Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Draft report for public consultation

Health technology assessment (HTA) of extending the national immunisation schedule to include HPV vaccination of boys

24 July 2018

1 Introduction

1.1 Background to the request

In June 2017, the Health Information and Quality Authority (HIQA) commenced work on a health technology assessment (HTA) in relation to proposed changes to the national human papillomavirus (HPV) immunisation programme. HIQA agreed to undertake the HTA following a formal request from the Department of Health for a HTA. The aim of the HTA is to establish the clinical and cost-effectiveness of extending the current immunisation programme, which offers HPV vaccination to all girls in their first year of second-level education (12 to 13 year olds), to a programme that also offers the vaccination to boys in their first year.

HPV is responsible for approximately 4.5% of the global cancer disease burden.[(1)] HPV is a double-stranded DNA virus that infects the skin and the mucosa of the anogenital and aerodigestive tracts. More than 200 HPV types have been identified.[(2)] Of the over 40 types proven to infect the epithelial cells of anogenital and oropharyngeal region, 12 types have been proven to be directly carcinogenic (the potential to cause cancer). In particular, HPV types 16 and 18 are responsible for the majority of HPV-associated cancers.

HPV is the most common sexually transmitted infection (STI).[(3)] It is mainly spread through skin-to-skin contact during sexual activity and around 90% (four out of five) of people will be infected at some point in their lives. It is transmitted sexually by both sexes.[(4)]

Persistent infection with oncogenic (cancer-causing) strains of HPV has a causative role in the development of invasive cervical, vaginal, vulvar, penile, anal, rectal and a subset of oropharyngeal cancers.[(5)] These cancers are broadly grouped as HPV-associated cancers, with cervical cancer by far the most common of these. The second most common HPV-associated tumour, oropharyngeal cancer, occurs three to four times more commonly in men than in women. HPV also has a causative role in the development of pre-cancerous lesions of the cervix, vulva, vagina, anus and penis.[(6)] It is strongly associated with anogenital warts with approximately 90% of anogenital warts directly attributable to HPV types 6 and 11.[(7)]

Ireland has a nationally funded, school-based, girls-only HPV immunisation programme. This programme commenced in 2010 with a three-dose schedule of the 4-valent (Gardasil®) vaccine. In line with recommendations from the World Health Organization (WHO), the current Irish national immunisation guidelines recommend a two-dose schedule for girls aged less than 15 years and three doses for girls aged 15 years and older or girls who are immunocompromised.

The efficacy of the HPV vaccine (which will be reviewed fully in Chapter 4) has been demonstrated in both male[8] and female populations.[9] Currently, 20 countries have recommended extending their national HPV immunisation programmes to include vaccination of boys. Austria was the first European country to recommend a national universal gender-neutral HPV immunisation programme in 2013 (although this was not publicly funded until 2014).[10] Other European countries that have since extended their programmes include Croatia, Germany, Italy, Norway, Serbia and Switzerland. Outside Europe, policy-makers in Australia, New Zealand, Canada and the US have also recommended universal gender-neutral HPV vaccination.

1.2 Terms of reference

This HTA is being carried out to assess the impact of changing from a policy of a girls-only school-based HPV immunisation programme to a policy of offering the HPV vaccine to both girls and boys (gender-neutral immunisation). The effect of different HPV vaccine uptake rates among girls on the clinical and cost-effectiveness of extending the immunisation schedule to include boys will also be assessed.

Based on this HTA, the Minister for Health will decide whether there should be a change in the national immunisation programme to extend the current programme, which offers HPV vaccination to all girls in their first year of second-level education (12 to 13 year olds), to a programme that also offers vaccination to boys. In consultation with the Department of Health, HIQA's Evaluation Team developed questions in relation to the critical information required to inform such a decision.

The Terms of Reference are to:

- describe the epidemiology of human papillomavirus (HPV) infection and HPV-related disease in Ireland
- perform a systematic review of the clinical effectiveness of HPV vaccines
- perform a systematic review of the safety of HPV vaccines
- perform a systematic review of the literature on the cost-effectiveness of HPV vaccination in males
- perform an economic evaluation of extending the current immunisation programme to include HPV vaccination of boys
- examine the effect of different HPV vaccine uptake rates among girls on the clinical and cost-effectiveness of extending the immunisation programme to boys
- estimate the budget impact of any changes to the current immunisation programme
- estimate the organisational and resource implications of any changes to the current immunisation programme
- consider any wider ethical or societal implications that HPV vaccination of boys

may have for patients, the general public or the healthcare system
- based on this assessment, advise on extending the national immunisation schedule to include HPV vaccination for boys.

1.3 Overall approach

Following an initial scoping of the technology, the Terms of Reference of this assessment were agreed between HIQA and the Department of Health.

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders including the Department of Health, the National Immunisation Office in the Health Service Executive (HSE), the National Cancer Registry, clinicians with specialist expertise, and public representation. The role of the Expert Advisory Group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group is available in the acknowledgements section of this report.

The Terms of Reference of the Expert Advisory Group are to:

- contribute to the provision of high-quality and considered advice by HIQA to the Minister for Health
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to HIQA regarding the scope of the analysis
- support the Evaluation Team led by HIQA during the assessment process by providing access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate
- contribute to HIQA's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

HIQA appointed an Evaluation Team comprising staff from the Health Technology Assessment Directorate to carry out the assessment.

The Terms of Reference of the HTA were reviewed by the Expert Advisory Group at the group's initial meeting. Draft findings on the epidemiology of HPV infection in Ireland, and findings from systematic reviews of the literature of clinical efficacy, clinical effectiveness and cost-effectiveness of HPV vaccination of boys were discussed at that meeting, as well as a plan for the economic evaluation. Vaccine safety and considerations regarding the cost-effectiveness, budget impact,

organisational, social and ethical implications of an extension of the current girls-only HPV immunisation programme to gender-neutral immunisation were discussed at subsequent meetings. Draft versions of this report were circulated for review by the Expert Advisory Group for their feedback.

HIQA is seeking the views of interested parties on the findings of this draft report through a public consultation taking place until 5pm on Friday 7 September 2018. Members of the public can participate in the public consultation on www.hiqa.ie.

Following the public consultation, a final draft report will be prepared and submitted to the Board of HIQA for approval. The completed assessment will be submitted to the Minister for Health and the Health Service Executive (HSE) as advice and published on the HIQA website.

2 Description of technology

2.1 Introduction

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract and is the cause of a range of conditions in both males and females, including a range of cancerous and precancerous lesions and anogenital warts. Although the majority of HPV infections do not cause symptoms and resolve spontaneously, persistent infection with HPV may result in disease.[5]

This chapter describes the three licensed HPV vaccines that serve as the primary prevention tool to prevent HPV infection and its sequelae. This chapter also provides background on HPV's potential as a pathogen and the resulting disease, which will be explored in greater detail in Chapter 3. The current adolescent school-based girls-only HPV immunisation programme in Ireland is described along with the range of HPV immunisation programmes found internationally.

2.2 Pathogen

Human papillomavirus (HPV) belongs to the family of viruses known as *Papillomaviridae*. Over 200 HPV types have been identified and characterised to date. HPV infects both cutaneous and mucosal epithelial cells and are highly tissue-specific.[11, 12]

Papillomavirus isolates are traditionally described as 'types'. HPV types may be classified in many ways, including the locations on the body that each virus tends to infect (cutaneous or mucosal types) and by their potential to cause cancer, that is, high-risk versus low-risk types. Twelve HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) are considered by the International Agency for Research on Cancer (IARC) to be carcinogenic (class I) and associated with a higher risk of progression to cancer; these are referred to as 'high-risk' HPV types.[13] HPV 66 is classified as probably carcinogenic (Group 2A) by the IARC, while 12 other types are considered possibly carcinogenic (Group 2B).[13]

HPV is the cause of almost all cervical cancer cases and is responsible for a substantial fraction of other anogenital cancers, oropharyngeal cancer and anogenital warts. HPV is responsible for approximately 4.5% of the global cancer disease burden,[5] with cervical cancer the most common cancer caused by HPV infection. Approximately 70% of cervical cancers are associated with HPV types 16 and 18.[14] These, in addition to HPV types 31, 33, 45, 52 and 58 account for approximately 90% of all invasive cervical cancer cases.[15] The IARC has also concluded that there is sufficient evidence to support a causal role of HPV 16 in cancers of the anus, penis, oropharynx, vulva and vagina.[16] The association

between HPV infection and invasive cancer at various anatomic locations is discussed in more detail in Section 3.6 of Chapter 3.

2.3 Disease

HPV viruses are spread through contact with infected genital skin, mucous membranes or bodily fluids and can be transmitted through intimate contact and sexual intercourse, including oral sex. The majority of HPV infections are asymptomatic and resolve spontaneously within one to two years.[5] Persistent infection with oncogenic (cancer-causing) strains of HPV is well-established as an important risk factor for invasive cervical, vaginal, vulvar, penile, anal, rectal and a subset of oropharyngeal cancers.[5]

Persistent HPV infection is defined by the presence of type-specific HPV DNA on repeated clinical biological samples over a period of time, usually six month periods, although this time period is not universally accepted.[17, 18] Once HPV is acquired, the median duration of HPV infection appears comparable between men[19] and women,[20] with genital HPV type 16 infections typically having a longer duration than most other HPV types in both men[19] and women.[21] About five to 10% of all infections may become persistent.

Persistent infections over months or years may progress towards premalignant glandular or squamous intra-epithelial lesions (precursors to invasive disease). In the cervix, they are classified histopathologically as cervical intra-epithelial neoplasia (CIN). CIN is further classified as: CIN 1: mild dysplasia; CIN 2: moderate to marked dysplasia; and CIN 3: severe dysplasia to carcinoma *in situ*. Most CIN lesions regress spontaneously; however, some lesions on the cervix can slowly become cancerous over a number of years. Squamous intra-epithelial lesions at other sites include vulvar intra-epithelial neoplasia (VIN), vaginal intra-epithelial neoplasia (VaIN), penile intra-epithelial neoplasia (PIN) and anal intra-epithelial neoplasia (AIN). A proportion of these premalignant lesions progress to invasive carcinomas. The interval between the acquisition of HPV infection and progression to invasive cancer is usually 20 years or longer.[5] The basis for this progression is not well understood.

HPV infection causes anogenital warts in females and males (condylomata acuminatae or venereal warts). Over 90% of these cases are associated with HPV types 6 and 11. These are usually referred to as 'low-risk' types indicating that they have a low, or no risk of causing cancer. The reported median time between infection with HPV types 6 or 11 and the development of anogenital warts is 11 to 12 months in young men and five to six months in young women.[22-24] Anogenital warts can be difficult to treat and may lead to psychological distress.

HPV types 6 and 11 can also cause a rare condition known as recurrent respiratory papillomatosis (RRP), in which warts form on the larynx or other parts of the

respiratory tract with the risk of airway obstruction.[25] RRP occurs in two forms:

- juvenile onset RRP which is caused by vertical transmission of HPV from mother to a susceptible child around the time of birth and usually presents in childhood,
- and adult onset RRP which is probably transmitted through sexual activity, with onset in young adulthood, typically in the third decade of life.[25]

RRP causes significant morbidity and may require multiple surgical interventions to maintain a patent airway to sustain life.

The epidemiology and burden of HPV-related disease is discussed in detail in Chapter 3.

2.4 Immune response after HPV infection

The median time from HPV infection to seroconversion (that is, the time period during which a specific antibody develops and becomes detectable in the blood) is approximately eight to 12 months, although immunological response varies significantly by individual and HPV type. As HPV infections are restricted to the epithelial layer of the mucosa, a vigorous immune response is not invoked.[17, 26]

The best-characterised and most type-specific HPV antibodies are those directed against the L1 protein of the virus. After natural infection, approximately 70 to 80% of women produce antibodies (seroconvert). Their antibody responses are typically slow to develop and of low titre and avidity. In men, seroconversion is rare as there is typically little response to HPV infection.[19] Even when seroconversion does happen in men, the antibodies produced are not generally protective.[27]

The available data are ambiguous as to whether natural infection with HPV induces protection against re-infection.[5] There appears to be a reduced risk of re-infection with the same HPV type, but infection does not seem to provide group-specific or general immune protection from infection with other HPV types. In most cases, those who develop lesions mount an effective cell-mediated immune response and the lesions regress.[28] Failure to develop an effective cell-mediated immune response to clear the infection results in persistent infection and, in the case of high-risk HPV types, an increased probability of progression to cancer.[17]

2.5 Detection of HPV

With the exception of cervical screening, patients are not usually screened or tested for HPV infection. Often there is little clinical utility in testing for HPV. For example, anogenital HPV infections are very common in young, sexually active populations;[20] in some studies, up to 70% of college-aged women are found to be HPV DNA

positive when tested.[21] The large majority of HPV infections are transient and asymptomatic and do not lead to disease.[22] In any case, no treatment exists for HPV infection.

The HPV virus cannot be cultured in tissue. For this reason, in most cases accurate identification of HPV is achieved through molecular biological techniques. Tests of choice for detecting HPV from clinical specimens include nucleic acid probe technology.[29] Direct detection of HPV genomes as well as transcripts can be achieved with hybridisation procedures. These include Southern and Northern blots, dot blots, in-situ hybridisation, signal-amplification molecular technology (Hybrid Capture assay [HC2]) and DNA sequencing of the genome. The only procedure that may be capable of recognising all HPV types and variants present in a biologic specimen is DNA sequencing of the viral genome, such as direct sequencing of a polymerase chain reaction (PCR) fragment.[22, 29]

The initial methods used to detect HPV were direct probe hybridisation, such as dot blot and Southern blot. Unfortunately these tests had low sensitivity and required large amounts of DNA in clinical samples. These methods have largely been replaced by amplification technology, which has allowed detection of low-level virus copy numbers in clinical samples. The established routine method for viral detection is the hybridisation of viral nucleic acids.

The two main techniques are:[22, 29, 30]

1) Signal amplification

The Hybrid Capture 2 (HC2) assay, which uses signal amplification, was the first technique to become commercially available. It can detect as little as 1 pg of HPV DNA per ml. Like other first-generation assays, HC2 assay detects HPV in aggregate (pooled positive or negative finding for five 'low-risk' [6, 11, 42, 43, 44] and 13 'high-risk' [16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68] HPV types) and does not specify the particular type(s) detected. The GP5+/6+ PCR-enzyme immunoassay (EIA) is a nucleic acid amplification assay that identifies 14 HPV types (the same types targeted by HC2, plus HPV 66). In 2009, an international expert committee proposed criteria for the validation of HPV assays in the context of primary screening for cervical cancer. It required that new tests should be highly reproducible and at least as accurate as the HC2 or GP5+/6+ PCR-EIA assay (defined as a relative sensitivity and specificity of ≥0.90 and ≥0.98, respectively to detect CIN 2+in a screening cohort aged 30 or older).[31]

2) Polymerase chain reaction (PCR)

PCR is a selective target amplification assay. It is capable of an exponential and reproducible increase in the HPV sequences present in biological specimens.

Theoretically, the amplification process can produce one billion copies from a single double stranded DNA molecule after 30 cycles of amplification.[25] Therefore, care must be taken to avoid false-positive results derived from cross-contaminated specimens or reagents. Testing for the presence of more than one HPV type in the biologic specimen is preferentially done by PCR-based methods, as it facilitates partial (for example, specific reporting of the presence of HPV 16 and or HPV 18 and pooled positive findings for other high-risk HPV types) and full genotyping (which allow all of the high-risk HPV genotypes to be distinguished in a single test).

In summary, HPV tests capture information differently. When considering HPV prevalence, it is important to take into consideration the testing platform used as it influences both the ability of the test to detect HPV (sensitivity and specificity) and the range of HPV types detected. As noted, for the purposes of cervical screening, it is recommended that the test used should be at least as accurate as HC2. PCR has the highest sensitivity, but is prone to false-positives due to cross-contamination. Testing for the presence of more than one HPV type in the biologic specimen is preferentially done by PCR-based methods.

2.6 Vaccines

2.6.1 Vaccine description

Three HPV vaccines are currently available and marketed in many countries worldwide for the prevention of HPV-related disease. The European Medicines Agency (EMA) first licensed the quadrivalent (or 4-valent) vaccine in September 2006, the bivalent (or 2-valent) vaccine in September 2007 and the nonavalent (or 9-valent) vaccine in June 2015.[32] For the remainder of this report, we will refer to these vaccines as 2-valent, 4-valent or 9-valent for clarity and consistency.

All of these vaccines are preventative and are intended to be administered, if possible, before a person becomes sexually active, that is, before a person is first exposed to HPV infection. Using recombinant deoxyribonucleic acid (DNA) technology, all three vaccines are prepared from the purified L1 structural proteins that self-assemble to form HPV type-specific empty shells, called virus-like particles (VLPs). None of the vaccines contain live biological products or viral DNA. Therefore, none of the vaccines are infectious. Neither do any of the vaccines contain antibiotics or preservative agents.

As of December 2017, three vaccines are licensed and marketed for use in Ireland to prevent HPV infections: the 2-valent vaccine Cervarix®, produced by GlaxoSmithKline which contains HPV 16 and 18 antigens;[33] the 4-valent vaccine Gardasil®, produced by MSD which contains HPV 6, 11, 16 and 18 antigens;[34] and the 9-valent vaccine Gardasil® 9, also produced by MSD which contains HPV 6, 11, 16, 18, 31, 33, 45, 52

and 58 antigens. A summary of the key characteristics of these vaccines including the indications for which they are currently licensed is included in Table 2.1.

All three vaccines protect against HPV types 16 and 18. These two HPV types are associated with 70% of precancerous cervical abnormalities and invasive cervical cancer. The 4-valent and 9-valent vaccines also provide protection against HPV types 6 and 11. While not oncogenic strains, HPV 6 and 11 are the causative agents for over 90% of anogenital warts. The 9-valent vaccine provides protection against five additional high-risk HPV types (31, 33, 45, 52 and 58). Overall, the seven high-risk HPV types included in the 9-valent vaccine are associated with almost 90% of precancerous cervical abnormalities and invasive cervical cancers. It is also known that the 2-valent and 4-valent vaccines confer a certain degree of cross-protection to the additional types included in the 9-valent vaccine, with the 2-valent vaccine conferring greater cross-protection than the 4-valent.[35]

Of note, Gardasil® 9 (the 9-valent vaccine licensed for use in Ireland) has been issued with a black triangle warning by the European Medicines Agency (EMA). This signifies that Gardasil® 9 is monitored even more intensively than other medicines. This is generally because there is less information available on it than on other medicines, for example a black triangle warning is often issued when a product is new to the market. The warning does not mean that the medicine is considered unsafe. In addition to Ireland, Gardasil® 9 has market authorisation in 50 other countries worldwide.

Table 2.1 Summary of key characteristics of the licensed HPV vaccines available in Ireland

Vaccine	2-valent	4-valent	9-valent
Trade name	Cervarix®	Gardasil®	Gardasil®9
Manufacturer	GlaxoSmithKline	MSD	MSD
Antigens	2-valent vaccine: Viral L1 protein for HPV types 16, 18	4-valent vaccine: Viral L1 protein for HPV types 6,11,16,18	9-valent vaccine: Viral L1 protein for HPV types 6,11,16,18,31,33,45,52,58
Formulation	Produced using a baculovirus expression system in Trichoplusia ni cells. Each 0.5 mL dose of the 2-valent vaccine contains 20µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto a proprietary adjuvant system containing 500 µg of aluminum hydroxide and 50 µg of 3-O-desacyl-4-monophosphoryl lipid A (AS04).	Produced using yeast substrate and includes amorphous aluminum hydroxyphosphate sulfate (AAHS) as adjuvant. Each 0.5 mL dose of this vaccine contains 20 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 40 µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto 225 µg of the adjuvant.	Produced using yeast substrate and includes the AAHS adjuvant. Each 0.5 mL dose of this vaccine contains 30 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 60 µg of HPV-16 L1 protein, 40 µg of HPV-18 L1 protein, 20 µg of HPV-31 L1 protein, 20 µg of HPV-33 L1 protein, 20 µg of HPV-45 L1 protein, 20 µg of HPV-52 L1 protein and 20 µg of HPV-58 L1 protein adsorbed on 500 µg AAHS.
Population	Girls and boys ≥9 years	Girls and boys ≥9 years	Girls and boys ≥9 years
Therapeutic indications	Prevention of the following conditions causally related to certain oncogenic HPV types: • Premalignant anogenital (cervical, vulval, vaginal and anal) lesions • Cervical cancer • Anal cancer	Prevention of the following conditions causally related to certain oncogenic HPV types: • Premalignant anogenital (cervical, vulval, vaginal and anal) lesions • Cervical cancer • Anal cancer • Prevention of anogenital warts (condyloma acuminata) causally related to specific HPV types	Prevention of the following conditions causally related to certain oncogenic HPV types: • Premalignant anogenital (cervical, vulval, vaginal and anal) lesions • Cervical cancer • Anal cancer • Prevention of anogenital warts (condyloma acuminata) causally related to specific HPV types

¥Reference: Summary of Product Characteristics – www.medicines.ie accessed 1/9/17[33, 34]
http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter10.pdf[36]

2.6.2 Administration, manufacturers' stipulated schedules and storage

For all HPV vaccines, the vaccination schedule stipulated by the manufacturer depends on the age of the vaccine recipient. The vaccines should be administered by intramuscular injection in the deltoid region of the upper arm.

2-valent HPV vaccine[37]

For girls and boys aged between nine and 14 years, a two-dose schedule (0.5 mL at zero and five to 13 months) is recommended. A minimum of five months must have elapsed between the first and second dose; if not, a third dose is required. If the age at the time of the first dose is 15 years or older, three doses (0.5 mL at zero, one and six months) are recommended. The need for a booster dose has not been established.

4-valent HPV vaccine[38]

For girls and boys aged nine to 13 years, a two dose schedule (0.5 mL at zero and six months) is recommended. If the second vaccine dose is administered earlier than six months after the first dose, a third dose is required. For girls and boys aged 14 years and older, the vaccine should be administered according to a three-dose schedule (0.5 mL at zero, two and six months). The second dose should be administered at least one month after the first dose and the third dose should be administered at least three months after the second dose. The need for a booster dose has not been established.

9-valent HPV vaccine[39]

For girls and boys aged nine to fourteen years, a two dose schedule (0.5 mL at 0 and five to 13 months) is recommended. If the second vaccine dose is administered earlier than five months after the first dose, a third dose is required. For individuals 15 years of age and older, the 9-valent vaccine should be administered according to a three-dose schedule (0.5 mL at zero, two and six months). The need for a booster dose has not been established.

Storage of HPV vaccines

HPV vaccines should be maintained between two and eight degrees Celsius (°C) and should not be frozen. They should be administered as soon as possible after being removed from the refrigerator.

For the 2-valent vaccine, stability has been demonstrated when stored outside the refrigerator for up to three days at temperatures between 8°C and 25°C, or for up to one day at temperatures between 25°C and 37°C. For the 4-valent vaccine, stability studies demonstrate that the vaccine is stable for three days when stored at temperatures of 8°C to 42°C. For the 9-valent vaccine, data indicate that the vaccine

components are stable for up to three days when stored at temperatures of 8°C to 25°C.

2.7 HPV immunisation programmes

2.7.1 Ireland's HPV immunisation programme

Ireland has a nationally funded, school-based, girls-only HPV immunisation programme. A pilot programme was first introduced in May 2010 in 20 Irish schools with a subsequent national programme rolled out in September 2010. The 2010-2011 programme initially consisted of a three-dose schedule of the 4-valent vaccine (Gardasil®) for girls in first and second year of second level schools and age-equivalent girls attending special schools or who were home schooled. A catch-up programme targeting girls in sixth year (final year) in second level schools and for age-equivalent girls attending special schools, home schooled, Youthreach, and community training centres was provided from September 2011 and repeated for girls in sixth year in 2012 and 2013. Since September 2014, the programme has targeted girls in first year.[40] As described in Section 2.6.2, the programme now consists of a two-dose schedule.

The current Irish national immunisation guidelines recommend a two-dose schedule for those aged nine to up to 15 years and three doses for those aged 15 years and older.[41] Uptake of the vaccine was initially high in Ireland with an 86.9% uptake for the two-dose schedule reported among girls in the first year of second level school (typically 12 to 13 years old) in the 2014 to 2015 academic year. There was some evidence of regional variation in uptake (77.4% to 90.8%) among the HSE's nine community healthcare organisations (CHOs), with eight achieving the target of at least 80% uptake. Uptake ranged from 75.1% to 96.9% in HSE local health offices; with 30 of 32 local health offices reaching the target of at least 80% uptake.[42]

For the 2015 to 2016 academic year, the national uptake of girls who completed the two-dose schedule was 72.3%, a significant decrease compared with the previous year. There was some regional variation evident, with uptake among the CHOs ranging from 66.3% to 77.6%.[43] For the 2016 to 2017 academic year, national uptake of girls who completed the two-dose schedule was 51%.[44] This constituted a large decline in uptake compared with previous academic years. There was some regional variation with uptake among the CHOs ranging from 47.5% to 61%. Among the local health offices, uptake ranged from 39.8% to 73.8%. Preliminary data from the 2017 to 2018 academic year indicate an increase in vaccine uptake to 61.7% (first dose completion), likely due in part to a targeted HPV vaccine information campaign launched by the HSE to raise awareness of the benefits of the vaccine. The prior decline was attributed to concerns about HPV vaccine safety following

high-profile negative publicity.[45] The safety of the HPV vaccines is reviewed in detail in Chapter 7.

A related decline in HPV vaccination rates due to local safety concerns was documented in a number of other countries including Denmark where rates of a three-dose schedule initially declined from 42% in 2014 to 24% of 13 year olds in 2015.[46] Vaccination is offered to girls in Denmark until age 18. However, a delayed vaccination pattern has been observed whereby a greater proportion initiate vaccination at age 14 than at age 13. A report in September 2017 indicated that overall uptake rates have increased again in Denmark, with 95% receiving their first dose by age 18.[38]

Japan witnessed the most severe drop in vaccination rates, with current vaccination coverage approaching zero. The significant decline occurred in girls who were born in the year 2000. In June 2013, the Japanese Ministry of Health, Labour, and Welfare suspended proactive recommendations for the HPV vaccine after unconfirmed reports of adverse events following vaccination appeared in the media.[47] In January 2014, the Vaccine Adverse Reactions Review Committee investigating these adverse events concluded that there was no evidence to suggest a causal association between the HPV vaccine and the reported adverse events after vaccination, but did not reinstate proactive recommendations for its use.[47]

High vaccination rates have been consistently maintained elsewhere, including Northern Ireland where vaccination is offered in year nine (12 to 13 year olds) and again in year 10 (13 to 14 year olds). By June 2017, 89.6% of girls had completed the two-dose schedule by the end of year 10.[48] A decrease in the first-dose uptake of the vaccine in year nine girls was noted between 2014 and 2017 (91.5% to 82.4%). The largest decrease occurred in the regions that border the Republic of Ireland, with the Southern and Western Health and Social Care Trusts experiencing decreases from 90.6% to 75% and from 92.4% to 79.5%, respectively. However, as noted in Denmark, the pattern appears to be one of delayed vaccination whereby a greater proportion chose to initiate vaccination at an older age. Despite the drop in uptake in these areas, by year 10 (13 to 14 year olds) all regions in Northern Ireland achieved a first dose coverage above 90% in 2017, which is very high by international standards.

Due to differences in the recommended HPV schedule and in the delivery of the two-dose schedule, vaccination uptake rates from other countries are not directly comparable. Nonetheless, vaccination uptake rates in the UK have been broadly comparable to those initially achieved in Ireland, with uptake rates of greater than 80% consistently achieved.[42] Countries that have a school-based HPV immunisation programme have reported higher vaccine uptake rates.[49]

As noted, Ireland's current immunisation programme is based on the 4-valent vaccine that protects against HPV types 6, 11, 16 and 18, thereby only protecting against approximately 70% of cervical cancer cases. Screening for cervical cancer is therefore still recommended for those who have received the vaccine. The first cohort of vaccinated girls (that is, those vaccinated as part of the catch-up programme in 2011) will be eligible for CervicalCheck, Ireland's national cervical screening programme, in 2018-2019.

While adolescent boys are not included in Ireland's national HPV immunisation programme, since January 2017 men who have sex with men (MSM) aged 16 to 26 years may avail of HPV vaccination through publicly-funded sexually transmitted infection (STI) clinics.[50] Additionally, both male and female patients who are HIV-positive (and under the age of 26) are offered HPV vaccination through HIV clinics.

2.7.2 International practice

HPV immunisation programmes vary greatly internationally. Examples of differences between programmes include the following:

- Population served (whether girls only or gender-neutral, and if targeted programmes for MSM and HIV-positive patients are in place)
- Funding mechanism (programmes may be included in the national schedule, but not necessarily reimbursed)
- Vaccination coverage or uptake rate
- Mode of delivery. While most programmes are school-based (which results in higher uptake rates[51]), programmes may also be delivered through a variety of community-based administration programmes.

As of December 2017, government-funded national HPV immunisation programmes are in place in 71 countries; 55 are female-only and 16 are gender-neutral programmes. Forty-one nationally-funded HPV programmes use Gardasil® with Germany, Denmark Italy, Portugal, Canada, Croatia, Slovenia, Austria, New Zealand and the US using Gardasil®9. Gardasil®9 was also adopted as part of the Australian HPV immunisation programme in 2018.[52] From 2006 until the end of the first quarter of 2017, 227 million doses of Gardasil® and 24 million doses of Gardasil®9 were distributed globally. Notable examples of countries that do not have a national HPV immunisation programme in place include China and India, with a combined population of over 1.4 billion people. The World Health Organization (WHO) has developed numerous initiatives to both improve acceptance and accelerate the granting of licenses for HPV vaccinations in these regions.

For a description of international immunisation programmes, for which information is available, see Appendix 2A.

In most European countries, a decision has not been made to recommend universal HPV vaccination of girls and boys (gender-neutral vaccination).[10] Austria was the first European country to recommend a national universal gender-neutral HPV immunisation programme in 2013 (although the programme was not publicly funded until 2014).[10] Elsewhere in Europe, a recommendation for gender-neutral vaccination is in place in Croatia, Czech Republic, Liechtenstein, Serbia, Switzerland and Norway. Vaccination of boys is also recommended and funded in nine Italian regions (Veneto, Puglia, Sardinia, Molise, Friuli Venezia, Giulia, Liguria, Sicilia, Calabria). In Germany, a permissive (Category B) recommendation for boys was issued in Saxony in 2013, that is, it was recommended that individual clinical decision-making be used to determine if HPV vaccination would be appropriate. This contrasts with a Category A recommendation which states that all members of a defined group should (or should not) be vaccinated. Vaccination is offered in Saxony to males through voluntary funding by some sick funds. In Ireland, a statement recommending vaccination of boys was issued by the National Immunisation Advisory Committee (NIAC) in 2013. Statements in favour of MSM vaccination were issued in the UK (JCVI, 2014) and Greece (January 2015).

A statement by the UK's Joint Committee on Vaccination and Immunisation (JCVI) in July 2018 reported that, when standard economic methodology is used, extending the girls-only programme in the UK to include boys would not be a cost-effective use of resources.[31] The statement argued however that the use of a lower 1.5% discount rate could be justified given the long natural history of HPV-associated disease. Gender neutral vaccination was predicted to be cost-effective compared with the existing girls-only programme if a discount rate of 1.5% is adopted, and on this basis the JCVI have advised that the current schedule in the UK should be extended to include boys.

Outside Europe, policy-makers in Australia, New Zealand, Canada and the US, among others, have recommended universal gender-neutral HPV vaccination. Australia extended the national HPV immunisation programme to include boys aged 12 to 13 years in 2013,[53] with a catch-up programme available for boys aged 14 to 15 years in 2013 and 2014.[54] In 2015, the reported uptake rate of a three-dose course was 77.8% in girls and 67% in boys.[55] In January 2017, vaccination of girls, boys, young women and young men age nine to 26 years with the 9-valent vaccine was introduced in New Zealand.[56] Table 2.2 lists all countries that have a gender-neutral HPV immunisation programme in place as of December 2017.

Table 2.2 Countries and regions that include HPV vaccination of boys in their national immunisation programme

Continent	Country and or region
Europe	Austria
	Croatia
	Czech Republic
	Germany (Saxony region only)
	Italy (nine regions only)
	Liechtenstein
	Serbia
	Switzerland
	Norway
North America	USA
	Canada
South America	Argentina
	Brazil
Caribbean and Central America	Puerto Rico
	Antigua
	Panama
	Bermuda
Middle East and Africa	Israel
Australasia	Australia
	New Zealand

Data accurate to December 2017

2.8 Discussion

Human papillomavirus (HPV) is the most common viral infection of the reproductive tract and is the cause of a range of conditions in both men and women. HPV is responsible for approximately 5% of the global cancer disease burden with cervical cancer the most common cancer caused by HPV infection. HPV also has a causal role in cancers of the anus, penis, oropharynx, vulva and vagina. HPV is responsible for a range of precancerous lesions and anogenital warts in men and women.

The large majority of HPV infections only last for a short while (are transient) and do not lead to disease. When considering HPV prevalence, it is important to take into consideration the testing platform used as HPV tests capture information differently (as discussed in section 2.5). Accurate identification of HPV infection is achieved through molecular biology techniques, such as signal amplification and polymerase chain reaction (PCR).

Three vaccines are licensed and marketed for use in Ireland to prevent HPV infections: the 2-valent vaccine Cervarix®, produced by GlaxoSmithKline which contains HPV 16 and 18 antigens; the 4-valent vaccine Gardasil®, produced by MSD

which contains HPV 6, 11, 16 and 18 antigens; and the 9-valent vaccine Gardasil® 9, also produced by MSD which contains HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antigens.

In common with the majority of countries worldwide, Ireland's national HPV immunisation programme involves girls-only vaccination using the 4-valent vaccine. While adolescent boys are not included in the school-based programme, men who have sex with men (MSM) aged 16 to 26 and HIV positive individuals (male and female under the age of 26) may avail of the vaccine through STI and HIV clinics in Ireland.

Since the license for the 9-valent vaccine was granted, many countries have replaced the 4-valent vaccine with the 9-valent vaccine. In total, 10 countries have made the change — all European countries apart from the US, Australia and New Zealand. The other recent change to HPV immunisation programmes worldwide is the expansion of girls-only programmes to include boys. To date, 20 countries have adopted gender-neutral immunisation recommendations. They include countries spread across six continents and include both high-income and middle-income economies.

Vaccine uptake rate (also called vaccine coverage) varies greatly between countries. Some are historically low, others are consistently high; others such as Ireland have seen a drop following negative publicity in recent years. The mechanism for vaccine reimbursement varies too, however it is most commonly through public funding. Most are delivered through schools, which has been shown to improve uptake rates.[51]

Key points

- Human papillomavirus (HPV) is the most common viral infection of the reproductive tract causing a number of conditions in both men and women, including a range of cancerous and precancerous lesions and anogenital warts.
- Papillomavirus isolates are traditionally described as 'types'. There are 12 HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) considered to be carcinogenic and associated with a higher risk of progression to cancer.
- As of December 2017, three vaccines are licensed and marketed for use in Ireland to prevent HPV infections. These contain antigens to two (Cervarix®), four (Gardasil®), and nine (Gardasil® 9) HPV types, respectively.
- All three vaccines protect against HPV types 16 and 18. These two HPV types are associated with 70% of precancerous cervical abnormalities and invasive cervical cancer. The 4-valent and 9-valent vaccines also provide protection against HPV 6 and 11. While not carcinogenic, HPV 6 and 11 are the causative agents for over 90% of anogenital warts.
- The 9-valent vaccine provides protection against five additional high-risk HPV types HPV types (31, 33, 45, 52 and 58). Overall, the seven high-risk HPV types included in the 9-valent vaccine are associated with almost 90% of precancerous cervical abnormalities and invasive cervical cancers.
- Since September 2010, Ireland has had a nationally funded, school-based, girls-only HPV vaccination programme in place.
- HPV vaccination has also been offered to HIV positive men and women under the age of 26 since 2016 through HIV clinics and, since January 2017, HPV vaccination has been offered to men who have sex with men (MSM) aged 16 to 26 through STI clinics in Ireland.
- Internationally, HPV vaccination programmes vary considerably in terms of target population, vaccine uptake rate, mechanism of funding and setting (school-based or community administration).
- Worldwide, 20 countries have either implemented, or plan to implement, a gender-neutral HPV vaccination programme.

3 Epidemiology

3.1 Introduction

This chapter describes the prevalence of HPV infection and the burden of disease associated with HPV infection in Ireland. Persistent infection with oncogenic (cancer-causing) strains of human papillomavirus (HPV) is well-established as a risk factor for developing cervical, vaginal, vulvar, penile, anal, rectal and a subset of oropharyngeal cancers. HPV infection is mainly spread through skin-to-skin contact during sexual activity and around 90% of people will be infected with HPV at some point in their lives. The cancer risk relates mainly to carcinomas of the cervix and to squamous cell carcinomas (SCCs) of the other sites. These specific cancers can be broadly grouped as HPV-associated cancers (although not all cases can be directly attributed to HPV infection). In addition to invasive cancerous lesions, HPV has a causative role in the development of pre-cancerous lesions of the cervix, vulva, vagina, anus and penis. HPV is also strongly associated with anogenital warts (also known as condyloma acuminatae); approximately 90% of anogenital warts (AGWs) are directly attributable to HPV types 6 and 11.

The average annual number of new cancers at these sites based on the sex- and age-specific cancer incidence data between 2009 and 2013, retrieved with permission from the National Cancer Registry Ireland, is presented in this chapter.[55] The National Cancer Registry Ireland (NCRI) is a publicly-appointed body, established in 1991, to collect and classify information on all cancer cases which occur in Ireland. Incidence data of precancerous lesions of the cervix (Cervical Intraepithelial Neoplasia [CIN]) is also presented (obtained from CervicalCheck, Ireland's national cervical screening service).

At present, no agency routinely collects comprehensive data from the general population on the incidence or prevalence of other precancerous lesions known to be associated with HPV infection. These include precancerous lesions of the anus (Anal Intraepithelial Neoplasia [AIN]), vulva (Vulvar Intraepithelial Neoplasia [VIN]), vagina (Vaginal Intraepithelial Neoplasia [VaIN]) and the penis (Penile Intraepithelial Neoplasia [PIN]). Only higher-grade (carcinoma in situ) lesions (e.g. AIN3, VIN3 etc) of these sites are currently registered by NCRI. Therefore, to estimate the total incidence of these lesions in Ireland, a literature review to identify countries that routinely collect these data was performed. The quality, completeness and representativeness of the collected data were then assessed. If transferable to the Irish context, the age-specific incidence rates were used to estimate the predicted annual incidence of such lesions in the Irish population.

Incidence data on the prevalence of HPV infection in cervical specimens were

obtained from CERVIVA (a multi-investigator research collaboration located in Ireland).[56] No Irish prevalence data on HPV infection in the general population at sites other than the cervix could be found. For this reason, a literature review was performed to identify international prevalence studies and their applicability to the Irish population was assessed.

This report distinguishes between HPV-associated and HPV-attributable tumours. 'HPV-associated' refers to tumours that are of squamous cell carcinoma (SCC) morphology and that occur at an anatomic location known to be associated with HPV (or any carcinoma of the cervix); however, not all of these tumours are directly caused by HPV. 'HPV-attributable' tumours refer to the proportion of HPV-associated disease causally related to infection with HPV.

The relative contribution of HPV ('HPV-attributable disease') in oropharyngeal carcinoma was estimated using data obtained from the NCRI[57] and from an Irish clinical audit.[58] Data on HPV-attributable disease in other tumours, and the relative contribution of specific HPV types in all tumours, were extracted from the most relevant published cancer site-specific data available in the scientific literature. The number of new cancers in Ireland attributable to HPV overall, to HPV types 16 and 18 (protection against which is provided by all three licensed vaccines available in Ireland), and to HPV types 16, 18, 31, 33, 45, 52 and 58 (protection against which is provided by the 9-valent vaccine, Gardasil®9) were then estimated by applying the corresponding cancer site-specific HPV prevalence to the average annual number of HPV-associated tumours in Ireland.

3.1.1 Overview of burden of HPV-associated cancers

On average, 539 cases of HPV-associated cancers were diagnosed every year in Ireland from 2009 to 2013 (see Table 3.1). Of these, three out of four (405) were in women and one out of four (134) in men (NCRI). Cervical cancer was the most frequent, with on average 308 cases per year (76% of all cases in women and 57% of the overall total of HPV-associated cancers). The next most frequent were oropharyngeal squamous cell carcinomas (123 per year or 23% of the total) and squamous cell carcinomas of the vulva (37 per year or 7% of the total), anus (28 per year or 5% of the total), penis (29 per year or 5% of the total), vagina (eight per year or 1% of the total) and rectum (six per year or 1% of the total).

Table 3.1: Average annual number of HPV-associated cancer cases, 2009-2013

Tumour	Case number	Proportion of total
Cervix	308	57%
Oropharynx	123	23%
Vulva	37	7%
Anus/Rectum	34	6%
Penis	29	5%
Vagina	8	1%

*Data courtesy of National Cancer Registry Ireland (NCRI)

HPV-related tumours account for 2.6% (4.1% for females and 1.3% for males) of all invasive cancers (excluding non-melanoma skin cancer) diagnosed in Ireland.[59] The three-fold difference in rates of HPV-associated invasive cancers between women and men is driven by the burden of cervical cancer cases. Rates of anal and or rectal squamous cell carcinoma were higher in women than in men, but rates of oropharyngeal squamous cell carcinoma were three to four times higher in men than in women.

3.2 Prevalence and natural history of HPV infection

3.2.1 Introduction

Many factors confound the calculation of the overall prevalence and transmission of HPV infection within a given population. Prevalence studies differ depending on the anatomic site and the population from which the sample is retrieved. As highlighted in Chapter 2, Section 2.5, prevalence studies also differ based on the testing platform used due to differences in the range of HPV types detected, the sensitivity and specificity of the test and how results are reported (aggregate, partial or full genotyping).

HPV infection can be detected at a range of anatomical sites, including oral, genital, anal and cervical mucosa. No studies have been completed in Ireland to date that estimate the population-level prevalence of HPV infection at anatomic sites other than the cervix.

A report by Giuliano et al. published in 2015, as part of the EUROGIN roadmap, reviewed the differences in HPV infection in terms of its natural history, transmission and incidence by gender and anatomic site of infection.[60] Few studies in the review included both men and women from the same underlying population and fewer still included sampling at multiple anatomic sites. The review concentrated on studies that employed similar methodologies and from comparable populations. In general there was a lack of HPV natural history publications for all anatomic sites other than the cervix. The review identified studies from North and Latin America that indicate

genital HPV prevalence is higher in men[60] than in women.[61, 62] Additionally, age does not appear to influence genital HPV prevalence in men,[63] but is strongly negatively associated with cervical HPV prevalence in women.[62] The proportion of high-risk (hrHPV) and low-risk (lrHPV) HPV infections in women[61, 62] appears equivalent (hrHPV: 14–15%; lrHPV: 18%); however, in men, the prevalence of lrHPV (39%) is substantially higher than hrHPV (30%).[63] Once HPV is acquired, the median duration of HPV infection appears comparable between men[19] and women,[20] with genital HPV 16 infections typically having a longer duration than most other hrHPV types in both men[19] and women.[21]

3.2.2 Genital infection

Only a few studies have evaluated genital HPV prevalence by anatomic site. In studies among men, HPV prevalence is highest at the penile shaft[64] and lowest at the urethra.[64, 65] Among women, HPV prevalence is highest at the cervix and vagina and appears lower at the vulvar epithelium.[65] This may be due to the unique vulnerability of the cervical transformation zone to infection. In contrast to women where there is marked reduction in prevalence with increasing age, HPV prevalence rates by age in men are relatively stable or slightly decrease with increasing age.[66]

3.2.2.1 Men

To our knowledge, no studies have been conducted to date that estimated the population-level prevalence of HPV infection in men in Ireland. Internationally, the prevalence of genital HPV infection in men has been found to vary substantially between different populations.

The most recent estimates of HPV infection in the general population emanate from the US.[67] In April 2017, the Centers for Disease Control and Prevention (CDC) reported on the prevalence of HPV infection at genital and oral sites in men and women between 2011 and 2014. It reported a prevalence of 'any genital' HPV of 42.5% (95% CI: 39.6 to 45.4) among adults aged 18 to 59 years during 2013 to 2014.[67] Gender-specific HPV prevalence was reported as 45.2% (95% CI: 41.5 to 49.0) among men and 39.9% (95% CI: 36.8 to 43.1) among women. In this study, 'any genital' HPV means they tested positive to one or more of the 37 HPV types from a penile or vaginal swab sample.

Another relatively recent prevalence study in men was published in 2015 in Denmark.[68] Penile swab samples from 2,460 male employees and conscripts at military barracks were tested for HPV DNA with the hybrid capture 2 (HC2) method and a polymerase chain reaction (PCR) assay. The overall HPV prevalence using HC2 was 22.2% (95% CI: 20.6 to 23.9) and 41.8% (95% CI: 39.9 to 43.8) using PCR. Prevalence of hrHPV was estimated at 17.8% (95% CI: 16.3 to 19.3) with the HC2 test and 30% (95% CI: 28.1 to 31.8) with the PCR test. Of the 24 HPV types tested

for in the PCR assay, HPV type 51 was the most prevalent at 20.8% (95% CI: 18.3 to 23.3). HPV type 16 was the second most prevalent at 13.8% (95% CI: 11.7 to 16.0). Age-specific prevalence of HPV infection was estimated when the HC2 results were stratified by high-risk and low-risk HPV types. The prevalence of both high-risk and low-risk HPV increased significantly to a peak at 26.6% (95% CI: 20.1 to 32.4) in men aged 22 to 24 years. Prevalence decreased with age thereafter.

Prior to this, a systematic review and meta-analysis of 10 studies which included 1,863 men was published in 2014.[(69)] An estimation of the pooled HPV prevalence of the general population in Europe was 12.4% (95% CI: 5.6 to 21.5). The HPV prevalence in Northern Europe (which included Ireland), was estimated at 13.7% (95% CI: 5.0 to 26). Most articles were published before 1999 and, in most studies, samples were collected from more than one anatomical site. The prevalence was estimated to be lower in both Southern Europe at 12.6% (95% CI: 0.0 to 42.4) and Western Europe at 5.9% (95% CI: 4.0 to 8.0). However, due to significant heterogeneity between studies the results of this meta-analysis must be viewed with caution. Studies differed considerably in terms of assay used for HPV detection, anatomical location of sampling and population from which samples were obtained.

A UK-based study[(70)] examining the NATSAL-3 trial recruited 15,162 women and men aged 16 to 74 years between 2010 and 2012. Urine samples from a sample of participants (1,885 males) aged 16 to 44 years, who reported at least one sexual partner over their lifetime, were tested for the presence of sexually transmitted infections (STIs). The prevalence of hrHPV amongst men of all ages was 8.4% (95% CI: 6.8 to 10.4). Prevalence was lowest in men aged 18 to 19 years at 4.0% (95% CI: 2.0 to 7.9) and highest in 25 to 34 year olds at 9.2% (95% CI: 6.6 to 12.6). The lower estimates observed in this study may be due to the sampling technique. Urine is a suboptimum specimen for the detection of STIs, particularly HPV in men. It is therefore likely that the prevalence estimates reported in this study are underestimated.

From the above studies, it is clear that the prevalence of genital HPV in men varies widely depending on the population sampled and the testing methodology employed. Earlier studies using less advanced HPV testing procedures tended to report lower estimates, with higher estimates observed in recent studies conducted in the US ('any HPV' of 45.2% [95% CI: 41.5 to 49.0])[(67)] and in Denmark ('any HPV' of 41.8% [95% CI: 39.9 to 43.8] and 'high risk' of 30% [95% CI: 28.1 to 31.8] by PCR).[(68)] The prevalence estimates identified in the Danish study appear most applicable to Ireland, as it is the most recently conducted study in Northern Europe and it employed advanced HPV testing techniques. Of note, however, the men recruited consisted of military conscripts as opposed to the general Danish male population.

3.2.2.2 Women

For women, Irish data are available for cervical HPV infection. Preliminary data from CERVIVA (the Irish Cervical Screening Research Consortium), in collaboration with CervicalCheck (Ireland's national cervical cancer screening programme), indicate a prevalence rate of hrHPV of 14.6% in cervical cytology of women in the general population.[71]

CERVIVA, an Irish multidisciplinary research consortium which focuses its research on cancer of the cervix and other HPV-associated cancers, is conducting an observational study to evaluate and compare different strategies for the triage of women with a high-risk HPV DNA/HPV mRNA positive primary screening test.[72] The cohort comprises women aged 23 to 60 years attending CervicalCheck for a routine cervical screening test. A residue of each smear sample is retained for high-risk HPV DNA and high-risk HPV mRNA testing. The study will determine a baseline population prevalence of high-risk HPV DNA and high-risk HPV mRNA. The study is ongoing and the results are yet to be published. However, preliminary data have been released to inform this HTA.[73] To date, 4,500 women have been recruited (median age 38 years [IQR 32-45 years]). Analysis was conducted on 3,222 samples. The rate of mRNA positivity was lower than the rate of DNA positivity, but this difference was not significant. For clarity, only the high-risk HPV DNA results are presented here. The prevalence of high-risk HPV was 14.6%. The genotype-specific prevalence of high-risk HPV (cobas® 4800 HPV test) is shown in Table 3.2. Prevalence was highest in those aged less than 30 years and decreased with increasing age.

Table 3.2 Genotype specific prevalence of high-risk HPV by DNA testing[72]

Age (years)	HPV 16 (%)	HPV 18 (%)	hrHPV *(%) (excluding HPV 16/18)
<30 (n=509)	9.2	2.2	20.4
30 to 39 (n=1,204)	3.5	1.0	10.8
40 to 49 (n=1,036)	2.0	0.5	5.9
50 years and older (n=473)	1.5	0.8	5.3
Total (n=3,222)	3.6	1.0	9.9

*hrHPV: high-risk HPV includes a pool of 12 genotypes (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68)

Internationally, there is evidence of substantial inter-country and intraregional heterogeneity in the prevalence of HPV, as evidenced by a systematic review and meta-analysis of 194 studies which included just over a million women with normal cervical cytology from 59 countries.[74] Worldwide, a peak in HPV infection was observed in women under the age of 25 years. Thereafter, it declined to a plateau.

Prevalence was higher with worsening dyskaryosis[1], and the five most prevalent genotypes were HPV 16 (3.2%), HPV 18 (1.4%), HPV 52 (0.9%), HPV 31 (0.8%), and HPV 58 (0.7%).(74)

As previously discussed, it is proposed that estimates from the Danish study by Hebnes et al. (2015) will be used as a surrogate HPV prevalence estimate for the Irish male population. For comparison, a study by Kjær et al. published in 2014 analysed residual specimens from liquid-based cytology samples from 40,382 women from 2002 to 2005 in Denmark.(75) Similar methods were employed as Ireland's CERVIVA study mentioned previously, whereby all samples were tested for hrHPV using the Hybrid Capture 2 technique, and genotyping was done using LiPa (Innogenetics). Study participants were 14 to 95 years of age at enrollment. The overall prevalence of high-risk HPV was 20.6 % ranging from 46% in 20 to 23-year-old women to 5.7% in women aged 65 years or older. It is notable that 43% of this sample was obtained from women aged 34 years or less whose hrHPV prevalence is highest. CERVIVA's estimates for Ireland, on the other hand, are based on comparably fewer samples from this age group which may explain the lower overall estimate for HPV prevalence among women in Ireland.

3.2.3 Oral infection

To our knowledge, no prevalence studies of oral HPV infection have been conducted in Ireland. In the US, the Centers for Disease Control and Prevention (CDC) reports an overall prevalence of oral HPV infection of 7.3% among adults aged 18 to 69 years during the period 2011 to 2014 (data obtained from the National Health and Nutrition Examination Survey 2011-2014).(67) 'Any' HPV refers to any HPV type detected. HPV prevalence was higher in men (11.5%) than women (3.3%).(67) The prevalence of oral hrHPV was 4% among adults aged 18 to 69 years; 6.8% among men and 1.2% among women.

The HPV Infection in Men (HIM) study was a large prospective study carried out to evaluate the natural history of oral infection with HPV.(27) It consisted of a multi-national cohort of over 4,000 men aged 18 to 70 years. The analysed cohort consisted of 1,626 men (499 from Brazil, 557 from Mexico, and 570 from the USA) who were provided oral rinse-and-gargle samples at two or more study visits and completed a minimum of two weeks of follow up. During the first 12 months of follow up, 4.4% (95% CI: 3.5–5.6) of men acquired a new oral HPV infection of any type, 1.7% (95% CI: 1.2–2.5) acquired a new oral high-risk HPV infection, and 0.6% (95% CI: 0.3–1.1) acquired a new oral HPV 16 infection. A long-term follow up of this study was subsequently conducted; 23 participants who provided an oral HPV-positive sample on two or more study visits were followed for a median of 44.4 months.(76) Of 13 incident infections, the median infection duration was seven months. Of 10 prevalent

[1] Dyskaryosis is an abnormality of nuclei seen in exfoliated cells, often cells from the uterine cervix.

infections, nine persisted for more than one year. Twelve-month persistence of incident infections increased significantly with age, potentially explaining the higher prevalence of oral HPV observed at older ages.

3.2.4 Anal infection

Anal HPV infection is common among women and men, including heterosexual men.[77-79] Anal HPV prevalence differs by gender[80]and male sexual orientation.[81, 82] Among men, anal HPV prevalence varies widely by sexual practice. Studies of anal HPV among heterosexual men show a prevalence of approximately 12%.[79] In contrast, studies among men who have sex with men (MSM) demonstrate a higher prevalence, with more than half of HIV-negative MSM having any type of anal HPV infection, depending on the population sample.[83, 84] In Ireland, a prevalence study of anal HPV infection in MSM attending a STI clinic reported that 69% had detectable HPV DNA, and 42% had a high-risk type.[85] Of note, over half (51%) of participants were HIV positive, and HIV-positive subjects were more likely than HIV-negative subjects to have any detectable HPV (77% versus 61%).

A US study conducted among 1,378 women over 18 years recruited from healthcare facilities estimated an anal HPV prevalence of 27%.[86] Studies among women that compare cervical and anal HPV infection have shown comparable prevalence estimates at both anatomic sites.[78, 86] Data on the persistence of anal HPV infection are lacking. However, as discussed in Section 3.6, invasive anal carcinoma is relatively rare in men and women.

3.2.5 HPV serology

Once infected, most individuals are able to naturally clear the infection through an immune response.[60] Nine to 24 months following initial HPV infection, a proportion of individuals develop detectable antibodies (seroconvert) to the specific HPV type.[87, 88] In one US study of 588 college women with incident HPV infections,[88] 59.5%, 54.1%, and 68.8% seroconverted for HPV types 16, 18, or 6, respectively, within 18 months of detecting the corresponding HPV DNA. In another US study, 58% to 67% of young women developed a detectable HPV 16 antibody within two years following an incident of HPV 16 infection, compared with only 7% to 11% of men.[89] Consistently, women demonstrate a higher HPV 16 seroprevalence than men, regardless of the population studied and despite higher genital and oral HPV DNA prevalence rates observed in men.[60]

The protection conferred by antibodies generated in response to infection against future HPV infections differs between men and women. Two studies (including the placebo arm of the Costa Rica HPV vaccine trial) describe a 50% reduction in risk against future HPV 16 infections among unvaccinated women who had high antibody titres for HPV 16, compared with HPV 16 seronegative women.[90, 91] Conversely, in

the prospective HIM Study, HPV 16 seropositivity in unvaccinated men was not associated with reduced risk of future HPV 16 infection, regardless of the level of antibody.[4]

3.2.6 Heterosexual transmission dynamics

As with all infectious agents, HPV transmission dynamics are dependent on both viral and host factors. Host susceptibility, contact rate per unit time, transmission probability and duration of infectiousness all influence transmission dynamics.[4] A meta-analysis of 30 HPV type-specific concordance studies[92] found that 26% of 2,972 couples were infected with one or more of the same genital HPV types, underscoring the high transmissibility of HPV. Concordance was even higher (63%) when the analysis was restricted to couples who were both genital HPV-positive.

Giuliano et al. (2015) identified five longitudinal heterosexual transmission studies with varying follow-up times, each of which recruited initially HPV-discordant couples.[60] In all studies, the incidence of transmission from men to women was lower than the incidence from women to men.

3.2.7 Type replacement

Due to the fact that current vaccines do not offer protection against all HPV types, there is a theoretical possibility that other types of HPV may emerge to fill the vacated ecological niche following elimination of vaccine-targeted HPV types. This theoretical concept is referred to as 'type replacement'.[93] Type replacement has been previously documented following pneumococcal vaccination.[94] The pneumococcal vaccine covered seven of the more than 92 pneumococcal serotypes, and following its introduction, the prevalence of non-vaccine targeted serotypes increased substantially among asymptomatic carriers.

Investigators have used observational (cohort or cross-sectional) data to evaluate HPV-type competition among unvaccinated women, with little evidence of competitive interactions observed.[93] Nonetheless, vaccination against only a portion of HPV types could introduce a competitive advantage for some HPV types not covered by the vaccine and could possibly lead to type replacement. Tota et al. (2017) investigated type replacement by pooling data from the Costa Rica Vaccine Trial and the PATRICIA trial, two large-scale, double-blind randomised controlled trials (RCTs) of the 2-valent vaccine.[95] Cumulative incidence of non-protected HPV infections across trial arms after four years were compared. The authors concluded that HPV-type replacement does not occur among vaccinated individuals within four years and is unlikely to occur in vaccinated populations.

3.2.8 Summary

In summary, there is evidence of substantial inter-country and intraregional

heterogeneity in the prevalence of HPV infection. HPV prevalence differs by gender and anatomic site, with a higher prevalence in the genital versus oral region.[67] There are limited published Irish HPV prevalence data. High-quality Irish data are available relating to cervical hrHPV prevalence in women who attend for cervical screening, which is estimated at 14.6%. No population-based prevalence studies were identified for men Ireland. A genital prevalence of hrHPV of 30% in men was estimated in Denmark.[68]

In contrast to women, where there is a marked reduction in prevalence with increasing age, HPV prevalence rates remain relatively stable or slightly decrease in men as they get older. A number of factors may contribute to this, including differences in transmission rates and immune response. Transmission rates differ by gender, with female-to-male transmission higher than male-to-female. The immune response to HPV also differs by gender and by anatomic site of infection. The immune response is stronger and more protective against re-infection in women than in men.

3.3 Cervical cancer and precancerous lesions

3.3.1 Introduction

Cervical cancer, mainly cervical carcinoma, is defined by its location. Cancers of the cervix uteri refer to those situated in the lower constricted part of the uterus or neck which connects the uterus to the vagina.[96] Invasive cervical cancer is usually preceded by precancerous abnormalities and pre-invasive cervical cancer (carcinoma *in situ*). Microscopically, this is characterised by abnormalities which progress from abnormal cervical cells (known as cervical intraepithelial neoplasia, CIN). The highest grade of CIN (CIN3) is considered equivalent to carcinoma in situ for purposes of cancer registration.

In Ireland, cervical cancer was the eighth most commonly diagnosed cancer in women between 2012 and 2014 (excluding non-melanoma skin cancer).[97] Cancer is the second most common cause of death in Ireland. Invasive cervical cancer was the twelfth most common cause of cancer death for women in Ireland between 2011 and 2012.[97]

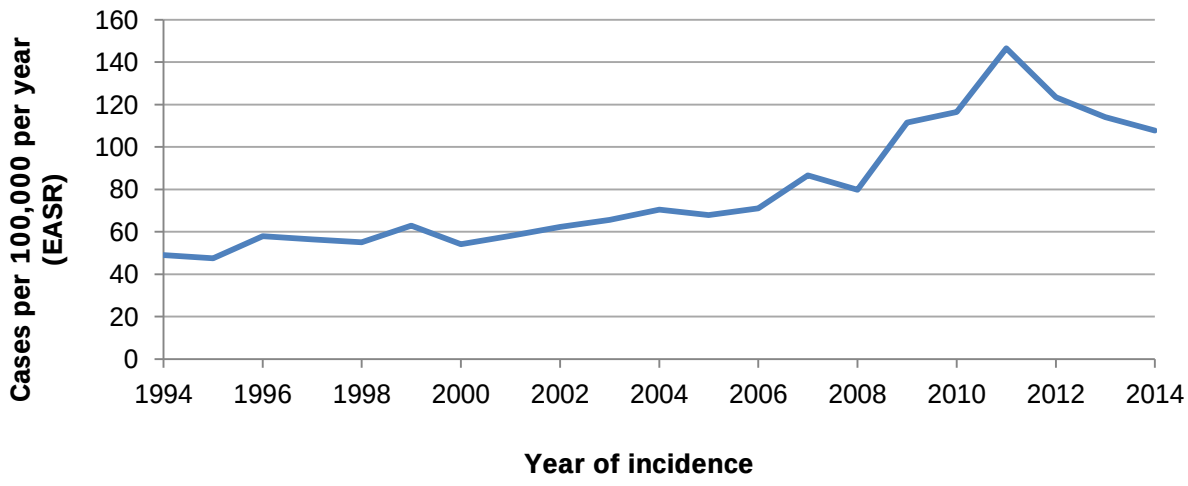
Within a European context, the estimated incidence of cervical cancer varies widely. In 2012, the estimated incidence in Ireland was 15.1 per 100,000 (European age-standardised rate [EASR]), compared with the EU27 incidence of 11.3 per 100,000.[98] Highest rates were recorded in Romania (34.9 per 100,000 EASR), with lowest rates in Switzerland (4.2 per 100,000 EASR). Ireland is ranked eighteenth within Europe, out of 40 countries, in terms of cervical cancer incidence.[98]

3.3.2 Incidence

Cervical carcinoma in situ

Carcinoma *in situ* refers to a cancer that has not spread and directly precedes invasive disease. Between 1994 and 2014, a total of 38,448 cases of cervical carcinoma *in situ* were diagnosed in Ireland. For the period 2012 to 2014, there were on average of 2,873 cases per year. There was an upward trend in the incidence of cervical carcinoma *in situ* in Ireland with age-standardised rates, increasing from 48.9 per 100,000 population at risk in 1994 to 107.7 per 100,000 population at risk in 2014 (Figure 3.1). The average incidence in the last three years of reporting (2012 to 2014) was 115.1 per 100,000 population at risk, corresponding with a cumulative lifetime risk of diagnosis of cervical carcinoma *in situ* (to age 74) of — one in every 13 women (Figure 3.1).

Figure 3.1 Age-standardised incidence rates of cervical carcinoma in situ* per 100,000 population at risk by year of diagnosis, Ireland 1994 - 2014



Data: National Cancer Registry Ireland, age–standardised to the European Standard Population (1976)

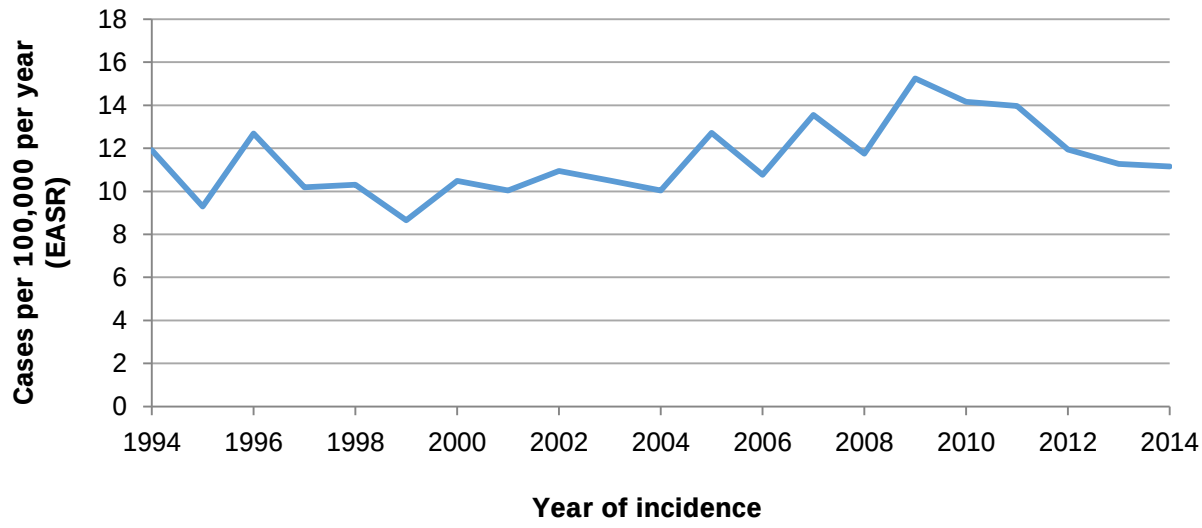
* Cervical carcinoma *in situ* corresponds with cervical intraepithelial neoplasia III (CIN 3) and adenocarcinoma in situ (AIS)

There was a marked increase in the reported incidence of cervical carcinoma *in situ* after 2008. This coincided with the introduction of CervicalCheck, and the high profile death in 2009 of a celebrity in the UK from invasive cervical cancer, publicity from which led to increased cervical screening uptake, particularly among those who hadn't received a previous smear.[99] Of note, these figures are based on incidence data for cervical carcinoma *in situ* provided by the National Cancer Registry in Ireland (NCRI). They differ from CervicalCheck treatment data (Section 3.3.5.1), as they do not include other conditions treated at colposcopy services such as CIN 2.

Invasive cervical cancer

Between 1994 and 2014, a total of 4,955 cases of invasive cervical cancer were diagnosed in Ireland. Almost 98% of these were regarded as a first significant tumour. Between 2012 and 2014, there were on average 277 cases diagnosed per year. The age-adjusted rate of invasive cervical cancer has increased slightly over time. The average incidence in the last three years of reporting (2012 to 2014) was 11.5 per 100,000 population at risk, corresponding with a cumulative lifetime risk of diagnosis (to age 74) of one in 112 women. Although there was some year-to-year variation, there was an overall slight increasing trend over time (Figure 3.2). When broken down into 30-year age bands, this trend was mirrored in the 30 to 59 year old age group. There was less clear evidence of trends in those aged under 30 and over 60 years, but these age groups accounted for fewer cases.

Figure 3.2 Age-standardised incidence rates of invasive cervical cancer per 100,000 population at risk by year of diagnosis, Ireland 1994 - 2014

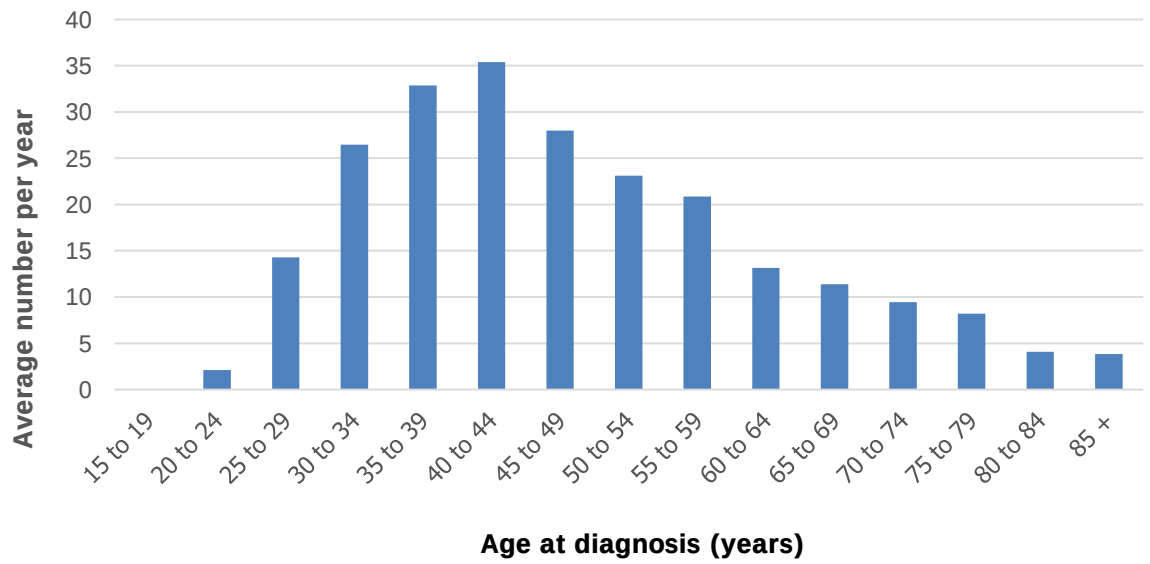


* Data: National Cancer Registry Ireland, age–standardised to the European Standard Population (1976)

A 2014 cancer projections report predicted that the numbers of invasive cervical cancers in Ireland would increase by 77% to 88% between 2010 and 2040, if trends in underlying rates up to 2010 continued, or by 18% if only demographic changes occurred.[100] Changing sexual behaviour and an increase in the prevalence of HPV were believed to be the most important factors influencing these trends.[100] However, these projections did not take into account the impact of CervicalCheck and the inclusion of HPV vaccination of schoolgirls in the national immunisation programme, and are well above those predicted based on demography alone which estimate an 18% increase in cases of cervical cancer by 2040.[100]

Cervical carcinoma is predominantly a disease of younger women. The average annual number of cases of invasive cervical cancer by age at diagnosis for the period 1994 to 2013 is shown in Figure 3.3. The most common age at diagnosis was between 40 and 44 years.

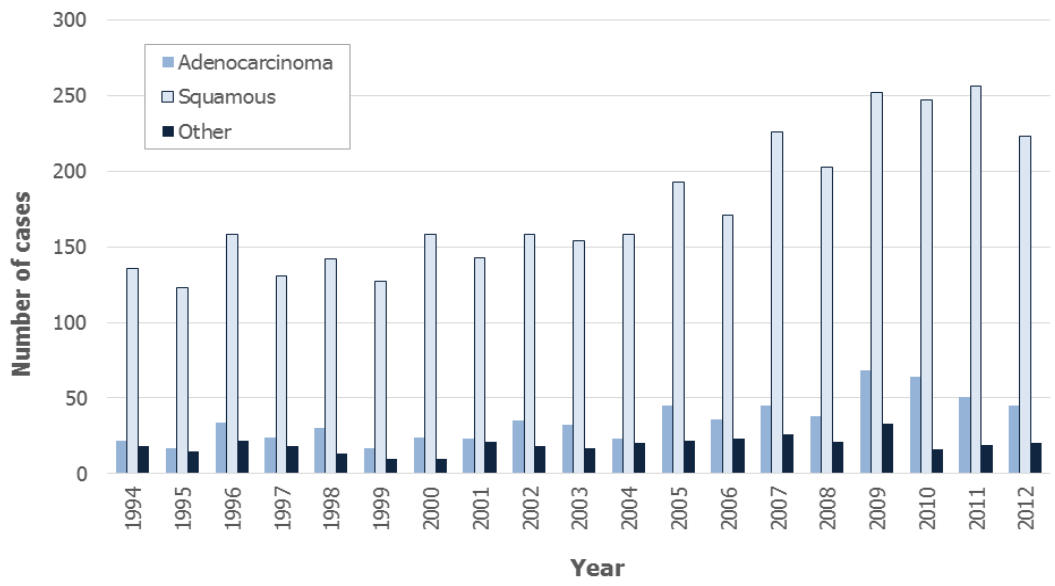
Figure 3.3 Average annual number of cases of invasive cervical cancer by age at diagnosis, 1994 to 2013



Data courtesy of National Cancer Registry, Ireland

Rates of invasive squamous cell carcinoma and invasive adenocarcinoma standardised to the European 1976 standard population are shown in Figure 3.4. These mirrored the overall age-standardised rate of invasive cervical cancer in this period. Peaks in the rates are seen in 2009 following the introduction of CervicalCheck in 2008.

Figure 3.4 Histological types of invasive cervical cancer by year of diagnosis, 1994 to 2012



Data courtesy of National Cancer Registry, Ireland

3.3.3 Precancerous lesions

CervicalCheck, Ireland's National Cervical Screening Programme, was introduced in September 2008. Originally, the screening strategy used liquid-based cytology (LBC) alone. In May 2015, the screening strategy was changed to include an additional reflex HPV testing (HPV triage) of low-grade cytological abnormalities. Between September 2015 and August 2016, a total of 272,086 women had a cervical screening test and 17,907 women attended colposcopy for the first time.[(101)]

In the first eight years of CervicalCheck up to August 2016, 1,269 invasive cancers, 50,302 cases of high-grade histological abnormalities (CIN 2, CIN 3 or AIS) and 36,619 cases of low-grade histological abnormalities were detected. Overall, for all women who attended colposcopy in 2016 (both new and follow-up appointments), 187 invasive cancers, 8,885 high-grade histological abnormalities and 7,114 low grade histological abnormalities were detected. This was the highest number of high-grade histological abnormalities recorded in a single year of operation since the start of CervicalCheck. The increase was almost certainly as a result of introducing the HPV triage strategy.

3.3.4 Calculation of HPV-attributable disease

Between 2009 and 2013, a total of 1,542 cases of invasive cervical cancer were diagnosed in Ireland. This gives an average incidence of 308 cases per year. It is generally accepted that persistent HPV infection is necessary for the development of

cervical carcinoma.[102] Thus, 100% of these cases are believed to be attributable to HPV.

A large-scale retrospective cross-sectional study designed and coordinated by the Institut Català d'Oncologia (ICO) in Barcelona, Spain, to estimate the prevalence of HPV DNA types in women with invasive cervical cancer during 1949 to 2009 was published by De Sanjose et al. in 2010.[103] Thirty-eight countries participated — Europe (Bosnia-Herzegovina, Croatia, Czech Republic, France, Greece, Italy, Netherlands, Poland, Portugal, and Spain); North America (the US); central South America (Argentina, Brazil, Chile, Colombia, Guatemala, Honduras, Mexico, Paraguay, Peru, and Venezuela); Africa (Algeria, Mozambique, Nigeria, and Uganda); Asia (Bangladesh, China, India, Israel, Japan, South Korea, Kuwait, Lebanon, Philippines, Taiwan, Thailand, and Turkey); and Oceania (Australia). In total, 22,661 cervical samples were obtained from 14,249 women. HPV types 16 and 18, included in the 4-valent HPV vaccine, were found to be the predominant types causing cervical cancer, accounting for 71% (95% CI: 70–72) of cases. High-risk HPV types 16, 18, 31, 33, 45, 52 and 58, included in the 9-valent vaccine, were found in 91% (95% CI 90–92) of cases. A full list of genotype distribution is provided in Table 3.3.

Table 3.3: Global HPV type distribution among invasive cervical cancer cases[104]

HPV type	HPV 6	HPV 11	HPV 16	HPV 18	HPV 31	HPV 33	HPV 45	HPV 52	HPV 58	All others
Total (n=8,977)	10 (<1%)	2 (<1%)	5439 (61%)	918 (10%)	335 (4%)	345 (4%)	528 (6%)	253 (3%)	203 (2%)	957 (11%)

A 2015 study by Hartwig et al. reported separately on samples from the European region of the study.[6] HPV types 16 and 18, included in the 4-valent HPV vaccine, were found to be the predominant types in cervical cancer, accounting for 72.8% (95% CI: 70.8–74.7) of cases. High-risk HPV types 16, 18, 31, 33, 45, 52 and 58, included in the 9-valent vaccine, were estimated to be responsible for 89.0% (95% CI: 87.5–90.3) of cases.[103]

Accordingly, a total of 224 cases of invasive cervical cancer cases are estimated to be attributable to HPV 16 and 18 annually in Ireland, versus 274 cases attributable to HPV 16, 18, 31, 33, 45, 52 and 58.

A 2014 report by Joura et al. estimated the proportion of CIN attributable to individual carcinogenic HPV subtypes, and the relative contribution of genotypes included in the 4-valent and 9-valent vaccines.[105] All CIN was found to be HPV-related, with HPV types included in the 4-valent vaccine accounting for 23-25% of CIN 1, 38.4–39% of CIN 2, and 58% of CIN 3. The HPV types targeted by the 9-valent vaccine account for 46-51% of CIN 1, 71-74.3% of CIN 2 and 85-90% of CIN

3. Hartwig, 2015 retrieved data from this study specific to the European region for CIN 2+ cases.[6] Adjusted for multiple infections, 45.5% of CIN 2+ cases are attributable to HPV types 16 and 18, with 82.3% attributable to HPV types 16, 18, 31, 33, 45, 52 and 58.

Between September 2015 and August 2016, a total of 8,885 cases of high grade CIN (CIN 2, CIN 3 and AIS) were diagnosed by CervicalCheck. Accordingly, an estimated 4,043 cases of CIN 2+ per year in Ireland are attributable to HPV types included in the 4-valent vaccine, and an estimated 7,312 cases of CIN 2+ are attributable the HPV types included in the 9-valent vaccine.

3.3.5 Treatment

3.3.5.1 Treatment of precancerous abnormalities

CervicalCheck, Ireland's National Cervical Screening Programme, aims to detect and treat women with precancerous abnormalities and early stage invasive cervical cancer. CervicalCheck classifies histological abnormalities according to CIN terminology. CIN describes squamous cell abnormalities which are classified histologically into low-grade abnormalities (CIN 1) and high-grade abnormalities (CIN 2 and CIN 3). CIN 3 is also called carcinoma *in situ*. CGIN (glandular cervical intraepithelial neoplasia) describe glandular cell abnormalities which are also classified into low-grade abnormalities and high-grade abnormalities; CGIN 3 is also called adenocarcinoma *in situ* (AIS).

Cold coagulation, large loop excision of the transformation zone (LLETZ), needle cone biopsy and cold knife cone biopsy are conservative methods for treating high-grade histological abnormalities.[106] LLETZ and cone biopsy completely remove the high-grade abnormality (including the transformation zone). A cone shaped wedge of cervical tissue is removed in a cone biopsy, hence the name. LLETZ and cold coagulation techniques are usually carried out under local anaesthesia in colposcopy clinics. Cold knife cone biopsy requires general anaesthesia.[106]

Between September 2015 and August 2016, 7,131 treatments were recorded at colposcopy by CervicalCheck in Ireland. LLETZ was performed in 5,173 (72.5%) cases and ablative treatment was used in 1,879 (26.3%) cases. Nineteen cone biopsies (0.3%), 57 hysterectomies (0.8%) and three trachelectomies (0.04%) were also performed. Almost all (97%) treatments were performed as outpatient procedures under local anaesthetic, exceeding the CervicalCheck target of 90%.

Overall, there is a substantial burden associated with the treatment of precancerous cervical abnormalities in Ireland. This includes the psychological burden associated with colposcopy, including general anxiety and screening-specific worries.[107]

3.3.5.2 Treatment of invasive cervical cancer

Squamous cell carcinoma is the most common histological type of invasive cervical cancer in Ireland. Between 1994 and 2012, it accounted for over 76% of invasive cervical cancers while adenocarcinoma accounted for just over 15%. Invasive cervical cancer is staged clinically according to the FIGO classification system. The stage of cervical cancer depends upon the size of the tumour, invasion of surrounding tissues, lymph node status and metastases. Risk assessment of a tumour incorporates the size of the tumour and depth of its invasion, histological genotype, stage, lymph node status and lymphovascular space involvement.[108] Primary treatment depends on the stage of the tumour and may consist of surgery, radiotherapy or a combination of chemotherapy and radiotherapy.[108] Management and treatment are recommended by a multidisciplinary team based on the stage, age and general health of the individual woman.

Early stage disease (FIGO stage IA1) may be managed conservatively with cone biopsy. Treatment options for women with FIGO stage IA2 to IVA include surgery, radiotherapy or the combination of chemotherapy and radiotherapy (chemoradiotherapy). Surgical treatment options for women with stage IA2 include radical hysterectomy and pelvic lymphadenectomy, large cone biopsy or radical trachalectomy and pelvic lymphadenectomy. Surgical treatment options for women with stage IB1, IB2 and IIA include radical hysterectomy and pelvic lympadenectomy. Surgery is the preferred treatment option in young women with stage IA2 and IB1 because it confers the benefit of conserving ovarian function, thus avoiding early menopause.[83] Radical trachelectomy is an alternative to radical hysterectomy for women with stage IB1 who wish to preserve fertility. Radical trachelectomy involves vaginal resection of the cervix, the upper vagina and the medial portions of the cardinal and uterosacral ligaments and prophylactic cervical cerclage. Radical hysterectomy involves the en-bloc removal of the uterus, cervix, parametrial tissues and upper vagina. This is usually combined with pelvic lymphadenectomy.

Women with stages IB2, IIA2 to IVA are generally treated with chemoradiotherapy.[83, 98] Surgery is not offered as a first resort to women with stage IB2, IIA2 to IVA because of the risk of positive margins and positive lymph nodes; however, it may be offered as adjuvant therapy where there is evidence of residual disease.[109, 110] Radiotherapy to the cervix is given by external beam radiotherapy or brachytherapy. Brachytherapy involves delivering radiotherapy into the uterus via the vagina. Women who present with metastatic or recurrent cervical cancer are commonly symptomatic.[108] They are generally offered palliative chemotherapy with or without immunotherapy and or individualised radiotherapy to relieve symptoms and to improve their quality of life.[108] Depending on previous care and the presence of central versus non-central disease, treatment may include exenteration with or without intraoperative radiotherapy, radical hysterectomy in carefully selected patients or brachytherapy. Complications associated with advanced

cervical cancer include pain, lymphoedema, fistulae, thrombosis, haemorrhage and renal failure.[109] Renal failure due to bilateral ureteric obstruction may require nephrostomy or ureteric stent placement.

According to NCRI data, since the year 2000 the proportion of women receiving different forms of treatment for invasive cervical cancer has been relatively stable (Table 3.4). Between 2000 and 2012, 63.3% received tumour-directed surgery, 39.8% received chemotherapy or immunotherapy, and 55.1% received radiotherapy. In the five years from 2008 and 2012, 39.7% of women had surgery alone, 20.2% had chemoradiotherapy and 15.9% had all three therapies.

Table 3.4 Treatment of invasive cervical cancer 2000 to 2012

Year	Tumour-directed surgery*$	Chemo or immunotherapy*	Radiotherapy*
2000	116	77	103
2001	107	78	106
2002	128	94	117
2003	127	78	128
2004	127	82	101
2005	155	119	152
2006	135	94	130
2007	192	119	155
2008	163	115	150
2009	240	136	182
2010	208	126	183
2011	232	106	170
2012	181	105	161

*Within a year of diagnosis
$ Surgeries for invasive cervical cancer include procedures such as LLETZ and cone biopsies as well as more extensive procedures such as hysterectomies.
Data courtesy of NCRI

Complications of treatment for invasive cervical cancer depend on the treatment modality used. Broadly speaking, complications impacting on quality of life can be categorised as: lymphoedema; bladder dysfunction and other urologic complications; bowel dysfunction and other gastrointestinal problems; sexual dysfunction; and psychosocial problems.[111] Treatment of advanced cervical cancer can lead to bladder dysfunction, detrusor overactivity, fistula and hydronephrosis.[112] Chemotherapy can result in toxicity-related adverse reactions although these may be short term. Radiation therapy is associated with haemorrhagic cystitis, ureteric stenosis, low-compliance bladder and fistula.[112] When multiple treatment approaches are used in combination, there may be a higher risk of long-term complications.[111]

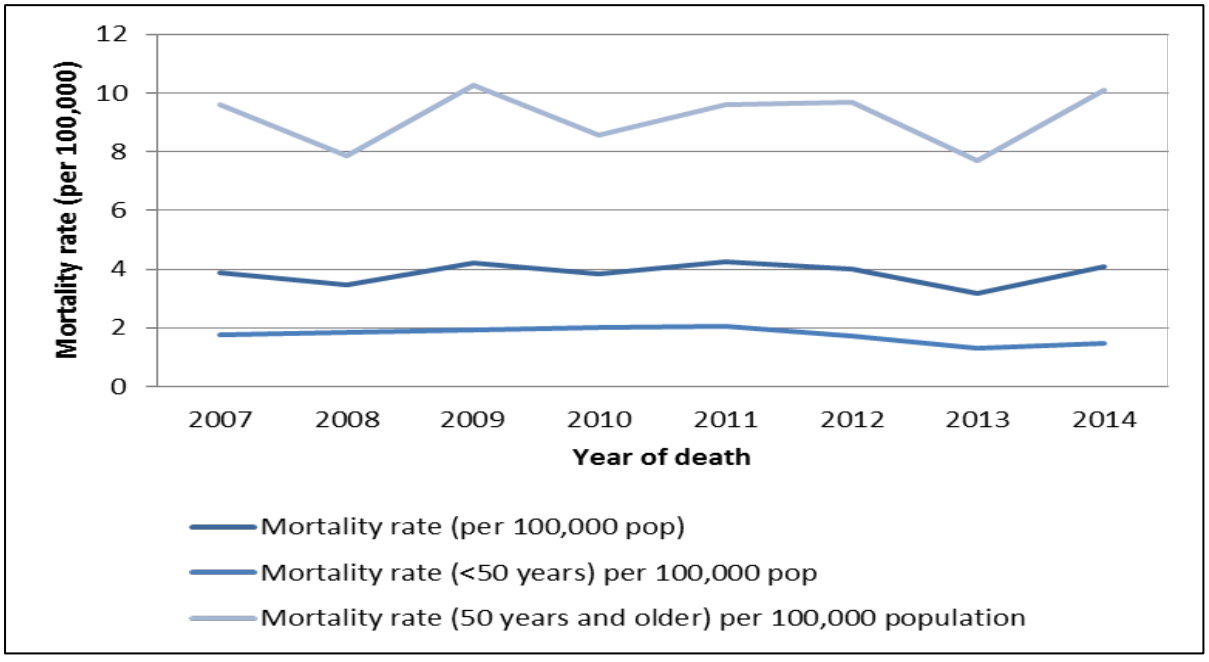
3.3.6 Mortality

The estimated annual age standardised mortality rate from invasive cervical cancer in 2012 was 4.3 per 100,000 in Ireland.[98] This was higher than the average annual rate for the 27 European Union member states (EU-27) which was 3.7 per 100,000 in 2012. The estimated age-standardised mortality rate from invasive cervical cancer in 40 European countries ranged from 14.2 per 100,000 (Romania) to 0.7 per 100,000 (Iceland) in 2012.[98] Ireland was ranked eighteenth.[98]

According to data from Ireland's Central Statistics Office (CSO), between 2007 and 2014, there were 710 deaths from invasive cervical cancer, an average of 89 deaths per year. The median age at death from invasive cervical cancer in Ireland is 56 years.[113] The annual number of deaths in women aged less than 50 years ranged from 22 to 35. This represents between 23% and 38% of all deaths from invasive cervical cancer.

Mortality rates for invasive cervical cancer, standardised to the European Standard population (ESP 1976), are shown in Figure 3.5. Although there has been year-on-year fluctuation, there has been no significant change in mortality between 2007 and 2014. Based on data from 2012 to 2014, the cumulative lifetime risk of death due to cervical cancer (to age 74) was one in 333 women.

Figure 3.5 Age-standardised mortality rates of invasive cervical cancer per 100,000 population by year of death in Ireland (2007 to 2014)



Data acquired from Central Statistics Office (CSO), standardised to the European Standard Population (1976)

In Ireland, mortality rates from invasive cervical cancer increased in the late 1960s and the early 1970s.[96] Rates subsequently declined somewhat; however, average mortality rates for invasive cervical cancer during 2010 to 2014 were approximately

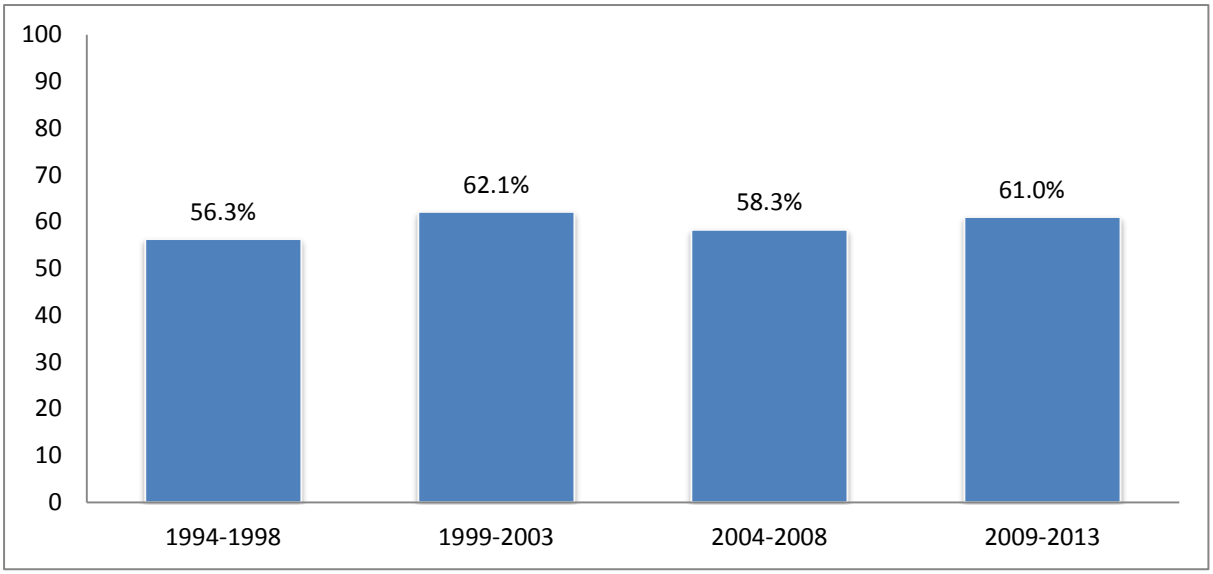
60% higher than in the early 1950s.[96] Relatively little change in the mortality rate from invasive cervical cancer has occurred in recent years.[96] When stratified by age at time of death, mortality rates are higher in women aged 50 years and over in comparison with younger women (Figure 3.5).

3.3.7 Survival

Based on data from the EUROCARE-5 study, the five-year relative survival for European women diagnosed with invasive cervical cancer between 2000 and 2007 was 62%.[114] Survival was lowest in Eastern Europe (57%), particularly in Bulgaria and Latvia (51%) and highest in Northern Europe (67%). Norway had the highest five-year relative survival at 71%. Ireland ranked 21 out of 28 countries with a five-year survival of 58.9%.[114] Across Europe, the study reported improvements in the age-standardised five-year relative survival rate from 61% (in 1999 to 2001) to 65% (in 2005 to 2007). However, it noted that exceptions to this trend were observed in Scotland and Ireland where a statistically significant reduction in five-year survival was observed.[114] In Ireland, five-year relative survival for these two periods were reported as 64% and 55%, respectively.[114]

The NCRI have estimated five-year survival using a cohort method (1994 to 1998, 1999 to 2003, 2004 to 2008) and a hybrid method (2009 to 2013). While relating to different time periods, five-year survival was estimated to have improved over time in Ireland from 56.3% in 1994 to 1998, to 61% in 2009 to 2013 (Figure 3.6).[115] The estimated trends in survival are clearly sensitive to the study periods and relatively small numbers of cases involved which may indicate that net five-year survival has remained largely static over the last 20 years.

Figure 3.6 Age-standardised net five-year survival for invasive cervical cancer in Ireland (1994 to 2013)

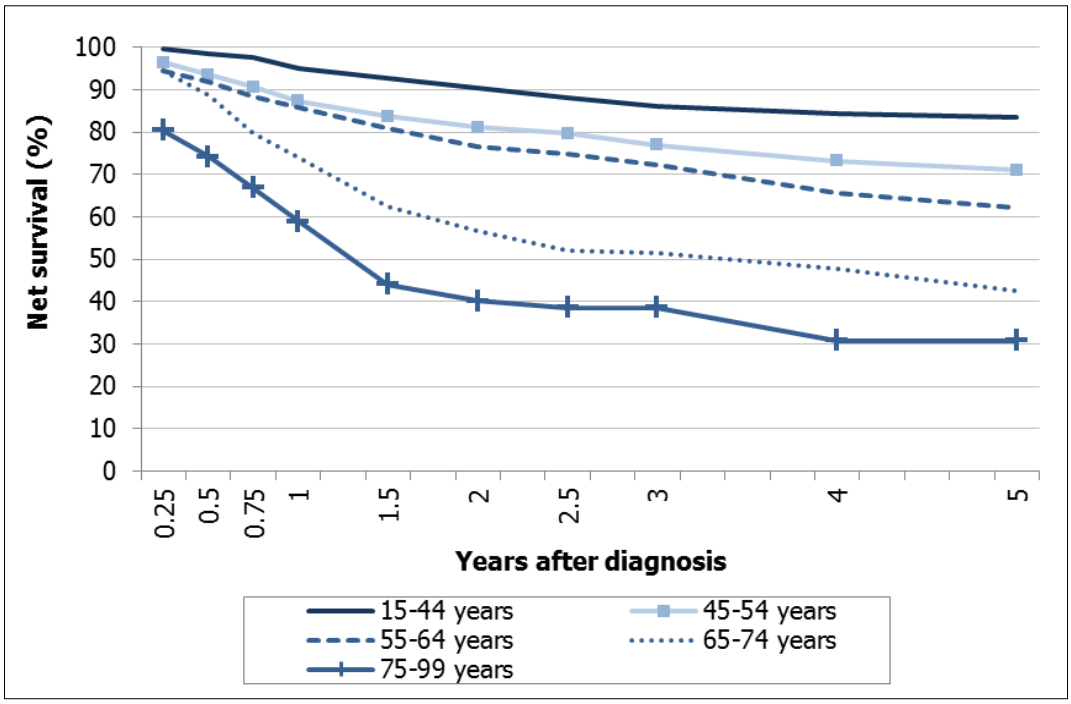


Figures acquired from NCRI, age-standardised

Age-standardised five-year relative survival in European women diagnosed with invasive cervical cancer between 2000 and 2007 reduced with advancing age.[116] Five-year relative survival in 15 to 44 year olds was 81%, but fell to 34% in those women aged 75 years and over at the time of diagnosis.[116]

This pattern was also observed in NCRI-calculated age-specific five-year relative survival for the time period 2008 to 2012 (Figure 3.7).[115] Those in the 15 to 44 year age group had a net five-year survival of 83.5%, whereas those aged 75 years and older at the time of diagnosis had a net five-year survival of 30.7%.

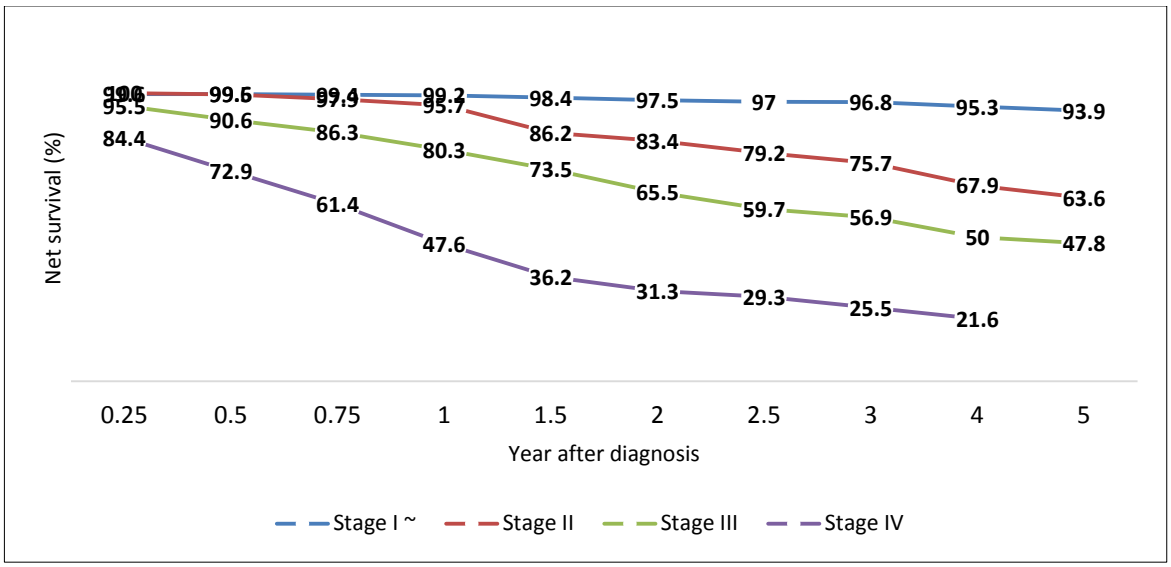
Figure 3.7 Net five-year survival for invasive cervical cancer by age, 2008 to 2012



Figures acquired from NCRI

The reduction in survival rates with increasing stage of tumour is well recognised.[25] NCRI age-standardised relative five-year survival calculations for the time period 2008 to 2012 are shown in Figure 3.8.[115] Net five-year survival for those diagnosed at stage II disease were 63.6%, at stage III were 47.8% and at stage IV were 21.6%. Note, age-standardised survival is unavailable for stage I as there were insufficient deaths in some age groups to allow age-standardisation calculations to be made. The five-year (un-standardised) survival for stage I disease was 93.9%.

Figure 3.8 Net five-year survival for invasive cervical cancer by stage, 2008 to 2012



Figures acquired from NCRI
~Data are age-standardised, with the exception of Stage I which is not age-standardised due to insufficient cases in some age groups

3.4 Vulvar cancer and precancerous lesions

3.4.1 Introduction

Cancer of the vulva is rare among women, with an estimated 27,000 new cases in 2008 worldwide, representing 4% of all gynaecologic cancers.[117] Approximately 60% of all vulvar cancer cases occur in more developed countries.

Vulvar cancer has two distinct histological patterns with two different risk factor profiles: basaloid or warty types and keratinising types.[118] Basaloid or warty lesions are more common in young women, are very often associated with HPV DNA detection (75-100%), and have a similar risk factor profile as cervical cancer. Keratinising vulvar carcinomas represent the majority of vulvar lesions (over 60%), they occur more often in older women and are more rarely associated with HPV.

3.4.2 Prevalence of invasive vulvar cancer and vulvar precancerous lesions

Between 2009 and 2013, NCRI data indicate that a total of 184 invasive squamous cell carcinomas of the vulva were diagnosed in Ireland. This gives an average annual figure of 37 cases per year during this period.

Population-level data on the incidence of pre-cancerous lesions of the vulva (vulvar intraepithelial neoplasia [VIN]) is not available in Ireland (with the exception of the highest grade lesion [VaIN 3]). These data are routinely collected in the Nordic countries however, where population-based cancer registries have been sources for

cancer statistics since the 1950s.[119] Cancer registration has been shown to be close to complete, timely and fairly accurate over time, and established routines for data quality assurance exist.[120]

A study by Nygard et al. published in 2014, collected data from four Nordic population-based registries over the period 2006 to 2008 (prior to the introduction of the HPV vaccine).[121] Age-standardised incidence rates of VIN 2 and VIN 3 ranged between 4.8 (Norway) and 8.8 (Iceland) per 100,000 woman-years. Table 3.5 lists the total number and age-adjusted (adjusted to the European standard population) incidence rates per 100,000 for each pre-invasive neoplasia.

Table 3.5: Age-adjusted incidence rates of cancer and pre-invasive neoplasia of the cervix, vulva and vagina, in Denmark, Iceland, Norway and Sweden (2004-2006)‡

	Denmark	Iceland	Norway	Sweden
Age-adjusted incidence rates per 100,000				
Cervical cancer	13.8	9.5	11.8	8.4
CIN 2/3 and AIS[a]	169.7	183.2	138.8	145.0
Vulvar cancer	3.1	1.3	2.9	1.8
VIN 2/3[b]	7.7	8.8	4.8	2.5*
Vaginal cancer	0.5	0.2	0.5	0.6
VaIN 2/3[c]	1.2	1.3	0.9	0.5*

‡ Ade-adjusted to the European standard population
[a]CIN2/3 and AIS - cervical intraepithelial neoplasia grade 2 and 3 and adenocarcinoma ***in situ***.
[b]VIN2/3 - vulvar intraepithelial neoplasia grade 2/3.
[c]VaIN2/3 - vaginal intraepithelial neoplasia grade 2/3.
*from Sweden only grade 3 VIN and VaIN were included.

Based on the age-specific incidence data from these countries, Hartwig et al. (2015) estimated that the annual number of new VIN 2 and VIN 3 cases in Ireland is between 108 and 220.[122]

3.4.3 Calculation of HPV-attributable proportion

A large-scale international collaborative study published by De Sanjose et al. in 2013[123] evaluated the HPV contribution and genotype distribution in invasive vulvar and vulvar intraepithelial neoplasia (VIN) lesions from pathological archives in 39 countries across five continents. The large-scale retrospective cross-sectional study was coordinated by the Catalan Institute of Oncology (ICO) and identified 2,296 specimens over a 30-year period (1980 to 2011). The European region covered Austria, Belarus, Bosnia-Herzegovina, Czech Republic, France, Germany, Greece, Italy, Poland, Portugal, Spain and the UK. Table 3.6 lists the relative contributions of each HPV type to HPV-DNA positive invasive vulvar cancer and VIN cases. Similar to other HPV-related tumours, HPV 16 is the most prevalent genotype.

Table 3.6 HPV genotype distribution amongst HPV-DNA VIN positive cases and invasive vulvar cancer cases that were both HPV-DNA and p16INK4A positive

HPV type	HPV-positive VIN		HPV and $p16^{INK4A}$ positive IVC	
	N	%	N	%
HPV 6	4	0.9	3	0.7
HPV 11	2	0.5	1	0.2
HPV 16	393	77.3	311	72.5
HPV 18	13	2.5	20	4.6
HPV 31	6	1.2	4	1
HPV 33	54	10.6	28	6.5
HPV 45	2	0.4	14	3.3
HPV 52	3	0.6	8	1.9
HPV 58	1	0.2	4	1
All other HPV types	28	5.8	34	8

HPV, human papillomavirus; VIN, vulvar intraepithelial neoplasia; IVC, invasive vulvar carcinoma

Hartwig (2015) reports on data from the ICO study specific to the European region.[6] The age-adjusted HPV-DNA and $p16^{INK4a}$ prevalence in invasive vulvar cancer was estimated at 19.3% (95% CI: 16.7–22.0). The $p16^{INK4a}$ protein is a surrogate marker of transforming infection. In normal cells it is expressed at a very low level and is almost undetectable; however, in cancerous and precancerous cells it is over-expressed. The addition of the $p16^{INK4a}$ biomarker was included as, contrary to cervical cancer where almost all cancer cases are reported to be $p16^{INK4a}$ positive, only 87.9% of the HPV-DNA positive invasive vulvar cancer cases were also $p16^{INK4a}$. The prevalence of HPV DNA in VIN cases was 86.9% (95% CI: 82.6–90.4).[6]

The relative contribution of HPV 16 and 18 and HPV 16, 18, 31, 33, 45, 52 and 58 are estimated at 73.6% (95% CI: 66.4–79.9) and 84.0% (95% CI: 77.6–89.0) of HPV-DNA positive invasive vulvar carcinomas, respectively.[123] The relative contribution of HPV 16 and 18 and HPV 16, 18, 31, 33, 45, 52 and 58 are estimated at 82.2% (95% CI: 77.2–86.6) and 94.4% (95% CI: 91.0–96.9) of VIN cases, respectively.[123]

3.4.4 HPV-attributable disease in Ireland

Given the overall HPV prevalence in invasive vulvar cancer in Europe of 19.3% (95% CI: 16.7–22.0),[123] it is estimated that seven invasive vulvar cancer cases are attributable to HPV annually in Ireland.

The relative contribution of HPV 16 and 18 and HPV 16, 18, 31, 33, 45, 52 and 58 are estimated at 73.6% (95% CI: 66.4–79.9) and 84.0% (95% CI: 77.6–89.0), respectively.[123]

After applying these relative contribution estimates, five cases are estimated to be attributable to HPV 16 and 18 (included in the 4-valent vaccine) and six cases attributable to HPV 16, 18, 31, 33, 45, 52 and 58 (included in the 9-valent vaccine).

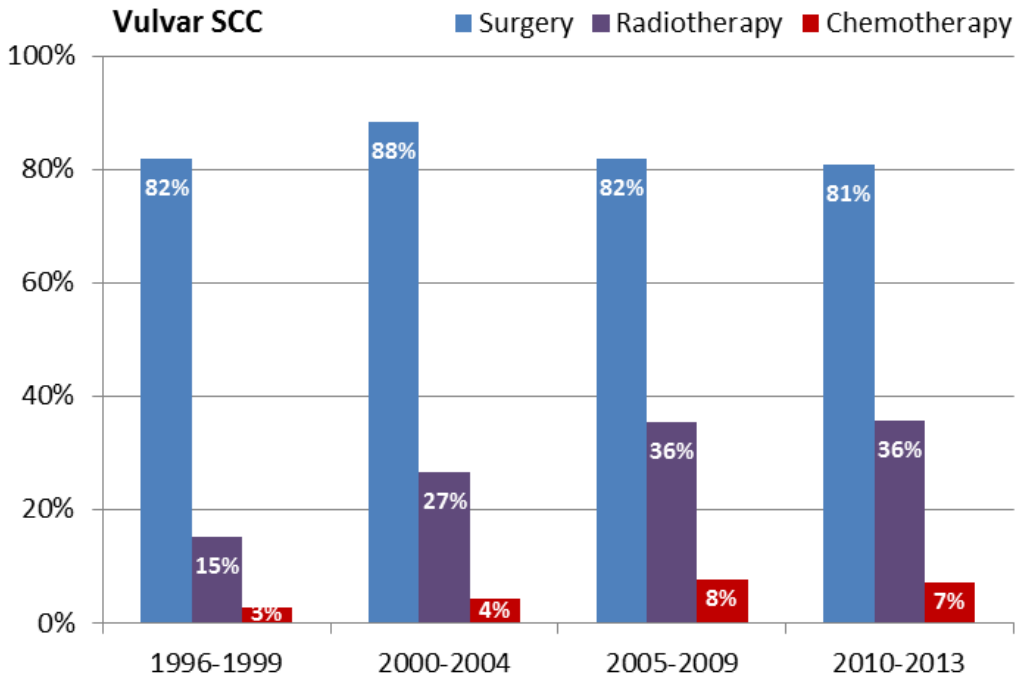
Using Nordic age-specific incidence data, Hartwig et al. (2015) estimated that the annual number of new VIN 2 and VIN 3 cases in Ireland is between 108 and 220.[122] Of these cases, 86.9% (95% CI: 82.6–90.4) are believed to be HPV-related, with HPV 16 and 18 accounting for 82.2% (95% CI: 77.2–86.6) and HPV 16, 18, 31, 33, 45, 52 and 58 accounting for 94.4% (95% CI: 91.0–96.9) of HPV-positive cases.[123]

After applying these relative contribution estimates, between 94 and 191 VIN 2 and VIN 3 cases in Ireland are estimated to be attributable to HPV. Furthermore, between 77 and 157 cases are attributable to HPV 16 and 18 (included in the 4-valent vaccine) and between 89 and 181 cases attributable to HPV 16, 18, 31, 33, 45, 52 and 58 (included in the 9-valent vaccine).

3.4.5 Tumour-directed treatment

During the period 2010-2013, data from the NCRI indicate that 81% of patients diagnosed with invasive vulvar cancer underwent surgical treatment, 36% underwent radiotherapy and 7% received chemotherapy. The proportion undergoing radiotherapy or chemotherapy increased over time, as illustrated in Figure 3.9.

Figure 3.9 Proportions of patients having tumour-directed treatment for vulvar cancer within 12 months after diagnosis, by diagnosis period [courtesy of NCRI].



3.4.6 Survival

Using NCRI data, the most recent estimate of five-year net survival (that is, survival relative to that expected in the general population) was 66% for patients with HPV-related invasive vulvar or vaginal cancer between 2010 and 2014.[59] No improvement in survival was noted over time (comparing the 1994-1998 to 2009-2013 diagnosis periods).

3.5 Vaginal cancer and precancerous lesions

3.5.1 Introduction

Cancer of the vagina is a rare cancer, with an estimated 13,000 new cases worldwide in 2008 — this represents 2% of all gynaecologic cancers.[124] Similar to cervical cancer, the majority of vaginal cancer cases (68%) occur in less developed countries.[125]

Most vaginal cancers are squamous cell carcinomas (90%), which are generally attributable to HPV, followed by clear cell adenocarcinomas and melanomas. Metastatic cervical cancer can be misclassified as cancer of the vagina. Invasive vaginal cancer is diagnosed primarily in older women (greater than 65 years) and the diagnosis is rare in women under 45 years, whereas the peak incidence of vaginal carcinoma *in situ* is observed between ages 55 and 70.

3.5.2 Incidence of invasive vaginal cancer and vaginal precancerous lesions

Between 2009 and 2013, NCRI data indicate that a total of 41 invasive squamous cell carcinomas of the vagina were diagnosed in Ireland. On average, eight cases were diagnosed per year during this period.

Population-level data on the incidence of pre-cancerous lesions of the vagina (vaginal intraepithelial neoplasia [VaIN]) are not available in Ireland. As outlined in Section 3.4.2, these data are routinely collected by the Nordic countries where population-based cancer registries have been sources for cancer statistics since the 1950s.[119] Using data from four Nordic population-based registries collected from 2006 to 2008 (prior to the introduction of the HPV vaccine), Nygard et al. reported age-standardised incidence rates of VaIN 2 and VaIN 3 ranging between 0.9 (Norway) and 1.3 (Iceland) per 100,000 woman-years (Section 3.4.2).[121] .

Based on the age-specific incidence data from these countries, Hartwig et al. (2015) estimated that the annual number of new VaIN 2 and VaIN 3 cases in Ireland is between 17 and 36.[122]

3.5.3 Calculation of HPV-attributable proportion

A large international collaborative study published by Alemany et al. in 2014[123] evaluated the HPV contribution and genotype distribution in invasive vaginal and vaginal intraepithelial neoplasia (VIN) lesions from pathological archives in 31 countries. The large-scale retrospective cross-sectional study was coordinated by the Catalan Institute of Oncology (ICO) and identified 408 invasive vaginal cancer specimens and 189 VaIN 2 and VaIN 3 lesions between 1986 and 2011. The European countries covered were Austria, Belarus, Czech Republic, France, Germany, Greece, Poland, Spain and the UK.

A study by Hartwig et al. published in 2015 reported on data from the European region.[6] The age-adjusted HPV-DNA prevalence in invasive vaginal cancer was 71.1% (95% CI 63.2-78.1%). This was substantially higher than that seen in vulvar cancer (Section 3.4). The HPV-DNA prevalence in VaIN 2 and VaIN 3 cases was 95.8% (95% CI: 91.8–98.2).[6]

Table 3.7 lists the relative contributions of each HPV type to HPV-DNA positive invasive vaginal cancer and VaIN 2 and VaIN 3 cases. Similar to other HPV-related cancers, HPV 16 is the most prevalent type detected.

Table 3.7 HPV type-specific relative contribution among HPV DNA positive VaIN 2 and VaIN3 and invasive vaginal cancer cases (full ICO cohort)

HPV Type	VaIN 2/3 (HPV+, *n* = 181)		Invasive vaginal cancer (HPV+, *n* = 303)	
	n	%	*n*	%
HPV 6	2	1%	2	<1%
HPV 11	–	–	1	<1%
HPV 16	95	53%	174	57%
HPV 18	10	6%	15	5%
HPV 31	1	<1%	16	5%
HPV 33	7	4%	14	5%
HPV 45	3	2%	10	3%
HPV 52	9	5%	8	3%
HPV 58	2	1%	11	(4%)
All others	50	27%	61	17%
Multiple	20	11%	12	4%

'VAIN 2/3': vaginal intraepithelial neoplasia; 'HPV + ': HPV DNA positive

3.5.4 HPV-attributable disease in Ireland

Between 2009 and 2013, NCRI data indicate that an average of eight new cases of invasive squamous cell carcinoma of the vagina were diagnosed each year. Of these cases, 5.5 are estimated to be attributable to HPV, assuming an overall HPV prevalence in vaginal cancer of 71.1% (95% CI: 63.2–78.1) in Europe.[124] The

relative contribution of HPV 16 and 18 and HPV 16, 18, 31, 33, 45, 52 and 58 are estimated to be 71.2% (95% CI: 61.8–79.6) and 85.6% (95% CI: 77.1–91.3), respectively.[124]

After applying these relative contribution estimates, four cases were estimated to be attributable to HPV 16 and 18 and 4.7 cases attributable to HPV 16, 18, 31, 33, 45, 52 and 58.

The age-standardised incidence rates of VaIN 2 and VaIN 3 in the three Nordic countries for which data were available ranged between 0.9 (Norway) and 1.3 (Iceland) per 100,000 woman-years (Table 3.5, Section 3.4.2). Based on the age-specific incidence data from these countries, Hartwig et al. (2015) estimates that the annual number of new VaIN 2 and VaIN 3 cases in Ireland is between 17 and 36.

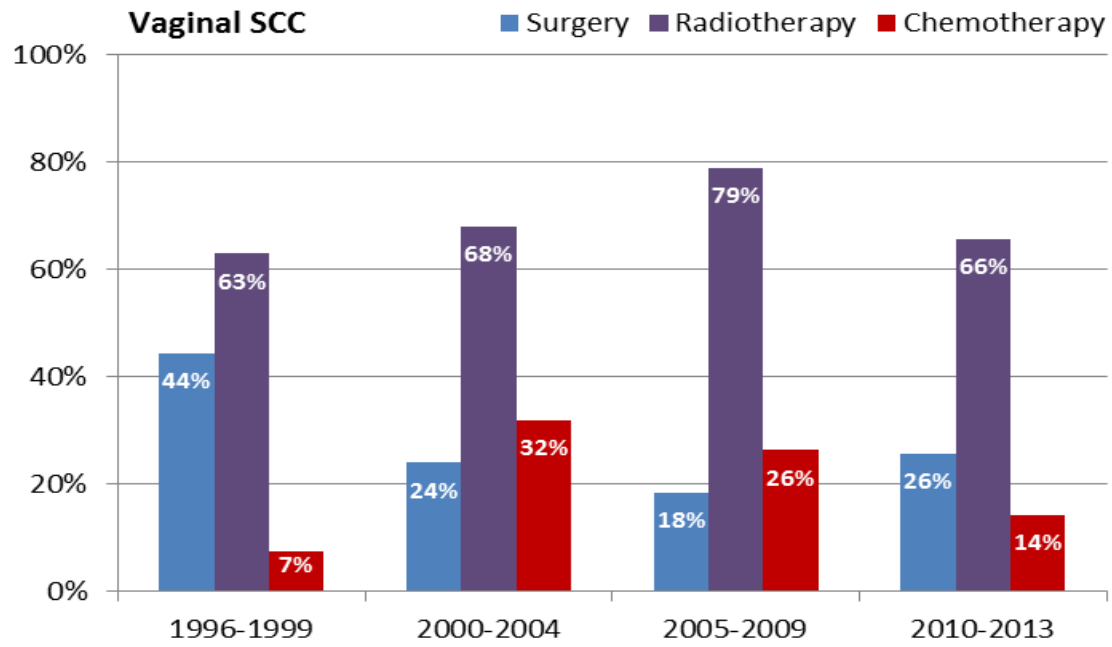
Of these cases, 95.8% (95% CI: 91.8–98.2) are expected to be HPV-related, with HPV 16 and 18 accounting for 64.1% (95% CI: 56.6–71.2) and HPV 16, 18, 31, 33, 45, 52 and 58 accounting for 77.6% (95% CI: 70.6–83.3) of HPV-positive cases.[6]

Based on these estimates, 17 to 35 of the estimated VaIN 2 and VaIN 3 cases in Ireland are predicted to be HPV-positive, with 11 to 22 cases attributable to HPV 16 and 18, and 13 to 27 attributable to HPV 16, 18, 31, 33, 45, 52 and 58.

3.5.5 Tumour-directed treatment

From 2010 to 2013, NCRI data indicate that over one in four (26%) patients diagnosed with invasive vaginal cancer underwent surgical treatment, two out of three (66%) underwent radiotherapy and 14% received chemotherapy. There have been no clear changes over time in treatment modalities, as illustrated in Figure 3.10.

Figure 3.10 Proportions of patients having tumour-directed treatment for vaginal cancer within 12 months after diagnosis, by diagnosis period [courtesy of NCRI]



3.5.6 Survival

The most recent NCRI estimate of five-year net survival (that is, survival relative to that expected in the general population) was two out of three (66%) patients diagnosed with HPV-related invasive vulvar or vaginal cancers between 2010 and 2014.[59] There was only limited evidence of improvement in survival over time (comparing 1994 to 1998 and 2009 to 2013 diagnosis periods).

3.6 Anal and rectal cancer and precancerous lesions

3.6.1 Introduction

Anal and rectal squamous cell carcinomas are relatively rare, with approximately 27,000 new cases diagnosed worldwide in 2008.[117] Age-adjusted incidence rates are estimated at approximately one per 100,000 population.[117] However, recent reports indicate an increase in incidence in some developed countries linked to several factors, for example changes in sexual behavior.[126, 127] Men having sex with men (MSM), particularly those infected by human immunodeficiency virus (HIV), represent a particularly high-risk group for developing anal cancer.[128, 129]

Anal intraepithelial neoplasia (AIN) is assumed to be the precursor lesion to anal cancer,[130] in that some cases of low-grade squamous intraepithelial lesions (LSILs) progress to high-grade squamous intraepithelial lesions (HSILs), and then to squamous cell carcinomas (SCCs). However, the rate and risk factors associated with

AIN progression, as well as the factors associated with regression, are poorly characterised. Several trials support the concept that AIN progresses to SCC.[131, 132]

3.6.2 Prevalence of anal and rectal cancer and AIN

The NCRI collected data on a total of 169 HPV-related anal and rectal cancers diagnosed in Ireland between 2009 and 2013, of which 108 were in women and 61 men. 'HPV-related' refers to primary squamous cell carcinomas of the anus or rectum, excluding tumours that are topographically or morphologically not associated with HPV. This gives an average annual incidence of 21.6 in women and 12.2 in men.

Prevalence studies of AIN have mostly been limited to high-risk groups to date, such as HIV-positive and MSM groups,[133-136] and little is known about prevalence in the general population. No population-level prevalence data has been obtained in Ireland. Denmark, on the other hand, has extensive registration of both anal cancer and AIN at the Danish Cancer Registry and the Danish Registry of Pathology. The Danish Registry of Pathology is a national register that contains information from all cytological and histological diagnoses, including AIN, performed in Denmark since 1978. Nielsen, 2012,[137] identified 608 cases of AIN 2 and AIN 3 in the period 1978-2008 from the Danish Registry of Pathology. The age-standardised incidence rate of AIN 2 and AIN 3 per 100,000 was 0.58 women and 0.43 in men between 2006 and 2008.

3.6.3 Calculation of HPV-attributable proportion

While a tumour may be HPV-related, due to its topographical and morphological characteristics, not all are directly attributable to HPV infection. A retrospective cross-sectional study by the Institut Català d'Oncologia (ICO) sought to estimate the HPV DNA prevalence and type distribution in patients with AIN 2 and AIN 3 and invasive anal cancers diagnosed from 1986 to 2011, from 24 countries worldwide, to determine the HPV-attributable proportion.[138] The Europe region contained data from nine countries: Bosnia-Herzegovina, Czech Republic, France, Germany, Poland, Portugal, Slovenia, Spain, and the United Kingdom.

The overall HPV DNA positivity was 95.3% (95% CI: 84.2–99.4%) for AIN 2 and 3 and 88.3% (95% CI: 85.1–91.0%) in invasive anal cancer. Within invasive cancer cases, HPV prevalence varied by geographical region with the highest prevalence in North America (95.8%; 95% CI: 89.7–98.9%) and the lowest in Africa (61.9%; 95% CI: 38.4–81.9%). No statistically significant differences were observed for gender or for period of diagnosis, neither in a five nor a 10-year period.

The most frequent HPV type was HPV 16 for both AIN 2 and AIN 3 (75.4% including multiple infections) and invasive anal cancer (80.7%). Among cancers, the second

most common type was HPV 18 (3.6%), accounting together with HPV 16 for 84.3% of HPV DNA-positive cases. Other HPV types detected were HPV 33 (2.7%), HPV 31 (1.9%), HPV 6 and HPV 58 (both 1.8%), HPV 35 (1.6%), and other types were identified in less than 1.5% of the specimens.

The overall HPV prevalence in anal cancer in the European region was 87.6% (95% CI: 81.6–92.1). The relative contribution of HPV 16 and 18 in HPV-positive anal cancers was estimated at 87.1% (95%CI: 80.7–92.1) and the relative contribution of HPV 16, 18, 31, 33, 45, 52 and 58 was estimated at 89.8% (95%CI: 83.8– 94.2).

The overall HPV prevalence in AIN 2 and AIN 3 in the European region was 95.3% (95% CI: 84.2–99.4%); the relative contribution of HPV 16 and 18 in HPV-positive AIS was 75.4% (95% CI: 59.4–87.4) and the relative contribution of HPV 16, 18, 31, 33, 45, 52 and 58 was 81.5% (95% CI: 66.4–91.9).

3.6.4 HPV-attributable disease in Ireland

3.6.4.1 Men

NCRI data indicate that the average incidence of anal and rectal squamous cell carcinomas in men was 12.2 per year between 2009 and 2013. Given the overall HPV prevalence in anal carcinoma of 87.6% (95% CI: 81.6–92.1),[138] 10.7 cases of anal and or rectal squamous cell carcinoma (95% bound: 8.0–9.0) were estimated to be attributable to HPV.

The relative contribution of HPV 16 and 18 in HPV-positive anal cancers is estimated at 87.1% (95% CI: 80.7–92.1) and the relative contribution of HPV 16, 18, 31, 33, 45, 52 and 58 is estimated at 89.8% (95% CI: 83.8–94.2).[138] After applying these relative contribution estimates, 9.3 cases of anal/rectal carcinoma are estimated to be attributable to HPV 16 and 18 and 9.6 cases attributable to HPV 16, 18, 31, 33, 45, 52 and 58.

Based on the trends in AIN incidence rates in Denmark,[137] Hartwig et al. (2015) estimate 10 new AIN 2 and AIN 3 cases occur each year in Ireland.[122] Of these cases, 95.3% (95% CI: 84.2–99.4%) are believed to be HPV-related with HPV 16 and 18 accounting for 75.4% (95% CI: 59.4–87.4) and HPV 16, 18, 31, 33, 45, 52 and 58 accounting for 81.5% (95% CI: 66.4–91.9) of HPV-positive cases.[138] Based on these estimates, 10 AIN 2 and AIN 3 cases in Ireland are estimated to be HPV-positive, with eight being preventable by vaccine.

3.6.4.2 Women

NCRI data indicate that the average incidence of anal and rectal squamous cell carincomas in women was 21.6 cases per year between 2009 and 2013. Given the overall HPV prevalence in anal cancer of 87.6% (95% CI: 81.6–92.1),[138] 18.9 cases

(95% bound: 15.0–16.9) are estimated to be attributable to HPV.

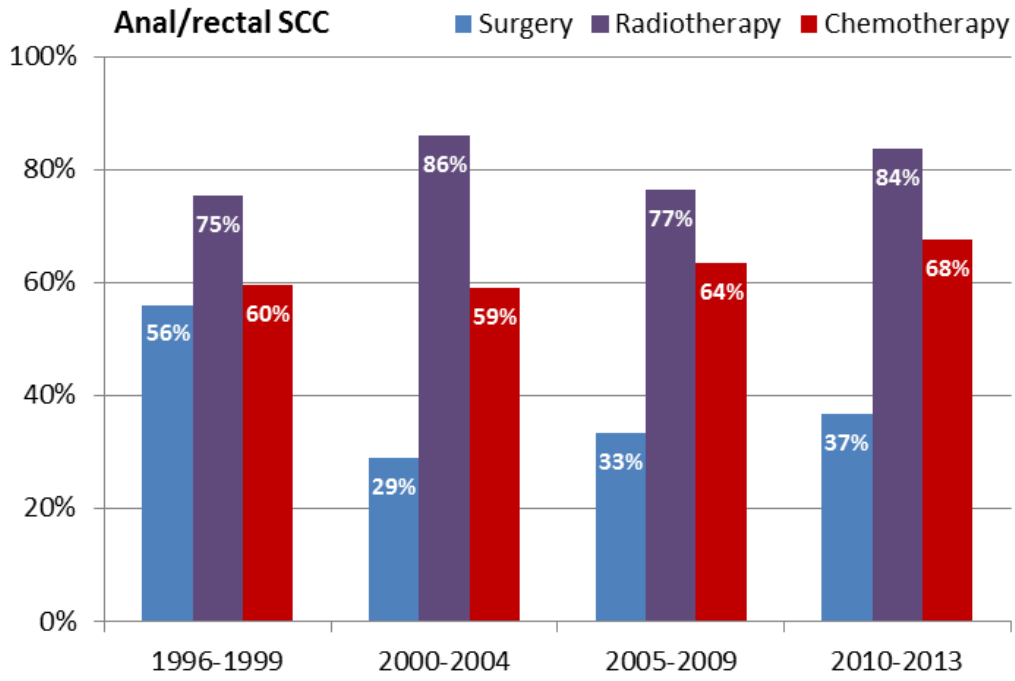
The relative contribution of HPV 16 and 18 in HPV-positive anal cancers is estimated at 87.1% (95% CI: 80.7–92.1) and the relative contribution of HPV 16, 18, 31, 33, 45, 52 and 58 at 89.8% (95% CI: 83.8–94.2).[138] After applying these relative contribution estimates, 16.5 cases of anal/rectal carcinoma are estimated to be attributable to HPV 16 and 18, and 17 cases attributable to HPV 16, 18, 31, 33, 45, 52 and 58.

Based on the trends in AIN incidence rates in Denmark,[137] Hartwig et al. (2015) estimated that 13 new AIN 2 and AIN 3 cases occur each year in Ireland.[122] Of these cases, 95.3% (95% CI: 84.2–99.4%) are believed to be HPV-related with HPV 16 and 18 accounting for 75.4% (95% CI: 59.4–87.4) and HPV 16, 18, 31, 33, 45, 52 and 58 accounting for 81.5% (95% CI: 66.4–91.9) of HPV-positive cases.[138] Based on these estimates, 13 of the AIN 2 and AIN 3 cases predicted to occur in Ireland are estimated to be HPV-positive, with 10 cases attributable to HPV 16 and 18 versus 11 attributable to HPV 16, 18, 31, 33, 45, 52 and 58.

3.6.5 Tumour-directed treatment

During the period 2010 to 2013, NCRI data indicate that 37% of patients diagnosed with anal or rectal squamous cell carcinoma underwent surgical treatment, 84% underwent radiotherapy and 68% received chemotherapy. Figure 3.11 demonstrates the change in treatment trends over time. A reduction in the proportion undergoing surgery in 2010 to 2013 compared with 1996 to 1999 is apparent.

Figure 3.11 Proportions of patients having tumour-directed treatment within 12 months after diagnosis, by diagnosis period [courtesy of NCRI]



3.6.6 Survival

The most recent NCRI estimate of five-year net survival (that is, survival relative to that expected in the general population) was 76% for patients with HPV-related invasive anal/rectal cancers between 2010 and 2014.[59] Following standardisation for age (age-standardised to the standard patient populations proposed by Corrazziari et al., 2004 [139]), five-year survival was 66% overall, with no significant difference by sex (67% in men and 62% in women). The age-standardised net survival improved significantly between diagnosis periods 1994 to 1998 and 2009 to 2013, from 33% to 65%.

3.7 Invasive penile cancer and precancerous penile lesions

3.7.1 Introduction

Penile cancer is a rare disease, with an estimated 22,000 cases globally each year.[117] The incidence is higher in the developing world, where penile cancer can account for up to 10% of cancers among men in some parts of Africa, South America, and Asia.[140] Precancerous penile lesions are similarly rare and precede penile cancer in up to 30% of cases.[141]

The pathogenesis of penile cancer can be described as occurring following two major pathways; the first is associated with HPV infection and the second associated with a

range of penile conditions (such as chronic inflammation, phimosis and prior lichen sclerosus and lichen planus).[142] Circumcision is known to be a protective factor, presumably by reducing HPV transmission or reducing the occurrence of penile conditions associated with penile carcinogenesis.[140, 143]

Cancers of the penis are primarily squamous cell carcinomas (95%), and the most common penile squamous cell carcinoma histologic sub-types are keratinising (49%), mixed warty-basaloid (17%), verrucous (8%) warty (6%), and basaloid (4%). HPV is most commonly detected in basaloid and warty tumours and is less commonly detected in keratinising and verrucous tumours.[118]

3.7.2 Incidence of invasive penile cancer and penile precancerous lesions

Between 2009 and 2013, NCRI data indicate a total of 145 invasive squamous cell carcinomas of the penis were diagnosed in Ireland. This gives an average annual figure of 29 cases per year during this period.

As of yet, no comprehensive data has been gathered on the incidence or prevalence of precancerous penile lesions in Ireland, with the except of in situ carcinomas registered by NCRI. However, a retrospective analysis of a nationwide registry in Denmark estimated the age specific incidence rate of high-grade squamous intraepithelial lesions (HGILs, defined as penile intraepithelial neoplasia grade 2 or 3) as 0.9 per 100,000 men between 2006 and 2008.[144] As the incidence of penile cancer was similar between Ireland and Denmark during this time period (1.21 per 100,000 men in Ireland versus 1.3 per 100,000 in Denmark), Denmark's estimate of 0.9 per 100,000 will be used as a surrogate incidence rate for the Irish population.

3.7.3 Calculation of HPV-attributable proportion

A recent, large-scale retrospective cross-sectional study by the Institut Catala d'Oncologia (ICO) investigated the proportion of high-grade squamous intraepithelial lesions (HGSILs) and invasive penile cancers attributable to HPV across 25 countries from Europe, North America, Latin America, Africa, Asia, and Oceania between 1983 and 2011.[145]

A total of 85 HGSILs and 1,010 invasive penile cancers were analysed for HPV DNA. Overall HPV DNA prevalence was 87.1% (95% CI: 78.0–93.4) in HGSILs and 33.1% (95% CI: 30.2–36.1) in invasive penile cancers. The investigators also reported by region. Countries participating in the European region included Czech Republic, France, Greece, Poland, Portugal, Spain and the United Kingdom. The overall HPV DNA prevalence was 32.2% (95% CI 27.8–36.9) in invasive penile cancer and 89.1% (95% CI 78.8–95.5) in HGSIL.

The most frequent HPV type in both penile HGSILs and invasive cancer was HPV 16

(79.6% and 68.7%, respectively). HPV 16 and 18 accounted together for approximately 70% of HPV DNA–positive penile cancers. The nine HPV types included in the 9-valent vaccine (HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) showed a combined prevalence among HPV DNA–positive cases of 92% in penile HGSILs and 84.6% in invasive penile cancers. It is important to highlight that the detection rates of low-risk HPV types (for example, HPV 6 and HPV 11) were higher in penile cancers (3.7% and 1.5%, respectively) compared with those observed in other HPV-related anogenital cancers.

Tables 3.7 and 3.8 show the HPV type–specific relative contribution among HPV DNA–positive invasive penile cancer and HGSIL cases by region. Accordingly, in Europe, the HPV types included in the 9-valent vaccine (6, 11, 16, 18, 31, 33, 45, 52, and 58) showed a combined prevalence among HPV DNA-positive tumours of 91.2% for HGSIL and 85.1% for invasive penile carcinomas. The HPV types (6, 11, 18 and 18) included in the 4-valent vaccine showed a combined prevalence of 82.3% for HGSILs and 74.7% for invasive penile cancers. Data are not available on the contribution of HPV 6 and 18 to HGSILs.

Table 3.7 HPV type-specific relative contribution among HPV DNA-positive penile invasive cancerous lesions

	TOTAL		Europe		North America		Central-South America		Africa		Asia		Oceania	
	(n=334)		(n=135)		(n=3)		(n=175)		(n=7)		(n=9)		(n=5)	
HPV Type	n	%	n	%	n	%	n	%	n	%	n	%	n	%
HPV 6	12	3.7	3	2.2	0	0.0	9	5.3	0	0.0	0	0.0	0	0.0
HPV 11	5	1.5	0	0.0	0	0.0	5	3.0	0	0.0	0	0.0	0	0.0
HPV 16	229	68.7	98	72.5	3	100.0	114	64.9	5	71.4	6	66.7	4	80.0
HPV 18	5	1.5	0	0.0	0	0.0	4	2.3	0	0.0	0	0.0	0	0.0
HPV 31	3	0.8	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
HPV 33	10	2.9	3	2.2	0	0.0	4	2.5	1	14.3	1	11.1	0	0.0
HPV 45	9	2.7	2	1.5	0	0.0	6	3.4	0	0.0	1	11.1	0	0.0
HPV 52	5	1.5	4	3.0	0	0.0	2	1.2	0	0.0	0	0.0	0	0.0
HPV 58	4	1.3	3	2.2	0	0.0	2	1.1	0	0.0	0	0.0	0	0.0
All other	44	13.5	18	12.9	0	0.0	24	13.9	1	14.3	1	11.1	1	20
HPV Undetermined	6	1.8	4	3.0	0	0.0	2	1.1	0	0.0	0	0.0	0	0.0
Multiple	30	9.0	9	6.7	0	0.0	18	10.3	1	14.3	0	0.0	2	40.0

Table 3.8 HPV type-specific relative contribution among HPV DNA-positive penile precancerous lesions, by region

	TOTAL		Europe		Central-South America		Asia		Oceania	
	(n=74)		(n=57)		(n=7)		(n=4)		(n=6)	
HPV Type	n	%	n	%	n	%	n	%	n	%
HPV 11	1	1.4	0	0.0	1	14.3	0	0.0	0	0.0
HPV 16	59	79.6	47	82.3	4	57.1	4	100.0	4	66.7
HPV 31	1	1.8	1	1.8	0	0.0	0	0.0	0	0.0
HPV 33	4	5.5	3	5.3	0	0.0	0	0.0	1	16.7
HPV 58	3	3.7	1	1.8	0	0.0	0	0.0	1	16.7
HPV 61	1	1.4	0	0.0	1	14.3	0	0.0	0	0.0
HPV Undetermined	2	2.7	2	3.5	0	0.0	0	0.0	0	0.0
Multiple	13	17.6	11	19.3	2	28.6	0	0.0	0	0.0

Note: Data not available for North America or Africa.

3.7.4 HPV-attributable disease in Ireland

On average, NCRI data indicate that 29 new penile cancer cases were diagnosed annually between 2009 and 2013. Given the overall HPV prevalence of 32.2% in penile cancer in the European region (95% CI 27.8–36.9),[145] nine cases are estimated to be attributable to HPV.

The relative contribution of HPV 16 and 18 (targeted by the 4-valent vaccine) in HPV-positive penile cancers is estimated at 74.7% and the relative contribution of HPV 16, 18, 31, 33, 45, 52, and 58 (targeted by the 9-valent vaccine) in HPV-positive penile cancers is estimated at 85.1%. After applying these relative contribution estimates, it is predicted that seven invasive penile cancer cases per year are attributable to HPV 16 and 18, and eight cases are attributable to HPV 16, 18, 31, 33, 45, 52, and 58.

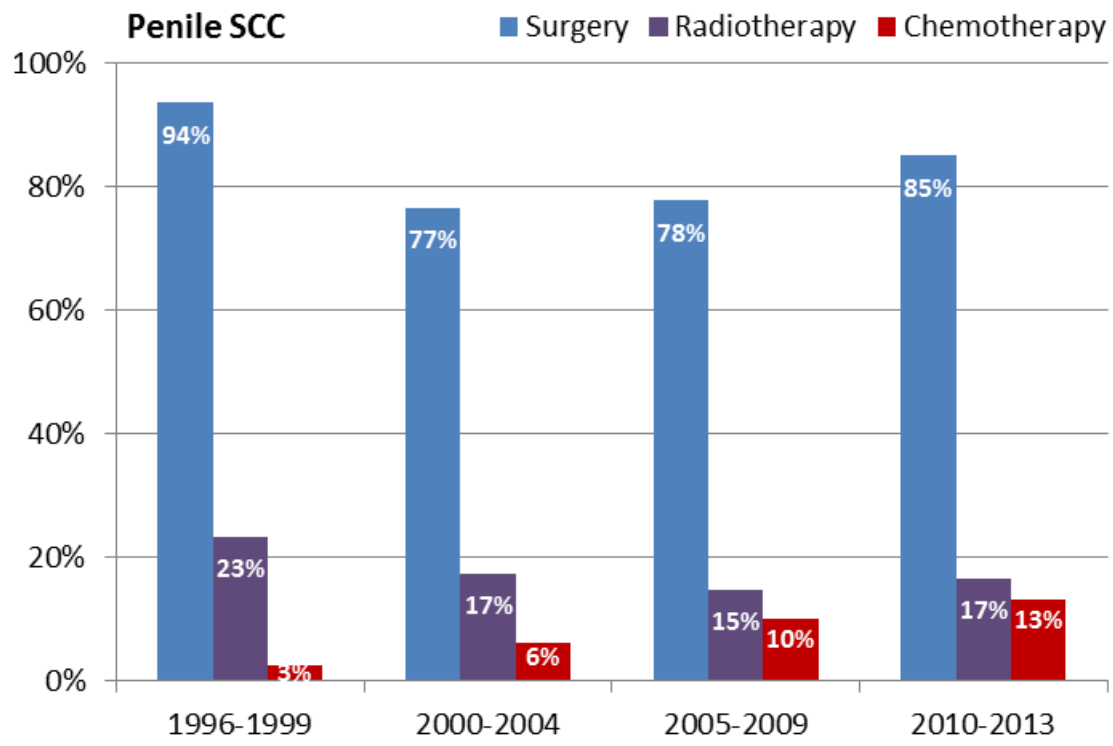
Given the overall HPV prevalence of 89.1% (95% CI 78.8–95.5) in HGSIL in the European region,[145] and applying the Danish age-specific incidence of penile precancerous lesions to the Irish population[144], an estimated 19 cases of HGSIL per year are estimated to be attributable to HPV Ireland.

The relative contribution of HPV 6, 11, 16 and 18 (targeted by the 4-valent vaccine) in HPV-positive HGSILs is estimated at 82.3% and the relative contribution of HPV 16, 18, 31, 33, 45, 52, and 58 (targeted by the 9-valent vaccine) in HPV-positive HGSILs is estimated at 91.2%. After applying these relative contribution estimates, it is predicted that there are 16 HGSILs per year attributable to HPV 16 and 18 and 17 cases attributable to HPV 16, 18, 31, 33, 45, 52, and 58.

3.7.5 Tumour-directed treatment

During the period 2010 to 2013, NCRI data indicate that 85% of patients diagnosed with invasive penile carcinoma underwent surgical treatment, 17% underwent radiotherapy and 13% received chemotherapy. Overall trends in treatment are somewhat unclear, with the exception of an increase in chemotherapy use, as illustrated in Figure 3.12.

Figure 3.12 Proportions of patients having tumour-directed treatment within 12 months after diagnosis, by diagnosis period [courtesy of NCRI]



3.7.6 Survival

The most recent NCRI estimate of five-year net survival (that is, survival relative to that expected in the general population) was 71% for patients with HPV-related invasive penile cancers between 2010 and 2014.[59] Following standardisation for age, five-year survival was 68% (age-standardised to the standard patient populations proposed by Corrazziari et al., 2004 [139]). No improvement in survival was noted over time (comparing 1994 to 1998 with 2010 to 2014 diagnosis periods).

3.8 Head and neck cancer

3.8.1 Introduction

Head and neck squamous cell carcinomas (SCCs) most commonly occur in the

epithelial lining of the oral cavity and are characterised by a high morbidity and mortality. Globally, the highest incidence rate estimated is in Europe with 99.6 cases per 100,000, while Middle Africa (3.4 per 100,000) has the lowest rate.[146, 147] There is a much higher proportion of head and neck cancer cases in males worldwide, estimated to be three times higher than that in females (male to female ratio ranges from 2:1 to 4:1).[146, 148] However, the mortality rate in females is higher. The global death rate from head and neck cancer is 4.4 per 100,000 population. Males show a mortality rate that is nearly four times higher than females (7.1 per 100,000 versus 2 per 100,000).[148]

Tobacco use and alcohol consumption are the well-known behavioural risk factors associated with head and neck cancer.[149] Other factors include genetics, environmental and occupational hazards and chewing betel quid or areca nut in Southern Asia.[149, 150] Over the past 15 years, strong evidence has emerged demonstrating an aetiological link between HPV infection and a subset of head and neck cancers (HNCs).[142]

HPV-associated HNCs have different risk factors, clinical characteristics and tumour biology when compared with tobacco and alcohol-associated HNC.[151] The disease characteristics of HPV-associated HNCs are remarkably distinct from those that are HPV-negative.[152] It has been demonstrated that HPV-positive cancers are driven by interaction of oncogenes E6 and E7 with p53 and pRb pathways, and have the feature of p16 upregulation.[151, 153-155] Contrastingly, HPV-negative HNCs are characterised by mutations in TP53 and pRb genes with p16 downregulation.[156, 157] HPV-associated HNCs tend to have more favourable survival outcomes compared with HPV-negative individuals.[156, 158] The most common alterations in HPV-negative HNCs are p53 mutations; these result in genomic instability, drug resistance and increased post-operative mortality.[157]

While virtually all cervical cancers are considered driven by HPV,[102] the quantitative assessment of the aetiological involvement of HPV in HNC is challenging. Analyses are frequently confounded by the multi-factorial aetiology of HNC, which are largely attributed to tobacco and alcohol use.[159] Consequently, the unequivocal fraction of HPV-DNA-positive HNCs for which HPV infection is the triggering carcinogenic event is unknown and its estimation remains a challenge.[160] Further, the mere presence of HPV DNA in HNCs is not sufficient to prove viral causation, as it might reflect a transient infection unrelated to the carcinogenic process.[161, 162]

There is strong and consistent molecular evidence demonstrating that HPV is an aetiological cause of cancer at the oropharyngeal site.[163, 164] HPV is detected in the tumour of oropharyngeal cancers. Importantly, at this location it is localised to the cell nuclei, transcriptionally active, clonal and not found in the surrounding benign tissue.

While HPV is an important cause of oropharyngeal cancer, it is currently unclear whether HPV has a causal role in other head and neck cancer sub-sites, such as laryngeal, oral cavity and nasopharyngeal carcinomas. HPV has been detected in a subset of oral cavity and laryngeal cancers in several studies,[165, 166] although the proportion of these cancers that are HPV-associated is notably smaller than that observed for oropharyngeal cancer. It is currently unclear whether HPV has a causal role in these other head and neck cancer sub-sites or may be explained by sub-site misclassification or undiagnosed oropharyngeal involvement.

Due to the uncertainty surrounding the involvement of HPV at these sites, this assessment will only focus on oropharyngeal sites (ICD-O-3 topography codes C01.9, C02.4, C02.8, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.0, C14.2 & C14.8). As mentioned previously, poor classification of the tumor subsite or overlap of some subsites may lead to misclassification of oropharyngeal carcinoma.[167] This may potentially lead to an underestimation of the true number of cases. For example, if an overlapping tumour is misclassified as originating in the oral cavity when in fact it originated in the oropharynx.

3.8.2 Incidence of HPV-related oropharyngeal cancer in Ireland

The NCRI collected data on a total of 613 HPV-related oropharyngeal cancers diagnosed in Ireland between 2009 and 2013; 148 in women and 465 in men. 'HPV-related' refers to primary squamous cell carcinomas located at anatomic sites known to be associated with HPV (ICD-O-3 topography codes C01.9, C02.4, C02.8, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.0, C14.2 & C14.8). This gives an average crude annual incidence of 29.6 in women and 93 in men. Of note, more recent clinical audit data from 2014 to 2018 (discussed in detail below) points to a 37% increase in cases compared to the case numbers recorded during the 2009-2013 period by the NCRI.

3.8.3 Calculation of HPV-attributable proportion

Most studies and meta-analyses assessing the quantitative contribution of HPV in HNCs have used the presence and detection of HPV-DNA in the tumour as the sole criterion to classify the tumour as HPV-driven. This probably results in an overestimation of the true impact of HPV in head and neck carcinogenesis. To accurately classify a tumour as HPV-driven, it is necessary to use other markers related to HPV-induced carcinogenesis, in addition to HPV-DNA detection, and thus assess the biological and oncogenic activity of the HPVs identified in HNCs. Testing positive for HPV-DNA in addition to the $p16^{INK4a}$ biomarker has the strongest diagnostic accuracy and prognostic value for HPV-attributable oropharyngeal cancer.[168]

To estimate the burden of oropharyngeal disease attributable to HPV in Ireland, data on oropharyngeal $p16^{INK4a}$ positivity were provided to the Evaluation Team by both the NCRI[57] and through a clinical audit conducted across eight hospitals in Ireland.[58]

In 2017, $p16^{INK4a}$ status was available for 77% of diagnosed oropharyngeal cancer cases in the NCRI database.[57] The provisional number (n=122) of cases of oropharyngeal cancer registered for 2017 currently stands at 80% of the average annual case-count for the years 2014-2016, thus a further 30 cases may yet be registered for 2017. Overall, 33% of oropharyngeal SCC cases diagnosed in 2017 (32% of female cases, 33% of male cases) were $p16^{INK4a}$-positive, but a further 23% had unknown $p16^{INK4a}$ status. Of $p16^{INK4a}$-tested oropharyngeal cases, 43% diagnosed in 2017 (47% of female cases, 42% of male cases) were $p16^{INK4a}$ positive. If these figures are representative of $p16^{INK4a}$ status for 2017 (when 2017 data are finalised including additional cases and test results), they suggest that somewhere in the range 33%-43% of all oropharyngeal cases diagnosed in 2017 were $p16^{INK4a}$ positive (range 32-47% of female cases, 33-42% of male cases), if untested cases are assumed to have the same or lower likelihood of testing positive for $p16^{INK4a}$.

The results of a clinical audit, conducted across eight cancer centres in Ireland, were also provided to the Evaluation Team.[58] The $p16^{INK4a}$ status of all available oropharyngeal cancer cases from 2014 to 2018 that were discussed at hospital-based multi-disciplinary meetings at the eight hospital centres were recorded. Over this time period, a total of 728 cancers were diagnosed. This represents a 37% increase in cases compared to the NCRI data from 2009-2013. The total number of $p16^{INK4a}$ positive cancers stood at 46% of the total (n=338). Consistent with NCRI data, oropharyngeal cancers were noted to occur much more frequently in men than in women. In fact, 77.5% of HPV-attributable tumours recorded in the clinical audit occurred in men.

Of note in this audit is that 19% of cases were not tested for p16, indicating that the overall positivity rate is higher. Nonetheless, the data from this audit and NCRI data indicate that close to half of all oropharyngeal cancer cases in Ireland may be directly attributable to HPV.

3.8.4 Fraction attributable to vaccine-targeted HPV subtypes

Data provided by the NCRI and the clinical audit did not perform HPV DNA partial genotyping on tumour specimens and therefore the proportion attributable to specific HPV types is unknown. In 2016, the Catalan Institute of Oncology (ICO) conducted a large international study explicitly designed to generate robust estimates of HPV-attributable fractions (AFs) in HNCs.[162] Formalin-fixed, paraffin-embedded cancer tissues of the oral cavity, oropharynx and larynx were collected from pathology archives in 29 countries worldwide, including the European region. It

was found that the distribution of individual HPV types is different in HNCs when compared with cervical cancers, as HPV 16 is systematically found in a much higher percentage of HPV-DNA positive HNCs than cervical cancers.

Confirming results from several other studies, the ICO study found that HPV 16 is the most frequently detected genotype among HPV-DNA positive cases (75.2%), but again with a wide range according to the cancer site: 83% in the oropharynx, 68.8% in the oral cavity and 50.8% in the larynx.[162] Table 3.11 lists the full breakdown of HPV type distribution at selected HPV-DNA positive HNC sites (from Castellsague et al., 2016).[162]

Table 3.11 Head and neck HPV type distribution by site

HPV-related markers	Oral cavity (n = 1,264) No. (%)	Oropharynx (n = 1,090) No. (%)	Larynx (n = 1,042) No. (%)
HPV DNA positivity*	93 (7.4)	271 (24.9)	59 (5.7)
HPV type distribution in single infection†			
HPV 6	0 (0.0)	1 (0.4)	4 (6.6)
HPV 11	1 (1.1)	0 (0.0)	1 (1.7)
HPV 13”	2 (2.2)	0 (0.0)	0 (0.0)
HPV 16	64 (68.8)	225 (83.0)	30 (50.8)
HPV 18	1 (1.1)	5 (1.8)	3 (5.1)
HPV 19”	0 (0.0)	1 (0.4)	0 (0.0)
HPV 26”	1 (1.1)	7 (2.6)	0 (0.0)
HPV 30”	0 (0.0)	1 (0.4)	0 (0.0)
HPV 31	0 (0.0)	0 (0.0)	2 (3.4)
HPV 33	0 (0.0)	9 (3.3)	2 (3.4)
HPV 35	2 (2.2)	6 (2.2)	1 (1.7)
HPV 39	1 (1.1)	1 (0.4)	3 (5.1)
HPV 45	0 (0.0)	1 (0.4)	5 (8.5)
HPV 51	2 (2.2)	2 (0.7)	0 (0.0)
HPV 52	4 (4.3)	0 (0.0)	0 (0.0)
HPV 53	1 (1.1)	1 (0.4)	0 (0.0)
HPV 56	0 (0.0)	0 (0.0)	1 (1.7)
HPV 58	1 (1.1)	2 (0.7)	1 (1.7)
HPV 59	0 (0.0)	1 (0.4)	0 (0.0)
HPV 66	0 (0.0)	1 (0.4)	0 (0.0)
HPV 67”	0 (0.0)	0 (0.0)	1 (1.7)
HPV 68	0 (0.0)	1 (0.4)	2 (3.4)
HPV 69”	0 (0.0)	2 (0.7)	0 (0.0)
HPV 90”	1 (1.1)	0 (0.0)	0 (0.0)
HPV types grouped by risk and vaccine†¶			
Only high-risk types	77 (82.8)	265 (97.8)	51 (86.4)
Only low-risk types	4 (4.3)	2 (0.7)	5 (8.5)
Types in bivalent vaccine	65 (69.9)	230 (84.9)	33 (55.9)
Types in 4-valent vaccine	66 (71.0)	231 (85.2)	38 (64.4)
Types in 9-valent vaccine	71 (76.3)	243 (89.7)	48 (81.4)

* Percentage of HPV-DNA positive cancers among all cancers tested by DNA enzyme immunoassay.
† Percentages among HPV-DNA positive cancers.
” Genotype identified by sequencing.
¶ Multiple infections (n = 7) are not included in these groups. Risk groups are defined according to the last International Agency for Research on Cancer classification high-risk HPV types the types included in Group 1, Group 2A, and Group 2B; other HPV types were classified as low-risk HPV types (27).

The Castellsague et al. paper also reports on HPV types grouped by risk and whether preventable by vaccine. Overall, high-risk HPV types are present in 82.8% of HPV-

DNA positive oral cancer, 97.8% of HPV-DNA positive oropharyngeal cancer and 86.4% of laryngeal cancer. The corresponding percentages for combined HPV types included in the 4-valent HPV vaccine (types 6, 11, 16, 18) were 71%, 85.2% and 64.4% for oral cavity, oropharyngeal and laryngeal HPV-DNA positive tumours, respectively. The corresponding percentages for combined HPV types included in the 9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) were 76.3%, 89.7%, and 81.4% for oral cavity, oropharyngeal and laryngeal HPV-DNA positive tumours, respectively.

3.8.5 Comparison with other studies

Recent US sources report a considerably higher HPV-AF for oropharyngeal cancer than our Irish estimates, at 70.1%.[169, 170] This figure emanates from the Centers for Disease Control and Prevention (CDC),[170] who accessed seven US population-based cancer registries to obtain archival tissue for cancers diagnosed from 1993 to 2005. Overall, HPV DNA was detected in 90.6% of cervical, 91.1% of anal, 75.0% of vaginal, 70.1% of oropharyngeal, 68.8% of vulvar, 63.3% of penile, 32.0% of oral cavity, and 20.9% of laryngeal cancers, as well as in 98.8% of cervical cancer *in situ*. As previously discussed, the presence of HPV DNA alone is not sufficient to infer viral causality. In addition, HPV prevalence varies substantially by geographical location, which may explain the difference.

The most recent systematic review and meta-analysis of HPV in HNCs identified reports similar HPV-AFs.[171] The review reported on 148 studies, contributing data for 12,163 cases of head and neck squamous cell carcinoma from 44 countries. By cancer site, pooled HPV-DNA prevalence estimates were 45.8% for oropharynx (95% CI 38.9–52.9), 22.1% for larynx (including hypopharynx) (16.4–28.3), and 24.2% for oral cavity (18.7–30.2). The estimate of HPV attributable fraction in oropharyngeal cancer defined by expression of positive cases of E6/E7 mRNA was 39.8%. Limitations of the systematic review were the low number of studies reporting on more than one marker and the differences in the geographic origin of the samples, as well as the high heterogeneity in the laboratory procedures and assays used across studies.

The ICO study, mentioned previously, reports HPV-AFs by geographical region.[162] While the overall HPV-AFs were estimated at 22.4% globally, Northern Europe recorded HPV-AFs of 50%. However, these data were based on relatively few studies. Ireland did not contribute data to this study.

3.8.6 Trends over time

In 2010, a pivotal paper by Ang et al. was published that alerted the scientific community to what seemed to be a ‘new’ disease; HPV-related oropharygeal carcinoma that appears to behave quite differently to HPV-negative oropharyngeal

carcinoma.[172] Evidence is accumulating to show that the incidence of oropharyngeal carcinoma is increasing rapidly in some countries. Authors in the US report on an alarming increase in oropharyngeal carcinomas in recent decades: one study reported that the population-level incidence of HPV-positive oropharyngeal cancers increased by 225% (95% CI, 208% to 242%) from 1988 to 2004 (from 0.8 per 100,000 to 2.6 per 100,000). During the same period, the incidence of HPV-negative cancers declined by 50% (95% CI, 47% to 53%; from 2.0 per 100,000 to 1.0 per 100,000).[173] The authors report that if recent incidence trends continue, the annual number of HPV-positive oropharyngeal cancers is expected to surpass the annual number of cervical cancers by the year 2020 in the US. However, noted limitations of the study were its small size (271 samples), non-representativeness of the tested patients and potential non-generalisability of observations from Hawaii, Iowa, and Los Angeles (the three participating registries of the study) to the rest of the US population.

Authors from the UK similarly noted a large increase in oropharyngeal cases. Schache et al., 2016, noted a near doubling in the annual number of oropharyngeal squamous cell carcinomas diagnosed between 2002 and 2011 across the UK.[174] However, the proportion of HPV positive cases remained static at approximately 50%. Therefore, the results argue that while the increase in incidence of oropharyngeal carcinoma is startling, the rapid increase in the UK cannot be solely attributable to the influence of HPV.

As noted previously, the Irish clinical audit provided to the Evaluation Team demonstrated a 37% increase in oropharyngeal cases comparing the 2009-2013 and 2014-2018 periods, consistent with increases observed internationally.

3.8.7 HPV-attributable HNC in Ireland

3.8.7.1 Men

NCRI data indicate an average of 93 new HPV-related HNC cases per year between 2009 and 2013 in Ireland, taking only into consideration SCCs at oropharyngeal sites. NCRI data also indicate that up to 42% of these are attributable to HPV in men.

This results in an estimated 39 cases, on average, attributable to HPV each year in Ireland. The relative contribution of HPV types included in the 4-valent HPV vaccine (types 6, 11, 16, 18) in HPV-positive oropharyngeal cancers is estimated at 85.2% and the relative contribution of HPV types included in the 9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) in HPV-positive oropharyngeal cancers is estimated at 89.%[162] After applying these relative contribution estimates, 33 cases per year in Ireland are estimated to be attributable to HPV types included in the 4-valent vaccine and 35 cases attributable to HPV types included in the 9-valent

vaccine.

3.8.7.2 Women

NCRI data indicate that there were on average 30 new HPV-related HNC cases per year in Ireland between 2009 and 2013, taking only into consideration SCCs at oropharyngeal sites. NCRI data also indicate that up to 47% of these are attributable to HPV in women.

This results in an estimated 14 cases attributable to HPV in Ireland. The relative contribution of HPV types included in the 4-valent HPV vaccine (types 6, 11, 16, 18) in HPV-positive oropharyngeal cancers is estimated at 85.2% and the relative contribution of HPV types included in the 9-valent HPV vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, and 58) in HPV-positive oropharyngeal cancers is estimated at 89.%[162] After applying these relative contribution estimates, 12 cases per year are estimated to be attributable to HPV types included in the 4-valent vaccine, with and 12.5 cases attributable in the 9-valent vaccine.

3.8.8 Treatment

3.8.8.1 Treatment overview

Traditionally, HNCs were treated using extensive surgical removal of tumours.[146] However, operative removal of tumours has a high rate of mortality due to the difficulty of accessing tumours within the oropharynx. In addition, these therapies affect critical functions such as speech and swallowing.[175] The paradigm has therefore shifted to more of a multi-modal approach that includes concurrent chemoradiotherapy, with the hope of improving vital functions after therapy. Concurrent chemotherapy and or radiotherapy have become widely accepted and have been shown to improve outcomes.[155, 175] As with most other solid tumours, the effectiveness of treatment reduces with the more advanced stage of the disease.[176]

The stage of disease largely dictates the treatment modality.[177] For early stage tumours (Stages I and II; T1–T2, N0), single modality treatment with either surgery or radiotherapy to the primary site and neck are recognised treatment approaches. Both claim excellent cure rates, but the short and long-term morbidity of each approach differs.[177] There have been rapid technological advances in both surgery and radiotherapy including transoral laser or robotic resections and Intensity Modulated Radiation Therapy (IMRT). For more advanced disease (greater than Stage II), the addition of chemotherapy or biological therapy to radiotherapy is well established.[177, 178]

To date, no single treatment modality has emerged as superior for treating HPV-associated HNCs.[179] Interventions should consider unique characteristics of the

tumor presentation in addition to patient preferences in order to optimise outcomes and quality of life, given the more prolonged survival of HPV-associated HNCs compared with HPV negative HNCs. Despite advances in the treatment of oropharyngeal carcinoma, surgery continues to carry a high risk of morbidity and chemotherapy increases the risk of swallowing dysfunctions following treatment.[179]

3.8.8.2 Surgical management of oropharyngeal carcinoma

Traditional surgical treatment with open resection usually required lip split and mandibulotomy.[180] This resulted in a high incidence of major complications such as wound dehiscence, pharyngocutaneous fistula, non-union and malunion of the mandible, with little apparent benefit over primary radiotherapy.[181] More recently, however, the development and refinement of new surgical techniques has resulted in a completely transoral approach for removal of selected oropharyngeal carcinomas.[180] This may be achieved using either laser or robotic assistance.[182, 183] Transoral laser surgery or transoral robotic surgery avoids most of the morbidity of traditional open surgical resection, accompanied by much faster recovery of a person's swallow function.[180]

Transoral laser or transoral robotic surgery is generally performed under high magnification using an operating microscope or endoscope.[182, 183] In the case of laser surgery, resection is effected using carbon dioxide (CO2) laser delivered by a fibreoptic cable. This allows complete transoral resection of tumours which would not be feasible using traditional instruments due to anatomical constraints. Concomitant or delayed neck dissection is generally required to deal with metastatic neck disease, or to exclude occult metastases in the case of patients with radiologically negative necks. For many patients, post-operative radiotherapy will still be required in the case of advanced stage neck disease (N2+), positive margins, or other adverse pathological features; however, this is generally a lower dose than given for primary chemoradiotherapy.

3.8.8.3 Chemotherapy and radiotherapy

Avoiding the high post-operative morbidity associated with traditional surgical techniques has seen a major shift towards non-surgical management from 2000 onwards. This coincided with the completion of landmark trials that demonstrated the superiority of chemoradiotherapy over radiotherapy alone.[184, 185]

The most commonly employed method of delivering radiation therapy for head and neck cancers is Intensity Modulated Radiation Treatment (IMRT). This technique allows the radiation oncologist to optimise treatment of the affected tissues while limiting the radiation dose to critical structures.[178] Radiation may also be associated with significant side effects, which vary depending upon the dose required and the tissues involved. Patients commonly complain of dry mouth, loss of taste, oral ulcers,

skin changes and swallowing difficulties. Significant swallow impairment may necessitate gastrostomy placement. Long-term side effects may include increased risk of carotid artery blockage, oesophageal strictures causing difficulty swallowing, weakness of the jaw bone that can result in jaw bone fracture (osteoradionecrosis) and the possibility of secondary cancers.

The primary chemotherapy used in head and neck cancer is cisplatin. While highly effective, toxicity includes nephrotoxicity, neurotoxicity and ototoxicity. If cisplatin is not tolerated, a second treatment option is cetuximab. Side effects of cetuximab include skin rashes, cardiotoxicity and pulmonary toxicity. Chemotherapy is useful in two ways. Firstly, it sensitises malignant cells to radiotherapy, rendering it more effective. Secondly it improves the control over metastatic disease to the lung, liver and bone.

In a study that compared radiation therapy alone with chemoradiotherapy in oropharyngeal tumours, significant improvement of up to three-years survival and a longer disease-free period in the combination therapy group was observed.[186] However, chemoradiotherapy is associated with a significantly higher incidence of major toxicity than radiotherapy alone,[185] including higher incidence of long-term swallowing problems and a high incidence of gastrostomy tube dependence.

3.8.8.4 Choice of therapy in early stage disease

The UK's National Institute for Health and Care Excellence (NICE) report on the evidence underpinning choice of treatment in early stage (T1–T2, N0) disease as part of their 2016 clinical guideline.[177] Only very low-quality evidence was available for the choice of transoral robotic surgery or intensity-modulated radiation therapy. Two-year overall survival ranged from 82% to 94% following transoral robotic surgery (two studies) and from 84% to 96% following IMRT (four studies). Two-year disease-free survival was 79% following transoral robotic surgery (one study), and ranged from 82% to 90% following IMRT (three studies).

Furthermore, the NICE guideline reports uncertainty about whether adding chemotherapy to locoregional treatment (surgery or radiotherapy) improves overall survival.[177] Uncertainty also surrounds whether conventional radiotherapy, altered fractionation radiotherapy or IMRT results in best overall survival.

3.8.8.5 Functional outcomes

Transoral laser or robotic surgery may offer significant advantages over chemoradiotherapy in its functional outcomes.[180] Even in cases where post-operative radiotherapy is recommended, the dose can usually be reduced compared with that given during primary chemoradiotherapy. The reduced radiotherapy dose to constrictor muscles and avoidance of chemotherapy-related toxicity lead to better

swallowing outcomes.

3.8.8.6 Palliation of breathing difficulties

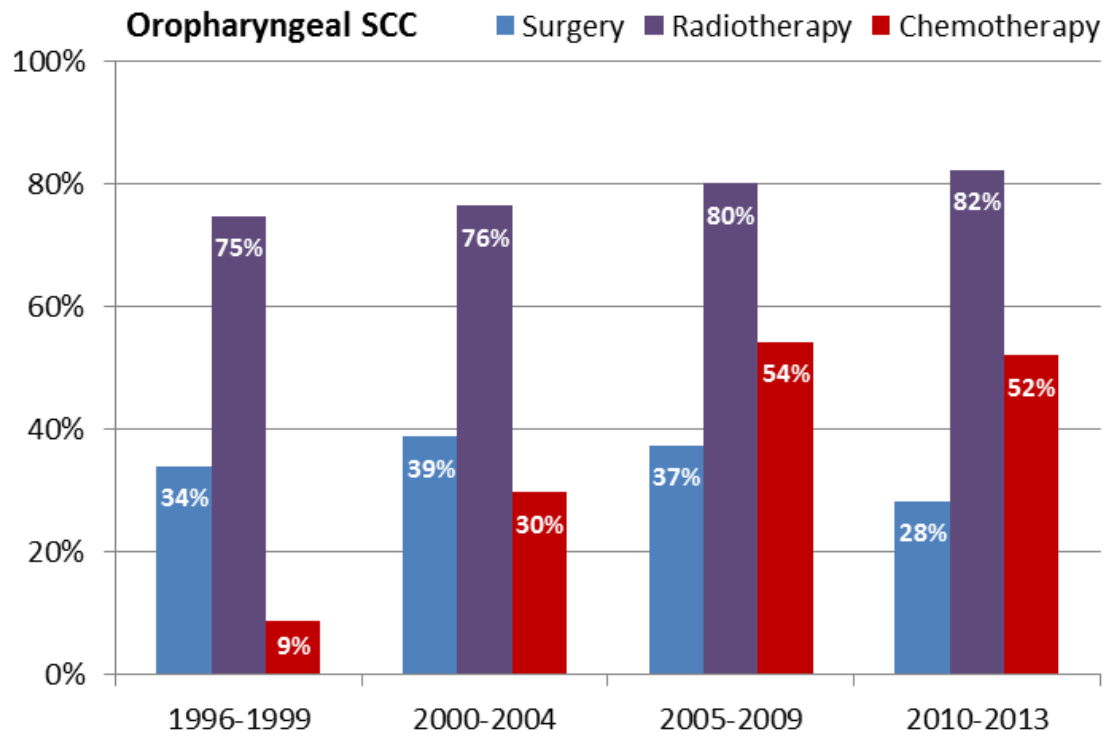
Respiratory complications are a significant cause of mortality and morbidity in patients with locally advanced and or metastatic oropharyngeal carcinoma.[177] Patients can experience distressing symptoms including stridor and dyspnoea as a result of upper airway obstruction. Strategies to reduce these symptoms can be challenging and will often require a combination of surgical and non-surgical interventions and palliative care. Tumour debulking, stenting or tracheostomy may be of benefit. The type of intervention depends on disease site and extent. There may be consequences which impact upon quality of life and place of care.

Chemotherapy and radiotherapy have significant side-effects which may make these therapies inappropriate or unacceptable to someone with advanced disease. Palliative care includes symptom control through the use of other drugs and planning end of life.

3.8.9 Tumour-directed treatment in Ireland

During the period 2010-2013, NCRI data indicate that 28% of patients diagnosed with oropharyngeal carcinoma underwent surgical treatment, 82% underwent radiotherapy and 52% received chemotherapy in Ireland. Figure 3.14 demonstrates the change in treatment trends over time. The increase in proportions receiving chemotherapy is notable; this may partly explain the improved survival over time (see Section 3.8.7).

Figure 3.14 Proportions of patients undergoing tumour-directed treatment within 12 months after diagnosis, by diagnosis period [courtesy of NCRI].

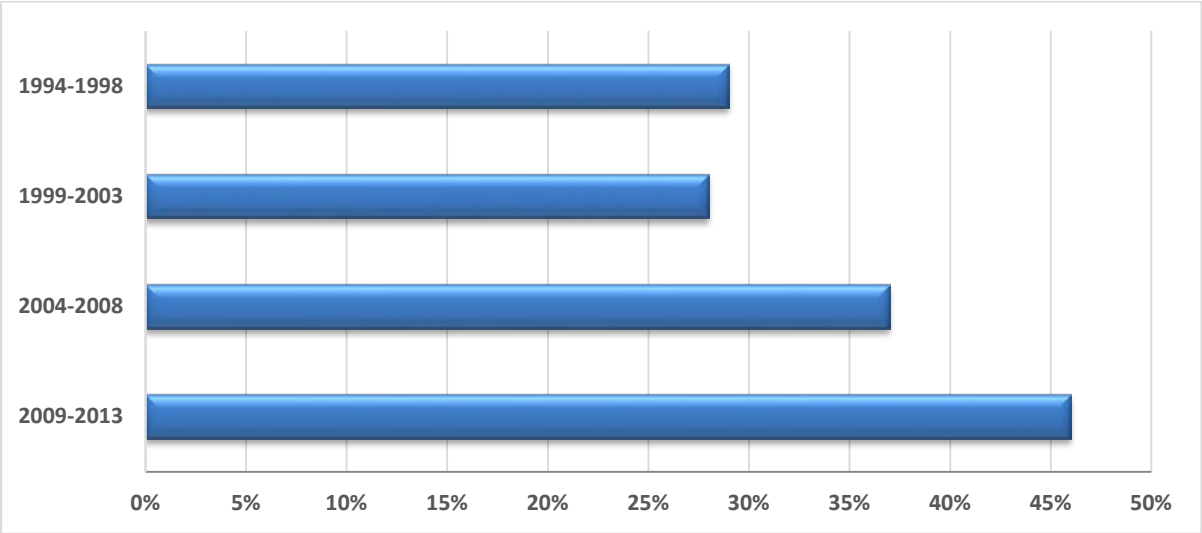


3.8.10 Survival

The most recent NCRI estimate of five-year net survival (that is, survival relative to that expected in the general population) was 53% for patients with HPV-related oropharyngeal cancers between 2010 and 2014.[59] Following standardisation for age, five-year survival was 45% overall and did not differ significantly by sex (44% in men and 47% in women)

The age-standardised net survival rate improved over time. Between diagnosis periods 1994 to 1998 and 2009 to 2013, five-year survival increased from 29% to 46% (see Table 3.15).

Table 3.15 Five-year survival by diagnosis period, age-standardised



As previously discussed, it is now known that patients with HPV-positive head and neck cancer have a better prognosis than non-HPV-positive cancers, although the underlying molecular mechanisms remain poorly understood.[187-189] Strikingly, patients with HPV-positive oropharyngeal tumours are highly curable with ionising radiation and have better survival rates compared with HPV-negative patients.[188] Possible trends in the HPV status of Irish cases may be contributing to the improved survival. As previously mentioned, the most common alterations in HPV-negative HNCs are p53 mutations that result in genomic instability, drug resistance and increased post-operative mortality.[157] As HPV-positive patients are younger, healthier and their tumour has a better prognosis then HPV-negative patients, long-term treatment side effects are becoming a major issue and de-escalation therapy is being investigated.[190] Approximately 20% of patients go on to develop distant cancers which are now increasingly being treated with costly immunotherapy.

Improved outcomes in HPV-positive oropharyngeal cancer patients have been consistently observed in single institution studies as well as large multi-centre trials performed by the Radiation Therapy Oncology Group,[172] Eastern Cooperative Oncology Group,[187] Trans Tasman Radiation Oncology Group,[191] and the Danish Head and Neck Cancer Group.[192] Although some reports have demonstrated this favorable HPV effect in the post-operative setting,[193] much of the data reflects patients treated with non-operative approaches.

3.9 Anogenital warts (condyloma acuminatae)

Anogenital warts (also known as condylomata acuminatae) are benign proliferative lesions caused by HPV, with HPV types 6 and 11 accounting for over 90% of lesions.[194] Anogenital warts are often also co-infected with oncogenic HPV types (such as HPV 16).[195] Genital warts are sexually transmitted, with transmission rates of approximately 60% between partners.[196]

3.9.1 Incidence

Anogenital warts (AGWs) have been designated as a notifiable disease since 1985 in Ireland. Notifications of AGWs are collected by Public Health departments and then notified to the Health Protection Surveillance Centre (HPSC) on a quarterly basis, in aggregate form. As of 4 October 2016, there were 1,843 cases of AGWs reported in Ireland in 2015 corresponding to a crude incidence rate (CIR) of 40.2 per 100,000 population, a decrease from 2014 (46.8 per 100,000).[197] The CIR among men was 45 per 100,000 and 28 per 100,000 among women.

However, in 2015 no data was received from the Mater clinic, the Gay Men's Health Service or the STI clinic in Galway. Therefore, incidence data on AGWs is unknown in Ireland due the under-estimation as a result of non-submission of data. Additionally, general practitioner (GP) notifications are sent to Public Health departments where they are entered and completeness of notification is unknown.

A review by Hartwig et al. published in 2015[6] identified two European publications that, based on their design, provided the most robust incidence data for AGWs in Europe.[198, 199] Both were retrospective cohort studies carried out using databases (one in Germany and the other in the UK) that included very large samples of routinely collected data.

Based on these studies, a lower incidence estimate of 142.0 per 100,000 woman-years[198] and an upper estimate of 191.1 per 100,000 woman-years[199] were reported for women. This corresponds to an estimated 3,356 to 4,516 number of new AGWs in women every year in Ireland. Assuming a prevalence of 90% for HPV 6 and 11 in AGWs,[43] between 3,020 and 4,064 of these cases are estimated to be attributable to HPV types 6 and 11 (included in both the 4-valent and 9-valent vaccines).

Based on these studies, a lower incidence estimate of 147.66 per 100,000 man-years[198] and an upper estimate of 167.7 per 100,000 man-years[199] were reported for men. This would correspond to an estimated 3,412 to 3,875 annual number of new AGWs in men in Ireland. Assuming a prevalence of 90% for HPV types 6 and 11 AGWs,[43] between 3,071 and 3,488 of these cases are estimated to be attributable to HPV types 6 and 11 (included in both the 4-valent and 9-valent vaccines).

3.9.2 Treatment

A number of treatments are available for the management of AGWs, with choice of treatment determined by number, location, morphology, distribution of warts and patient and provider preference.[200] The British Association for Sexual Health and HIV (BASHH) and European guidelines emphasise the importance of providing patients with information about their condition and discussing the treatment options

available.[195, 201] Importantly, not treating AGWs initially is also an option as spontaneous clearance may occur in certain patients.

Podophyllotoxin (available as a solution and a cream) and imiquimod 5% cream are the mainstay of the patient-applied therapies, having superseded interferons and 5-fluorouracil which are no longer recommended for the routine management of AGWs because of their toxicity.[200, 201] Other topical treatment options applied by a clinician are trichloroacetic acid and podophyllin, although routine use of podophyllin is no longer recommended.[195] Physical ablative therapies, performed by a clinician, include cryotherapy, electrosurgery, excision, curettage and laser. Topical and ablative treatment may be combined.

Lacey et al. (2011)[195] updated the European Guideline for the Management of Anogenital Warts. A systematic review of randomised controlled trials (RCTs) was performed and formulated in the structure of a clinical guideline. In general, the data confirmed that only surgical therapies have primary clearance rates approaching 100%. Recurrences, including new lesions at previously treated or new sites, occur after all therapies, and recurrence rates are often 20%-30% or more. All therapies are associated with local skin reactions including itching, burning, erosions and pain.

Within these caveats, the recommended treatment modalities include the following:[195]

1) Home therapy

    a. Podophyllotoxin (0.15% cream or 0.5% solution)

       Podophyllotoxin is usually recommended to treat clusters of small AGWs. It is in liquid form and has a toxic effect on the cells of the AGW.

    b. Imiquimod (5% cream)

       Imiquimod is a type of cream usually recommended to treat larger AGWs. It stimulates the immune system to target the AGW.

2) Clinic therapy

    a. Cryotherapy

       Cryotherapy involves freezing the AGW using liquid nitrogen and is usually recommended to treat multiple small AGWs, particularly those that develop on the shaft of the penis or on, or near, the vulva.

    b. Trichloroacetic acid

       Trichloroacetic acid (TCA) may be recommended to treat small AGWs that

are very hard. Its mechanism of action is the destruction of the proteins inside the cells of the AGW. However if not applied correctly, TCA can damage healthy skin.

c. Electrosurgery, scissors excision, curettage and laser therapy

Excision is sometimes recommended to treat small hardened AGWs, particularly where this is a combination of smaller AGWs that have joined together to form a cauliflower shape.

Electrosurgery is often combined with excision to treat large AGWs that develop around the anus or vulva that have failed to respond to topical treatments. Excision is first used to remove the outer bulk of the AGW. A metal loop is then pressed against the AGW. An electric current is passed through the loop to burn away the remaining part of the AGW.

Laser surgery may be recommended to treat large AGWs that cannot be treated using other methods of physical ablation because they are difficult to access.

Not recommended is the routine use of podophyllin or interferons. Podophyllin 20-25%, a non-standardised resin extract from the Podophyllum plant, is inexpensive to produce but is associated with only moderate efficacy. The recommended choice of therapy depends on the morphology and extent of AGWs and should be made by mutual agreement between the physician and the patient. Patients with limited disease (1–5 warts) will often opt for immediate therapy in clinic. As previously noted, AGWs regress spontaneously in some patients, therefore no treatment is an option for AGWs at any site.

3.9.3 Morbidity and reduction in quality of life

Buckley et al. published a systematic review in 2016, on behalf of Cochrane Response, on the incidence, prevalence and self-reported history and quality of life of patients who suffer from anogenital warts.[7] In studies that compared overall health status in people with AGW with the general population, EQ-5D health status index scores were lower in three of four studies identified. In one study that utilised the *QHO Quality of Life Questionnaire*, overall quality of life was poorer in people with AGW than healthy controls. The factors thought to contribute to the decrement in health status appeared to be related to anxiety and depression.

3.10 Recurrent respiratory papillomatosis

A rare condition, known as recurrent respiratory papillomatosis (RRP), can be caused by HPV types 6 and 11. Patients with this disease experience recurrent papillomae (or warts) anywhere along the respiratory tract and have a high risk of airway

obstruction. Papillomae most commonly occur in the larynx (laryngeal papillomatosis). RRP occurs in two forms: juvenile onset RRP which is caused by vertical transmission of HPV from mother to a susceptible child perinatally and usually presents in childhood, and adult onset RRP which is transmitted horizontally through sexual activity with onset in young adulthood.[57, 58] RRP causes significant morbidity and may require multiple surgical interventions to maintain a patent airway. It can be fatal and lesions may undergo malignant change.[57]

There are no estimates for the prevalence of RRP in Ireland. In the UK, Donne et al. (2017) estimated the number of patients with RRP currently managed in secondary and tertiary healthcare.[202] The study consisted of a cross-sectional survey of Ear, Nose and Throat (ENT) consultants in the UK (283 consultants from 128 UK National Health Service [NHS] healthcare trusts and health boards) with validation using Hospital Episode Statistics inpatient data. The authors estimated that the prevalence rate of RRP at 1.42 per 100,000 in the general UK population.

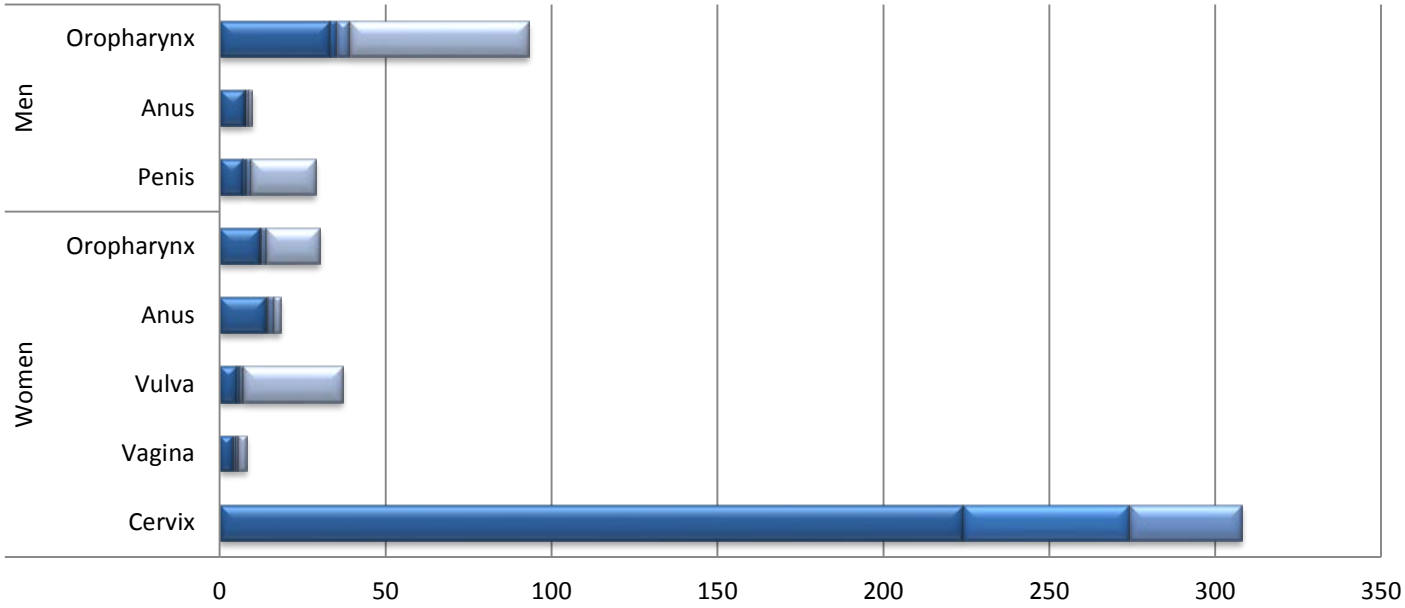
3.11 Discussion

HPV is the cause of almost all cervical cancer cases and is responsible for a substantial fraction of other anogenital cancers, oropharyngeal cancer and anogenital warts. The burden of disease associated with HPV is substantial. Globally, 4.5% of all cancers (630,000 new cancer cases per year) are attributable to HPV.[117]

In the preceding sections, the relative contribution of HPV to each HPV-associated tumour in Ireland was calculated. Additionally, the relative contribution was presented by HPV type, and grouped by vaccine-preventable HPV types (types that are targeted by the 4-valent and 9-valent vaccines).

Figure 3.16 summarises these findings, giving the average annual case numbers for each cancer (over the period 2009-2013) in Ireland, incorporating the number estimated to be attributable to HPV 16 and 18 (included in the 4- and 9-valent vaccines) and attributable to HPV 31, 33, 45, 52 and 58 (the additional benefit provided by the 9-valent vaccine). Other HPV types that are not vaccine-preventable are also presented, as are HPV-negative cases.

Figure 3.16 Average annual case numbers of all HPV-associated tumours in Ireland, by vaccine-preventable HPV type



	Women					Men		
	Cervix	Vagina	Vulva	Anus	Oropharynx	Penis	Anus	Oropharynx
HPV 16/18 (included in 4- and 9-valent vaccines)	224	4	5	14	12	6.9	7.5	33
HPV 31/33/45/52/58 (included in 9-valent vaccine)	50	0.7	1	0.5	0.5	1	0.2	2
Other HPV types (not vaccine-preventable)	34	0.8	1	1.6	1.5	1.4	0.9	4
HPV-negative	0	2.5	30	2.3	16	19.7	1.2	54

The data estimate that, across all HPV-related cancers, 383 cases per year are directly attributable to HPV in Ireland. Of these, 285 are attributable to HPV 16 and 18 (included in the 4-valent and 9-valent vaccines) and a further 55 cases are attributable to HPV 31, 33, 45, 52 and 58 (the additional benefit provided by the 9-valent vaccine). As expected, cervical cancer is by far the most common HPV-associated tumour in Ireland, with an estimated 274 cases attributable to vaccine-preventable HPV types occurring each year. The additional benefit of the 9-valent vaccine is clear, as an estimated 50 cervical cancer cases are attributable to HPV 31, 33, 45, 52 and 58 annually. The next most common tumour, oropharyngeal carcinoma, also occurs in considerable numbers, with an estimated 48 cases attributable to vaccine-preventable HPV types occurring each year.

Overall rates of HPV-associated invasive cancers appear to be increasing. The NCRI estimate that between 1994 and 2014 there has been a 2% increase per year for both sexes.[59] However, female rates fell from 2011 to 2014, possibly reflecting benefits from the introduction of organised population-based cervical screening through the CervicalCheck programme in 2009 which has led to an increase in the detection and treatment of pre-invasive cervical cancers. By comparison, cancer rates as a whole in Ireland have increased more slowly over the same period.[203]

Across all HPV-associated cancers, radiotherapy and surgery were the most frequent treatment types (60% of patients diagnosed during 2010-2013 had radiotherapy and 57% had surgery as part of their initial treatment).[59] Chemotherapy use was also substantial at 40%. Treatment varied by cancer site. Surgery was the most frequent treatment for vulvar and penile cancer and, to a lesser extent, cervical cancer; radiotherapy for oropharyngeal, anal, rectal and vaginal cancer. Chemotherapy use increased markedly over time for most sites, notably oropharyngeal cancer and cervical cancer. Approximately equal numbers of patients had single-modality (one) (most commonly surgical) and multi-modality (more than one) treatments (most commonly radiotherapy and chemotherapy).

Overall, age-standardised five-year survival for all HPV tumours averaged 61% for both sexes over the period 2010-2014.[59] The five-year net survival ranged from 53% for patients with oropharyngeal squamous cell carcinomas (SCCs) to 76% for patients with anal or rectal cell carcinomas, before standardising for age. The age-standardised net survival improved significantly between diagnosis periods 1994-1998 and 2009-2013 for oropharyngeal SCC, from 29% to 46%, and for anal and rectal SCC, from 33% to 65%. However, there was only limited evidence of any improvement for cervical cancer or vaginal and vulvar SCC, and none for penile SCC. A range of factors likely impacted on the improving prognosis observed in oropharyngeal and anal and rectal cancers. As stated previously, HPV-positive oropharyngeal cancers have a better prognosis than HPV-negative cancers.

A substantial number of pre-cancerous lesions (cervical, vulvar, vaginal, penile and anal) occur in Ireland each year. For all lesions, most result from infection with vaccine-preventable HPV types. The most significant lesion is CIN 2+, with 8,885 new cases diagnosed between September 2015 and August 2016 in Ireland. A reduction of incident pre-cancerous lesions through vaccination has clear implications for the State's screening services.

An estimated 3,020 to 4,064 anogenital warts (AGWs) in women and 3,071 to 3,488 AGWs in men are attributable to HPV 6 and 11 in Ireland each year. While not fatal, they are associated with psychological morbidity and frequently recur following treatment. Additionally, due to their high incidence, there are resource implications for STI and primary care services. HPV types 6 and 11 are also the causative agents in a rare condition known as recurrent respiratory papillomatosis (RRP). Both the 4-valent and 9-valent vaccines target HPV types 6 and 11.

3.12 Key points

- Persistent infection with certain oncogenic (cancer-causing) strains of HPV (denoted hrHPV) is well-established as an important risk factor for cervical, vaginal, vulvar, penile, anorectal and a subset of oropharyngeal cancers. Non-oncogenic strains are associated with anogenital warts.
- 'HPV-associated' tumours are tumours of squamous cell carcinoma (SCC) morphology that occur at an anatomic location known to be associated with HPV. 'HPV-attributable' tumours refer to the proportion of HPV-associated disease causally related to infection with HPV.
- Many factors confound the calculation of the overall prevalence and transmission of HPV infection within a given population. Prevalence studies differ depending on the anatomic site the sample is taken from, the testing platform used and the population from which the sample is retrieved.
- Across all HPV-attributable tumours, HPV 16 is the most common causative type. Of interest is the quantification of the relative contribution of vaccine-preventable HPV types: the 2-valent and 4-valent (HPV 16 and 18) and the 9-valent (HPV 16, 18, 31, 33, 45, 52 and 58) vaccine types.
- The estimated prevalence of hrHPV in cervical specimens is 14.6% in Ireland. No data are available on the prevalence of HPV in men in Ireland. A Danish study reported a prevalence of hrHPV of 30% among genital samples of men.
- Data on HPV-related disease in Ireland include data on invasive cancers from the National Cancer Registry Ireland (2009-2013) and Cervical Intraepithelial Neoplasia from CervicalCheck (2008-2016). In the absence of reliable Irish data, estimates for other precancerous lesions and anogenital warts must be derived from international sources.

Cervical cancer and precancerous lesions

- On average, 308 new invasive cervical cancer cases are diagnosed annually in Ireland. HPV types 16 and 18 account for almost three out of four (72.8%) cases (n=224) and HPV types 16, 18, 31, 33, 45, 52 and 58 for 89% of cases (n=274).
- Cervical intraepithelial neoplasia (CIN) is the precancerous lesion that precedes invasive disease. In 2015 to 2016, a total of 8,885 cases of high-grade histological abnormalities (CIN2+) were diagnosed in Ireland, 45.5% (n=4,043) of which are attributable to HPV 16 and 18 and 82.3% (n=7,312) to HPV 16, 18, 31, 33, 45, 52 and 58.
- Cervical cancer results in an average of 88 deaths per year in Ireland, with a five-year survival of 61%.

Vulvar cancer and precancerous lesions

- On average, 37 new invasive vulvar cancer cases are diagnosed annually in Ireland. Assuming a HPV prevalence of 19.3% in vulvar cancer, seven cases are estimated to be attributable to HPV. Five cases are estimated to be attributable to HPV 16 and 18 and six cases to HPV 16, 18, 31, 33, 45, 52 and 58.
- Between 108 and 220 new vulvar intraepithelial neoplasia (VIN) 2 and VIN 3 cases are estimated to occur annually in Ireland, of which 71.7% (n=77 to 157) cases are attributable to HPV 16 and 18 and 82.0% (n=80 to 181) cases are attributable to HPV 16, 18, 31, 33, 45, 52 and 58.
- HPV-related invasive vulvar or vaginal cancer has a five-year survival of 66%.

Vaginal cancer and precancerous lesions

- On average, eight new invasive vaginal cancer cases are diagnosed annually in Ireland. Assuming a HPV prevalence of 71.1% in vaginal cancer, 5.5 of these cases are estimated to be attributable to HPV, of which four cases are attributable to HPV 16 and 18 and 4.7 cases to HPV 16, 18, 31, 33, 45, 52 and 58.
- Between 17 and 36 new vaginal intraepithelial neoplasia (VaIN) 2 and VaIN 3 cases are estimated to occur annually in Ireland, of which between 11 and 22 cases are attributable to HPV 16 and 18, and 13 and 27 cases are attributable to HPV 16, 18, 31, 33, 45, 52 and 58.

Penile cancer and precancerous lesions

- On average, 29 new penile cancer cases are diagnosed annually in Ireland. Assuming a HPV prevalence of 32.2% in penile cancer, nine of these cases are estimated to be attributable to HPV, of which seven cases are attributable to HPV 16 and 18 and eight cases to HPV 16, 18, 31, 33, 45, 52 and 58.
- An estimated 19 cases of of high-grade squamous intraepithelial lesions (HGSIL) are estimated to be attributable to HPV in Ireland each year, of which 16 cases are attributable to HPV 16 and 18 and 17 cases to HPV 16, 18, 31, 33, 45, 52 and 58.
- HPV-related invasive penile cancer has a five-year survival of 66%.

Anal and rectal cancer and precancerous lesions

- On average, 12.2 new invasive anal and rectal squamous cell cancer cases are diagnosed annually in men in Ireland. Given a prevalence of HPV in anal cancer of 87.6%, 10.7 of these cases are estimated to be attributable to HPV, of which 9.3 are attributable to HPV 16 and 18 and 9.6 cases to HPV 16, 18, 31, 33, 45, 52 and 58.

- On average, 21.6 new invasive anal and rectal squamous cell cancer cases are diagnosed annually in women in Ireland. Given a prevalence of HPV in anal cancer of 87.6%, 18.9 of these cases are estimated to be attributable to HPV, of which 16.5 cases are attributable to HPV 16 and 18 and 17 to HPV 16, 18, 31, 33, 45, 52 and 58.
- An estimated 10 new cases of anal intraepithelial neoplasia (AIN) occur in men and 13 in women in Ireland annually. Nearly all AIN 2 and AIN 3 cases are believed to be HPV-related, with HPV 16 and 18 accounting for 75.4% and HPV 16, 18, 31, 33, 45, 52 and 58 accounting for 81.5% of cases.
- Age-standardised five-year survival for invasive anal cancer is 66% in Ireland, with no significant difference by sex (67% in men and 62% in women).

Head and neck cancer

- Head and neck squamous cell carcinomas most commonly occur in the epithelial lining of the oral cavity. Tobacco use and alcohol consumption are well-known behavioural risk factors; however, strong evidence has also accumulated of an aetiological link between HPV infection and a subset of head and neck squamous cell carcinomas. While HPV is known to be associated with oropharyngeal cancer, it is currently unclear whether HPV has a role in other head and neck cancer sub-sites.
- On average, 93 new HPV-related oropharyngeal cancers are diagnosed in men annually in Ireland. An estimated 42% (n=39) of these are attributable to HPV, of which, 33 cases are estimated to be attributable to HPV 16 and 18 and 35 cases to HPV 16, 18, 31, 33, 45, 52 and 58.
- On average, 30 new HPV-related oropharyngeal cases are diagnosed in women annually in Ireland. An estimated 47% (n=14) of these are attributable to HPV, of which, 12 cases are attributable to HPV 16 and 18 and 12.5 cases attributable to HPV 16, 18, 31, 33, 45, 52 and 58.
- A recent clinical audit on oropharyngeal cases diagnosed between 2014 and 2018 in Ireland found a 37% increase in cases compared to the 2009-2013 NCRI data. Overall, 77.5% of cases were in men and approximately half are thought to be HPV-driven.
- Age-standardised five -year mortality from oropharyngeal cancer is 45% overall in Ireland, with no significant difference by sex (44% in men and 47% in women).

Anogenital warts (AGWs)

- An estimated 3,412 to 3,875 new cases of AGWs occur in men and an estimated 3,356 to 4,516 new cases occur in women in Ireland annually. Approximately 90% of these are attributable to HPV 6 and 11, covered by all HPV vaccines.

Recurrent respiratory papillomatosis (RRP)

- RRP is a rare condition, caused by HPV types 6 and 11. RRP is estimated to occur in 1.42 per 100,000 in the general UK population. Some patients with RRP suffer significant morbidity and mortality due to airway obstruction.

4. Clinical efficacy and immunogenicity of HPV vaccines

Persistent infection with oncogenic (cancer-causing) strains of HPV is well-established as having a causative role in developing invasive cervical, vaginal, vulvar, penile, anal, rectal and a subset of oropharyngeal cancers.[204] HPV also has a role in the development of pre-cancerous lesions of the cervix, vulva, vagina, anus and penis.[6] It is strongly associated with anal and genital warts, with approximately 90% of anogenital warts directly attributable to HPV types 6 and 11.[7]

This chapter will summarise the available evidence regarding the efficacy of HPV vaccination as primary prevention for these conditions. It also considers the immunogenicity of HPV vaccines, that is, the vaccine's ability to provoke an efficient, long lasting, HPV-specific immune response in vaccinated individuals and the duration of the immune response. In line with the agreed scope of the health technology assessment (HTA), this chapter aims to identify and evaluate the clinical efficacy and immunogenicity of a two-dose schedule of the 4-valent and 9-valent HPV vaccines (administered at zero and six months) in 12 to 13 year old boys and girls.

The inherent dilemma is that there are no direct clinical outcome data reported from clinical trials to demonstrate the clinical efficacy of a two-dose HPV vaccination in 12 to 13 year old boys. This is due to the ethical and legal constraints in conducting such trials in pre and early adolescents. In order to demonstrate evidence of clinical efficacy, the first step is to establish evidence of efficacy in adults. The initial vaccine trials relate to a three-dose schedule of the 4-valent HPV vaccine in adult females. Subsequently, the efficacy of the 4-valent vaccine in males was established.

Outcomes in the clinical trials are reported for a number of different populations which depend on the extent to which the trial protocol was adhered to (per-protocol or intention-to-treat) and the HPV status of participants at baseline (no restriction or restricted to those negative for selected HPV types at baseline plus/minus having a negative cervical smear at baseline). Examples of different populations for which data are reported in the published studies are outlined in Table 4.1. Given the scope of this assessment, the cohort of interest is the one that provides the best approximation for the primary target group for HPV vaccination, that is, pre and early adolescent girls and boys who have not yet become sexually active (that is HPV naïve at baseline) and who receive one or more doses of the HPV vaccine.

Table 4.1 Different patient populations analysed for efficacy of 4-valent HPV vaccine in adult females (FUTURE I and II trials)

Population	Number of vaccination doses received	Baseline HPV status for inclusion	Follow-up visits	Starting date for case counting	Analyses of disease
Per-protocol susceptible	3	Negative for HPV types 6/11/16/18 at day 1 and through month 7	Generally did not deviate from the study protocol	Month 7	Related to HPV types 6/11/16 & 18
Intention-to-treat (ITT)	≥1	No exclusion based on baseline HPV status at day 1	Had any follow-up visit	Day 1	Related to HPV types 6/11/16 & 18 and any HPV type
Unrestricted susceptible (Modified ITT)	≥1	Negative for HPV types 6/11/16/18 at day 1	Had any follow-up visit	Day 1	Related to HPV types 6/11/16 & 18
Generally HPV-naïve (Restricted MITT)	≥1	Negative for HPV types 6/11/16/18 /31/33/35/39/45/ 51/52/56/58/59 at day 1 and had a negative cervical smear test result on day 1	Had any follow-up visit	Day 1	Related to any HPV type

FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical Disease) I (n=5,455) and II (n=12,167) trials were 16-country randomised controlled trials that assessed the efficacy of the 4-valent HPV vaccine (Gardasil®) in women aged 16 to 26 years.

The generally HPV-naïve (also referred to as the restricted modified intention-to-treat [MITT]) population was selected as the population that most closely represents the population of interest in this assessment. It excludes individuals with evidence of prevalent infection at baseline by any of the genital HPV types evaluated (up to 14 types for restricted MITT) or serological evidence of past exposure to the vaccine-targeted types. It also excludes those with evidence of cervical cytology abnormalities at baseline.

The clinical efficacy of the three-dose schedule of the 4-valent HPV vaccine in adult males is also evaluated for HPV-naïve populations; any of the reported clinical outcomes achieved with the 9-valent compared with the 4-valent HPV vaccine in adult females and males for modified intention-to-treat populations will be examined, where reported.

Next, the immunogenicity analyses used in the bridging studies are appraised to extend vaccination recommendations to newer HPV vaccines (for example, 9-valent vaccine), dosage regimens (for example, two-dose schedule) and different age groups (or example, pre and early adolescents) for per-protocol populations. These immunobridging trials were acceptable to the European Medicines Agency (EMA) for demonstrating the clinical efficacy of the 4-valent and 9-valent HPV vaccines in pre-adolescent and adolescent girls and boys.[205, 206]

This approach was also endorsed by the World Health Organization's (WHO's) International Agency for Research on Cancer (IARC) Working Group in the report on 'Primary end-points for prophylactic HPV vaccine trials' in September 2013:[207]

> 'After a vaccine has been shown to be effective in one population group (e.g. individuals aged 16 to 26 years), immunobridging is sufficient for extending licensure to other population groups (e.g. individuals aged < 16 years). The IARC Working Group recommended that immunological non-inferiority is an appropriate end-point in such situations, independent of the number of vaccine doses used to demonstrate such non-inferiority, with reduction in disease being verified by post-licensure monitoring. The need for standardization of virological and immunological assays was emphasized'.

Finally, this chapter reports on the persistence of HPV-antibody responses over time for the HPV vaccine in the relevant identified primary and follow-up studies for per-protocol populations. These data provide evidence of the likely duration of protection provided by the HPV vaccine.

4.1 Search strategy and methodology

4.1.1 Literature search

Electronic searches

The reporting of this systematic review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[208] The following electronic databases were systematically searched: Medline (via PubMed), EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify reports of randomised controlled trials (RCTs) of prophylactic HPV vaccines up until July 2017, using a combination of index terms: "*HPV vaccine**", "*Human Papillomavirus vaccine**", "*HPV immuni**". Limits applied included by study design (RCTs only) and

studies including humans only. There were no date or language restrictions applied. The search terms and methodology used are further outlined in Appendix 1.

Searching other resources

A systematic review of RCTs of HPV vaccines,[209] prepared for the WHO Strategic Advisory Group of Experts (SAGE) on Immunization in June 2016, identified six relevant evidence reviews. The results of this systematic search were compared with the individual searches from the Cochrane review to ensure all relevant studies were adequately captured. In addition, the citation lists of other relevant high-quality systematic reviews identified,[210] as well as the reference lists of all included studies, were cross-referenced to ensure the capture of all relevant publications.

The registry of randomised controlled trials (www.clinicaltrials.gov) was reviewed to ensure that any relevant ongoing studies, including published papers, were identified. Furthermore, the pharmaceutical company with market authorisation for the 4-valent and 9-valent HPV vaccine in Ireland, Merck Sharp and Dohme, was contacted to obtain additional information.

4.1.2 Selection criteria

Inclusion criteria

The PICOS (Population, Intervention, Comparator, Outcomes, Study design) concept used to formulate the review question is presented in Table 4.2.

Table 4.2 PICOS criteria for identification of relevant studies for the systematic review of efficacy of HPV vaccines in boys

Population	9 to 26 years old males and females
Intervention	4-valent [types 6, 11, 16, and 18] HPV vaccine (Gardasil®) or 9-valent [types 6, 11, 16, 18, 31, 33, 45, 52, 58] HPV vaccine (Gardasil® 9);
Comparator	Placebo, no vaccine, co-administration with other vaccine or alternative age of vaccination.
Outcomes	Clinical efficacy to be classified as: a. Clinical efficacy outcomes based on reduction in: ▪ HPV infection ▪ anogenital warts ▪ pre-cancerous lesions (adenocarcinoma-in-situ [AIS] or intra-epithelial neoplasia) ▪ cancers of the cervix, vagina, vulva, penis, anus or oropharynx b. Intermediary immunogenicity outcomes based on non-inferiority of: ▪ Geometric mean titres (GMTs) ▪ Seroconversion rates (or seropositivity rates)
Study design	Randomised controlled trials (RCTs)

Exclusion criteria

The following specific population subgroups were excluded from the search results on screening:

- HIV positive and immuno-compromised patients,
- MSM (men who have sex with men),
- cohort and ad-hoc analyses in specific subgroups.

Studies examining the 2-valent HPV vaccine were also excluded from this review. In the case where interim and final analyses were reported in a RCT, the final analyses with complete follow up were used. Where the event rates or population sizes of individual RCTs were not powered to adequately detect clinical outcomes, combined or pooled analyses of multiple RCTs were included. Research letters and conference abstracts were excluded.

4.1.3 Data collection and analysis

Identification of studies

All titles and abstracts retrieved by electronic searching were downloaded to the reference manager EndNote (version 7). Duplicates were removed and citations were screened by one reviewer to eliminate clearly irrelevant studies. One reviewer independently screened the remaining citations. Full texts were obtained and reviewed as per the inclusion criteria.

Data extraction and management

Data extraction using a standardised data extraction form (created based on a combination of the Cochrane Risk of Bias form[211] and SAGE recommendations[212] for data extraction forms) was performed independently by two reviewers, with any disagreements being resolved by discussion or inclusion of a third reviewer.

Data extracted included:

- study author and title,
- year,
- study design and length of follow up,
- country and setting,
- inclusion and exclusion criteria,
- non-respondents and or loss to follow up,
- population characteristics (that is, age, gender, ethnicity),
- intervention characteristics (type of vaccine, dose and vaccination schedule),
- comparator characteristics,
- outcomes,
- and summary of results.

Where necessary, the study author was contacted to obtain available data already published, but not sufficiently detailed, and outcome data that were not reported.

Assessment of risk of bias and quality of evidence

The risk of bias of included studies was assessed by two reviewers independently using the Cochrane Collaboration's tool and the criteria specified in the Cochrane Handbook for Systematic Reviews of Interventions,[211] with any disagreement being resolved by discussion or inclusion of a third reviewer. This included assessment of sequence generation; allocation concealment; blinding (of participants, healthcare providers and outcome assessors); incomplete outcome data; selective reporting of

outcomes; other possible sources of bias. Risk of bias for each domain was categorised as low, unclear or high. Results were presented in a risk of bias graph and risk of bias summary.

GRADE profiler (GRADE pro) software was used to assess the overall quality of evidence for each outcome collected based on the following factors:

- risk of bias due to study design limitations,
- inconsistency of evidence (that is, unexplained heterogeneity),
- indirectness of evidence,
- imprecision of results and publication bias. [213-215]

GRADE assessments were undertaken by a single reviewer and checked by a second reviewer. Results are presented in summary of findings (SOF) tables, grading the quality of evidence for each outcome as 'high', 'moderate', 'low' or 'very low'.

Measures of treatment effect and data synthesis

Risk ratios (RRs) and associated 95% confidence intervals (CIs) were calculated from the proportion of participants showing treatment effects in the treatment arms relative to a control for dichotomous variables using the Mantel-Haenszel method.[216] A risk ratio of less than one suggests vaccine protection against a specific clinical outcome.

Studies where clinical outcomes were reported in events per number of person years at risk (PYR) were extracted verbatim. However, to ensure methodological consistency in calculating risk ratios (RRs) across all studies, the number of events in the appropriate HPV-naïve population was chosen to show the treatment effects of the vaccine.

Data on two immunogenicity outcomes were captured:

- geometric mean titres (GMTs)
- seroconversion (or seropositivity) rates.

As GMT data are reported as a continuous variable, the mean differences on the log scale were expressed as GMT ratios using the generic inverse variance method. A GMT ratio of greater than one suggests vaccine superiority for the GMT immunogenicity outcome in the intervention over the comparator group. A fixed-effect model was applied to obtain pooled estimates, if appropriate. Where heterogeneity was deemed to be significant (I^2 >40%) according to the Cochrane criteria, the random-effects model was applied.[217] Review Manager (version 5.3) software was used for the meta-analysis.

4.1.4 Methodology

The systematic review results and evidence synthesis are categorised into six evidence summaries:

1) Efficacy of HPV vaccine against persistent infection and disease related to HPV types 6, 11, 16, and 18
2) Efficacy of HPV vaccine against persistent infection and disease related to types 31, 33, 45, 52, and 58 (and types 35, 39, 51, 56 and 59 if reported)
3) Immunogenicity outcomes of the 4-valent HPV vaccine in adult females and males (and reported immune-persistence rates)
4) Non-inferior immunogenicity of the 9-valent versus 4-valent HPV vaccine for the common HPV types
5) Non-inferior immunogenicity of three-dose HPV vaccination in males compared with females
6) Non-inferior immunogenicity of two-dose versus three-dose HPV vaccine schedules

The clinical efficacy outcomes of the three-dose schedule of the 4-valent HPV vaccine (versus placebo or control) in adult males and females focus on the reduction in the incidence of:

- HPV infection
- anogenital warts
- pre-cancerous lesions (adenocarcinoma-in-situ [AIS] or intra-epithelial neoplasia) and
- cancers of the cervix, vagina, vulva, penis, anus or oropharynx.

As outlined earlier, where reported, the outcomes were taken from modified intention-to-treat populations (that is, those who were HPV-naïve at baseline) as these cohorts are currently the best approximation for the primary target group for HPV vaccination, pre and early adolescent girls (and boys) who have not yet become sexually active.

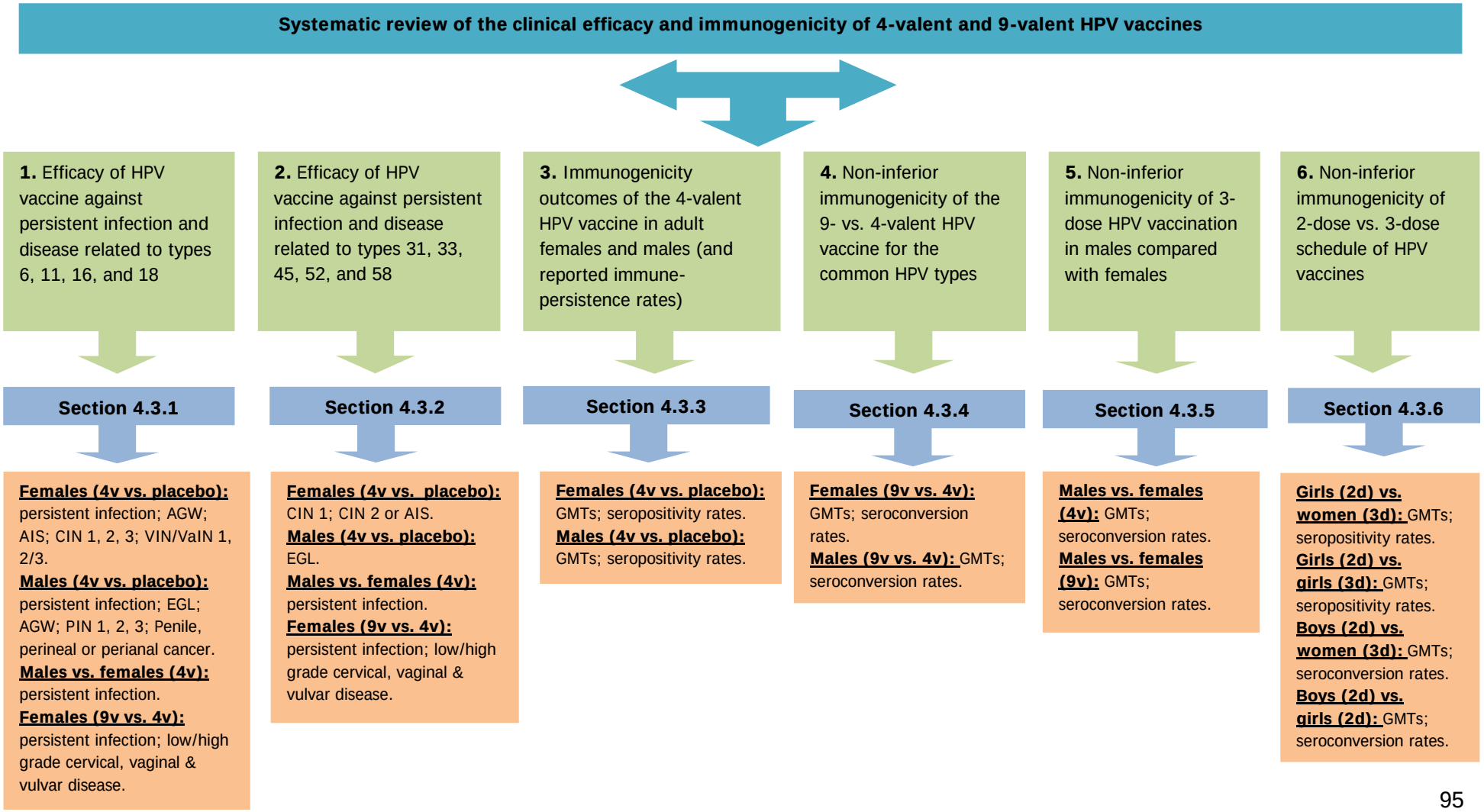
The clinical efficacy in nine to 15 year old boys and girls is demonstrated by comparing GMTs and seroconversion rates versus those achieved in adult populations. These immunobridging trials must exceed pre-defined non-inferiority thresholds to demonstrate HPV vaccine efficacy in these younger boys and girls.

This approach of demonstrating HPV vaccine efficacy by achieving non-inferior immunogenicity outcomes is also used in the bridging studies to extend vaccination recommendations to newer HPV vaccines (for example, 9-valent versus 4-valent HPV vaccine) and alternative HPV vaccine dosage regimens (for example, two-dose versus three-dose schedule).

The long-term persistence of HPV-antibody responses of the 4-valent HPV vaccine over time is reported for the relevant primary and follow-up studies in adult females and males.

A flowchart of the six evidence summaries included in the systematic review, the interventions and comparators for the relevant populations of interest, and the reported clinical efficacy and immunogenicity outcomes for the 4-valent and 9-valent HPV vaccines in the published papers is illustrated in Figure 4.1.

Figure 4.1 Overview of evidence summaries in the systematic review of the clinical efficacy and immunogenicity of 4-valent and 9-valent HPV vaccines



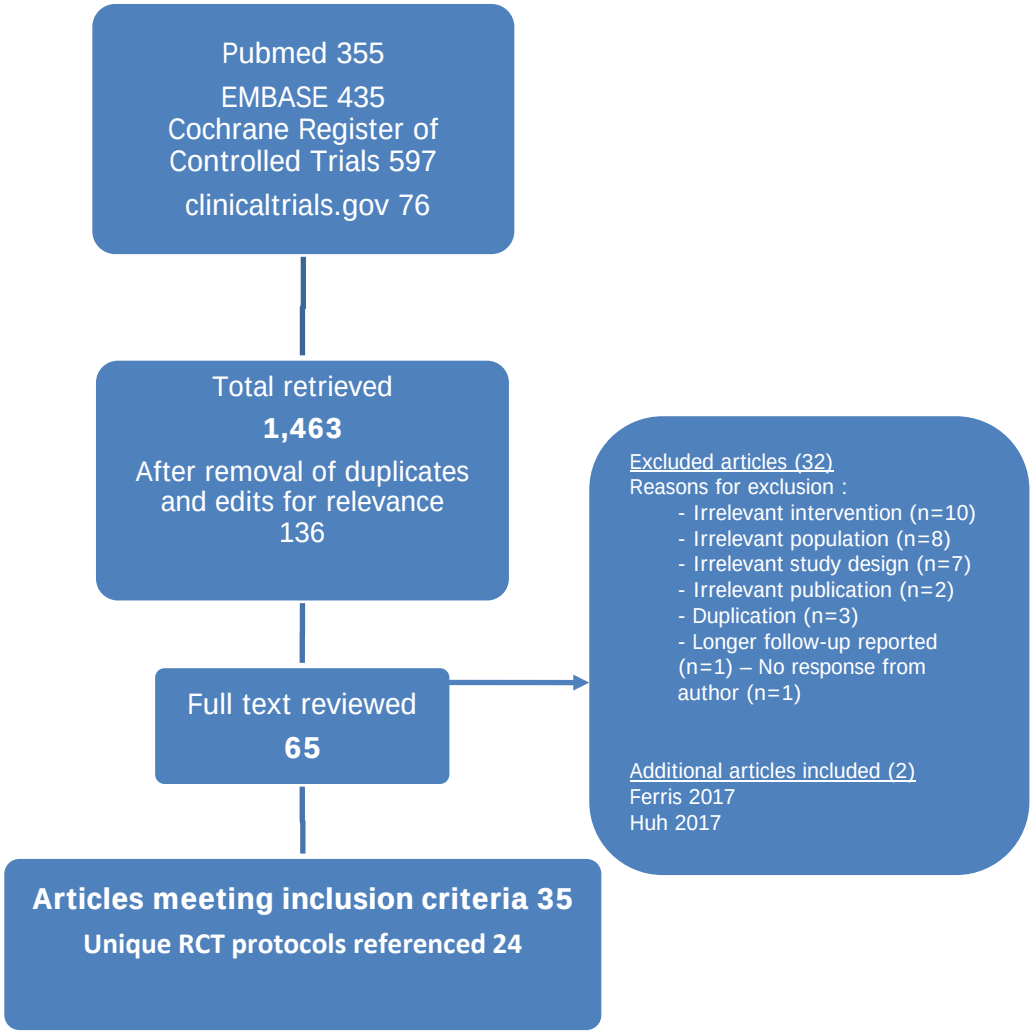
4.2 Results

This section presents the results from the studies identified as part of the systematic search. The summaries and synthesis of the evidence are presented in Section 4.3. To facilitate clear presentation of the data, all forest plots (Figures 4.6 to 4.37) are in Appendix 4.3. The tables detailing supplementary summary of findings (Tables 4.33 to 4.39) are in Appendix 4.4.

4.2.1 Results of literature search

The literature search for RCTs on HPV vaccines was conducted during July 2017. Of the 1,463 titles retrieved, 65 titles were identified to be potentially relevant, and full text copies were reviewed. Thirty-five published articles met the pre-specified inclusion criteria (Figure 4.1), and reference 24 unique RCTs. Details of the studies excluded from the review and the reason for their exclusion are provided in Appendix 4.2.

Figure 4.2 PRISMA flowchart of RCT studies included in the review



4.2.2 Description of included literature

The characteristics of 31 of the 35 published papers included in the review are summarised in Table 4.2. Unique publications are identified according to the first author. The majority of publications (n=26) refer to multinational trials; the five other studies reported data for Canada, China, Japan, Korea and Mexico.

The study sizes in the review ranged from 176 to 20,583 participants. The FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical Disease) I (n=5,455 in protocol 013) and II (n=12,167 in protocol 015) trials were large 16-country randomised controlled trials that assessed the efficacy of the 4-valent HPV vaccine (Gardasil®) in women aged 16 to 26 years. There were 11 published studies included in the review that reported on these two trials individually (or in combination with other trial protocols for combined or pooled analysis). The trials reporting exclusively on immunogenicity outcomes (n=13) were of smaller size ranging from 176 to 4,065.

Eligibility criteria varied, but common criteria for those conducted in females included a history of four or fewer lifetime sexual partners, general good health, and for women to be not pregnant and have no previous abnormal cervical test (Pap smear) results. Competitive Luminex immunoassay (cLIA) was performed in the majority of trials for detection of HPV subtype immune response. Polymerase chain reaction (PCR) testing was also available at enrolment to determine HPV-naïve populations in trials. Tissues from definitive therapy and excisions (including biopsy specimens) were tested with a PCR-based assay for 14 HPV types, including the four subtypes in the 4-valent vaccine (that is, HPV 6, 11, 16, and 18) and the 10 other oncogenic HPV subtypes. Uniform to all two and three-dose trials was the timing of administration of the vaccine at zero and six months, and zero, two and six months, respectively.

For the clinical outcomes referenced in the table, the populations of interest were the restricted or unrestricted modified intention-to-treat populations unless otherwise stated. All immunogenicity outcomes are reported for a per-protocol population. Seroconversion rates are reported where trial participants were defined as seronegative at baseline; otherwise trial publications report absolute seropositivity rates at pre-specified timelines.[218-225] Participants were considered anti-HPV 6, 11, 16 or 18 seropositive when their anti-HPV antibody titres were equal to or exceeded 20mMU/mL, 16mMU/mL, 20mMU/mL and 24mMU/mL, respectively.

The other four publications examine the administration of HPV vaccines with co-administered vaccines appropriate for school-based vaccination programs. These papers by Vesikari (2010),[226] Reisinger (2010),[227] Kosalaraksa (2015)[228] and Schilling (2015)[229] fall outside the evidence summaries for this review.

Table 4.3 Characteristics of studies retrieved

Author (Year)	Study type	Setting	Intervention	Control	Study size (N)	Max length of follow-up	Persistent infection	Clinical outcomes	Immunological outcomes
Ault (2007)[230]	Pooled analysis of 4 RCTs* (Protocols 005/007/013/015) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	20,583	36 months	N/R	HPV 16/18-related CIN 2, CIN 3 AIS, Cervical cancer	N/R
Block (2006)[231]	Non-inferiority immunogenicity	Multinational	3d of 4v (boys & girls 10-15 yo)	3d of 4v (women 16-23 yo)	1,529	7 months	N/R	N/R	GMTs Seroconversion rates
Brown (2009)[232]	Pooled analysis of 2 RCTs* (Protocols 013/015) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	17,622	42 months	Cross protection against infection (PPE)	Cross protection against HPV – related (other than 16/18) CIN 1, CIN 2/3 or AIS disease	N/R
Castellsague (2015)[233]	Non-inferiority immunogenicity	Multinational	3d of 9v (men 16-26 yo)	3d 9v (women 16-26 yo)	2,520	7 months	N/R	N/R	GMTs Seroconversion rates
Dillner (2010)[234]	Pooled analysis of 2 RCTs* (Protocols 013/015) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	17,622	42 months	N/R	CIN 1, AGW, VIN/VaIN 1	N/R
Dobson (2013)[218]	Non-inferiority immunogenicity	Canada	2d of 4v (girls 9-13 yo)	3d of 4v (girls 9-13 yo) and 3d of 4v (women 16-26 yo)	830	36 months	N/R	N/R	GMTs Seropositivity rates
Ferris (2014)[219]	Long term follow-up study	Multinational	3d of 4v (boys & girls 9-15 yo 0 to 6 months)	3 dose 4v (boys & girls 9-15 yo 30 to 36 months)	1,661	96 months	4v HPV-related persistent infection (EVG ITT)	4v HPV-related disease (any type, CIN, EGL) (EVG ITT)	GMTs Seropositivity rates (to 96 months)

Table 4.3 continued (Characteristics of studies retrieved)

Author (Year)	Study type	Setting	Intervention	Control	Study size (N)	Max length of follow-up	Persistent infection	Clinical outcomes	Immunological outcomes
Ferris (2017)[220]	Long term follow-up study	Multinational	3d of 4v (boys & girls 9-15 yo 0 to 6 months)	3 dose 4v (boys & girls 9-15 yo 30 to 36 months)	803	120 months	4v HPV-related persistent infection (EVG PPE)	4v HPV-related EGL, CIN (EVG PPE) and Non-vaccine HPV-related EGL, CIN (EVG ITT)	GMTs Seropositivity rates (to 120 months)
FUTURE II Study Group (2007a)[235]	RCT (FUTURE II) (Protocol 015)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	12,167	36 months	N/R	HPV 16/18-related CIN 2, CIN 3, AIS, cervical cancer	N/R
Garland (2007)[236]	RCT (FUTURE I) (Protocol 013)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	5,455	42 months	N/R	4v HPV-related CIN 1, CIN 2, CIN 3, AIS, AGW, VIN/VaIN 1, VIN/VaIN 2-3	N/R
Guiliano (2011)[237]	RCT	Multinational	3d of 4v (men 16-26 yo)	3d of placebo (men 16-26 yo)	4,065	Median 2.9yrs	4v HPV-related persistent HPV infection	4v HPV-related AGW, PIN 1, PIN 2-3, Penile/perianal /perineal cancer,	N/R
Goldstone (2013)[238]	RCT	Multinational	3d of 4v (men 16-26 yo)	3d of placebo (men 16-26 yo)	4,065	Mean 2.5 years	N/R	4v HPV-related, 10 non-vaccine HPV type related and other HPV-related EGLs, AGW, PIN 1+, PIN 2+	N/R

Table 4.3 continued (Characteristics of studies retrieved)

Author (Year)	Study type	Setting	Intervention	Control	Study size (N)	Max length of follow-up	Persistent infection	Clinical outcomes	Immunological outcomes
Hernandez-Avila (2016)[221]	Non-inferiority immunogenicity	Mexico	2d of 4v (girls 9-10 yo)	3d of 4v (girls 9-10 yo) 3d of 4v (women 18-24 yo)	450	21 months	N/R	N/R	GMTs Seropositivity rates
Hillman (2012)[239]	RCT	Multinational	3d of 4v (men 16-26 yo)	3d of placebo (men 16-26 yo)	4,065	36 months	N/R	N/R	GMTs Seroconversion rates
Huh (2017)[222]	RCT	Multinational	3d of 9v (women 16-26 yo)	3d of placebo (women 16-26 yo)	14,215	60 months	Persistent HPV infection (>6 mo & >12mo)	Combined incidence of high grade cervical, vulvar and vaginal disease	GMTs Seropositivity rates (to 60 months)
Iversen (2016)[223]	Non-inferiority immunogenicity	Multinational	2d of 9v (girls 9-15 yo)	3d of 9v (women 15-26 yo)	1,518	7 months	N/R	N/R	GMTs Seropositivity rates
Joura (2007)[240]	Pooled analysis 3 RCTs* (Protocols 007/013/015) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	18,174	36 months	N/R	HPV 16/18-related VIN/VaIN 2-3	N/R
Joura (2008)[241]	Pooled analysis 2 RCTs* (Protocols 013/015) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	17,622	44 months	N/R	AIS, CIN 1+, CIN 2+, CIN 3+ (PPE)	GMTs Seroconversion rates

Table 4.3 continued (Characteristics of studies retrieved)

Author (Year)	Study type	Setting	Intervention	Control	Study size (N)	Max length of follow-up	Persistent infection	Clinical outcomes	Immunological outcomes
Joura (2015)[224]	RCT	Multinational	3d of 9v (women 16-26 yo)	3d of 4v (women 16-26 yo)	14,215	48 months	Persistent HPV infection (>6 mo & >12mo)	Low-grade disease (AGW, CIN 1, VIN 1, VaIN 1); High-grade disease (AIS,CIN 2-3, cervical cancer, VIN 2-3, VaIN 2-3, vaginal or vulvar cancer	GMTs Seropositivity rates (to 24 months only)
Kang (2008)[242]	RCT	Korea	3d of 4v (females 9-23 yo)	3d of placebo (females 9-23 yo)	176	7 months	N/R	N/R	GMTs Seroconversion rates
Kjaer (2009)[243]	Pooled analysis 3 RCTs* (Protocols 007/013/015) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	18,174	42 months	N/R	4v HPV-related CIN 2+, VIN/VaIN 2-3+	N/R
Li (2012)[244]	RCT	China	3d of 4v (boys 9-15 yo)	3d of 4v (girls 9-15 yo)	600	7 months	N/R	N/R	GMTs Seroconversion rates
Majewski (2009)[245]	Pooled analysis 4 RCTs* (Protocols 007/013/015/016) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	9,265	36 months	N/R	4v HPV-related CIN 1+, CIN 2+, CIN 3+, AIS, AGW, VIN/VaIN 1, VIN/VaIN 2+	N/R
Munoz (2010)[9]	Pooled analysis 2 RCTs* (Protocols 013/015) (FUTURE I & II)	Multinational	3d of 4v (women 16-26 yo)	3d of placebo (women 16-26 yo)	17,622	42 months	N/R	4v HPV-related CIN 1, CIN 2, CIN 3, AIS, AGW, VIN/VaIN 1, VIN/VaIN 2-3	N/R

Table 4.3 continued (Characteristics of studies retrieved)

Author (Year)	Study type	Setting	Intervention	Control	Study size (N)	Max length of follow-up	Persistent infection	Clinical outcomes	Immunological outcomes
Nygard (2015)[225]	RCT (Protocol 015-21 follow-up to FUTURE II)	Multinational (Nordic countries)	3d of 4v (women 16-23 yo)	3d of placebo (women 16-23 yo)	1,598	108 months	N/R	N/R	GMTs Seropositivity rates
Reisinger (2007)[246]	RCT	Multinational	3d of 4v (boys 9-15 yo)	3d of 4v (girls 9-15 yo)	1,781	18 months	N/R	N/R	GMTs Seroconversion rates
Van Damme (2015)[247]	Non-inferiority immunogenicity	Multinational	3d of 9v (boys & girls 9-15 yo)	3d of 9v (women 16-26 yo)	3,074	36 months	N/R	N/R	GMTs Seroconversion rates
Van Damme (2016)[248]	RCT	Multinational	3d of 9v (males 16-26 yo)	3d of 4v (males 16-26 yo)	500	7 months	N/R	N/R	GMTs Seroconversion rates
Vesikari (2015)[249]	RCT	Multinational (Europe)	3d of 9v (girls 9-15 yo)	3d of 4v (girls 9-15 yo)	600	7 months	N/R	N/R	GMTs Seroconversion rates
Villa (2006)[250]	RCT (Protocol 007) (long term follow-up to phase 2-b)	Multinational	3d of 4v (women 16-23)	3d of placebo (women 16-23)	1,158	60 months	HPV related persistent infection	4v HPV-related AGW, CIN 1-3	GMTs (to 60 months)
Yoshikawa (2013)[251]	RCT	Japan	3d of 4v (women 18-26)	3d of placebo (women 18-26)	1,021	30 months	HPV related persistent infection or disease	Composite of 4v HPV-related genital disease (PPE)	GMTs Seroconversion rates (in text)

* Study conducted in at least two settings with outcomes reported separately. Figures reported here correspond to combined participant numbers.

Key: AIS, adenocarcinoma in situ; AGW, anogenital warts; CC, case-control study; CIN, cervical intraepithelial neoplasia; CVG, catch-up vaccination group; 2d, two doses; 3d, three doses; EVG, early vaccination group; EGL, external genital lesions; GMT, geometric mean titre; HPV, human papilloma virus; ITT, intention-to-treat population; N/R, not reported; PIN, penile intraepithelial neoplasia; PPE, per-protocol efficacy population; RCT, randomised controlled trial; VaIN, vaginal intra-epithelial neoplasia; VIN, vulval intraepithelial neoplasia yo, years old.

4.2.3 Risk of bias in included studies

A detailed summary of the risk of bias assessment of the included studies is provided in Table 4.4. The majority of included studies were considered to have a low risk of bias, as they satisfy at least five of the seven risk of bias domains. The notable exceptions that were judged to be of a high risk of bias were (with the type of bias in bracketed text):

- Block 2006[231] — the study was not blinded or randomised (selection and performance bias)
- Castellsague 2015[233] — non-randomised comparison where participants and personnel appear not to be blinded in the study (selection and performance bias)
- Dobson 2013[218] — open-label study with non-blinding of participants; adult females were not randomised (selection and performance bias)
- Ferris 2014[219] and Ferris 2017[220] — non-randomised comparison. Cross over from placebo group to the vaccine intervention. Reported on different populations and inclusion criteria depending on the outcomes leading to very unclear presentation of data and results (unclear or high risk of bias across all the domains)
- Hernandez-Avila 2016[221] — open-label, unblinded, non-randomised clinical trial. Cluster allocation of interventions (selection and performance bias)
- Iversen 2016[223] — open-label unblinded clinical trial with non-randomised allocation (selection and performance bias)
- Li 2012[244] — small sample sizes from one country. No seroconversion rates reported
- Van Damme 2015[247] — allocation concealment for girls only. Unblinded participants and staff for the immunogenicity study. Difference in populations selected for reporting immunogenicity outcome versus antibody persistence (selection, detection performance, and reporting bias).
- Vesikari 2015[249] displayed high risk of bias in reporting of results.

Table 4.4 Risk of bias appraisal of the included studies

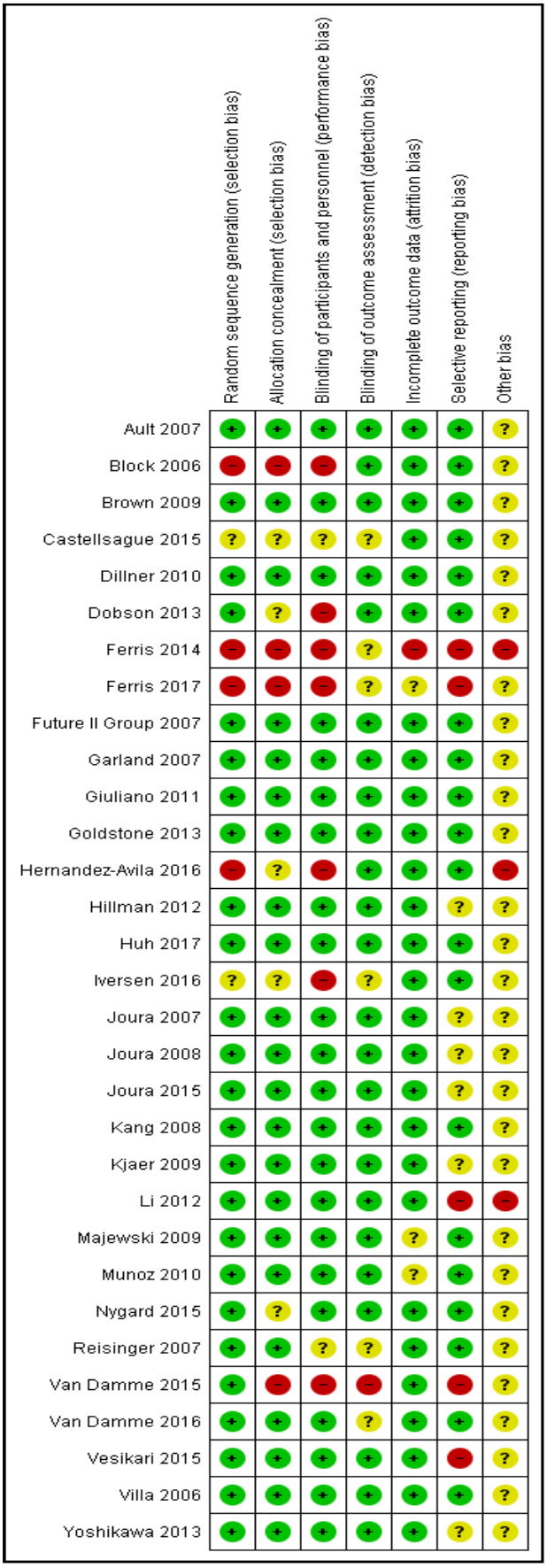
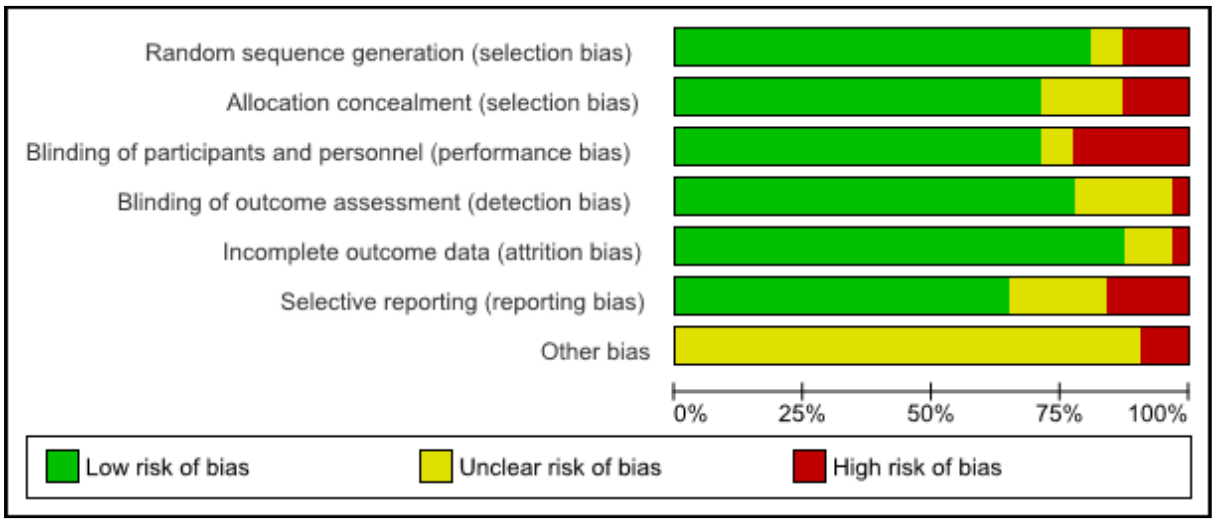


Figure 4.3 summarises the risk of bias appraisal for the included studies. Overall, it confirms that the majority of studies can be classified as having a low risk of bias for six of the seven risk of bias domains. The 'other bias' domain shows an unclear risk of bias for the majority of studies. This classification is primarily due to the majority of studies having the vaccine manufacturer as a funding source.

Figure 4.3 Risk of bias graph



4.3 Evidence synthesis and summaries of results

4.3.1 Efficacy of HPV vaccine against persistent infection and disease related to HPV types 6, 11, 16 and 18

Females - HPV vaccine versus control (placebo or other vaccine)

Persistent infection

One study reported the effect of the 4-valent HPV vaccine on persistent HPV infection in women aged 16 to 23 years after 60 months follow up.[250] The outcome is reported in an unrestricted susceptible population of women aged 16 to 23 years, and is presented as related to the HPV types included in the vaccine. The certainty of the evidence for this outcome is assessed to be 'moderate' (Table 4.5).

Table 4.5 Estimate of effect on persistent infection comparing the 4-valent HPV vaccine to placebo in women aged 16 to 23 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 6/11/16 or 18-related Persistent infection: Follow up: 60 months Unrestricted susceptible	228 per 1,000	**16 per 1,000** (7 to 43)	**RR 0.07** (0.03 to 0.19)	510 (1 RCT)[250]	⨁⨁⨁◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). [250] **Villa 2006.** a. Downgraded one level for imprecision: small sample size.

The effect estimate for this outcome showed a 93% reduction in the risk of persistent infection in the vaccine group compared with the control group (RR: 0.07; 95% CI: 0.03, 0.19) (Figure 4.6).

Anogenital warts (condyloma acuminata)

Three studies reported the effect of the 4-valent HPV vaccine on anogenital warts in females after 36 and 42 months.[9, 234, 245] The outcome is reported both in generally HPV-naïve and unrestricted susceptible populations of women aged 15 to 26 years. The outcome is presented as related to the HPV types included in the vaccine or any HPV type. The certainty of the evidence for this outcome is assessed to be 'low' (Table 4.6).

Table 4.6 Estimate of effect on anogenital warts comparing the 4-valent HPV vaccine to placebo in women aged 15 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16 or 18-related Anogenital warts Follow up: 42 months Generally HPV-naive	30 per 1,000	**1 per 1,000** (0 to 3)	**RR 0.04** (0.01 to 0.09)	9424 (2 RCTs from 1 study)[9]	⨁⨁◯◯ LOW [a, b]
HPV 06/11/16 or 18-related Anogenital warts Follow up: 42 months Unrestricted susceptible	29 per 1,000	**1 per 1,000** (1 to 2)	**RR 0.04** (0.02 to 0.08)	17029 (2 RCTs from 1 study)[234]	⨁⨁◯◯ LOW [a ,b]
Any HPV type- related Anogenital warts Follow up: 36 months Generally HPV-naive	33 per 1,000	**4 per 1,000** (2 to 7)	**RR 0.11** (0.06 to 0.22)	5040 (4 RCTs from 1 study)[245]	⨁⨁◯◯ LOW [a, b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI__). [234] Dillner 2010, [245] Majewski 2009, [9] Munoz 2010__. a. Downgraded one level for risk of bias: pooled analysis of populations from multiple trial protocols, b. Downgraded one level for imprecision: low event rates.

The effect estimate for this outcome showed a 96% reduction in the risk of HPV 6, 11, 16 or 18-related anogenital warts in the vaccine group compared with the control group for both the generally HPV-naïve population (RR: 0.04; 95% CI: 0.01, 0.09) and the unrestricted susceptible population (RR: 0.04; 95% CI: 0.02, 0.08). For any HPV type-related anogenital warts in the generally HPV-naïve population, there is an 89% reduction in the risk for the vaccine group compared with the control group (RR: 0.11; 95% CI: 0.06, 0.22). Details of forest plot summaries are provided in figures 4.7, 4.8 and 4.9 in Appendix 4.3.

Adenocarcinoma-in-situ (AIS)

Three studies reported the effect of the 4-valent HPV vaccine on adenocarcinoma-in-situ (AIS) in females after 36 and 42 months.[9, 230, 245] The outcome is reported both in generally HPV-naïve and unrestricted susceptible populations of women aged 15 to 26 years, and is presented as related to the HPV types included in the vaccine, HPV 16 or 18 or any HPV type. The certainty of the evidence for this outcome is assessed to be 'very low' to 'low' (Table 4.7).

Table 4.7 Estimate of effect on adenocarcinoma-in-situ (AIS) comparing the 4-valent HPV vaccine to placebo in women aged 15 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16 or 18-related AIS Follow up: 42 months Generally HPV-naive	1 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.14** (0.01 to 2.80)	9296 (2 RCTs from 1 study)[9]	⊕◯◯◯ VERY LOW [a, b ,c]
HPV 16/18-related AIS Follow up: 36 months Unrestricted susceptible	1 per 1,000	**0 per 1,000** (0 to 1)	**RR 0.05** (0.00 to 0.81)	19466 (4 RCTs from 1 study)[230]	⊕⊕◯◯ LOW [a, b]
Any HPV type- related AIS Follow up: 36 months Generally HPV-naive	0 per 1,000	**0 per 1,000** (0 to 3)	**RR 0.34** (0.01 to 8.37)	4997 (4 RCTs from 1 study)[245]	⊕◯◯◯ VERY LOW [a ,b, c]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI__).__ [230] __Ault 2007,__ [245] __Majewski 2009,__ [9] __Munoz 2010__. a. Downgraded one level for risk of bias: pooled analysis of populations from multiple trial protocols, b. Downgraded one level for imprecision: low event rates; c. Downgraded another level for imprecision: 95% CI varies widely around the effect estimate includes potential benefits for the intervention and the control, along with the line of no-effect.

The effect estimate for this outcome showed a 86% reduction in the risk of HPV 6, 11, 16 or 18-related AIS in the vaccine group compared with the control group for the generally HPV-naïve population (RR: 0.14; 95% CI: 0.01, 2.80). It also estimated a 95% reduction in the risk of HPV 16 or 18-related AIS in the vaccine group compared with the control group for the unrestricted susceptible population (RR: 0.05; 95% CI: 0.00, 0.81). For any HPV type-related AIS in the generally HPV-naïve population, there is a 66% reduction in the risk for the vaccine group compared with the control group (RR: 0.34; 95% CI: 0.01, 8.37).

In general, very few AIS cases were observed across both groups in all populations. For example, the results reported in the generally HPV-naïve populations observed no cases of HPV 6, 11, 16 or 18-related AIS in the intervention group (n=4,616) and only three cases in the placebo group (n=4,680). The results reported in the generally HPV-naïve populations observed no cases of any HPV type-related AIS in the intervention group (n=2,470) and only one case in the placebo group (n=2,527). The effect sizes are rendered very uncertain due to low event rates and the very wide 95% CIs reported around the effect estimates, which include potential benefits for the intervention and the control, along with the no-effect. See details of forest plot summaries in figures 4.7, 4.8 and 4.9 in Appendix 4.3.

However, the estimate of 95% reduction of HPV 16 or 18-related AIS reported in the larger study of an unrestricted susceptible population also had no cases in the intervention group (n=9,729), but 10 cases in the placebo group (n=9,737). There was greater statistical significance associated with this result, despite the low event rates.

Cervical intraepithelial neoplasia (CIN)

Five studies reported the effect of the 4-valent HPV vaccine on cervical intraepithelial neoplasia (CIN) in females after 36 and 42 months.[9, 230, 234, 243, 245] The outcome is reported both in generally HPV-naïve and unrestricted susceptible populations of women aged 15 to 26 years, and is presented as related to the HPV types included in the vaccine, HPV 16 or 18 or any HPV type. The certainty of the evidence for this outcome is assessed to be 'low' (Tables 4.8).

Table 4.8 Estimate of effect on cervical intraepithelial neoplasia (CIN) comparing the 4-valent HPV vaccine to placebo in women aged 15 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16 or 18-related **CIN 1** Follow up: 42 months Generally HPV-naive	29 per 1,000	**1 per 1,000** (0 to 2)	**RR 0.02** (0.01 to 0.07)	9296 (2 RCTs from 1 study)[9]	⊕⊕◯◯ LOW [a, b]
HPV 06/11/16 or 18-related CIN 1 Follow up: 42 months Unrestricted susceptible	28 per 1,000	**1 per 1,000** (1 to 3)	**RR 0.05** (0.03 to 0.09)	16805 (2 RCTs from 1 study)[234]	⊕⊕◯◯ LOW [a, b]
Any HPV type-related CIN 1 or worse Follow up: 36 months Generally HPV-naive	50 per 1,000	**36 per 1,000** (27 to 47)	**RR 0.71** (0.54 to 0.93)	4997 (4 RCTs from 1 study)[245]	⊕⊕◯◯ LOW [a, b]
HPV 06/11/16 or 18-related **CIN 2** Follow up: 42 months Generally HPV-naive	10 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.01** (0.00 to 0.17)	9296 (2 RCTs from 1 study)[9]	⊕⊕◯◯ LOW [a, b]
HPV 06/11/16 or 18-related CIN 2 follow up: 42 months Unrestricted susceptible	15 per 1,000	**1 per 1,000** (0 to 2)	**RR 0.04** (0.02 to 0.11)	12782 (3 RCTs from 1 study)[243]	⊕⊕◯◯ LOW [a ,b]

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
Any HPV type-related CIN 2 or worse Follow up: 36 months Generally HPV-naive	21 per 1,000	**9 per 1,000** (6 to 15)	**RR 0.44** (0.27 to 0.71)	4997 (4 RCTs from 1 study)[245]	⊕⊕◯◯ LOW [a, b]
HPV 06/11/16 or 18-related **CIN 3** Follow up: 42 months Generally HPV-naive	9 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.01** (0.00 to 0.20)	9296 (2 RCTs from 1 study)[9]	⊕⊕◯◯ LOW [a ,b]
HPV 16/18-related CIN 3 Follow up: 36 months Unrestricted susceptible	8 per 1,000	**0 per 1,000** (0 to 1)	**RR 0.03** (0.01 to 0.11)	19466 (4 RCTs from 1 study)[230]	⊕⊕◯◯ LOW [a, b]
Any HPV type-related CIN 3 or worse Follow up: 36 months Generally HPV-naive	13 per 1,000	**5 per 1,000** (3 to 10)	**RR 0.42** (0.22 to 0.79)	4997 (4 RCTs from 1 study)[245]	⊕⊕◯◯ LOW [a, b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI__). [230] Ault 2007, [234] Dillner 2010, [243] Kjaer 2009, [245] Majewski 2009, [9] Munoz 2010.__ a. Downgraded one level for risk of bias: pooled analysis of populations from multiple trial protocols, b. Downgraded one level for imprecision: low event rates.

The effect estimate for this outcome showed a 98% reduction in the risk of HPV 6, 11, 16 or 18-related CIN 1 in the vaccine group compared with the control group for the generally HPV-naïve population (RR: 0.02; 95% CI: 0.01, 0.07), and a 95% reduction for the unrestricted susceptible population (RR: 0.05; 95% CI: 0.03, 0.09). For any HPV type-related CIN 1 or worse in the generally HPV-naïve population, there is a 29% reduction in the risk for the vaccine group compared with the control group (RR: 0.71; 95% CI: 0.54, 0.93).

The effect estimate showed a 99% reduction in the risk of HPV 6, 11, 16 or 18-related CIN 2 in the vaccine group compared with the control group for the generally HPV-naive population (RR: 0.01; 95% CI: 0.01, 0.17), and a 97% reduction for the unrestricted susceptible population (RR: 0.04; 95% CI: 0.02, 0.11). For any HPV type-related CIN 2 or worse in the generally HPV-naïve population, there is a 56% reduction in the risk for the vaccine group compared with the control group (RR: 0.44; 95% CI: 0.27, 0.71).

The effect estimate showed a 99% reduction in the risk of in the risk of HPV 6, 11, 16 or 18-related CIN 3 in the vaccine group compared with the control group for the generally HPV-naïve population (RR: 0.01; 95% CI: 0.00, 0.20), and a 97% reduction in the risk of HPV 16 or 18-related CIN 3 in the vaccine group compared

with the control group for the unrestricted susceptible population (RR: 0.03; 95% CI: 0.01, 0.11). For any HPV type-related CIN 3 or worse in the generally HPV-naïve population, there is a 58% reduction in the risk for the vaccine group compared with the control group (RR: 0.42; 95% CI: 0.22, 0.79). See details of forest plot summaries in figures 4.7, 4.8 and 4.9 in Appendix 4.3.

Vulvar and vaginal intraepithelial neoplasia (VIN and VaIN)

Four studies reported the effect of the 4-valent HPV vaccine on vulvar and vaginal intraepithelial neoplasia (VIN and VaIN) in females after 36 and 42 months.[9, 234, 243, 245] The outcome is reported both in generally HPV-naïve and unrestricted susceptible populations of women aged 15 to 26 years, and is presented as related to the HPV types included in the vaccine or any HPV type. The certainty of the evidence for this outcome is assessed to be 'very low' to 'low' (Tables 4.9).

Table 4.9 Estimate of effect on vulvar and vaginal intraepithelial neoplasia (VIN and VaIN) comparing the 4-valent HPV vaccine to placebo in women aged 15 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16 or 18-related **VIN/VaIN 1** Follow up: 42 months Generally HPV-naive	4 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.05** (0.01 to 0.36)	9424 (2 RCTs from 1 study)[9]	⨁⨁◯◯ LOW [a, b]
HPV 06/11/16 or 18-related VIN/VaIN 1 Follow up: 42 months Unrestricted susceptible	4 per 1,000	**0 per 1,000** (0 to 4)	**RR 0.05** (0.01 to 0.22)	17029 (2 RCTs from 1 study)[234]	⨁⨁◯◯ LOW [a ,b]
Any HPV type-related VIN/VaIN 1 Follow up: 36 months Generally HPV-naive	5 per 1,000	**2 per 1,000** (1 to 6)	**RR 0.39** (0.14 to 1.10)	5040 (4 RCTs from 1 study)[245]	⨁◯◯◯ VERY LOW [a ,b, c]
HPV 06/11/16 or 18-related **VIN/VaIN 2/3** Follow up: 42 months Generally HPV-naive	5 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.05** (0.01 to 0.34)	9424 (2 RCTs from 1 study)[9]	⨁⨁◯◯ LOW [a, b]
HPV 06/11/16 or 18-related VIN/VaIN 2/3 Follow up: 42 months Unrestricted susceptible	5 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.03** (0.00 to 0.21)	12955 (3 RCTs from 1 study)[243]	⨁⨁◯◯ LOW [a, b]

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
Any HPV type-related VIN/VaIN 2/3 or worse Follow up: 36 months Generally HPV-naive	4 per 1,000	**0 per 1,000** (0 to 3)	**RR 0.05** (0.00 to 0.83)	5040 (4 RCTs from 1 study)[245]	⨁⨁◯◯ LOW [a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI__). [234] Dillner 2010, [243] Kjaer 2009, [245] Majewski 2009, [9] Munoz 2010.__. a. Downgraded one level for risk of bias: pooled analysis of populations from multiple trial protocols, b. Downgraded one level for imprecision: low event rates; Downgraded another level for imprecision: 95% CI varies widely around the effect estimate includes potential benefits for the intervention and the control, along with the line of no-effect.

The effect estimate for this outcome showed a 95% reduction in the risk of HPV 6, 11, 16 or 18-related VIN 1 and VaIN 1 in the vaccine group compared with the control group for both the generally HPV-naïve population (RR: 0.05; 95% CI: 0.01, 0.36) and the unrestricted susceptible population (RR: 0.05; 95% CI: 0.01, 0.22). For any HPV type-related VIN 1 and VaIN 1 in the generally HPV-naïve population, there is a 61% reduction in the risk for the vaccine group compared with the control group (RR: 0.39; 95% CI: 0.14, 1.10).

The effect showed a 95% reduction in the risk of in the risk of HPV 6, 11, 16 or 18-related VIN 2 or 3 and VaIN 2 or 3 in the vaccine group compared with the control group for the generally HPV-naïve population (RR: 0.05; 95% CI: 0.01, 0.34), and a 97% reduction in the unrestricted susceptible population (RR: 0.03; 95% CI: 0.00, 0.21). For any HPV type-related VIN and VaIN 2 or worse in the generally HPV-naïve population, there is a 95% reduction in the risk for the vaccine group compared with the control group (RR: 0.05; 95% CI: 0.0, 0.83). See details of forest plot summaries in figures 4.7, 4.8 and 4.9 in Appendix 4.3.

Summary

In an unrestricted susceptible population of 16 to 23 year old females, the 4-valent HPV vaccine is shown to have a significant effect at preventing persistent HPV 6, 11, 16 or 18-related infections at five years.

In the generally HPV-naïve population of 15 to 26 year old females, the 4-valent HPV vaccine is shown to have a significant effect at preventing external genital lesions and anogenital warts up to 42 months. The vaccine also demonstrates a significant effect in reducing the events associated with HPV 6, 11, 16 or 18-related CIN 1, CIN 2, CIN 3, VIN 1, VaIN 1,VIN 2 and VaIN 2 up to 42 months. There also is a reduction in HPV 6, 11, 16 or 18-related AIS between the 4-valent HPV vaccine and placebo groups. However, there is considerable uncertainty due to the very low event rates and associated wide CIs. A similar effect size with associated uncertainty also occurs for any-HPV type related AIS in a European adult female population.

There is similar supportive evidence provided for all these outcomes for up to 42 months in the unrestricted susceptible population of 15 to 26 year old females.

Males - HPV vaccine versus control (placebo or other vaccine)

Persistent infection

One study reported the effect of the 4-valent HPV vaccine on persistent infection in males after 2.9 years.[237] The outcome is reported for infections longer than six months in a naïve-to-relevant HPV type2 (NRT) population of men aged 16 to 26 years, and is presented as related to the HPV types included in the vaccine. The certainty of the evidence for this outcome is assessed to be 'moderate' (Table 4.10).

Table 4.10 Estimate of effect on persistent infection (over six months) comparing the 4-valent HPV vaccine to placebo in men aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 6/11/16 or 18-related Persistent infection: Follow up: median 2.9 years Naive to relevant HPV type	105 per 1,000	**35 per 1,000** (26 to 46)	**RR 0.33** (0.25 to 0.44)	3333 (1 RCT)[237]	⨁⨁⨁◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). [237] **Giuliano 2011.** a. Downgraded one level for imprecision: low rate of events.

The effect estimate for this outcome showed a 67% reduction in the risk of persistent infection in the vaccine group compared with the control group (RR: 0.33; 95% CI: 0.25, 0.44) (Figure 4.10).

External genital lesions

Two studies reported from one trial (NCT00090285), which compared the 4-valent HPV vaccine versus placebo in 4,065 males aged 16 to 26 years. The trial reported on the outcome of external genital lesions, which is a combination of anogenital warts, PIN1, PIN2 and PIN3 in addition to penile, perianal and perineal cancer.[237, 238]

The outcome is reported for external genital lesions in a naïve-to-relevant HPV type[2] (NRT) and HPV-naïve[3] populations of men aged 16 to 26 years after 2.9 and 2.5 years respectively, and is presented as related to the HPV types included in the vaccine or any HPV type. The certainty of the evidence for this outcome is assessed to be 'moderate' (Table 4.11). The studies found fewer males with external genital

[2] Naïve to the relevant HPV type (HPV-naïve (that is, seronegative and PCR negative) to the four vaccine HPV types being analysed at day one.
[3] HPV-naïve populations (that is naïve to 14 HPV types at the time of enrolment).

lesions in the vaccine group compared to the control group for both modified intention-to-treat populations — naïve to the vaccine types and naïve to 14 HPV types at enrolment.

Table 4.11 Estimate of effect on comparing the 4-valent HPV vaccine to placebo in external genital lesions in men 16-26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16/18-related **External GLs** Follow up: median 2.9 yrs Naive to relevant HPV type	29 per 1,000	**7 per 1,000** (4 to 14)	**RR 0.25** (0.14 to 0.46)	3545 (1 RCT)[237]	⊕⊕⊕◯ MODERATE [a]
HPV 06/11/16 or 18-related External GLs Follow up: mean 2.5 yrs HPV-naive	25 per 1,000	**2 per 1,000** (1 to 8)	**RR 0.09** (0.03 to 0.30)	2545 (1 RCT)[238]	⊕⊕⊕◯ MODERATE [a]
Any HPV type External GLs Follow up: mean 2.5 yrs HPV-naive	29 per 1,000	**6 per 1,000** (2 to 12)	**RR 0.19** (0.08 to 0.42)	2545 (1 RCT)[238]	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI**).** [237] **Giuliano 2011,** [238] **Goldstone 2013.** a. Downgraded one level for imprecision: low rate of events.

The effect estimate for this outcome showed a 91% and 75% reduction in the risk of HPV 6, 11, 16 or 18-related external genital lesions in the vaccine group compared with the control group for both the HPV-naïve (RR: 0.09; 95% CI: 0.03, 0.30) and the naïve-to-relevant HPV type population (RR: 0.25; 95% CI: 0.14, 0.46) respectively (Figure 4.11 and 4.12). For any HPV type-related external genital lesions in the HPV-naïve population, there is an 81% reduction in the risk for the vaccine group compared with the control group (RR: 0.19; 95% CI: 0.08, 0.42) (Figure 4.12).

Anogenital warts (condyloma acuminata)

Two studies reported the effect of the 4-valent HPV vaccine on anogenital warts in males after 2.9 and 2.5 years respectively.[237, 238] The outcome is reported both in naïve to relevant HPV type2 (NRT) and HPV-naïve3 populations of men aged 16 to 26 years, and is presented as related to the HPV types included in the vaccine or all HPV type. The certainty of the evidence for this outcome is assessed to be 'moderate' (Tables 4.12). The studies found fewer males with anogenital warts in the vaccine group compared to the control group for each modified intention-to-treat population — the naïve to the vaccine types and the naive to 14 HPV types at

enrolment.

Table 4.12 Estimate of effect on comparing the 4-valent HPV vaccine to placebo in anogenital warts in men aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16/18-related **Anogenital warts** Follow up: median 2.9 yrs Naive to relevant HPV type	27 per 1,000	**6 per 1,000** (3 to 11)	**RR 0.21** (0.11 to 0.41)	3545 (1 RCT)[237]	⊕⊕⊕◯ MODERATE [a]
All HPV type-related Anogenital warts Follow up: mean 2.5 yrs HPV-naive	26 per 1,000	**4 per 1,000** (2 to 10)	**RR 0.15** (0.06 to 0.39)	2545 (1 RCT)[238]	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI**). [237] Giuliano 2011, [238] Goldstone 2013.** a. Downgraded one level for imprecision: low rate of events.

The effect estimate for this outcome showed a 79% reduction in the risk of HPV 6, 11, 16 or 18-related anogenital warts in the vaccine group compared with the control group for the naive to relevant HPV type population (RR: 0.21; 95% CI: 0.11, 0.41) (Figure 4.11). For all HPV type-related anogenital warts in the HPV-naïve population, there is an 85% reduction in the risk for the vaccine group compared with the control group (RR: 0.15; 95% CI: 0.06, 0.39) (Figure 4.12).

Penile, perianal or perineal intraepithelial neoplasia (PIN)

Two studies reported the effect of the 4-valent HPV vaccine on penile, perianal or perineal intraepithelial neoplasia (PIN) in males after 2.9 and 2.5 years respectively.[237, 238] The outcome is reported both in naïve-to-relevant HPV type[4] (NRT) and HPV-naïve[5] populations of men aged 16 to 26 years, and is presented as related to the HPV types included in the vaccine or all HPV type. Given all results show low event rates and wide CIs that cross the line of no-effect, the certainty of the evidence for this outcome is assessed to be 'low' (Tables 4.13).

[4] Naïve to the relevant HPV type (HPV-naïve (that is, seronegative and PCR negative) to the four vaccine HPV types being analysed at day one.
[5] HPV-naïve populations (that is naïve to 14 HPV types at the time of enrolment).

Table 4.13 Estimate of effect on comparing the 4-valent HPV vaccine to placebo in penile, perianal or perineal intraepithelial neoplasia (PIN) in men aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16/18-related **PIN Grade 1 lesions** Follow up: median 2.9 yrs Naive to relevant HPV type	2 per 1,000	**1 per 1,000** (0 to 7)	**RR 0.66** (0.11 to 3.97)	3545 (1 RCT)[237]	⊕⊕◯◯ LOW [a,b]
All HPV type-related PIN Grade 1 or worse Follow up: mean 2.5 yrs HPV-naive	3 per 1,000	**2 per 1,000** (0 to 9)	**RR 0.50** (0.09 to 2.71)	2545 (1 RCT)[238]	⊕⊕◯◯ LOW [a,b]
HPV 06/11/16/18-related **PIN Grade 2 or 3 lesions** Follow up: median 2.9 yrs Naive to relevant HPV type	1 per 1,000	**1 per 1,000** (0 to 12)	**RR 1.99** (0.18 to 21.97)	3545 (1 RCT)[237]	⊕⊕◯◯ LOW [a, b]
All HPV type-related PIN Grade 2 or worse Follow up: mean 2.5 yrs HPV-naive	2 per 1,000	**0 per 1,000** (0 to 7)	**RR 0.20** (0.01 to 4.15)	2545 (1 RCT)[238]	⊕⊕◯◯ LOW [a,b]
HPV 06/11/16/18-related **All PIN Lesions** Follow up: median 2.9 yrs Naive to relevant HPV type	2 per 1,000	**2 per 1,000** (1 to 9)	**RR 1.00** (0.25 to 3.98)	3545 (1 RCT)[237]	⊕⊕◯◯ LOW [a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI__).__ [237] __Giuliano 2011,__ [238] __Goldstone 2013.__ a. Downgraded one level for imprecision: low rate of events; b. Downgraded another level for imprecision: 95% CI around the effect estimate includes potential benefits for the intervention and the control, along with the no-effect.

The effect estimate for this outcome showed a 34% reduction in the risk of HPV 6, 11, 16 or 18-related PIN 1 in the vaccine group compared with the control group for the naïve-to-relevant HPV type population (RR: 0.66; 95% CI: 0.11, 3.97). For all HPV type-related PIN 1 or worse in the HPV-naïve population, there is a 50% reduction in the risk for the vaccine group compared with the control group (RR: 0.50; 95% CI: 0.09, 2.71).

There was no significant difference in PIN 2 or 3 cases between the HPV vaccine and the placebo group in the NRT population, with identical absolute effects of one case per 1,000 for both groups. The relative effect for this outcome showed RR= 1.20; 95% CI=0.18, 21.97). However, for all HPV type-related PIN 2 or worse in the HPV-naïve population, there is an 80% reduction in the risk for the vaccine group

compared with the control group (RR: 0.20; 95% CI: 0.01, 4.15).

There was no significant difference in all PIN lesions between the HPV vaccine and the placebo group in the NRT population, with identical absolute effects of two cases per 1,000 for both groups. The relative effect for this outcome showed RR= 1.00; 95% CI=0.25, 3.98.

For any-HPV type-related PIN grade 1 and grade 2 or worse in the HPV-naïve population, there was evidence of a 50% and 80% reduction in events. Despite this sizeable effect size, very few PIN cases were observed across the intervention and placebo groups in all populations. The very wide 95% CIs reported around the effect estimates, that include potential benefits for the intervention and the control, along with the no-effect, rendered the results inconclusive. See details of forest plot summaries in Figures 4.11 and 4.12 in Appendix 4.3.

Penile, perianal or perineal cancer

One study reported the effect of the 4-valent HPV vaccine on penile, perianal or perineal cancer in males after 2.9 years.[237] However, there were no cases of penile, perianal or perineal cancer reported in either the HPV vaccine or the placebo group (Table 4.14). The relative effect was not estimable, and the result is inconclusive (Figure 4.11).

Table 4.14 Estimate of effect on comparing the 4-valent HPV vaccine to placebo in penile, perianal or perineal cancer in men 16-26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 06/11/16/18-related Penile/perianal/perineal cancer follow up: median 2.9 yrs	0 per 1,000	**0 per 1,000** (0 to 0)	**Not estimable**	3545 (1 RCT)[237]	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI__).__ [237] __Giuliano 2011.__ a. Downgraded one level for imprecision: low rate of events.

Summary

The 4-valent HPV vaccine is also shown to be effective at preventing persistent HPV 6, 11, 16 or 18-related infections in adult males aged 16-26 years. The vaccine is also effective at preventing external genital lesions and anogenital warts at three years; but given the low event rates observed, there appears to be no conclusive evidence of a significant clinical difference compared with placebo for PIN lesions at three years. There were no observed events of penile, perianal or perineal cancer in either the intervention of placebo group at three years.

One study reported the effect of the 4-valent HPV vaccine on persistent infection and or disease in males compared to females from 42 to 96 months.[219] The outcome is reported for persistent infection and or disease in an intention-to-treat population of women aged nine to 15 years, and is presented as related to the HPV types included in the vaccine. The certainty of the evidence for this outcome is assessed to be 'very low' (Table 4.15).

Table 4.15 Estimate of effect on comparing 4-valent HPV vaccination in persistent infection and or disease in boys versus girls aged nine to 15 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	9 to 15 year old females	**9 to 15 year old males**			
HPV 06/11/16 or 18-related Persistent Infection Follow up: 96 months EVG ITT Population	8 per 1,000	**12 per 1,000** (2 to 82)	**RR 1.40** (0.20 to 9.87)	411 (1 RCT)[219]	⨁◯◯◯ VERY LOW [a, b]
HPV 06/11/16 or 18-related Persistent Infection or Disease Follow up: 96 months EVG ITT Population	8 per 1,000	**12 per 1,000** (2 to 81)	**RR 1.48** (0.21 to 10.41)	429 (1 RCT)[219]	⨁◯◯◯ VERY LOW [a, b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). [219] __Ferris 2014__. a. Downgraded two levels for risk of bias: non-randomised comparison with cross-over of placebo group to catch up vaccination group and high loss to follow up (attrition bias). b. Downgraded one level for imprecision: low event rates and very wide CIs and crosses line of no effect.

There was no significant difference in the number of events of persistent infection and or disease related to HPV 6, 11, 16 or 18 with 4-valent HPV vaccine, between males and females The event rates were low for very small sample sizes, and displayed wide confidence intervals which cross the line of on-effect, rendering the results quite uncertain (Figure 4.13).[219]

Females (9-valent compared to 4-valent HPV vaccine)

Persistent infection

One study reported the effect of the 9-valent HPV vaccine versus 4-valent HPV vaccine on persistent infection in females after 48 months.[224] The outcomes are reported for infections longer than six and 12 months in a modified intention-to-treat population[6] of women aged 16 to 26 years, and are presented as related to the HPV

[6] Mostly HPV-naïve subjects who at day one were negative for squamous intraepithelial lesion, were seronegative for the 9-vaccine HPV types, and PCR-negative for the 14 HPV types tested during the study.

types included in the vaccine. The certainty of the evidence for this outcome is assessed to be 'moderate' (Table 4.16).

Table 4.16 Estimate of effect on HPV 6, 11, 16 & 18-related persistent infections comparing 9-valent HPV to 4-valent HPV vaccination in women aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	4-valent vaccine	**9-valent vaccine**			
HPV 6/11/16/18-related Persistent HPV Infection >6 months Follow up: 48 months Mostly HPV-naive	20 per 1,000	**15 per 1,000** (10 to 21)	**RR 0.74** (0.50 to 1.09)	5967 (1 RCT)[224]	⊕⊕⊕◯ MODERATE [a]
HPV 6/11/16/18-related Persistent HPV Infection >12 months Follow up: 48 months Mostly HPV-naive	9 per 1,000	**9 per 1,000** (6 to 16)	**RR 1.05** (0.62 to 1.78)	5967 (1 RCT)[224]	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). [224] __Joura 2015__. a. Downgraded one level for imprecision: low event rates.

The effect estimate for persistent infection longer than six months showed a 26% reduction in the risk of persistent infection in the 9-valent HPV vaccine group compared with the 4-valent HPV vaccine group (RR: 0.74; 95% CI: 0.50, 1.09), while there are identical absolute effects for persistent infection longer than 12 months (nine per 1,000) for both the 9-valent and 4-valent HPV vaccines (Figure 4.14).

Low-grade and high-grade cervical, vaginal and vulvar disease

The same study reported the effect of the 9-valent HPV vaccine versus 4-valent HPV vaccine on low-grade and high-grade cervical disease in females after 48 months.[224] The outcome is reported in the same population of women aged 16 to 26 years, and is presented as related to the HPV types included in the vaccine. The certainty of the evidence for this outcome is assessed to be 'low' to 'moderate' (Table 4.17).

Table 4.17 Estimate of effect on comparing 9-valent and 4-valent HPV vaccination in HPV 6, 11, 16 & 18-related low grade and high grade cervical, vaginal and vulvar disease in women aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	4-valent vaccine	**9-valent vaccine**			
HPV 6/11/16/18-related Cervical, vulvar and vaginal disease (any grade or severity) Follow up: 48 months Mostly HPV-naive	0 per 1,000	**1 per 1,000** (0 to 12)	**RR 4.06** (0.45 to 36.29)	6108 (1 RCT)[224]	⊕⊕◯◯ LOW [a, b]
HPV 6/11/16/18-related Low grade disease (Condyloma, CIN1, VIN1 and VaIN1) Follow up: 48 months Mostly HPV-naive	0 per 1,000	**1 per 1,000** (0 to 12)	**RR 4.06** (0.45 to 36.29)	6108 (1 RCT)[224]	⊕⊕◯◯ LOW [a ,b]
HPV 6/11/16/18-related High Grade disease (CIN2/3, AIS, cervical cancer, VIN 2/3, vulvar cancer, VaIN 2/3 and vaginal cancer) Follow up: 48 months Mostly HPV-naive	0 per 1,000	**0 per 1,000** (0 to 0)	**Not estimable**	6108 (1 RCT)[224]	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). [224] __Joura 2015__. a. Downgraded one level for imprecision: low event rates. b. Downgraded one further level for imprecision: very wide CIs and crosses line of no effect.

There was no significant difference between 9-valent and 4-valent HPV vaccines in the clinical outcomes — cervical, vaginal and vulvar diseases — related to the HPV 6, 11, 16, and 18 types for women. It should be noted that there were more observed events (albeit very small numbers) for any or low-grade cervical, vaginal and vulvar diseases in the 9-valent vaccine group. However, these effects are not statistically significant due to the presence of extremely wide CIs that cross the line of no-effect (Figure 4.14). There were no events observed in either vaccine group in the case of high-grades of these diseases.

4.3.2 Efficacy of HPV vaccine against persistent infection and disease related to types 31, 33, 45, 52, and 58 (and types 35, 39, 51, 56 and 59 if reported)

Females - HPV vaccine versus control (placebo or other vaccine)

Cervical intraepithelial neoplasia (CIN)

One study reported the effect of the 4-valent HPV vaccine on cervical intraepithelial neoplasia (CIN) in females after 42 months.[232] The outcome is reported in a generally HPV-naïve population of women aged 16 to 26 years, and is presented as related to the 10 HPV types not included in the vaccine (that is, HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59). The certainty of the evidence for this outcome is assessed to be 'very low' to 'low' (Tables 4.18).

Table 4.18 Estimate of effect on cervical intraepithelial neoplasia (CIN) comparing the 4-valent HPV vaccine to placebo in women aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 31/33/35/39/45/51/52/56/58 or 59-related **CIN 1** Follow up: 42 months Generally HPV-naive	38 per 1,000	**31 per 1,000** (25 to 39)	**RR 0.82** (0.66 to 1.02)	9296 (2 RCTs from 1 study)[232]	⊕◯◯◯ VERY LOW [a, b ,c]
HPV 31/33/35/39/45/51/52/56/58 or 59-related **CIN 2-3 or AIS** Follow up: 42 months Generally HPV-naive	20 per 1,000	**14 per 1,000** (10 to 18)	**RR 0.68** (0.49 to 0.93)	9296 (2 RCTs from 1 study)[232]	⊕⊕◯◯ LOW [a, b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI__). [232] Brown 2009__. a. Downgraded one level for risk of bias: pooled analysis of populations from multiple trial protocols, b. Downgraded one level for imprecision: low event rates; c. Downgraded another level for imprecision: 95% CI varies around the effect estimate includes potential benefits for the intervention and the control, along with the line of no-effect.

The effect estimate for this outcome showed an 18% reduction in the risk of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59-related CIN 1 in the vaccine group compared with the control group for the generally HPV-naïve population (RR: 0.82; 95% CI: 0.66, 1.02). However, the event rates are low for the reported outcome, and the confidence interval for the CIN 1 estimate crossed the line of no-effect rendering this evidence quite uncertain (Figure 4.15). The effect estimate showed a 32% reduction in the risk of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59-related CIN 2-3 or AIS in

the vaccine group compared with the control group for the generally HPV-naïve population (RR: 0.68; 95% CI: 0.49, 0.93).

Males - HPV vaccine versus control (placebo or other vaccine)

External genital lesions

One study reported on the outcome of external genital lesions in a HPV-naive[7] population of men aged 16 to 26 years after 2.5 years, and is presented as related to the 10 HPV types not included in the vaccine (that is, HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59).(238) The certainty of the evidence for this outcome is assessed to be 'low' (Table 4.19).

Table 4.19 Estimate of effect of 4-valent HPV vaccine versus placebo in HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59-related external genital lesions in men aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Placebo	**4-valent vaccine**			
HPV 31/33/35/39/45/51/52/56/58/59-related **External GLs** Follow up: mean 2.5 yrs HPV-naive	5 per 1,000	**2 per 1,000** (0 to 8)	**RR 0.33** (0.07 to 1.64)	2545 (1 RCT)(238)	⊕⊕◯◯ LOW [a, b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI**). (238) Goldstone 2013.** a. Downgraded one level for imprecision: low rate of events; b. Downgraded another level for imprecision:

The effect estimate for this outcome showed a 67% reduction in the risk of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59-related external genital lesions in the vaccine group compared with the control group for the HPV-naïve population (RR: 0.33; 95% CI: 0.07, 1.64). The study found fewer males with external genital lesions in the vaccine group compared to the control group; albeit the study reported low event rates and the wide CI crossed the line of no-effect (Figure 4.12)

Males compared to females (4-valent HPV vaccine)

Persistent infection and external genital lesions

One study reported the effect of the 4-valent HPV vaccine on persistent infection and external genital lesions in males compared to females from 42 to 120 months.(220) The outcomes are reported in an intention-to-treat population of boys and girls aged nine to 15 years, and are presented as related to the 10 HPV types not included in the vaccine (that is, HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59).

[7] HPV-naïve populations (that is naïve to 14 HPV types at the time of enrolment).

The certainty of the evidence for these outcomes is assessed to be 'very low' to 'low' (Table 4.20).[8]

Table 4.20 Estimate of effect of 4-valent HPV vaccination in HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59-related persistent infection and external genital lesions in boys versus girls aged 9 to 15 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	9 to 15 year old females	**9 to 15 year old males**			
HPV 31/33/35/39/45/51/52/56/58 & 59-related **persistent infection** Follow up: 120 months EVG ITT Population	147 per 1,000	**60 per 1,000** (41 to 88)	**RR 0.41** (0.28 to 0.60)	1179 (1 RCT)[220]	⨁⨁◯◯ LOW [a]
HPV 31/33/35/39/45/51/52/56/58 & 59-related **external genital lesions** Follow up: 120 months EVG ITT Population	3 per 1,000	**1 per 1,000** (0 to 15)	**RR 0.22** (0.01 to 4.52)	1179 (1 RCT)[220]	⨁◯◯◯ VERY LOW [a, b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). [220] __Ferris 2017__. a. Downgraded two levels for risk of bias: non-randomised comparison with cross-over of placebo group to catch up vaccination group with very serious risk of bias for selection, performance and reporting biases and unclear for all other risk of bias domains b. Downgraded one level for imprecision: low event rates and very wide CIs and crosses line of no effect.

The effect estimate for this outcome showed a 59% reduction in the risk of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59-related persistent infection in the vaccinated males compared with the vaccinated females (RR: 0.41; 95% CI: 0.28, 0.60) (Figure 4.16) The study found fewer males with non-vaccine HPV type related persistent infection in compared to females.

The effect estimate for this outcome showed a 78% reduction in the risk of HPV 31, 33, 35, 39, 45, 51, 52, 56, 58 or 59-related external genital lesions in the vaccinated males compared with the vaccinated females (RR: 0.22; 95% CI: 0.01, 4.52). The study found fewer males with non-vaccine HPV type related external genital lesions in the vaccine group compared to the control group; however, the result observed for external genital lesions was very uncertain due to extremely low event rates in participants (that is, one per 1,000 compared to 3 per 1,000), and the wide CI crossed the line of no-effect.

[8] The paper by Ferris et al. (2017) was classified as high risk of bias for selection, performance and reporting biases and unclear for all other risk of bias domains. The authors did not provide GMT immunogenicity data comparing males versus females at different time points; seropositivity rates were reported for 10 years post-first vaccination dose, but there were no patient numbers provided for this analysis. Clinical outcomes for HPV 6, 11, 16 and 18-related infection and diseases were reported for a per-protocol efficacy population only. It was decided by the reviewers that it was not appropriate to include this data in the review.

Females (9-valent compared to 4-valent HPV vaccine)

Persistent infection

One study reported the effect of the 9-valent HPV vaccine versus 4-valent HPV vaccine on persistent infection in females after 48 months.[224] The outcomes are reported for infections longer than six and 12 months in mostly HPV-naïve women aged 16 to 26 years, and are presented as related to the HPV types not common to both vaccines (that is, HPV 31, 33, 45, 52 and 58). The certainty of the evidence for this outcome is assessed to be 'moderate' to 'high' (Table 4.21).

Table 4.21 Estimate of effect on HPV 31, 33, 45, 52 & 58-related persistent infections comparing 9-valent HPV to 4-valent HPV vaccination in women aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	4-valent vaccine	**9-valent vaccine**			
HPV 31/33/45/52/58-related Persistent HPV infection >6 months Follow up: 48 months Mostly HPV-naïve	148 per 1,000	**9 per 1,000** (6 to 13)	**RR 0.06** (0.04 to 0.09)	5967 (1 RCT)[224]	⨁⨁⨁⨁ HIGH
HPV 31/33/45/52/58-related Persistent HPV infection >12 months Follow up: 48 months Mostly HPV-naïve	107 per 1,000	**6 per 1,000** (4 to 10)	**RR 0.06** (0.04 to 0.09)	5967 (1 RCT)[224]	⨁⨁⨁◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). [224] __Joura 2015__. a. Downgraded one level for imprecision: low event rates.

The effect estimate for HPV 31, 33, 45, 52 and 58-related persistent infection longer than six and 12 months both showed a 94% reduction in the risk for the 9-valent HPV vaccine group compared with the 4-valent HPV vaccine group (RR: 0.06; 95% CI: 0.04, 0.09) (Figure 4.17).

Low and high-grade cervical, vaginal and vulvar disease

The same study reported the effect of the 9-valent HPV vaccine versus 4-valent HPV vaccine on low-grade and high-grade cervical disease in females after 48 months.[224] The outcome is reported in the same population of women aged 16 to 26 years, and is presented as related to the HPV types not common to both vaccines (that is, HPV 31, 33, 45, 52 and 58). The certainty of the evidence for this outcome is assessed to be 'moderate' (Table 4.22).

Table 4.22 Estimate of effect on comparing 9-valent and 4-valent HPV vaccination in HPV 31, 33, 45, 52 & 58-related low-grade and high-grade cervical, vaginal and vulvar disease in women aged 16 to 26 years

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	4-valent vaccine	**9-valent vaccine**			
HPV 31/33/45/52/58-related Cervical, vulvar and vaginal disease (any grade or severity) Follow up: 48 months Mostly HPV-naïve	22 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.02** (0.00 to 0.11)	6108 (1 RCT)[224]	⊕⊕⊕◯ MODERATE [a]
HPV 31/33/45/52/58-related Low grade disease (Condyloma, CIN1, VIN1 and VaIN1) Follow up: 48 months Mostly HPV-naïve	18 per 1,000	**0 per 1,000** (0 to 2)	**RR 0.02** (0.00 to 0.13)	6108 (1 RCT)[224]	⊕⊕⊕◯ MODERATE [a]
HPV 31/33/45/52/58-related High Grade disease (CIN2/3, AIS, cervical cancer, VIN 2/3, vulvar cancer, VaIN 2/3 & vaginal cancer) Follow up: 48 months Mostly HPV-naïve	7 per 1,000	**0 per 1,000** (0 to 3)	**RR 0.02** (0.00 to 0.41)	6108 (1 RCT)[224]	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). [224] **Joura 2015**. a. Downgraded one level for imprecision: low event rates.

The effect estimate for HPV 31, 33, 45, 52 and 58-related cervical, vulvar and vaginal disease (any grade or severity [ags], low grade [lg] and high grade [hg]) all showed a 98% reduction in the risk for these clinical outcomes for the 9-valent HPV vaccine group compared with the 4-valent HPV vaccine group (RR: 0.02; 95% CIs: [ags] 0.00, 0.11; [lg] 0.00, 0.13; [hg] 0.00, 0.41) (Figure 4.17).

4.3.3 Immunogenicity outcomes of the 4-valent HPV vaccine in adult females and males (and reported immune-persistence rates)

Females – 4-valent HPV vaccine versus control (placebo)

GMTs and seropositivity rates

Five studies reported the effect of the 4-valent HPV vaccine on immunogenicity outcomes in females after seven months.[225, 241, 242, 250, 251] The outcomes are

reported for geometric mean titres (GMTs) of antibodies and seropositivity rates to the vaccine HPV types in per-protocol immunogenicity populations of women aged nine to 26 years in Table 4.23.

The GMTs reported in the studies by Joura (2008)[241] and Nygard (2015)[225] fall within similar confidence intervals. The other studies by Kang (2008),[242] Villa (2006)[250] and Yoshikawa (2013)[251] do not report similar results — except in regards HPV 6. It should be noted that Kang (2008) and Villa (2006) have small participant numbers, while Yoshikawa (2013) did not report confidence intervals around results or explicit results for the placebo group. The seropositivity rates for the 4-valent HPV vaccine in females aged nine to 26 years are all similar at seven months ranging from 98.1% to 100% across the studies.

Immune-persistence rates

For immune-persistence rates reported over time in females aged 16 to 23 years,[250] the 4-valent vaccine increased GMTs for HPV 6, 16 and 18 when compared with placebo from seven to 60 months. However, there appeared to be an anomalous result reported for the HPV 11 type GMT in the placebo group (which included only two patients for analysis). This very-low certainty evidence provided an inferior GMT ratio for this HPV type at month 60.

In a population of females aged 16 to 26 years, the 4-valent vaccine increased GMTs for HPV 6, 11, 16 and 18 when compared with placebo from seven to 44 months.[241] Note, the GMTs for the placebo group were not reported. There was a trend across all four HPV types towards GMTs peaking at month seven followed by a gradual reduction over 43 months to an apparent plateau level of persistence of immuno-protection against HPV infection caused by the four vaccine HPV types.

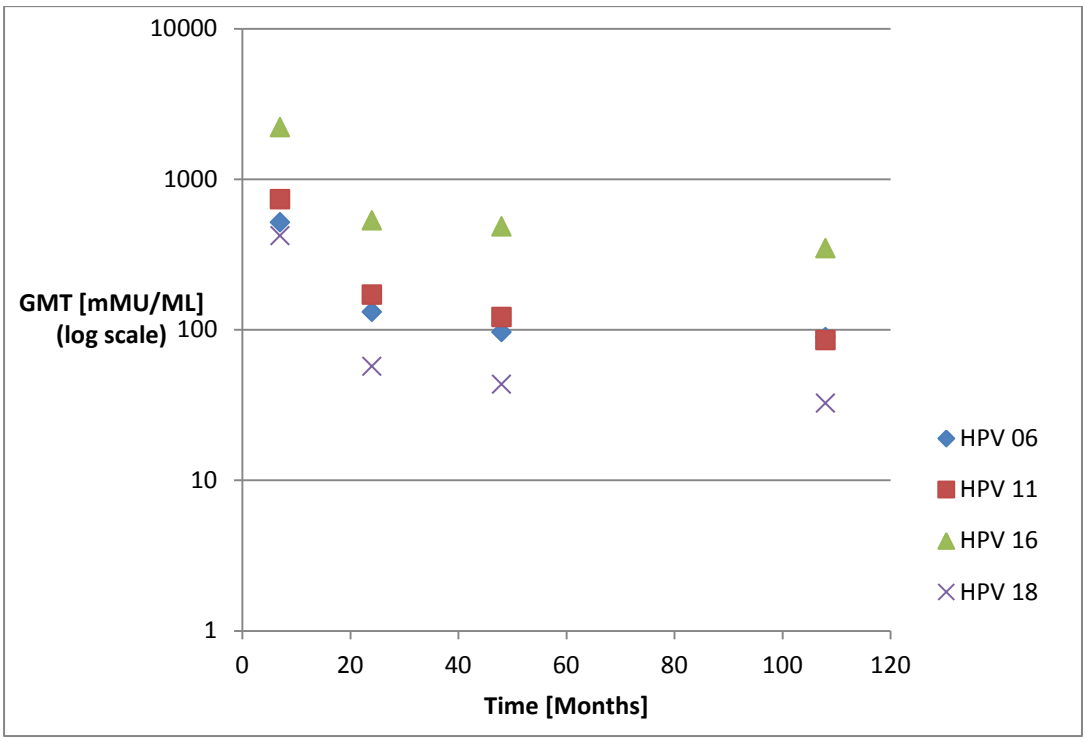
In another population of females aged 16 to 23 years, the 4-valent vaccine again increased GMTs for HPV 6, 11, 16 and 18 when compared with placebo from seven to 108 months.[225] Note, the GMTs for the placebo group were not reported.

Figure 4.4 shows the results from Nygard et al., which shows a similar trend across all four HPV types towards GMTs peaking at month seven followed by a gradual reduction over 101 months to an apparent plateau level of persistence of immuno-protection against HPV infection caused by the four vaccine HPV types.[225]

Table 4.23 GMTs and seropositivity rates to HPV 6, 11, 16 and 18 post-vaccination with the 4-valent HPV vaccine in females aged nine to 26 years at seven months

GMTs and seropositivity rates of antibodies to HPV 6, 11, 16 & 18	Study publications - immunogenicity outcomes at month 7				
	Villa 2006[250]	Joura 2008[241]	Kang 2008[242]	Yoshikawa 2013[251]	Nygard 2015[225]
GMT - HPV 6 mMU/mL (95% CI)	559.7 (466.5-671.5) [n=77]	542.7 (526.3-559.6) [n=2635]	565 (440-726) [n=111]	390.8 [n=459]	517.6 (466.0-574.9) [n=237]
GMT - HPV 11 mMU/mL (95% CI)	642.4 (530.3-778.2) [n=83]	761.6 (735.4-788.6) [n=2659]	1005 (817-1235) [n=112]	579.8 [n=459]	736.3 (656.2-826.0) [n=238]
GMT - HPV 16 mMU/mL (95% CI)	3889.1 (3147.1-4806.1) [n=78]	2294.0 (2185.2-2408.1) [n=2573]	5181 (4006-6700) [n=113]	2396.4 [n=459]	2213.0 (1871.6-2616.8) [n=228]
GMT - HPV 18 mMU/mL (95% CI)	755.5 (582.3-980.1) [n=82]	461.6 (443.9-479.9) [n=2800]	886 (687-1142) [n=110]	369.0 [n=459]	420.9 (368.6-480.6) [n=259]
Seropositivity-HPV 6 n (%) (95% CI)	Not reported	2630/2635 (99.8%) (99.6-99.9)	109/111 (98.2%) (93.6-99.8)	458/459 (99.7%)	236/237 (99.6%) (97.7-100)
Seropositivity-HPV 11 n (%) (95% CI)	Not reported	2651/2659 (99.7%) (99.5-99.9)	112/112 (98.2%) (96.8-100)	459/459 (100%)	237/238 (99.6%) (97.7-100)
Seropositivity-HPV 16 n (%) (95% CI)	Not reported	2568/2573 (99.8%) (99.5-99.9)	112/113 (99.1%) (95.2-100)	459/459 (100%)	228/228 (100%) (98.4-100)
Seropositivity-HPV 18 n (%) (95% CI)	Not reported	2786/2800 (99.5%) (99.1-99.7)	109/110 (99.1) (95.0-100)	458/459 (99.6%)	254/259 (98.1%) (95.6-99.4)

Figure 4.4 GMTs for HPV 6, 11, 16 and 18 following three doses of 4-valent HPV vaccine in women aged 16 to 26 years at seven, 24, 48 and 108 months



Another study reported similar persistence of GMTs over time for a vaccinated cohort of Japanese women with neutralising antibody titres starting to decline after seven months, while remaining above the titre recorded for women who received placebo at month 30.[251]

Seropositivity rates for all HPV vaccine types demonstrated high levels of persistence from month seven to 108 months; however, in this time frame, the HPV 18 type seropositivity rate dropped from 98.1% to 60.0%.[225] The lower seropositivity rate for HPV 18 was also observed at month 44.[241] However, this difference does not appear to affect the anamnestic response to the HPV 18 type.[225, 241]

The certainty of the evidence for these outcomes is assessed to be 'moderate' for the studies by Joura 2008 and Nygard 2015; while those of Villa 2006 are assessed to be 'very low' to 'low' (Table 4.24).

Table 4.24 Immune-persistence (GMTs and seropositivity rates) to HPV 6, 11, 16 and 18 following three doses of 4-valent HPV vaccine versus placebo in females aged 16 to 26 years from 7 to 108 months

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Placebo	**4-valent HPV vaccine**			
GMTs - HPV 06	Nygard 2015 month 7	Not reported	**517.6 mMU/mL** (466.0 – 574.9)	**Not estimable**	237 (1 RCT)[225])	⨁⨁⨁◯ MODERATE [a]
	Nygard 2015 month 108	Not reported	**89.3 mMU/mL** (84.8 – 94.0)	**Not estimable**	1233 (1 RCT)[225]	⨁⨁⨁◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**542.7 mMU/mL** (526.3 – 559.6)	**Not estimable**	2635 (1 RCT)[241]	⨁⨁⨁◯ MODERATE [a]
	Joura 2008 month 44	Not reported	**74.6 mMU/mL** (71.6 – 77.7)	**Not estimable**	2375 (1 RCT)[241]	⨁⨁⨁◯ MODERATE [a]
	Villa 2006 month 7	31.3 mMU/mL (14.9 – 65.7)	**559.7 mMU/mL** (466.5 – 671.5)	**GMT Ratio 17.88**	86 of 241 (1 RCT)[250]	⨁⨁◯◯ LOW [a, b]
	Villa 2006 month 60	30.5 mMU/mL (14.9 – 62.5)	**66.5 mMU/mL** (52.3 – 84.6)	**GMT Ratio 2.18**	86 of 241 (1 RCT)[250]	⨁⨁◯◯ LOW [a, b]
GMTs - HPV 11	Nygard 2015 month 7	Not reported	**736.3 mMU/mL** (656.2 – 826.0)	**Not estimable**	238 (1 RCT)[225]	⨁⨁⨁◯ MODERATE [a]
	Nygard 2015 month 108	Not reported	**85.2 mMU/mL** (80.7 – 90.0)	**Not estimable**	1233 (1 RCT)[225]	⨁⨁⨁◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**761.6 mMU/mL** (735.4 – 788.6)	**Not estimable**	2659 (1 RCT)[241]	⨁⨁⨁◯ MODERATE [a]
	Joura 2008 month 44	Not reported	**90.3 mMU/mL** (86.6 – 94.1)	**Not estimable**	2399 (1 RCT)[241]	⨁⨁⨁◯ MODERATE [a]
	Villa 2006 month 7	342.7 mMU/mL (No CI reported)	**642.4 mMU/mL** (530.3 – 778.2)	**GMT Ratio 1.87**	85 of 241 (1 RCT)[250]	⨁◯◯◯ VERY LOW [a, b, c, d]
	Villa 2006 month 60	150.4 mMU/mL (No CI reported)	**67.6 mMU/mL** (51.1 – 89.3)	**GMT Ratio 0.45**	85 of 241 (1 RCT)[250]	⨁◯◯◯ VERY LOW [a, b, d]
GMTs - HPV 16	Nygard 2015 month 7	Not reported	**2213.0 mMU/mL** (1,871.6 – 2,616.8)	**Not estimable**	228 (1 RCT)[225]	⨁⨁⨁◯ MODERATE [a]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Placebo	**4-valent HPV vaccine**			
	Nygard 2015 month 108	Not reported	**348.3 mMU/mL** (328.0 – 369.9)	**Not estimable**	1178 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**2294.0** (2185.2 – 2408.1)	**Not estimable**	2573 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 44	Not reported	**334.6** (319.4 – 350.5)	**Not estimable**	2330 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
	Villa 2006 month 7	42.0 mMU/mL (13.8 – 128.3)	**3889.1 mMU/mL** (3147.1 – 4806.1)	**GMT Ratio 92.60**	87 of 241 (1 RCT)[250]	⊕◯◯◯ VERY LOW [a, b, c]
	Villa 2006 month 60	16.0 mMU/mL (<12 – 52.2)	**395.4 mMU/mL** (303.2 – 515.7)	**GMT Ratio 24.71**	86 of 241 (1 RCT)[250]	⊕⊕◯◯ LOW [a, b]
GMTs - HPV 18	Nygard 2015 month 7	Not reported	**420.9 mMU/mL** (368.6 – 480.6)	**Not estimable**	259 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Nygard 2015 month 108	Not reported	**32.5 mMU/mL** (30.3 – 34.9)	**Not estimable**	1331 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**461.6 mMU/mL** (443.9 – 479.9)	**Not estimable**	2800 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 44	Not reported	**33.8 mMU/mL** (32.0 – 35.7)	**Not estimable**	2536 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
	Villa 2006 month 7	36.4 mMU/mL (12.3 – 107.5)	**755.5 mMU/mL** (582.3 – 980.1)	**GMT Ratio 20.76**	89 of 241 (1 RCT)[250]	⊕◯◯◯ VERY LOW [a, b, c]
	Villa 2006 month 60	32.7 mMU/mL (9.3 – 115.0)	**43.7 mMU/mL** (30.8 – 62.1)	**GMT Ratio 1.34**	89 of 241 (1 RCT)[250]	⊕⊕◯◯ LOW [a, b]
Seropositivity - HPV 06	Nygard 2015 month 7	Not reported	**236/237 (99.6%)** (97.7 – 100%)	**Not estimable**	237 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Nygard 2015 month 108	Not reported	**1164/1233 (94.4%)** (93.0 – 95.6%)	**Not estimable**	1233 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**2630/2635 (99.8%)** (99.6% - 99.9%)	**Not estimable**	2635 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Placebo	**4-valent HPV vaccine**			
	Joura 2008 month 44	Not reported	**2130/2375 (89.7%)** (88.4% - 90.9%)	**Not estimable**	2375 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 11	Nygard 2015 month 7	Not reported	**237/238 (99.6%)** (97.7 – 100%)	**Not estimable**	238 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Nygard 2015 month 108	Not reported	**1178/1233 (95.5%)** (94.1 – 96.6%)	**Not estimable**	1233 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**2651/2659 (99.7%)** (99.5% - 99.9%)	**Not estimable**	2659 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 44	Not reported	**2267/2399 (94.5%)** (93.5% - 95.4%)	**Not estimable**	2399 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 16	Nygard 2015 month 7	Not reported	**228/228 (100%)** (98.4 – 100%)	**Not estimable**	228 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Nygard 2015 month 108	Not reported	**1167/1178 (99.1%)** (98.3 – 99.5%)	**Not estimable**	1178 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**2568/2573 (99.8%)** (99.5% - 99.9%)	**Not estimable**	2573 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 44	Not reported	**2293/2330 (98.4%)** (97.8% - 98.9%)	**Not estimable**	2330 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 18	Nygard 2015 month 7	Not reported	**254/259 (98.1%)** (95.6 – 99.4%)	**Not estimable**	259 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Nygard 2015 month 108	Not reported	**799/1331 (60.0%)** (57.3 – 62.6%)	**Not estimable**	1331 (1 RCT)[225]	⊕⊕⊕◯ MODERATE [a]
	Joura 2008 month 7	Not reported	**2786/2800 (99.5%)** (99.1% - 99.7%)	**Not estimable**	2800 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Placebo	**4-valent HPV vaccine**			
	Joura 2008 month 44	Not reported	**1529/2536 (60.3%)** (58.4% - 62.2%)	**Not estimable**	2536 (1 RCT)[241]	⊕⊕⊕◯ MODERATE [a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).). [225] **Nygard 2015,** [241] **Joura 2008,** [250] **Villa 2006.**
a. Downgraded one level for risk of bias: selective outcome reporting — no immunogenicity outcome data reported for the placebo group (or if reported based on single digit patient numbers), b. Downgraded one level for imprecision: small sample size, c. Downgraded one level for inconsistency: heterogeneity between GMT results for Villa at month 7, d. Downgraded another level for imprecision: baseline GMT for HPV 11 in placebo group appears too high compared with other GMT readings.

Summary

The evidence demonstrates that the 4-valent HPV vaccine appears to be effective for up to 108 months for all immunogenicity outcomes in 16 to 23 year old females. Seropositivity rates for HPV 6, 11 and 16 remained at 94.4%, 95.5% and 99.1% by the end of year nine; however, the rates for HPV 18 did taper to 60%.

Males – 4-valent HPV vaccine versus control (placebo)

GMTs, seropositivity rates and immune-persistence

One study reported the effect of the 4-valent HPV vaccine on immunogenicity outcomes in males after seven and 36 months.[239] The outcomes are reported for GMTs of antibodies and seropositivity rates to the vaccine HPV types in a per-protocol immunogenicity population of men aged 16 to 26 years. The certainty of the evidence for these outcomes is assessed to be 'moderate' (Table 4.25).

Table 4.25 Immune-persistence (GMTs and seropositivity rates) to HPV 6, 11, 16 and 18 following three doses of 4-valent HPV vaccine versus placebo in males aged 16 to 26 years from seven to 36 months

Outcomes		Absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies) [9]	Certainty of the evidence (GRADE)
		Placebo	4-valent HPV vaccine			
GMTs - HPV 06	Hillman 2012 month 7	7.0 mMU/mL	**473.9 mMU/mL** (446.8 – 502.7)	**GMT Ratio 67.70**	978 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
	Hillman 2012 month 36	7.0 mMU/mL	**73.4 mMU/mL** (69.2 – 77.8)	**GMT Ratio 10.49**	792 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 11	Hillman 2012 month 7	8.4 mMU/mL	**651.5 mMU/mL** (620.7 – 683.7)	**GMT Ratio 77.56**	978 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
	Hillman 2012 month 36	8.3 mMU/mL	**83.8 mMU/mL** (79.4 – 88.5)	**GMT Ratio 10.10**	792 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 16	Hillman 2012 month 7	11.0 mMU/mL	**2,622.1 mMU/mL** (2,484.9 – 2,766.9)	**GMT Ratio 238.37**	999 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
	Hillman 2012 month 36	10.8 mMU/mL	**309.3 mMU/mL** (291.5 – 328.1)	**GMT Ratio 28.64**	811 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
GMTs - HPV 18	Hillman 2012 month 7	9.7 mMU/mL	**439.3 mMU/mL** (415.7 – 464.3)	**GMT Ratio 45.29**	1032 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
	Hillman 2012 month 36	9.6 mMU/mL	**33.9 mMU/mL** (31.6 – 36.4)	**GMT Ratio 3.53**	836 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 06	Hillman 2012 month 7	Not reported	**970/978 (99.2%)** (98.4 – 99.6%)	**Not estimable**	978 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]

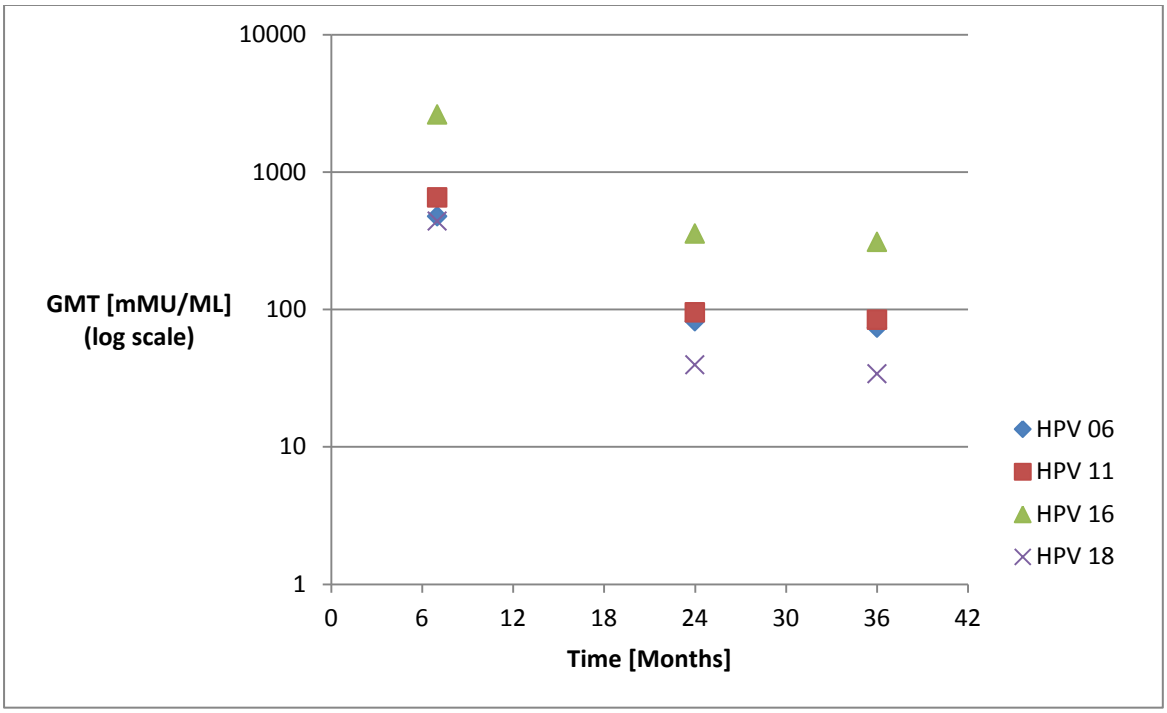
[9] Participant numbers reported only for the HPV vaccine intervention.

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies) [9]	Certainty of the evidence (GRADE)
		Placebo	**4-valent HPV vaccine**			
	Hillman 2012 month 36	Not reported	**709/792 (89.5%)** (87.2 – 91.6%)	**Not estimable**	792 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 11	Hillman 2012 month 7	Not reported	**972/978 (99.4%)** (98.74– 99.7)	**Not estimable**	978 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
	Hillman 2012 month 36	Not reported	**747/792 (94.3%)** (92.5 – 95.8)	**Not estimable**	792 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 16	Hillman 2012 month 7	Not reported	**993/999 (99.4%)** (98.7 – 99.8)	**Not estimable**	999 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
	Hillman 2012 month 36	Not reported	**797/811 (98.3%)** (97.1 – 99.1)	**Not estimable**	811 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
Seropositivity - HPV 18	Hillman 2012 month 7	Not reported	**1015/1032 (98.4%)** (97.5 – 99.1)	**Not estimable**	1032 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]
	Hillman 2012 month 36	Not reported	**479/836 (57.3%)** (53.9 – 60.7)	**Not estimable**	836 (1 RCT)[239]	⊕⊕⊕◯ MODERATE [a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).[239] **Hillman 2012.** a. Downgraded one level for risk of bias: no immunogenicity outcome data reported for the placebo group.

Figure 4.5 shows a trend across all four HPV types towards GMTs peaking at month seven after 4-valent HPV vaccination followed by a gradual reduction over 29 months to an apparent plateau level of persistence of immuno-protection against HPV infection.[239] No immunogenicity outcome data were reported for the placebo group.

Figure 4.5 GMTs for HPV 6, 11, 16 and 18 following three doses of 4-valent HPV vaccine in men aged 16 to 26 years from seven to 36 months



Comparative data between the 4-valent vaccine and placebo were not available for the seropositivity rates. At seven months, seropositivity rates for HPV 6, 11, 16 and 18 in the vaccine group was ≥98.4%; At 36 months, seropositivity rates for HPV 6, 11 and 16 in the vaccine group was ≥89.5%, but only 57.3% for HPV 18. Interestingly, this HPV type-specific drop also occurs for females.

Summary

The evidence demonstrates that the 4-valent HPV vaccine appears to be effective for up to 36 months for all immunogenicity outcomes in 16 to 26 year old males. Seropositivity rates for HPV 6, 11 and 16 remained at 89.5%, 94.3% and 98.3% by the end of year three; however, the rates for HPV 18 did taper to 57.3%.

4.3.4 Non-inferior immunogenicity of the 9-valent versus 4-valent HPV vaccine for the common HPV types

Females – 9-valent versus 4-valent HPV vaccine

Two studies reported the effect of the 9-valent HPV vaccine compared to the 4-valent HPV vaccine on immunogenicity outcomes in females after seven and 42 months.[222, 249] The outcomes are reported for GMTs of antibodies and seropositivity rates to the vaccine HPV types in per-protocol immunogenicity populations of women aged nine to 26 years (Tables 4.33 and 4.34). The non-inferiority threshold for the GMT ratios of 9-valent HPV vaccine versus 4-valent HPV vaccine in females was 0.5.

For the 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26 year old females at seven months, there was comparable GMTs for the HPV 6 and 16 types.[222] The 4-valent HPV vaccine produced higher GMTs for the HPV 11 type, but the 9-valent HPV vaccine was non-inferior; the 9-valent vaccine yielded superior GMTs for the HPV 18 type (Figure 4.18). At 42 months, the GMT ratios for all four HPV types were comparable to those at seven months (Table 4.33). The 9-valent HPV vaccine produced substantially superior GMTs for the HPV 31, 33, 45, 52, and 58 types at seven and 42 months (Table 4.34). At seven months, the seropositivity rates for the four common HPV types in both vaccines were comparable with similar effect estimates at 42 months; however, for HPV 18 at 42 months, the seropositivity rate favoured the 9-valent vaccine. The 9-valent vaccine produced higher seropositivity rates for HPV 31, 33, 45, 52, and 58 types at seven and 42 months (Figure 4.19). The certainty of the evidence for all immunogenicity outcomes in women aged 16-26 years at months seven and 42 is assessed to be ‘high’ and ‘moderate’ respectively (Table 4.33).

For the 9-valent HPV vaccine versus 4-valent HPV vaccine in nine to 15 year old females at seven months, there were also comparable GMTs for the HPV 6, 11, 16, and 18 types.[249] The 9-valent HPV vaccine again produced substantially superior GMTs for the HPV 31, 33, 45, 52, and 58 types compared to the 4-valent HPV vaccine in this population (Figure 4.20). At seven months, the seropositivity rates for the HPV 6, 11, 16, and 18 types were identical for both the 9-valent and 4-valent HPV vaccine. The seropositivity rate data were not reported for the HPV 33, 45, and 52 types; however, the seropositivity rates reported for the HPV 31 and 58 were superior for the 9-valent HPV vaccine (Figure 4.21). The certainty of the evidence for all immunogenicity outcomes in girls aged nine to 15 years at seven months is assessed to be ‘high’ (Table 4.34).

Males – 9-valent versus 4-valent HPV vaccine

GMTs and seropositivity rates

One study reported the effect of the 9-valent HPV vaccine compared to the 4-valent HPV vaccine on immunogenicity outcomes in males after seven months.[248] The outcomes are reported for GMTs of antibodies and seropositivity rates to the vaccine HPV types in per-protocol immunogenicity populations of men aged 16 to 26 years in Table 4.35. The certainty of the evidence for these outcomes is assessed to be 'high'. The non-inferiority threshold for the GMT ratios of 9-valent HPV vaccine versus 4-valent HPV vaccine in males was 0.5.

For the 9-valent HPV vaccine versus 4-valent HPV vaccine in 16 to 26 year old males, there was no significant difference between 9-valent vaccine and 4-valent vaccine for the HPV 6, 11, 16 and 18 types. There were substantially superior GMTs with the 9-valent vaccine for the HPV 31, 33, 45, 52 and 58 types (that is to say, those not included in the 4-valent vaccine) (Figure 4.22). Likewise, there was no significant difference in seropositivity rates between 9-valent vaccine and 4-valent vaccine for the HPV 6, 11, 16 and 18 types, and there were substantially higher seropositivity rates for the HPV 31, 33, 45, 52 and 58 types with the 9-valent vaccine compared with the 4-valent vaccine (Figure 4.23).

Comparison of immune responses for the 9-valent HPV vaccine versus the 4-valent HPV vaccine in males (aged 16 to 26 years) and females (aged 9 to 26 years)

Table 4.26 compares the immunogenicity outcomes for HPV subtypes 6, 11, 16 and 18 of the 9-valent HPV vaccine with the 4-valent HPV vaccine by study population for the included studies at seven months. GMTs for anti-HPV 6, 11, 16 and 18 are summarised on a logarithmic scale for girls (aged nine to 15 years), women (aged 16 to 26 years) and men (aged 16 to 26 years) in Figure 4.6.

The 9-valent HPV vaccine demonstrated:

- non-inferiority as compared with the 4-valent HPV vaccine for HPV types 6, 11, 16, and 18 in females and males aged 16 to 26 years, with GMT ratios ranging from 0·80 to 1·19,[222] and from 0·89 to 1·23[248]
- non-inferiority as compared with the 4-valent HPV vaccine for HPV types 6, 11, 16, and 18 in females aged nine to 15 years, with GMT ratios ranging from 0·93 to 1·08[249]
- no significant difference in GMTs compared with the 4-valent HPV vaccine in any age group with seroconversion rates for the 9-valent HPV vaccine

ranging between 98.2% and100% for the HPV 6, 11, 16 and 18 subtypes across the studies (Figure 4.6) (Tables 4.33, 4.34 and 4.35)

- almost 100% seroconversion for the majority of participants for HPV types 31, 33, 45, 52 and 58 at month seven in females aged nine to 26 years, and in males aged 16 to 26 years (with seroconversion for the 9-valent HPV vaccine ranging from 99.6-100%).[222, 248, 249]

Table 4.26 Immunogenicity comparison of the 9-valent HPV vaccine with the 4-valent HPV vaccine by study population at seven months

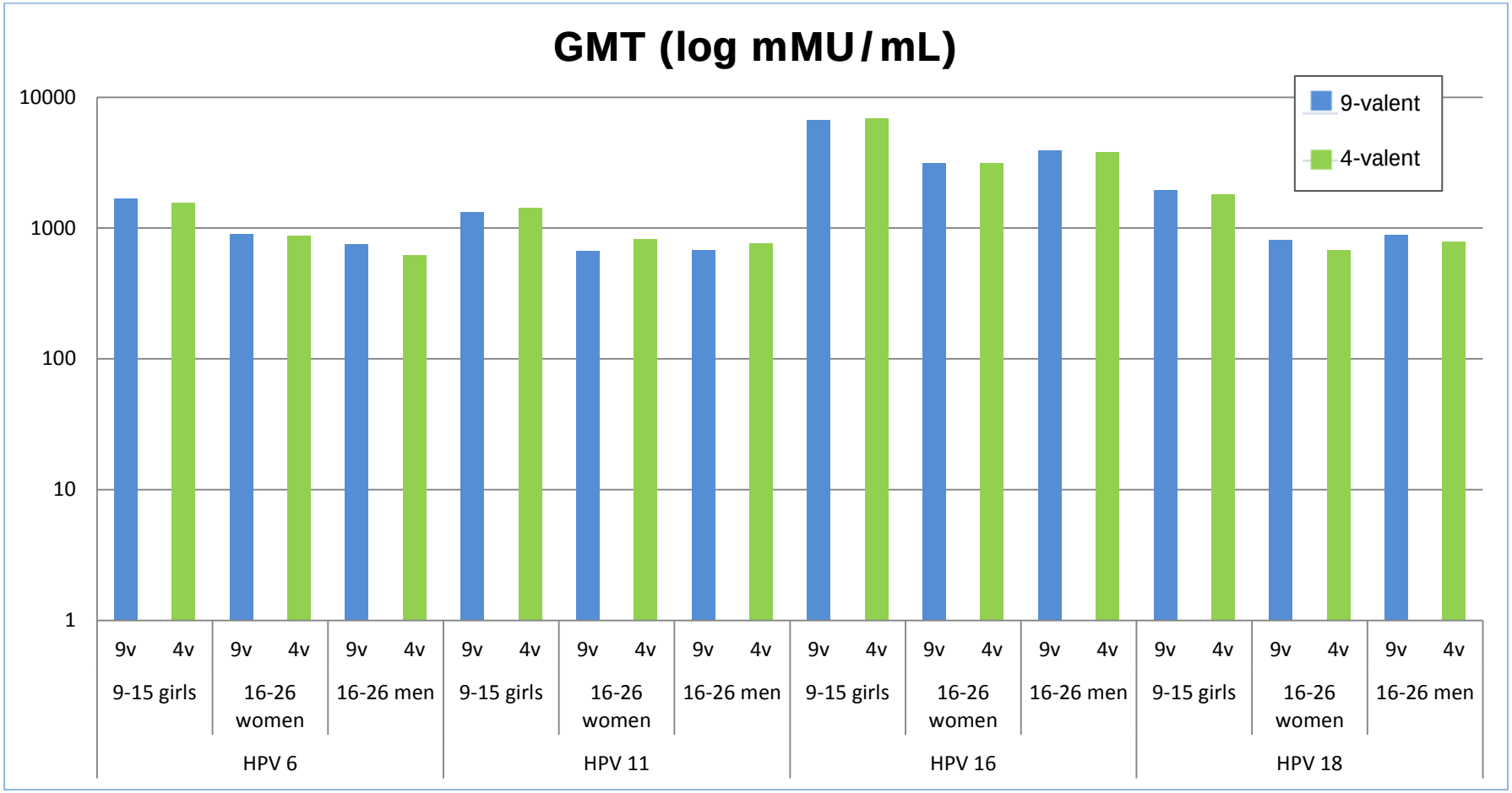
Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
		4-valent vaccine	**9-valent vaccine**			
GMTs - HPV 06 Follow up: 7 months	Females 16-26 (Huh 2017)	875.2 mMU/mL (854.2 – 896.8)	**893.1 mMU/mL** (871.7 – 915.1)	**GMT Ratio 1.02** (0.99 to 1.05)	7968 (1 RCT)[222])	⊕⊕⊕⊕ HIGH
	Females 9-15 (Vesikari 2015)	1565.9 mMU/mL (1412.2 – 1736.3)	**1679.4 mMU/mL** (1518.9 – 1856.9)	**GMT Ratio 1.07** (0.93 to 1.23)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
	Males 16-26 (Van Damme 2016)	618.4 mMU/mL (554.0 – 690.3)	**758.3 mMU/mL** (665.9 – 863.4)	**GMT Ratio 1.23** (1.04 to 1.45)	454 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
GMTs - HPV 11 Follow up: 7 months	Females 16-26 (Huh 2017)	830.0 mMU/mL (809.2 – 851.4)	**666.3 mMU/mL** (649.6 – 683.4)	**GMT Ratio 0.80** (0.77 to 0.83)	7977 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Females 9-15 (Vesikari 2015)	1417.3 mMU/mL (1274.2 – 1576.5)	**1315.6 mMU/mL** (1183.8 – 1462.0)	**GMT Ratio 0.93** (0.80 to 1.08)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
	Males 16-26 (Van Damme 2016)	769.1 mMU/mL (683.5 – 865.3)	**681.7 mMU/mL** (608.9 – 763.4)	**GMT Ratio 0.89** (0.76 to 1.04)	454 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
GMTs - HPV 16 Follow up: 7 months	Females 16-26 (Huh 2017)	3156.6 mMU/mL (3082.3 – 3232.7)	**3131.1 mMU/mL** (3057.1 – 3206.9)	**GMT Ratio 0.99** (0.96 to 1.02)	8094 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
	Females 9-15 (Vesikari 2015)	6887.4 mMU/mL (6220.8 – 7625.5)	**6739.5 mMU/mL** (6134.5 – 7404.1)	**GMT Ratio 0.97** (0.85 to 1.11)	546 (1 RCT)[249]	⊕⊕⊕⊕ HIGH

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		4-valent vaccine	**9-valent vaccine**			
	Males 16-26 (Van Damme 2016)	3787.9 mMU/mL (3378.4 – 4247.0)	**3924.1 mMU/mL** (3513.8 – 4382.3)	**GMT Ratio 1.04** (0.89 to 1.21)	471 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
GMTs - HPV 18	Females 16-26 (Huh 2017)	678.7 mMU/mL (660.2 – 697.7)	**804.6 mMU/mL** (782.7 – 827.1)	**GMT Ratio 1.19** (1.14 to 1.24)	9080 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
Follow up: 7 months	Females 9-15 (Vesikari 2015)	1795.6 mMU/mL (1567.2 – 2057.3)	**1956.6 mMU/mL** (1737.3 – 2203.7)	**GMT Ratio 1.08** (0.91 to 1.28)	545 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
	Males 16-26 (Van Damme 2016)	790.9 mMU/mL (683.0 – 915.7)	**884.3 mMU/mL** (766.4 – 1020.4)	**GMT Ratio 1.12** (0.91 to 1.37)	470 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 06	Females 16-26 (Huh 2017)	3967/3975 (99.8%) (99.7 – 99.9%)	**3985/3993 (99.8%)** (99.6 – 99.9%)	**RR 1.00**(1.00 to 1.00)	7968 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
Follow up: 7 months	Females 9-15 (Vesikari 2015)	261/261 (100%)	**273/273 (100%)**	**RR 1.00** (0.99 to 1.01)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
	Males 16-26 (Van Damme 2016)	223/226 (98.7%) (96.2 – 99.7%)	**224/228 (98.2%)** (95.6 – 99.5%)	**RR 1.00** (0.97 to 1.02)	454 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 11	Females 16-26 (Huh 2017)	3978/3982 (99.9%) (99.8 – 100%)	**3994/3995 (100%)** (99.9 – 100%)	**RR 1.00** (1.00 to 1.00)	7977 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
Follow up: 7 months	Females 9-15 (Vesikari 2015)	261/261 (100%)	**273/273 (100%)**	**RR 1.00** (0.99 to 1.01)	534 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
	Males 16-26 (Van Damme 2016)	226/226 (100%) (98.4 – 100%)	**228/228 (100%)** (98.4 – 100%)	**RR 1.00** (0.99 to 1.01)	454 (1 RCT)[248]	⊕⊕⊕⊕ HIGH
Seropositivity - HPV 16	Females 16-26 (Huh 2017)	4060/4062 (100%) (99.8 – 100%)	**4031/4032 (100%)** (99.9 – 100%)	**RR 1.00** (1.00 to 1.00)	8094 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
Follow up: 7 months	Females 9-15 (Vesikari 2015)	270/270 (100%)	**276/276 (100%)**	**RR 1.00** (0.99 to 1.01)	546 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
	Males 16-26 (Van Damme 2016)	237/237 (100%) (98.5 – 100%)	**234/234 (100%)** (98.4 – 100%)	**RR 1.00** (0.99 to 1.01)	471 (1 RCT[248])	⊕⊕⊕⊕ HIGH

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
		4-valent vaccine	**9-valent vaccine**			
Seropositivity - HPV 18	Females 16-26 (Huh 2017)	4528/4541 (99.7%) (99.5 – 99.8%)	**4532/4539 (99.8%)** (99.7 – 99.9%)	**RR 1.00** (1.00 to 1.00)	9080 (1 RCT)[222]	⊕⊕⊕⊕ HIGH
Follow up: 7 months	Females 9-15 (Vesikari 2015)	269/269 (100%)	**276/276 (100%)**	**RR 1.00** (0.99 to 1.01)	545 (1 RCT)[249]	⊕⊕⊕⊕ HIGH
	Males 16-26 (Van Damme 2016)	235/236 (99.6%) (97.7 – 100%)	**233/234 (99.6%)** (97.6 – 100%)	**RR 1.00** (0.99 to 1.01)	470 (1 RCT)[248]	⊕⊕⊕⊕ HIGH

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). [222] **Huh 2017,** [249] **Vesikari 2015,** [248] **Van Damme 2016.**

Figure 4.6 Comparison of immune responses (GMTs) to HPV 6, 11, 16 and 18 for 9-valent vs. 4-valent HPV vaccine by study population* at seven months



*Huh 2017 (females 16-26); Vesikari 2015 (females 9-15); Van Damme 2016 (males 16-26).

4.3.5 Non-inferior immunogenicity of three-dose HPV vaccination in males compared with females

4-valent HPV vaccine

GMTs and seropositivity rates

Four studies reported the effect of the 4-valent HPV vaccine on immunogenicity outcomes in males compared to females after seven months and 96 months respectively.[219, 231, 244, 246] The study by Ferris et al. (2014)[219] is a long-term follow up of the early vaccination and catch-up vaccination groups from the participants in the original trial reported on by Reisinger et al. (2007).[246] Li et al. (2012) reports on the immunogenicity outcomes for the 4-valent HPV vaccine versus placebo for 100 males (aged nine to 15 years) and 500 females (aged nine to 45 years), of which 100 girls are aged nine to 15 years.[244] The outcomes in the studies are reported for GMTs of antibodies and seroconversion rates to the vaccine HPV types in per-protocol immunogenicity populations of boys compared to girls aged nine to 15 years, and cohorts of boys and girls aged nine to 15 years compared with adult females aged 16 to 26 years (or 16 to 45 years for the Chinese study).

The statistical criterion for non-inferiority of GMTs in the immunobridging studies (by Block and Reisinger) was established when the lower bound of the two-sided 95% CI of GMT ratio was greater than 0.5 for each HPV type.[231, 246] Assessment of non-inferiority of seroconversion rates was based on four one-sided tests of non-inferiority (one corresponding to each vaccine HPV type) at the 0.025 level (defined as the lower bound of the two-sided 95% CI for the differences in seroconversion rates being >-5 percentage points for each of the four HPV types). The Chinese study (Li et al. 2012) reports on GMT responses to the vaccine and does not specify non-inferiority thresholds for comparing immunogenicity in males to females. The certainty of the evidence for these outcomes is assessed to be 'very low' to 'moderate'.

The first reported evidence for the 4-valent HPV vaccine comparing the anti-HPV GMTs in young males and females versus adult females was reported in 2006.[231] By month seven, anti-HPV GMTs in boys aged 10 to 15 years were non-inferior and were of 1.81 to 2.68 fold higher than older females aged 16 to 23 years old, and were of 1.09 to 1.32 fold higher than younger females aged 10 to 15 years old. The anti-HPV GMTs reported in the long-term follow-up study[219] for boys aged nine to 15 years were similarly non-inferior to females aged nine to 15 years old, that is, 1.01 to 1.31 fold higher (Table 4.36). The results from the small Chinese study[244] reported non-inferior GMTs for males versus females for all HPV types, with the exception of the HPV 6 type. However, it should be noted that the GMT results from this trial fall outside the confidence intervals of results reported in the other included

studies (Figure 4.24). There was no significant difference in seroconversion rates between males and females for all four HPV vaccine types based on gender at seven months and 18 months (Figure 4.25).

The evidence in Table 4.27 compares the immunogenicity outcomes of the 4-valent HPV vaccine in younger males compared with younger females (by study population) for the included studies at seven months.

Focusing on the results from the two multinational trials, the 4-valent HPV vaccine demonstrated:

- higher immune responses (GMTs) for all four HPV types in vaccinated males than females aged nine to 15 years at seven months. GMT ratios were superior in males and ranged between 1.09 and 1.32,[231] and 1.01 and 1.31 for this younger aged cohort.[219]
- GMTs appear to favour females over time as evidenced at 96 months for boys and girls (Table 4.36); yet those GMTs for all four HPV vaccine types remained non-inferior for males versus females at month 96.[219]
- seroconversion non-inferiority in more than 99% of the study participants, indicating no relative differences in seroconversion rates between males and females aged nine to 15 years.[231, 246]

Table 4.27 Immunogenicity comparison of the 4-valent HPV vaccine in males versus females aged nine to 15 years at seven months

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	**9 to 15 year old males**			
GMTs - HPV 06 Follow up: 7 months	Li 2012 month 7	744 mMU/mL	**580 mMU/mL**	**GMT Ratio 0.78** (0.46 to 1.32)	94 (1 RCT)[244]	⨁◯◯◯ VERY LOW [a, b, c, d]
	Ferris 2014 month 7	893.9 mMU/mL (818.7 – 976.0)	**962.7 mMU/mL** (874.2 – 1060.1)	**GMT Ratio 1.08** (0.95 to 1.23)	957 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, d, e]
	Block 2006 month 7	959 mMU/mL	**1042 mMU/mL**	**GMT Ratio 1.09**	851 (1 RCT)[231]	⨁◯◯◯ VERY LOW [a, b]
GMTs - HPV 11	Li 2012 month 7	1225 mMU/mL	**1040 mMU/mL**	**GMT Ratio 0.85** (0.58 to 1.25)	96 (1 RCT)[244]	⨁◯◯◯ VERY LOW [a, b, c, d]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	**9 to 15 year old males**			
Follow up: 7 months	Ferris 2014 month 7	1356.8 mMU/mL (1245.1 – 1478.6)	**1370.8 mMU/mL** (1249.6 – 1503.8)	**GMT Ratio 1.01** (0.89 to 1.15)	958 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, d, e]
	Block 2006 month 7	1220 mMU/mL	**1318 mMU/mL**	**GMT Ratio 1.08**	851 (1 RCT)[231]	⨁◯◯◯ VERY LOW [a, b]
GMTs - HPV 16 Follow up: 7 months	Li 2012 month 7	4410 mMU/mL	**4032 mMU/mL**	**GMT Ratio 0.91** (0.55 to 1.51)	96 (1 RCT)[244]	⨁◯◯◯ VERY LOW [a, b, c, d]
	Ferris 2014 month 7	4992.2 mMU/mL (4501.9 – 5535.9)	**6091.0 mMU/mL** (5447.0 – 6811.0)	**GMT Ratio 1.22** (1.05 to 1.42)	953 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, e]
	Block 2006 month 7	4697 mMU/mL	**5638 mMU/mL**	**GMT Ratio 1.20**	851 (1 RCT)[231]	⨁◯◯◯ VERY LOW [a, b]
GMTs - HPV 18 Follow up: 7 months	Li 2012 month 7	1263 mMU/mL	**1365 mMU/mL**	**GMT Ratio 1.08** (0.71 to 1.64)	96 (1 RCT)[244]	⨁◯◯◯ VERY LOW [a, b, c, d]
	Ferris 2014 month 7	1130.8 mMU/mL (1018.3 – 1255.7)	**1470.7 mMU/mL** (1311.2 – 1649.5)	**GMT Ratio 1.30** (1.11 to 1.52)	961 (1 RCT)[219]	⨁◯◯◯ VERY LOW [b, e]
	Block 2006 month 7	916 mMU/mL	**1212 mMU/mL**	**GMT Ratio 1.32**	855 (1 RCT)[231]	⨁◯◯◯ VERY LOW [a, b]
Seropositivity - HPV 06 Follow up: 7 months	Reisinger 2007 month 7	491/492 (99.8%)	**455/456 (99.8%)**	**RR 1.00** (0.99 to 1.01)	948 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
	Block 2006 month 7	423/423 (100%)	**428/428 (100%)**	**Not estimable**	851 (1 RCT)[231]	⨁◯◯◯ VERY LOW [a, b]
Seropositivity -HPV 11 Follow up: 7 months	Reisinger 2007 month 7	491/492 (99.8%)	**456/457 (99.8%)**	**RR 1.00** (0.99 to 1.01)	949 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
	Block 2006 month 7	423/423 (100%)	**428/428 (100%)**	**Not estimable**	851 (1 RCT)[231]	⨁◯◯◯ VERY LOW [a, b]
Seropositivity - HPV 16 Follow up: 7 months	Reisinger 2007 month 7	488/489 (99.8%)	**453/455 (99.5%)**	**RR 1.00** (0.99 to 1.00)	944 (1 RCT)[246]	⨁⨁⨁◯ MODERATE [a]
	Block 2006 month 7	424/424 (100%)	**427/427 (100%)**	**Not estimable**	851 (1 RCT)[231]	⨁◯◯◯ VERY LOW [a, b]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
		9 to 15 year old females	**9 to 15 year old males**			
Seropositivity - HPV 18 Follow up: 7 months	Reisinger 2007 month 7	442/483 (91.5%)	**417/451 (92.5%)**	**RR 1.01** (0.97 to 1.05)	934 (1 RCT)[246]	⊕⊕⊕◯ MODERATE [a]
	Block 2006 month 7	426/426 (100%)	**428/429 (99.7%)**	**RR 1.00**	855 (1 RCT)[231]	⊕◯◯◯ VERY LOW [a, b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). [219] **Ferris 2014,** [244] **Li 2012,** [246] **Reisinger 2007.** a. Downgraded one level for risk of bias: non-randomised comparison. b. Downgraded one level for inconsistency: heterogeneity between the studies at 7 months c. Downgraded one level for imprecision: very small sample size d. Downgraded one level for imprecision: the 95% CI overlaps line of no effect e. Downgraded two levels for risk of bias: non-randomised comparison with cross-over of placebo group to catch up vaccination group; suspected reporting bias in presentation of results and high loss to follow up at the later timepoint (attrition bias). [231] **Block 2006.** a. Downgraded two levels for risk of bias: non-randomised indirect comparison of populations with performance bias (lack of blinding of trial personnel) b. Downgraded one level for imprecision: no 95% confidence intervals reported for GMT ratios.

9-valent HPV vaccine

GMTs and seropositivity rates

Two studies reported the effect of the 9-valent HPV vaccine on immunogenicity outcomes in males compared to females after seven months and 36 months respectively.[233, 247] These two published immunobridging efficacy studies inferred 9-valent HPV efficacy in males and females aged 9nine to 15 years,[247]and in heterosexual males and in men who have sex with men (MSM) aged 16 to 26 years,[233] by comparing immunogenicity data between the individuals in the intervention arms and 16 to 26 year old female controls. The outcomes in the studies are reported for GMTs of antibodies and seroconversion rates to the vaccine HPV types in per-protocol immunogenicity populations of adult heterosexual males and females aged 16 to 26 years, and boys and girls aged nine to 15 years compared with adult females aged 16 to 26 years.

The statistical criterion for non-inferiority of GMTs was established when the lower bound of the two-sided 95% CI of GMT ratio was greater than 0.67 for each HPV type. Assessment of non-inferiority of seroconversion rates was based on nine one-sided tests of non-inferiority (one corresponding to each vaccine HPV type) at the 0.025 level (defined as the lower bound of the two-sided 95% CI for the differences in seroconversion rates being >−5 percentage points for each 9vHPV HPV type). The certainty of the evidence for these outcomes is assessed to be ‘very low’ to ‘low’.

For three doses of the 9-valent HPV vaccine in males versus females aged 16 to 26 years at seven months, there was evidence of superior GMT responses in males (Figure 4.26), and no significant difference in seroconversion rates for all nine HPV vaccine types based on gender (Figure 4.27). Comparing GMT ratios and seroconversion rates in males versus females aged nine to 15 years at seven

months, there was also evidence of superior GMT responses for all nine HPV vaccine types in males, with the exception of the HPV 52 type which still exceeded the non-inferiority threshold. At 36 months, there were non-inferior GMT results for all nine HPV types in young males compared to young females (Figure 4.28). At seven months and 36 months, there was no significant difference in the seropositivity rates for all nine HPV vaccine types for males compared to females at the respective timelines (Figure 4.29).

The evidence in Table 4.28 compares the immunogenicity outcomes of the 9-valent HPV vaccine in males compared with females (by study population) for the included studies at seven months. GMTs for anti-HPV 31, 33, 45, 52 and 58 for the 9-valent HPV vaccine are summarised on a logarithmic scale for boys and girls (aged nine to 15 years), and men and women (aged 16 to 26 years) in Figure 4.7.

The 9-valent HPV vaccine demonstrated:

- higher immune responses (GMTs) for all nine HPV types in vaccinated males compared with females. GMT ratios were superior in males; 1.09 to 1.27 in those aged 16 to 26 years,[233] and 1.07 to 1.36 in those aged nine to 15 years.[247]
- the immune response to the HPV types exclusive to the vaccine (that is, HPV 31, 33, 45, 52 and 58) was comparable between the sexes; although higher immune responses were observed in the younger pre-adolescent and adolescent cohorts aged nine to 15 years in comparison with women and men aged 16 to 26 years (Figure 4.7).
- vaccinated males tend to have higher GMTs than vaccinated females at seven months. GMTs appear to favour females over time as evidenced at 36 months for boys and girls (see table 4.37);[247] yet those GMTs for males continue to persist and exceed the non-inferiority threshold.
- seroconversion non-inferiority in more than 99% of the study participants, indicating no relative differences in seroconversion rates between males and females aged nine to 26 years.[233, 247]

Table 4.28 Immunogenicity comparison of the 9-valent HPV vaccine in males versus females by study population at seven months

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
		Females	**Males**			
GMTs - HPV 06 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	703.9 mMU/mL (660.6, 749.9)	**782.0 mMU/mL** (738.0 – 828.7)	**GMT Ratio 1.11** (1.02 to 1.21)	1555 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1712.0 mMU/mL (1638.9–1788.4)	**2084.7 mMU/mL** (1940.9 – 2239.2)	**GMT Ratio 1.22** (1.12 to 1.33)	2156 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
GMTs - HPV 11 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	564.9 mMU/mL (530.6 – 601.3)	**616.7 mMU/mL** (582.4 – 653.0)	**GMT Ratio 1.09** (1.00 to 1.19)	1563 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1278.7 mMU/mL (1223.1–1336.8)	**1487.1 mMU/mL** (1385.0 – 1596.7)	**GMT Ratio 1.16** (1.07 to 1.26)	2156 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
GMTs - HPV 16 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	2788.3 mMU/mL (2621.4 – 2965.8)	**3346.0 mMU/mL** (3158.9 – 3544.1)	**GMT Ratio 1.20** (1.10 to 1.31)	1680 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	7071.6 mMU/mL (6776.1–7380.1)	**8628.9 mMU/mL** (8077.5 – 9218.0)	**GMT Ratio 1.22** (1.13 to 1.32)	2196 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
GMTs - HPV 18 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	679.8 mMU/mL (633.1 – 730.1)	**808.2 mMU/mL** (754.9 – 865.4)	**GMT Ratio 1.19** (1.08 to 1.31)	1737 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	2081.2 mMU/mL (1978.8–2188.9)	**2822.8 mMU/mL** (2609.0 – 3054.2)	**GMT Ratio 1.36** (1.24 to 1.49)	2208 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
GMTs - HPV 31 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	570.1 mMU/mL (531.5 – 611.5)	**708.5 mMU/mL** (662.7 – 757.6)	**GMT Ratio 1.24** (1.13 to 1.36)	1734 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1879.3 mMU/mL (1791.3–1971.6)	**2221.2 mMU/mL** (2056.4 – 2399.1)	**GMT Ratio 1.18** (1.08 to 1.29)	2181 (1 RCT)[247]	⊕⊕◯◯ LOW [a]

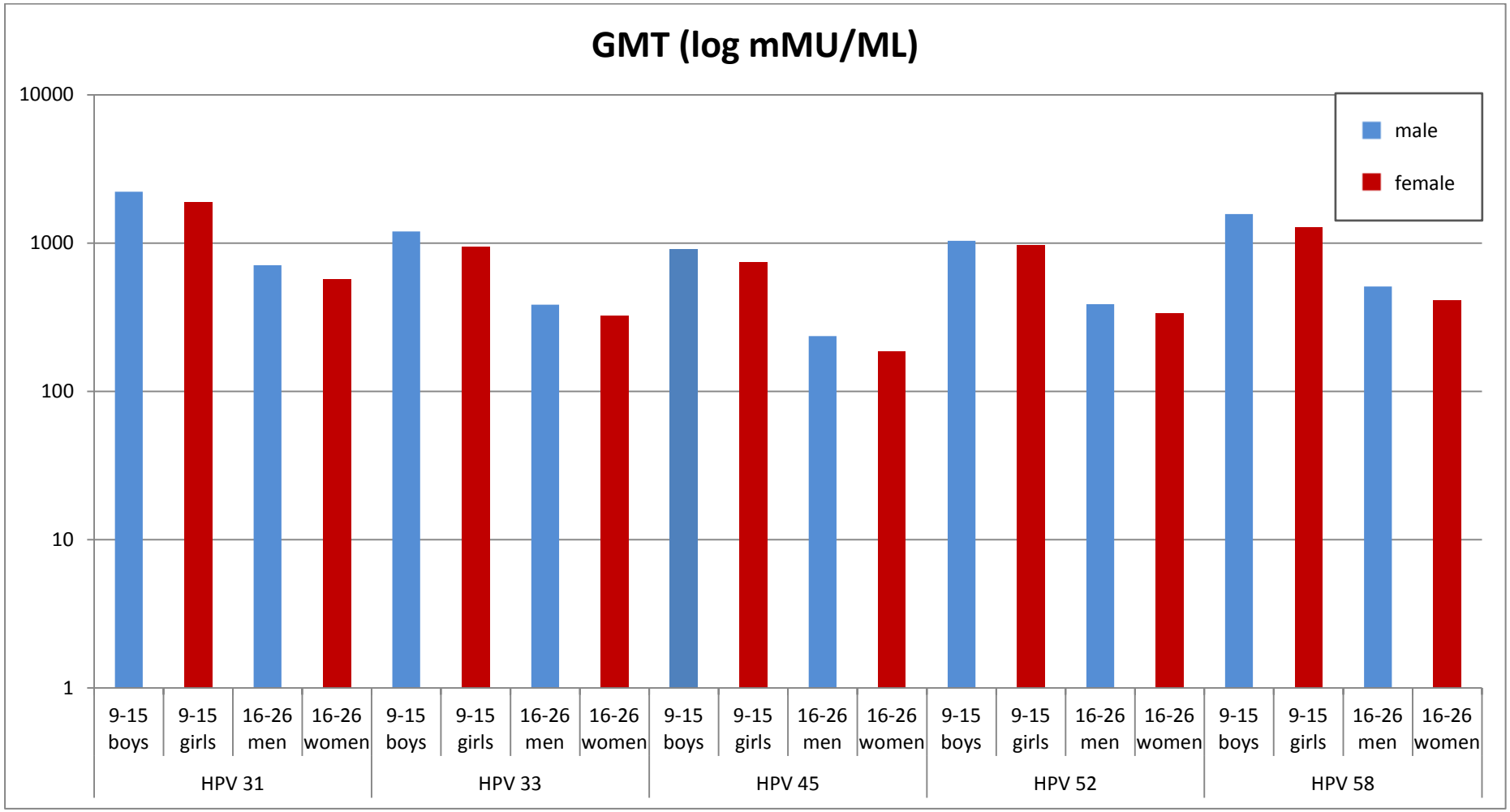
Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
		Females	**Males**			
GMTs - HPV 33 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	322.0 mMU/mL (302.9 – 342.3)	**384.8 mMU/mL** (362.5 – 408.4)	**GMT Ratio 1.20** (1.10 to 1.31)	1754 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	944.1 mMU/mL (904.3–985.7)	**1198.7 mMU/mL** (1117.3 – 1285.9)	**GMT Ratio 1.27** (1.17 to 1.38)	2204 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
GMTs - HPV 45 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	185.7 mMU/mL (172.3 – 200.2)	**235.6 mMU/mL** (219.0 – 253.6)	**GMT Ratio 1.27** (1.14 to 1.41)	1780 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	737.1 mMU/mL (698.4–777.8)	**907.0 mMU/mL** (830.0 – 991.2)	**GMT Ratio 1.23** (1.11 to 1.38)	2217 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
GMTs - HPV 52 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	335.2 mMU/mL (314.3 – 357.6)	**386.8 mMU/mL** (363.4 – 411.6)	**GMT Ratio 1.15** (1.05 to 1.26)	1756 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	970.5 mMU/mL (927.1–1016.0)	**1037.8 mMU/mL** (962.9 – 1118.6)	**GMT Ratio 1.07** (0.98 to 1.17)	2210 (1 RCT)[247]	⊕◯◯◯ VERY LOW [a,b]
GMTs - HPV 58 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	409.3 mMU/mL (384.5 – 435.7)	**509.8 mMU/mL** (479.9 – 541.6)	**GMT Ratio 1.25** (1.14 to 1.37)	1736 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1277.7 mMU/mL (1222.0–1336.0)	**1567.7 mMU/mL** (1461.2 – 1682.0)	**GMT Ratio 1.23** (1.13 to 1.34)	2196 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 06 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	705/708 (99.6%) (98.8%-99.9%)	**844/847 (99.6%)** (99%-99.9%)	**RR 1.00** (0.99 to 1.01)	1555 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1591/1597 (99.6%) (99.2 – 99.9)	**558/559 (99.8%)** (99.0 – 100)	**RR 1.00** (1.00 to 1.01)	2156 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 11 Follow up: 7	Adults 16-26 (Castellsague 2015)	711/712 (99.9%) (99.2%-100%)	**851/851 (100%)** (99.6%-100%)	**RR 1.00** (1.00 to 1.01)	1563 (1 RCT)[233]	⊕⊕◯◯ LOW [a]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		Females	**Males**			
months	Boys & girls 9-15 (Van Damme 2015)	1595/1597 (99.9%) (99.5 – 100)	**559/559 (100%)** (99.3 – 100)	**RR 1.00** (1.00 to 1.00)	2156 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 16 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	780/781 (99.9%) (99.3%-100%)	**899/899 (100%)** (99.6%-100%)	**RR 1.00** (1.00 to 1.00)	1680 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1625/1627 (99.9%) (99.6 – 100)	**569/569 (100%)** (99.4 – 100)	**RR 1.00** (1.00 to 1.00)	2196 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 18 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	829/831 (99.8%) (99.1%-100%)	**905/906 (99.9%)** (99.4%-100%)	**RR 1.00** (1.00 to 1.01)	1737 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1638/1641 (99.8%) (99.5 – 100)	**567/567 (100%)** (99.4 – 100)	**RR 1.00** (1.00 to 1.00)	2208 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 31 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	826/826 (100%) (99.6%-100%)	**908/908 (100%)** (99.6%-100%)	**RR 1.00** (1.00 to 1.00)	1734 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1615/1617 (99.9%) (99.7 – 100)	**564/564 (100%)** (99.3 – 100)	**RR 1.00** (1.00 to 1.00)	2181 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 33 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	852/853 (99.9%) (99.3%-100%)	**901/901 (100%)** (99.6% - 100%)	**RR 1.00** (1.00 to 1.00)	1754 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1635/1637 (99.9%) (99.6 – 100)	**567/567 (100%)** (99.4 – 100)	**RR 1.00** (1.00 to 1.00)	2204 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 45 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	867/871 (99.5%) (98.8%-99.9%)	**907/909 (99.8%)** (99.2%-100%)	**RR 1.00** (1.00 to 1.01)	1780 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1644/1647 (99.8%) (99.5 – 100)	**570/570 (100%)** (99.4 – 100)	**RR 1.00** (1.00 to 1.00)	2217 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 52 Follow up: 7	Adults 16-26 (Castellsague 2015)	847/849 (99.8%) (99.2%-100%)	**907/907 (100%)** (99.6%-100%)	**RR 1.00** (1.00 to 1.01)	1756 (1 RCT)[233]	⊕⊕◯◯ LOW [a]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
		Females	**Males**			
months	Boys & girls 9-15 (Van Damme 2015)	1640/1642 (99.9%) (99.6 – 100)	**568/568 (100%)** (99.4 – 100)	**RR 1.00** (1.00 to 1.00)	2210 (1 RCT)[247]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 58 Follow up: 7 months	Adults 16-26 (Castellsague 2015)	837/839 (99.8%) (99.1%-100%)	**897/897 (100%)** (99.6%-100%)	**RR 1.00** (1.00 to 1.01)	1736 (1 RCT)[233]	⊕⊕◯◯ LOW [a]
	Boys & girls 9-15 (Van Damme 2015)	1628/1630 (99.9%) (99.6 – 100)	**566/566 (100%)** (99.4 – 100)	**RR 1.00** (1.00 to 1.00)	2196 (1 RCT)[247]	⊕⊕◯◯ LOW [a]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). [233] **Castellsague 2015.** a. Downgraded two levels for risk of bias: non-randomised comparison; participants and personnel appear not to be blinded in the study. [247] **Van Damme 2015.** a. Downgraded two levels for risk of bias: non-randomised comparison with allocation concealment for girls only. Unblinded participants and staff for the immunogenicity study. Difference in approach to populations selected for reporting immunogenicity outcome vs. antibody persistence (selection, performance, detection and reporting bias). Also: High loss to follow up (attrition bias).b. Downgraded one level for imprecision: the 95% CI overlaps line of no effect.

Figure 4.7 Comparison of immune responses (GMTs) to HPV 31, 33, 45, 52 and 58 for the 9-valent HPV vaccine in males versus females at seven months



Castellsague 2015 (men vs. women 16-26); Van Damme 2015 (boys vs. girls 9-15).

4.3.6 Non-inferior immunogenicity of two-dose versus three-dose HPV vaccine schedules

Two doses of HPV vaccine in younger females (nine to 14 years) versus three doses of HPV vaccine in women (16 to 26 years)

Three studies reported the effect on immunogenicity outcomes of two-dose HPV vaccination schedules in younger females (aged nine to 14 years) versus three-dose HPV vaccination schedules in older females (aged 16 to 26 years).[218, 221, 223] Two published immuno-bridging efficacy studies inferred HPV efficacy for a two-dose schedule of the 4-valent vaccine in younger females, aged nine to 13 years and nine to 10 years respectively, [218] [221] by comparing immunogenicity data between the individuals in the intervention arms and the respective 16–26 and 18-24 year old female controls who received three doses of the vaccine. The third study inferred HPV efficacy by comparing similar immunogenicity outcomes for a two-dose schedule of the 9-valent vaccine in females aged nine to 14 compared with a three-dose schedule in older females aged 16 to 26 years.[223] The outcomes in the studies are reported for GMTs of antibodies and seropositivity rates (also reported as seroconversion non-inferiority for the 9-valent HPV vaccine) to the vaccine HPV types in per-protocol immunogenicity populations; all studies reported data at seven months, while the 4-valent HPV vaccine studies reported follow-up data to 21 month and 36 month timelines respectively.

The non-inferiority threshold for the GMT ratios in two-dose regimens in younger females versus three-dose regimens in older females was 0.5 for the 4-valent HPV vaccine and a more conservative 0.67 for the 9-valent HPV vaccine. Assessment of non-inferiority of seroconversion rates was carried out for the study of the 9-valent HPV vaccine. It was based on nine one-sided tests of non-inferiority (one corresponding to each vaccine HPV type) at the 0.025 level (defined as the lower bound of the two-sided 95% CI for the differences in seroconversion rates being >-5 percentage points for each 9vHPV HPV type). The certainty of the evidence for these outcomes is assessed to be ‘very low’ to ‘low’.

For two doses of HPV vaccine in younger females versus three doses of HPV vaccine in older females at seven months, there was evidence of substantially higher GMTs and non-inferior GMT ratios for younger females (two doses) when compared with older females (three doses) for the HPV 6, 11, 16 and 18 subtypes; the GMT ratios were 1.63, 1.92, 2.32 and 2.01. There was high heterogeneity for HPV 6, 11 and 18 (Figure 4.30). One possible source of heterogeneity was the study from Mexico,[221] which included both seronegative and seropositive participants at baseline.

The GMTs reported for HPV 31, 33, 45, 52, and 58 post-vaccination with the 9-valent HPV vaccine were 1.6 to 2.96 fold higher in younger females (two-dose

schedule) compared with older females (three-dose schedule). For seropositivity rates to all HPV subtypes measured, the relative risks (RRs) recorded were predominantly 1.0 indicating no significant difference between younger (two-dose schedule) and older (three-dose schedule) at seven months (Figure 4.31).

For the comparison of immunogenicity outcomes for the different dosage schedules with the 4-valent HPV vaccine in the intervention and comparator cohorts, there was evidence of substantially higher GMTs for HPV 11, 16 and 18 in younger females (two-dose schedule), that were non-inferior when compared to older females (three-dose schedule) at seven months (Figure 4.32). However, there was serious inconsistency between the two studies for the evidence of non-inferiority for the HPV 6 subtype at this point in time, with GMT ratios reported at 0.79 and 2.33 respectively. The study by Hernandez-Avila et al. (2016) provides the anomalous result. There was consistent evidence of superior GMT responses for the two-dose vaccinated younger females after follow up at 21 and 36 months, with similar GMT ratios (and overlapping CIs) reported at these points in time (Table 4.38). Focusing on the paper by Dobson, there was almost 100% seropositivity rates with relative risks of 1.0 reported for the 4-valent HPV subtypes in two-dose vaccinated younger females versus three-dose vaccinated older females at seven months.[218] The seropositivity rates remained at 100% for HPV 6, 11 and 16 at 36 months; while the HPV 18 subtype reported a relative risk of 1.09 favouring the two-dose schedule, with declines of 14% for the girls and 21% for the women at 36 months (Figure 4.33). Seroconversion non-inferiority in more than 99% of the study participants in the 9-valent HPV vaccine study, indicating no relative differences in seroconversion rates between the girls who received two doses and the women who received three doses of the vaccine.

The evidence in Table 4.29 compares the immunogenicity outcomes for a two-dose schedule of the HPV vaccine in adolescent females versus three-dose schedule of the HPV vaccine in adult females at seven months.

The two-dose vaccination schedule of the HPV vaccine in girls (aged nine to 14 years) demonstrated:

- higher GMT responses with non-inferior GMT ratios when compared with three-dose HPV vaccination schedules in older females at seven months,[218, 221, 223] which appear to be sustained in the longer-term (up to 36 months with 4-valent vaccines).[218] There does appear to be a narrowing of the superiority of the relative effect over time without ever falling below the non-inferiority threshold.

- no significant differences in seropositivity rates compared with the older females at seven months (or at longer follow-up times for the 4-valent HPV vaccine).[218, 221, 223]

Table 4.29 Immunogenicity comparison of two doses of the HPV vaccine in adolescent females versus three doses of the HPV vaccine (4-valent and 9-valent) in adult females at seven months

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Older (15 to 26 year old) females	**Younger (9 to 14 year old) females**			
GMTs - HPV 06 Follow up: 7 months	387.3 to 938 mMU/mL	**306.2 to 2186 mMU/mL**	GMT Ratio 1.63 (0.98 to 2.70)	1271 (3 RCTs)[218, 221, 223]	⨁◯◯◯ VERY LOW [a, b, c]
GMTs - HPV 11 Follow up: 7 months	580.5 to 1277 mMU/mL	**968.3 to 2348 mMU/mL**	GMT Ratio 1.92 (1.51 to 2.43)	1293 (3 RCTs)[218, 221, 223]	⨁◯◯◯ VERY LOW [a, b]
GMTs - HPV 16 Follow up: 7 months	2408.8 to 3574 mMU/mL	**5136.7 to 8004.9 mMU/mL**	GMT Ratio 2.32 (2.02 to 2.65)	1296 (3 RCTs)[218, 221, 223]	⨁⨁◯◯ LOW [a]
GMTs - HPV 18 Follow up: 7 months	343.7 to 761.5 mMU/mL	**605 to 1872.8 mMU/mL**	GMT Ratio 2.01 (1.62 to 2.50)	1332 (3 RCTs)[218, 221, 223]	⨁◯◯◯ VERY LOW [a, b]
GMTs - HPV 31 Follow up: 7 months	572.1 mMU/mL (505.8 – 647.2)	**1436.3 mMU/mL** (1272.1 – 1621.8)	GMT Ratio 2.51 (2.10 to 3.00)	536 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
GMTs - HPV 33 Follow up: 7 months	348.1 mMU/mL (311.5 – 389.1)	**1030.0 mMU/mL** (920.4 – 1152.7)	GMT Ratio 2.96 (2.50 to 3.50)	552 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
GMTs - HPV 45 Follow up: 7 months	213.6 mMU/mL (187.7 – 243.2)	**357.6 mMU/mL** (313.7 – 407.6)	GMT Ratio 1.67 (1.38 to 2.02)	554 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
GMTs - HPV 52 Follow up: 7 months	364.2 mMU/mL (327.0 – 405.6)	**581.1 mMU/mL** (521.9 – 647.1)	GMT Ratio 1.60 (1.36 to 1.88)	543 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
GMTs - HPV 58 Follow up: 7 months	491.1 mMU/mL (438.6 – 549.8)	**1251.2 mMU/mL** (1119.6 – 1398.4)	GMT Ratio 2.55 (2.15 to 3.02)	531 (1 RCT)[223]	⨁⨁◯◯ LOW [a]

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Older (15 to 26 year old) females	**Younger (9 to 14 year old) females**			
Seropositivity - HPV 06 Follow up: 7 months	629/635 (99.1%)	**638/644 (99.1%)**	RR 1.00 (0.99 to 1.01)	1279 (3 RCTs)[218, 221, 223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 11 Follow up: 7 months	647/648 (99.8%)	**645/646 (99.8%)**	RR 1.00 (0.99 to 1.01)	1294 (3 RCTs)[218, 221, 223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 16 Follow up: 7 months	635/636 (99.8%)	**660/660 (100%)**	RR 1.00 (1.00 to 1.01)	1296 (3 RCTs)[218, 221, 223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 18 Follow up: 7 months	668/672 (99.4%)	**660/660 (100%)**	RR 1.00 (0.99 to 1.01)	1332 (3 RCTs)[218, 221, 223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 31 Follow up: 7 months	263/264 (99.6%) (97.9 – 100%)	**271/272 (99.6%)** (98.0 – 100%)	RR 1.00 (0.99 to 1.01)	536 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 33 Follow up: 7 months	278/279 (99.6%) (98.0 – 100%)	**272/273 (99.6%)** (98.0 – 100%)	RR 1.00 (0.99 to 1.01)	552 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 45 Follow up: 7 months	274/280 (97.9%) (95.4 – 99.2%)	**272/274 (99.3%)** (97.4 – 99.9%)	RR 1.01 (0.99 to 1.04)	554 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 52 Follow up: 7 months	270/271 (99.6%) (98.0 – 100%)	**271/272 (99.6%)** (98.0 – 100%)	RR 1.00 (0.99 to 1.01)	543 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 58 Follow up: 7 months	260/261 (99.6%) (97.9 – 100%)	**270/270 (100%)** (98.6 – 100%)	RR 1.00 (0.99 to 1.01)	531 (1 RCT)[223]	⨁⨁◯◯ LOW [a]

The risk in the intervention group* *(and its 95% confidence interval) is based on the assumed risk in the comparison group and the* ***relative effect* *of the intervention (and its 95% CI).* [218] **Dobson 2013 ,** [221] **Hernandez-Avila 2016 ,** [223] **Iversen 2016.** a. Downgraded two levels for risk of bias: non-random sequence generation; open-label trials with unclear allocation concealment. b. Downgraded one level for inconsistency: high heterogeneity (>70%) for GMTs of HPV 6/11/18

subtypes. c. Downgraded one level for imprecision: the 95% CI overlaps line of no effect for GMT of HPV 6 subtype (Hernandez-Avila 2016).

Two doses versus three doses of HPV vaccine in younger females (nine to 14 years)

Two studies reported the effect on immunogenicity outcomes of two-dose versus three-dose HPV vaccination schedules in younger females (aged nine to 14 years).[218, 223] One published immunobridging efficacy study inferred HPV efficacy for a two-dose schedule of the 4-valent vaccine in younger females (aged nine to 13 years),[218] by comparing immunogenicity data from this intervention arm with the female controls who received three doses of the vaccine. The second included study inferred HPV efficacy comparing similar immunogenicity outcomes for a two-dose versus three-dose schedule of the 9-valent vaccine in females (aged nine to 14 years).[223] The outcomes in the studies are reported for GMTs of antibodies and seropositivity rates (also reported as seroconversion non-inferiority for the 9-valent HPV vaccine) to the vaccine HPV types in per-protocol immunogenicity populations; each study reported data at seven months, while the 4-valent HPV vaccine study reported follow-up data to 36 months.

The non-inferiority threshold for the GMT ratios in two-dose versus three-dose regimens in younger females was 0.5 for the 4-valent HPV vaccine and a more conservative 0.67 for the 9-valent HPV vaccine. Assessment of non-inferiority of seroconversion rates was carried out for the study of the 9-valent HPV vaccine. It was based on nine one-sided tests of non-inferiority (one corresponding to each vaccine HPV type) at the 0.025 level (defined as the lower bound of the two-sided 95% CI for the differences in seroconversion rates being >-5 percentage points for each 9vHPV HPV type). All participants in the analyses were seronegative at baseline. The certainty of the evidence for these outcomes is assessed to be 'very low' to 'low'.

For the two-dose versus three-dose regimens of 4-valent and 9-valent HPV vaccines in younger females at seven months, there was evidence of higher GMTs for the HPV 6, 11, 16 and 33 subtypes (that is, GMTs were 1.13, 1.08, 1.10 and 1.29 folder higher), and non-inferior GMT ratios of 0.82 for the HPV 18 and 31 subtypes. The GMTs were almost identical between the intervention and comparison groups for the HPV 58 subtype; while there were inferior GMT ratios of 0.54 and 0.64 observed for the HPV 45 and 52 subtypes (Figure 4.34). For seropositivity rates to all HPV subtypes measured, the relative risks recorded were all 1.0 indicating no significant difference between two-dose and three-dose HPV vaccination schedules at seven months (Figure 4.35). Seroconversion non-inferiority in more than 99% of the study participants in the 9-valent HPV vaccine study, indicating no relative differences in seroconversion rates between the girls who received two doses and the women who received three doses of the vaccine.

For the two-dose versus three-dose regimen of the 4-valent HPV vaccine at 36 months, there was evidence that GMTs for the two dose group were non-inferior to the three dose group for the HPV 11 and 16 subtypes, with respective GMT ratios of 0.73 and 0.81. However, the results for the HPV 6 and 18 subtypes were inferior for the two-dose versus the three-dose regimen, with lower bound CIs of 0.46 and 0.26 reported (Table 4.39 and Figure 4.36).

The seropositivity rates remained at 100% for HPV 6, 11 and 16 at 36 months; while the HPV 18 subtype reported a relative risk of 0.90 favouring the three-dose schedule at the same point in time, with declines of 14% for the two-dose cohort and 5% for the three-dose cohort (Table 4.39 and Figure 4.37).

The evidence in Table 4.30 compares the immunogenicity outcomes for a two-dose versus three-dose vaccination schedule of the HPV vaccine in girls (aged nine to 14 years) at seven months.

The two-dose vaccination schedule of the HPV vaccine in girls (aged nine to 14 years) demonstrated:

- higher GMT responses for HPV 6, 11, 16 and 33 subtypes and non-inferior GMT ratios for HPV 18, 31 and 58 subtypes when compared with three-dose HPV vaccination schedules at seven months,[218, 223] which appear to be sustained for the HPV 11 and 16 subtypes in the longer term (up to 36 months with 4-valent vaccines).[218]

- inferior GMT ratios for the HPV 45 and 52 subtypes when compared with the three-dose schedule of the 9-valent vaccine at seven months.[223] There were also inferior GMT ratios for the comparison relating to the HPV 6 and 18 subtypes in the longer term (up to 36 months with 4-valent vaccines).[218] The trend appears to favour the immune response from a three-dose schedule over time.

- no significant differences in seropositivity rates compared with the three dose vaccination schedule at seven months (or at longer follow-up times for the 4-valent HPV vaccine).[218, 223]

Table 4.30 Immunogenicity comparison of two doses versus three doses of the HPV vaccine (4-valent and 9-valent) in adolescent females at seven months

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Three doses (9 to 14 year old) females	**Two doses (9 to 14 year old) females**			
GMTs - HPV 06 Follow up: 7 months	1496.1 – 1856 mMU/mL	**1657.9 - 2186 mMU/mL**	RR 1.13 (0.98 to 1.30)	1001 (2 RCTs)[218, 223]	⊕◯◯◯ VERY LOW [a, b]
GMTs - HPV 11 Follow up: 7 months	1306.3 – 2096 mMU/mL	**1388.9 - 2348 mMU/mL**	RR 1.08 (0.96 to 1.23)	1006 (2 RCTs)[218, 223]	⊕◯◯◯ VERY LOW [a, b]
GMTs - HPV 16 Follow up: 7 months	6996.0 - 7640 mMU/mL	**7457 - 8004.9 mMU/mL**	RR 1.10 (0.96 to 1.25)	1035 (2 RCTs)[218, 223]	⊕◯◯◯ VERY LOW [a, b]
GMTs - HPV 18 Follow up: 7 months	1703 - 2049.3 mMU/mL	**1207 - 1872.8 mMU/mL**	RR 0.82 (0.64 to 1.04)	1037 (2 RCTs)[218, 223]	⊕◯◯◯ VERY LOW [a, b, c]
GMTs - HPV 31 Follow up: 7 months	1748.3 mMU/mL	**1436.3 mMU/mL**	RR 0.82 (0.69 to 0.97)	543 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
GMTs - HPV 33 Follow up: 7 months	796.4 mMU/mL	**1030.0 mMU/mL**	RR 1.29 (1.10 to 1.51)	548 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
GMTs - HPV 45 Follow up: 7 months	661.7 mMU/mL	**357.6 mMU/mL**	RR 0.54 (0.45 to 0.65)	549 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
GMTs - HPV 52 Follow up: 7 months	909.9 mMU/mL	**581.1 mMU/mL**	RR 0.64 (0.55 to 0.74)	547 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
GMTs - HPV 58 Follow up: 7 months	1229.3 mMU/mL	**1251.2 mMU/mL**	RR 1.02 (0.87 to 1.20)	543 (1 RCT)[223]	⊕◯◯◯ VERY LOW [a, b]
Seropositivity - HPV 06 Follow up: 7 months	500/502 (99.6%)	**497/499 (99.6%)**	RR 1.00 (0.99 to 1.01)	1001 (2 RCTs)[218, 223]	⊕⊕◯◯ LOW [a]

Outcomes	**Absolute effects** (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)
	Three doses (9 to 14 year old) females	**Two doses (9 to 14 year old) females**			
Seropositivity - HPV 11 Follow up: 7 months	504/505 (99.8%)	**501/501 (100%)**	RR 1.00 (0.99 to 1.01)	1006 (2 RCTs)[218, 223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 16 Follow up: 7 months	520/520 (100%)	**515/515 (100%)**	RR 1.00 (0.99 to 1.01)	1035 (2 RCTs)[218, 223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 18 Follow up: 7 months	521/522 (99.8%)	**515/515 (100%)**	RR 1.00 (1.00 to 1.01)	1037 (2 RCTs)[218, 223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 31 Follow up: 7 months	271/271 (100%)	**271/272 (99.6%)**	RR 1.00 (0.99 to 1.01)	543 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 33 Follow up: 7 months	275/275 (100%)	**272/273 (99.6%)**	RR 1.00 (0.99 to 1.01)	548 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 45 Follow up: 7 months	273/275 (99.3%)	**272/274 (99.3%)**	RR 1.00 (0.99 to 1.01)	549 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 52 Follow up: 7 months	274/275 (99.6%)	**271/272 (99.6%)**	RR 1.00 (0.99 to 1.01)	547 (1 RCT)[223]	⨁⨁◯◯ LOW [a]
Seropositivity - HPV 58 Follow up: 7 months	272/273 (99.6%)	**270/270 (100%)**	RR 1.00 (0.99 to 1.01)	543 (1 RCT)[223]	⨁⨁◯◯ LOW [a]

The risk in the intervention group* *(and its 95% confidence interval) is based on the assumed risk in the comparison group and the* ***relative effect* *of the intervention (and its 95% CI).* [218] **Dobson 2013 ,** [223] **Iversen 2016.** a. Downgraded two levels for risk of bias: non-random sequence generation; open-label trials with unclear allocation concealment. b. Downgraded one level for imprecision: the 95% CI overlaps line of no effect. c. Downgraded one level for inconsistency: heterogeneity between studies for HPV 18.

Two doses of HPV vaccine in younger males (nine to 14 years) versus three doses of HPV vaccine in women (16 to 26 years)

One published immunobridging efficacy study inferred HPV efficacy for a two-dose schedule of the 9-valent HPV vaccine in younger males, aged nine to 14 years by comparing immunogenicity data between the individuals in the intervention arm and the 16–26 year old female controls who received three doses of the vaccine.[223] The outcomes in the study are reported for GMTs of antibodies and seropositivity rates (also reported as seroconversion non-inferiority) to the vaccine HPV types in per-protocol immunogenicity populations at seven months.

The statistical criterion for non-inferiority of GMTs was established when the lower bound of the two-sided 95% CI of GMT ratio was greater than 0.67 for each HPV type. Assessment of non-inferiority of seroconversion rates was based on nine one-sided tests of non-inferiority (one corresponding to each vaccine HPV type) at the 0.025 level (defined as the lower bound of the two-sided 95% CI for the differences in seroconversion rates being >-5 percentage points for each of the vaccine HPV types). The certainty of the evidence for these outcomes is assessed to be 'very low' to 'low'.

For two doses of HPV vaccine in younger males versus three doses of the 9-valent HPV vaccine in older females at seven months, there was evidence of substantially higher GMTs and superior GMT ratios for younger males (two doses) when compared with older females (three doses) for the HPV 6, 11, 16 and 18 subtypes; the GMT ratios were 2.02, 2.45, 2.69 and 2.44. The GMTs reported for HPV 31, 33, 45, 52, and 58 post-vaccination with the 9-valent HPV vaccine were 1.65 to 2.99 fold higher in younger males (two doses) compared with older females (three doses).

For seropositivity rates to all HPV subtypes measured, the relative risks recorded were predominantly 1.0 indicating no significant difference between younger (two doses) and older (three doses) at seven months. There was 100% seroconversion for the two-dose schedule in younger males for all HPV subtypes, with the exception of HPV 45 (99.3%). Seroconversion non-inferiority was evident for all the study participants in the 9-valent HPV vaccine study, indicating no relative differences in seroconversion rates between the adolescent males who received two doses and the adult females who received three doses of the vaccine.

The evidence in Table 4.31 compares the immunogenicity outcomes for a two-dose schedule of the 9-valent HPV vaccine in adolescent males versus a three-dose schedule of the 9-valent HPV vaccine in adult females at seven months

The two-dose vaccination schedule of the HPV vaccine in adolescent males (aged nine to 14 years) demonstrated:

- higher GMT responses with superior GMT ratios when compared with three-dose HPV vaccination schedules in older females at seven months.[223]
- no significant differences in seroconversion rates compared with the older females at seven months.[223]

Table 4.31 Immunogenicity comparison of two doses of the 9-valent HPV vaccine in adolescent males versus three doses of the 9-valent HPV vaccine in adult females at seven months

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		15 to 26 year old females	**9 to 14 year old males**			
GMTs - HPV 06 Follow up: 7 months	Iversen 2016	770.9 mMU/mL (684.8 – 867.9)	**1557.4 mMU/mL** (1391.5 – 1743.1)	**GMT Ratio 2.02**	501 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 11 Follow up: 7 months	Iversen 2016	580.5 mMU/mL (516.0 – 653.0)	**1423.9 mMU/mL** (1273.2 – 1592.3)	**GMT Ratio 2.45**	502 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 16 Follow up: 7 months	Iversen 2016	3154.0 mMU/mL (2807.1 – 3543.7)	**8474.8 mMU/mL** (7582.4 – 9472.3)	**GMT Ratio 2.69**	522 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 18 Follow up: 7 months	Iversen 2016	761.5 mMU/mL (670.8 – 864.5)	**1860.9 mMU/mL** (1641.1 – 2110.2)	**GMT Ratio 2.44**	539 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 31 Follow up: 7 months	Iversen 2016	572.1 mMU/mL (505.8 – 647.2)	**1498.2 mMU/mL** (1326.5 – 1692.0)	**GMT Ratio 2.62**	535 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 33 Follow up: 7 months	Iversen 2016	348.1 mMU/mL (311.5 – 389.1)	**1040.0 mMU/mL** (928.9 – 1164.3)	**GMT Ratio 2.99**	550 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 45 Follow up: 7 months	Iversen 2016	213.6 mMU/mL (187.7 – 243.2)	**352.3 mMU/mL** (309.0 – 401.7)	**GMT Ratio 1.65**	553 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		15 to 26 year old females	**9 to 14 year old males**			
GMTs - HPV 52 Follow up: 7 months	Iversen 2016	364.2 mMU/mL (327.0 – 405.6)	**640.4 mMU/mL** (575.2 – 713.0)	**GMT Ratio 1.76**	544 (1 RCT)[223]	⊕◯◯◯ VERY LOW [a,b]
GMTs - HPV 58 Follow up: 7 months	Iversen 2016	491.1 mMU/mL (438.6 – 549.8)	**1325.7 mMU/mL** (1186.2 – 1481.6)	**GMT Ratio 2.70**	531 (1 RCT)[223]	⊕◯◯◯ VERY LOW [a,b]
Seropositivity - HPV 06 Follow up: 7 months	Iversen 2016	237/238 (99.6%) (97.7 – 100%)	**263/263 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	501 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 11 Follow up: 7 months	Iversen 2016	237/238 (99.6%) (97.7 – 100%)	**264/264 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	502 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 16 Follow up: 7 months	Iversen 2016	248/249 (99.6%) (97.8 – 100%)	**273/273 (100%)** (98.7 – 100%)	**RR 1.00** (0.99 to 1.01)	522 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 18 Follow up: 7 months	Iversen 2016	263/267 (98.5%) (96.2 – 99.6%)	**272/272 (100%)** (98.7 – 100%)	**RR 1.02** (0.99 to 1.04)	539 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 31 Follow up: 7 months	Iversen 2016	263/264 (99.6%) (97.9 – 100%)	**271/271 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	535 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 33 Follow up: 7 months	Iversen 2016	278/279 (99.6%) (98.0 – 100%)	**271/271 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	550 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 45 Follow up: 7 months	Iversen 2016	274/280 (97.9%) (95.4 – 99.2%)	**271/273 (99.3%)** (97.4 – 99.9%)	**RR 1.01** (0.98 to 1.03)	553 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 52 Follow up: 7 months	Iversen 2016	270/271 (99.6%) (98.0 – 100%)	**273/273 (100%)** (98.7 – 100%)	**RR 1.00** (0.99 to 1.01)	544 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 58 Follow up: 7 months	Iversen 2016	260/261 (99.6%) (97.9 – 100%)	**270/270 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	531 (1 RCT)[223]	⊕⊕◯◯ LOW [a]

The risk in the intervention group* *(and its 95% confidence interval) is based on the assumed risk in the comparison group and the* ***relative effect* *of the intervention (and its 95% CI).* [223] **Iversen 2016.** a. Downgraded two levels for risk of bias: non-randomised comparison in an open label study; participants were not blinded and personnel would have been aware of schedules.

Comparison of two doses of HPV vaccine in younger males (nine to 14 years) versus younger females (nine to 14 years)

One published immunobridging efficacy study inferred HPV efficacy for a two-dose schedule of the 9-valent HPV vaccine in younger males and females, aged nine to 14 years by comparing immunogenicity data between the individuals in the intervention arms and the 16 to 26 year old female controls who received three doses of the vaccine.[223] The results from this study of a two-dose vaccine schedule for adolescents by gender versus a three-dose vaccine schedule in the adult female population can also be used to compare the immune response to the two-dose HPV vaccine schedule among adolescents by gender. As described earlier, the outcomes in the study are reported for GMTs of antibodies and seropositivity rates (also reported as seroconversion non-inferiority) to the vaccine HPV types in per-protocol immunogenicity populations at seven months.

For two doses of the 9-valent HPV vaccine in younger males versus younger females at seven months, there was evidence of slightly higher GMTs for younger males for the HPV 11, 16, 31, 33, 52 and 58 subtypes; the GMT ratios were 1.03, 1.06, 1.04, 1.01, 1.10 and 1.06. The GMT ratio of 0.94 reported for the HPV 6 subtype favoured younger females compared with younger males. The GMTs for the HPV 18 and 45 subtypes were almost identical (GMT ratios 0.99).

For seroconversion rates to all HPV subtypes measured, the relative risks (RRs) recorded were 1.0 indicating no significant difference between two doses of the vaccine in younger males and females at seven months. There was 100% seroconversion for the two-dose schedule in younger males for all HPV subtypes, with the exception of HPV 45 (99.3%). In females, there was >99% seroconversion for all HPV vaccine types at seven months.

The evidence in Table 4.32 compares the immunogenicity outcomes for a two-dose schedule of the 9-valent HPV vaccine in adolescent males versus adolescent females at seven months. GMTs for anti-HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 for the 9-valent HPV vaccine at seven months are summarised on a logarithmic scale for two-dose schedule in boys and girls (aged nine to 14 years), and three-dose schedule in girls (aged nine to 14 years) and women (aged 16 to 26 years) in Figure 4.8.

The two-dose vaccination schedule of the 9-valent HPV vaccine in boys (aged nine to 14 years) demonstrated:

- almost identical GMT responses (with overlapping CIs for all HPV subtypes) when compared with the same vaccination schedules in adolescent females at seven months[223]

- no significant differences in seroconversion rates compared with the adolescent females at seven months.[223]

The two-dose vaccination schedule of the 9-valent HPV vaccine in boys and girls (aged nine to 14 years) demonstrated:

- higher GMTs than those for women (aged 16 to 26 years) who received the three-dose vaccine schedule
- GMTs that were numerically lower for some vaccine subtypes (that is, HPV 18, 31, 45 and 52) than those observed in girls (aged nine to 14 years) who received the three-dose vaccine schedule
- the GMT ratios in girls (aged nine to 14 years) for two-dose versus three-dose schedules were only inferior for the HPV 45 and 52 subtypes at seven months.

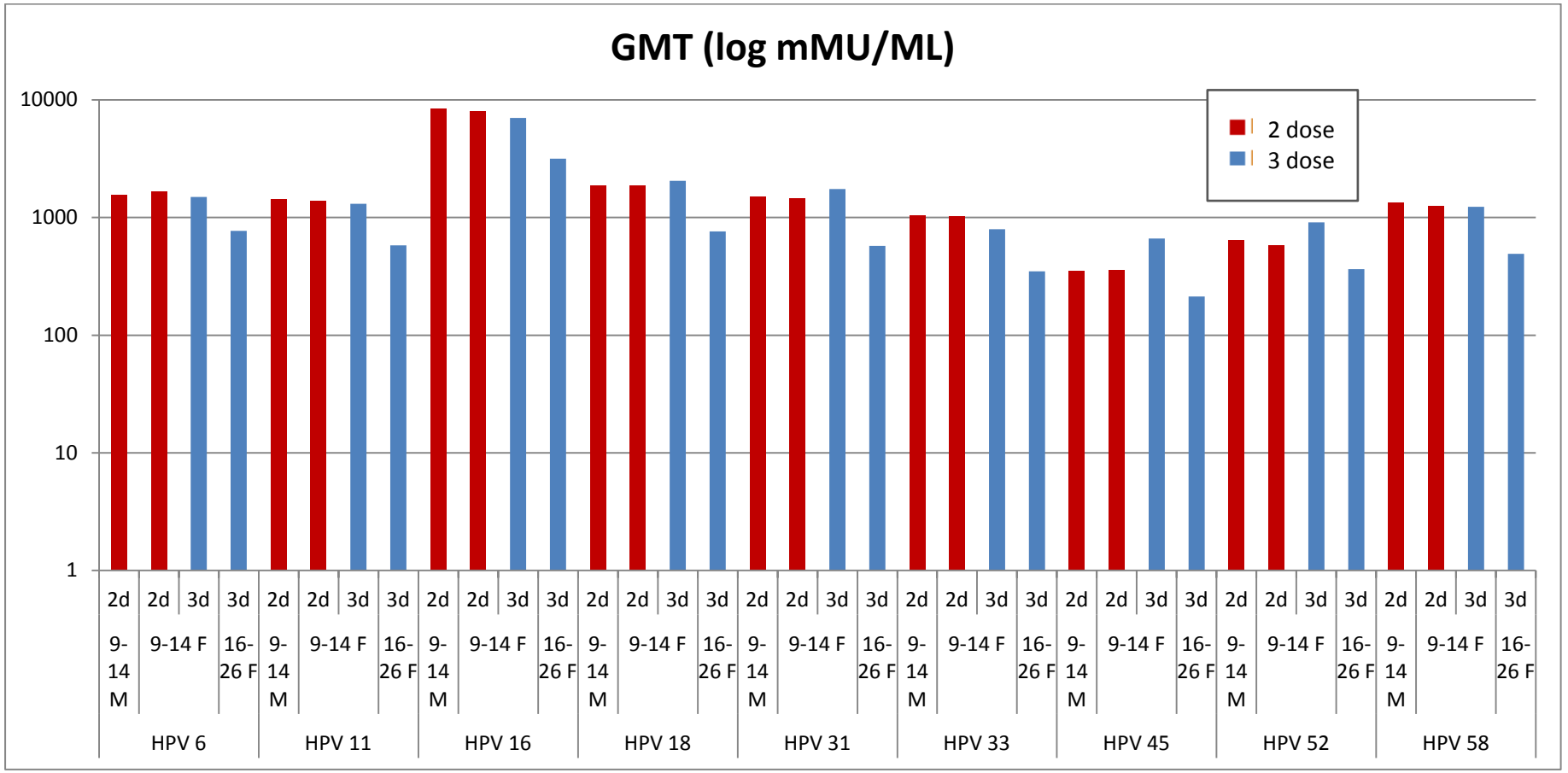
Table 4.32 Immunogenicity comparison of two doses of the 9-valent HPV vaccine in adolescent males versus females at seven months

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 14 year old females	**9 to 14 year old males**			
GMTs - HPV 06 Follow up: 7 months	Iversen 2016	1657.9 mMU/mL (1479.6 – 1857.6)	**1557.4 mMU/mL** (1391.5 – 1743.1)	**GMT Ratio 0.94**	521 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 11 Follow up: 7 months	Iversen 2016	1388.9 mMU/mL (1240.4 – 1555.3)	**1423.9 mMU/mL** (1273.2 – 1592.3)	**GMT Ratio 1.03**	522 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 16 Follow up: 7 months	Iversen 2016	8004.9 mMU/mL (7160.5 – 8948.8)	**8474.8 mMU/mL** (7582.4 – 9472.3)	**GMT Ratio 1.06**	545 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 18 Follow up: 7 months	Iversen 2016	1872.8 mMU/mL (1651.6 – 2123.6)	**1860.9 mMU/mL** (1641.1 – 2110.2)	**GMT Ratio 0.99**	544 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 31 Follow up: 7 months	Iversen 2016	1436.3 mMU/mL (1272.1 – 1621.8)	**1498.2 mMU/mL** (1326.5 – 1692.0)	**GMT Ratio 1.04**	543 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 33 Follow up: 7 months	Iversen 2016	1030.0 mMU/mL (920.4 – 1152.7)	**1040.0 mMU/mL** (928.9 – 1164.3)	**GMT Ratio 1.01**	544 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 45 Follow up: 7 months	Iversen 2016	357.6 mMU/mL (313.7 – 407.6)	**352.3 mMU/mL** (309.0 – 401.7)	**GMT Ratio 0.99**	547 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 52 Follow up: 7 months	Iversen 2016	581.1 mMU/mL (521.9 – 647.1)	**640.4 mMU/mL** (575.2 – 713.0)	**GMT Ratio 1.10**	545 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]
GMTs - HPV 58 Follow up: 7 months	Iversen 2016	1251.2 mMU/mL (1119.6 – 1398.4)	**1325.7 mMU/mL** (1186.2 – 1481.6)	**GMT Ratio 1.06**	540 (1 RCT)[223]	⨁◯◯◯ VERY LOW [a,b]

Outcomes		**Absolute effects** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
		9 to 14 year old females	**9 to 14 year old males**			
Seropositivity - HPV 06 Follow up: 7 months	Iversen 2016	257/258 (99.6%) (97.9 – 100%)	**263/263 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	521 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 11 Follow up: 7 months	Iversen 2016	258/258 (100%) (98.6 – 100%)	**264/264 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	522 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 16 Follow up: 7 months	Iversen 2016	272/272 (100%) (98.7 – 100%)	**273/273 (100%)** (98.7 – 100%)	**RR 1.00** (0.99 to 1.01)	545 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 18 Follow up: 7 months	Iversen 2016	272/272 (100%) (98.7 – 100%)	**272/272 (100%)** (98.7 – 100%)	**RR 1.00** (0.99 to 1.01)	544 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 31 Follow up: 7 months	Iversen 2016	271/272 (99.6%) (98.0 – 100%)	**271/271 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	543 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 33 Follow up: 7 months	Iversen 2016	272/273 (99.6%) (98.0 – 100%)	**271/271 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	544 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 45 Follow up: 7 months	Iversen 2016	272/274 (99.3%) (97.4 – 99.9%)	**271/273 (99.3%)** (97.4 – 99.9%)	**RR 1.00** (0.99 to 1.01)	547 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 52 Follow up: 7 months	Iversen 2016	271/272 (99.6%) (98.0 – 100%)	**273/273 (100%)** (98.7 – 100%)	**RR 1.00** (0.99 to 1.01)	545 (1 RCT)[223]	⊕⊕◯◯ LOW [a]
Seropositivity - HPV 58 Follow up: 7 months	Iversen 2016	270/270 (100%) (98.6 – 100%)	**270/270 (100%)** (98.6 – 100%)	**RR 1.00** (0.99 to 1.01)	540 (1 RCT)[223]	⊕⊕◯◯ LOW [a]

__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).* [223] **Iversen 2016. a. Downgraded two levels for risk of bias: non-randomised comparison in an open label study; participants were not blinded and personnel would have been aware of schedules.

Figure 4.8 Comparison of immunogenicity outcomes for the two-dose versus three-dose 9-valent vaccine schedules (nine to 14 years versus 16 to 26 years)



Iversen 2016 (data reported for two dose girls [9-14] vs. three dose women [16-26]; two dose girls [9-14] vs. three dose girls [9-14]; two dose boys [9-14] vs. three dose women [16-26]).

4.4 Discussion

This systematic review was undertaken to identify the evidence for the clinical efficacy and immunogenicity of 4-valent and 9-valent HPV vaccines from relevant published studies. Clinical efficacy studies of HPV vaccines have not been conducted in adolescent girls and boys, the primary target of the Irish HPV vaccination programme, for ethical and legal reasons. However, HPV vaccines have been approved by regulatory agencies based on bridging studies that generate immunogenicity data to support the extrapolation of data on efficacy obtained under specific circumstances of use (such as, the three-dose 4-valent HPV vaccine efficacy in 16 to 26 year old females and males) to different HPV vaccine types, different age groups, different populations and different dosage schedules.[252]

In order to overcome the lack of direct clinical outcome data available in published studies for two-dose HPV vaccination in 12 to 13 year old boys and girls, it was necessary to firstly establish the clinical efficacy of the HPV vaccines in HPV-naïve populations of adult females and males. These populations provide the best approximation for pre and early adolescent girls and boys, who have not yet become sexually active. Secondly, the bridging studies, that were approved by regulators to infer HPV vaccine efficacy, were analysed to compare any reported immunogenicity outcome differences by vaccine type (9-valent versus 4-valent), gender (male versus female) and dosage schedule (two doses versus three doses). Thirdly, the persistence of HPV-antibody responses over time for the 4-valent HPV vaccine in the per-protocol populations of identified long-term follow-up studies was examined to establish the duration of protection of the HPV vaccine post-vaccination. This three-step process involved the completion of six distinct evidence summary reviews, as illustrated earlier in section 4.1.4.

There were 35 studies identified that met the inclusion criteria. Exclusion criteria applied to studies that focused exclusively on adults over 26 years, the men who sex with men (MSM) population and trials of patients with acquired immuno-deficiencies as these were not generally representative of the target population. The 2-valent HPV vaccine was not included in the review, as it was assumed that this technology would not be considered for a gender-neutral vaccination programme, as it does not offer protection against anogenital warts. The 2-valent HPV vaccine has been shown to confer greater levels of cross-protection against non-vaccine HPV-types when compared with the 4-valent HPV vaccine.[253] Hence, it was considered likely to bias the efficacy results for HPV vaccine upwards if included in the review.

From the 31 studies included in the evidence summaries, the systematic review has shown that for the clinical efficacy outcomes in HPV-naïve females aged 15 to 26 years old (the population that most closely matches that of pre and early adolescent girls), the 4-valent HPV vaccine has demonstrated a significant effect at reducing

events[10] associated with persistent HPV 6, 11, 16 or 18-related infections (93%), anogenital warts (89-96%), and HPV 6, 11, 16 and 18-related CIN 1 (95-97%), CIN 2 (96-99%), CIN 3 (97-99%), VIN/VaIN 1 (95%) and VIN/VaIN 2/3 (95-97%).[9, 230, 243, 245, 250]

There was an estimated 95% reduction in HPV 16 or 18-related adenocarcinoma *in situ* (AIS) cases in a large study of an unrestricted susceptible population. Despite the low event rates (10 cases in ≤ 20,000 participants), the estimate was statistically significant.[230] For non-vaccine HPV type-related CIN 2 or AIS in a generally HPV-naïve female population, the 4-valent HPV vaccine appears to be associated with reduced event rates (32% reduction).[232] For the 9-valent versus 4-valent HPV vaccine in HPV-naïve adult females, there is no significant difference in the effect on clinical outcomes observed for the HPV subtypes common to both vaccines (that is HPV 6, 11, 16 and 18). However, there is a significant reduction in the events associated with HPV 31, 33, 45, 52 and 58 type-related persistent infection (94%) and cervical, vaginal and vulvar diseases (98%) reported for the 9-valent HPV vaccine in this population.[224]

In HPV-naïve adult males (the population that most closely matches that of pre and early adolescent boys), the 4-valent HPV vaccine is also shown to be effective at reducing events associated with persistent HPV 6, 11, 16 or 18-related infections (67%), external genital lesions (75-91%) and anogenital warts (79%) in this population.[237, 238] For any HPV type-related PIN grade 1 and grade 2 or worse lesions in the HPV-naïve population, there was evidence of 50% and 80% reduction in events. Despite this sizeable effect size, very few PIN cases were observed across the intervention and placebo groups in all populations. The very wide 95% CIs reported around the effect estimates rendered the results inconclusive. Further evidence from future large scale trials with longer follow-up periods are required to conclusively establish the efficacy of the vaccine in the prevention of PIN lesions and related cancer. For non-vaccine HPV type-related external genital lesions in a HPV-naïve male population, the 4-valent HPV vaccine appears to be associated with reduced event rates (67%).[238] There are no studies identified that compared clinical outcomes for the 9-valent versus 4-valent HPV vaccine in adult heterosexual males.

There was no conclusive evidence of a significant clinical difference in the efficacy of the 4-valent vaccine on comparable clinical outcomes, such as vaccine HPV type-related persistent infection or external genital lesions, between sexes.[219, 237, 238] The only exception was the report of less incidents of persistent infection (related to 10 oncogenic non-vaccine HPV-related subtypes) in a follow-up study of young males compared to young females.[220] However, this paper by Ferris (2017) reported on a different population (EVG ITT), and was assessed to have a high risk of bias.

[10] Percentage reduction in brackets.

For the immunobridging studies comparing the 9-valent and 4-valent HPV vaccine in females[222] [249] and males,[248] there were non-inferior GMT ratios and comparable seroconversion rates for the four HPV subtypes common to both vaccines. As expected, the 9-valent vaccine produces substantial GMT responses for the HPV 31, 33, 45, 52 and 58 subtypes for all ages in each gender group studied. Seroconversion for HPV types 31, 33, 45, 52 and 58 ranged from 99.6-100%.

The studies comparing the immunogenicity outcomes for 4-valent[219, 231, 244, 246] and 9-valent[233, 247] HPV vaccines in males versus females demonstrated higher immune responses (GMTs) with superior GMT ratios for all vaccine-related HPV types in vaccinated males. GMTs appear to favour females over time, but the GMTs for males continue to persist and exceed the non-inferiority threshold. Higher immune responses were evident in the younger pre-adolescent and adolescent cohorts aged nine to 15 years compared with older cohorts aged 16 to 26 years. Seroconversion non-inferiority occurred in >99% of study participants, indicating no relative differences in seroconversion rates between males and females aged nine to 26 years.

The studies comparing the immunogenicity outcomes of a two-dose versus three-dose vaccination schedule of the HPV vaccine in boys and girls (aged nine to 15 years) versus older females (aged 16 to 26 years) demonstrated higher immune responses (GMTs) with non-inferior GMT ratios in the two-dose HPV vaccination schedules for the younger cohort.[218, 221, 223] This non-inferiority is sustained in the longer term for young females (up to 36 months with the 4-valent HPV vaccine). There appears to be a narrowing of the superiority of this relative effect over time, but never falls below the non-inferiority threshold.[218, 221] The two-dose versus three-dose vaccination schedule of the HPV vaccine in girls (aged nine to 15 years) demonstrated higher or non-inferior GMT responses for seven of the nine HPV subtypes.[223] Inferior GMT ratios were reported for the HPV 45 and 52 subtypes of the 9-valent vaccine. The clinical relevance of this finding is unclear. The trend of the immunogenicity data appears to favour the immune response from a three-dose regimen over time. For all the two-dose versus three-dose comparisons (girls versus women; girls versus girls; boys versus women), there was almost 100% seropositivity rates, that tended to persist over time. There were comparable immune responses between the two-dose schedules of the 9-valent HPV vaccine in boys and girls.[223]

The 4-valent HPV vaccine was shown to produce durable HPV-antibody responses up to 108 months in adult females,[225] and up to 36 months in adult males.[239] However, there was no GMT data reported for placebo groups in these studies to facilitate comparison with the HPV vaccine intervention.[225, 239] Of interest, despite persistence of seroconversion rates for all other vaccine HPV subtypes over time, the

HPV 18 subtype did taper to 60% for each gender. However, this has been shown not to affect the anamnestic response to the HPV 18 subtype.[225, 239]

Immunogenicity data for females was reported from five studies. The most reliable and consistent evidence was from the Nordic population in a study that followed the FUTURE II trial.[225] Despite a narrower multinational focus, the robust and durable nature of the evidence has contributed to an assumption of lifelong duration of efficacy of the 4-valent HPV vaccine. A sensitivity analysis is conducted to assess the impact of a 10-year duration of efficacy in the economic evaluation of the vaccine in Chapter 8.

The findings of this review are consistent with the systematic review of randomised controlled trials (RCTs) of HPV vaccines commissioned by the WHO in 2016.[209] However, the authors (Cochrane Response, London) did not summarise evidence of the efficacy of the 4-valent HPV vaccine versus placebo in females. The Cochrane systematic review by Arbyn et al. (2018) evaluated the immunogenicity, clinical efficacy and safety of prophylactic HPV vaccines (that is 1-valent, 2-valent and 4-valent) in females.[254] It concluded that the HPV vaccines protect against cervical pre-cancer in adolescent girls and young women aged 15 to 26 years, and the effect is higher for lesions associated with HPV 16 and 18 than for lesions irrespective of HPV type. The findings of this review also report superior efficacy of the 4-valent HPV vaccine against vaccine HPV-type related lesions of the cervix in females than those attributable to 'any HPV type'.

Arbyn et al. (2018) noted that the effect of the HPV vaccine is greater in those who are negative for high-risk HPV or HPV 16 and 18 DNA at enrolment than those unselected for HPV DNA status.[254] This observation validates the methodological approach taken to focus on the efficacy of the vaccines in HPV-naïve populations to approximate the baseline sexual history characteristics of the target population for the HPV vaccination programme. It should be noted that this review has a slightly different methodological approach.

Delere et al. (2014) completed a systematic review and meta-analysis on the efficacy and duration of vaccine protection against HPV infection and CIN lesions.[255] This work also focused on study participants in whom incident HPV infection with the vaccine-HPV types was ruled out at enrolment. The long-term observation of these authors also did not indicate any loss of anti-viral protection after vaccination against the HPV 16 and 18-related infections and cervical disease. Signorelli et al. (2017) reports the same 9-valent HPV vaccine efficacy against composite high-grade cervical, vaginal or vulvar disease related to HPV types 31, 33, 45, 52 and 58, and also concludes that the 9-valent HPV vaccine appears to be non-inferior to other HPV vaccines in terms of short-term immunogenicity and efficacy against common HPV types.[256]

The non-inferiority findings for the two-dose 4-valent HPV vaccine schedule are consistent with those of D'Addario et al. (2017), who also found that after seven months there was no comparison in which girls who received a two-dose schedule (of either 2-valent or 4-valent HPV vaccine) had antibody responses that were inferior to those of girls who received three doses.[(210)]

There are gaps in the evidence presented for the efficacy of the HPV vaccine in certain clinical outcomes. Due to the exclusion of the MSM population from the inclusion criteria of the review, there are no data reported on pre-cancerous lesions or cancer of the anus in the review of clinical efficacy. However, it should be noted that anal intraepithelial neoplasia (AIN) and anal cancer outcomes were reported for a MSM population by Giuliano 2011.[(237)] The end-of-study results from the Protocol 020 MSM substudy was the basis for demonstrating the use of Gardasil® to prevent anal intraepithelial neoplasia (AIN) and anal cancer in males, and led to the approval of Gardasil® for these indications in men and women by the Food and Drug Administration (FDA) in 2010.

In contrast to the extensive data reported on the efficacy of HPV vaccination against anogenital HPV-related infection and disease in this chapter, there is no completed RCT that assesses HPV vaccine efficacy against oropharyngeal HPV-related infection and disease. This may be attributable to the extreme difficulty in identifying HPV-related pre-malignant precursors of oropharyngeal cancer, making the design of RCTs using intra-epithelial neoplasia as a surrogate endpoint extremely difficult.[(257)] The clinical effectiveness of the HPV vaccine against anal and oropharyngeal HPV-related infection and diseases is examined at a population level in Chapter 5.

Since other vaccines are routinely given to pre and early adolescents, it is also important to determine if they can be co-administered with the HPV vaccines. All students in first year of second level schools in Ireland are also offered a booster dose of the Meningococcal C (MenC) vaccine, and a booster dose of tetanus, low dose diphtheria and low dose pertussis (whooping cough) (Tdap) vaccine.[(258)] The systematic review of human papillomavirus (HPV) vaccine co-administration (2014)[(259)] concluded that non-inferiority of immune response and an acceptable safety profile were demonstrated when 2-valent or 4-valent HPV vaccine was co-administered with other vaccines (includes gender-neutral vaccination studies by Vesikari (2010)[(226)] on Repevax® (diphtheria, tetanus, acellular pertusis, inactive polio) and by Reisinger (2010)[(227)] on Menactra® (meningococcal conjugate) plus Adacel® (diphtheria, tetanus, acellular pertusis). Further studies in boys and girls, examining concomitant administration of the 9-valent HPV vaccine with Repevax® by Kosalaraksa (2015)[(228)] and with Menactra® plus Adacel® by Schilling (2015),[(229)] found that the 9-valent HPV vaccine was generally well-tolerated and did not interfere with the antibody response to any of these vaccines. This strategy minimises the number of visits required to deliver each vaccine dose individually.

The review has strengths and limitations. In regards limitations, it was difficult to carry out quantitative pooling of retrieved data, particularly due to the heterogeneity of studies by population type (generally HPV naïve versus unrestricted susceptible) and differences in the HPV type(s) related to the outcomes of interest. To overcome this impediment, it was possible to interpret the findings of identified published studies that were combined or pooled analyses of multiple RCTs of clinical efficacy outcomes for the 4-valent HPV vaccine versus placebo in females. It is necessary to acknowledge that some of the certainty around the evidence reported was categorised as 'low' or 'very low'. The use of GRADEpro can be subjective. However, there was a high level of agreement between both independent reviewers in producing a transparent assessment of the quality of the evidence. The majority of the trials identified in the review are sponsored or funded by the manufacturer. This was flagged as an unclear risk of bias under 'other biases'. However, these trials tended to be international, multi-centre trials with large population numbers. As referenced in section 4.2.3, the risk of bias graph confirms the majority of studies can be classified as having a 'low' risk of bias for six of the seven risk of bias domains.

The evidence collated within this chapter on the efficacy of the 4-valent and 9-valent HPV vaccines in reducing the prevalence of HPV infections, where deemed sufficiently applicable, are used to underpin the economic modelling in Chapter 8. Chapter 8 evaluates the relative cost-effectiveness and resource implications of introducing gender-neutral HPV immunisation for early adolescents, who have not yet become sexually active.

4.5 Key messages

- A systematic review was undertaken to identify the evidence for the clinical efficacy and immunogenicity of 4-valent and 9-valent HPV vaccines from relevant published studies.
- Clinical efficacy studies of HPV vaccines have not been conducted in adolescent girls and boys. HPV vaccines have been approved by regulatory agencies based on bridging studies that generate immunogenicity data to support the extrapolation of data on efficacy from adult cohorts to adolescent cohorts.
- For clinical outcomes from randomised controlled trials (RCTs) on the efficacy of the HPV vaccine, the focus was on HPV-naïve populations to provide the best approximation for pre and early adolescent girls and boys, who are not yet sexually active.
- For immunogenicity outcomes, the population of interest was per-protocol.
- From the 35 studies identified that met the inclusion criteria, 31 were included in the six evidence summaries.
- The 4-valent HPV vaccine demonstrated a significant effect at reducing events associated with persistent HPV 6, 11, 16 or 18-related infections (93%), anogenital warts (89-96%), and HPV 6, 11, 16 and 18-related CIN 1 (95-97%) , CIN 2 (96-99%), CIN 3 (97-99%), VIN/VaIN 1 (95%) and VIN/VaIN 2/3 (95-97%) in HPV-naïve women. Despite low event rates for AIS in the studies, the vaccine showed a 95% reduction in HPV 16 or 18-related AIS cases.
- The 4-valent HPV vaccine is also shown to be effective at reducing events associated with persistent HPV 6, 11, 16 or 18-related infections (67%), external genital lesions (75-91%) and anogenital warts (79%) in HPV-naïve men. Despite a sizeable reduction in any-HPV type-related PIN 1 (50%) and PIN 2+ lesions (80%) in a HPV-naïve male population, there is considerable uncertainty around the effect size of the 4-valent HPV vaccine on PIN lesions and penile, perineal and perianal cancer in men, due to statistical insignificance around reported estimates and very low event rates among study participants.
- There was no conclusive evidence of a significant clinical difference in the efficacy of the 4-valent vaccine on comparable clinical outcomes, such as vaccine HPV type-related persistent infection or external genital lesions, between sexes.
- For non-vaccine HPV type-related CIN 2 or AIS in generally HPV-naïve women, the 4-valent HPV vaccine appears to be associated with reduced event rates (32% reduction). For non-vaccine HPV type-related external genital lesions in a HPV-naïve male population, the 4-valent HPV vaccine appears to be associated with reduced event rates (67% reduction).
- For the 9-valent versus 4-valent HPV vaccine in HPV-naïve adult females, there is no significant difference in the effect on clinical outcomes observed for the HPV

subtypes common to both vaccines (HPV 6, 11, 16 and 18). However, there is a significant reduction in the events associated with HPV 31, 33, 45, 52 and 58 type-related persistent infection (94%) and cervical, vaginal and vulvar diseases (98%) reported for the 9-valent HPV vaccine.

- There is evidence that the 4-valent HPV vaccine produces durable HPV-antibody responses up to 108 months in adult females, and up to 36 months in adult males. The robust and durable nature of the evidence has contributed to an assumption of lifelong duration of efficacy of the 4-valent HPV vaccine.
- For immunobridging studies comparing the 9-valent and 4-valent HPV vaccine in females and males, there were non-inferior geometric mean titre (GMT) ratios and comparable seroconversion rates for the four HPV subtypes common to both vaccines.
- For the 4-valent and 9-valent HPV vaccine in males versus females, vaccinated males tended to have higher GMTs than vaccinated females at seven months. GMTs appear to favour females over time, with those for males continuing to exceed the non-inferiority threshold. This was evident in boys versus girls for both HPV vaccines and in men versus women for the 9-valent HPV vaccine.
- The immunobridging studies emphasise either superior or non-inferior immune responses for two-dose versus three-dose schedules for 4-valent and 9-valent HPV vaccines for all comparisons of girls versus women, girls versus girls and boys versus women at seven months. There are comparable immune responses between the two-dose schedules of the 9-valent HPV vaccine in boys and girls at seven months.
- For all immunobridging studies comparing both dosage schedules, there was no significant difference in seropositivity rates between males and females at seven months, and this seroconversion persisted over time.
- To summarise, the key immunogenicity data for HPV vaccines at seven months demonstrates:
  - Adolescents display superior immune responses to adults
  - Males display superior immune responses to females
  - 9-valent vaccine produces similar immune response to 4-valent vaccine for the common HPV types
  - Two-dose vaccine schedules are non-inferior to three-dose vaccine schedules
  - Seroconversion was >98% for all participants across comparisons.
- The immunogenicity data from all bridging studies demonstrates that GMT responses to HPV vaccines persist over time with durable seropositivity rates.
- No clinical outcome data were available from included studies for HPV-related infection or disease of the anus or the oropharynx.
- The 2-valent HPV vaccine was not included in the systematic review of efficacy

and immunogenicity.

5 Population-level effectiveness of HPV immunisation programmes

5.1 Introduction

It has been more than 10 years since the implementation of the first HPV immunisation programme in Ireland in 2007. Since then, an increasing number of published surveillance studies have documented trends in HPV-related disease, such as the incidence or prevalence of anal and genital warts or high-grade cervical lesions. The population-level effect of HPV immunisation programmes is expected to vary substantially between countries due to the vaccine used (the 2-valent vaccine does not provide protection against anogenital warts) and the vaccine coverage achieved.

This chapter summarises the available evidence regarding the population-level effect of HPV immunisation programmes. Data from pre-vaccination and post-vaccination periods are compared to assess the impact of the programmes on the prevalence of HPV infection and HPV-related disease (namely, anogenital warts or high-grade cervical lesions). Through time-trend analysis of observational studies, it is possible to investigate whether or not the high efficacy reported in randomised controlled trials (RCTs) translates into real-world effectiveness.

As this systematic review retrieves real-world data on the effectiveness of HPV vaccination, it differs from the systematic review of the efficacy of the HPV vaccine (Chapter 4) in a number of ways. In contrast to the efficacy review which only included RCT data, an effectiveness review considers observational studies. While the efficacy data were limited to populations that were HPV seronegative at baseline, the effectiveness data may include those previously exposed to HPV as HPV immunisation programmes do not stipulate sexual naïvety nor HPV seronegativity prior to vaccination. Thirdly, in addition to the 4-valent and 9-valent vaccines, it considers immunisation programmes based on the 2-valent vaccine. While the 2-valent vaccine is not under consideration for boys in Ireland, certain jurisdictions (such as the UK) first introduced the 2-valent vaccine for their girls-only HPV immunisation programmes prior to changing to the 4-valent vaccine. This chapter reviews all evidence of effectiveness of real-world immunisation programmes, rather than excluding valuable data on early immunisation programmes due to different vaccine formulations.

The systematic review aims to answer the following questions:

- Following the implementation of a HPV immunisation programme in a given population, is there evidence of a reduction in HPV-related infection or disease?

- Do real-world data (in the form of observational studies) support the observed high efficacy of the HPV vaccine in RCTs?

5.2 Methods

A systematic review was undertaken to assess the population-level effectiveness of HPV immunisation programmes.

5.2.1 Criteria for selection of studies

Table 5.1 outlines the population, intervention, comparator, outcomes and study design (PICOS) criteria for selection of studies.

Table 5.1: PICOS criteria

Population	Any group or population of people who were administered the HPV vaccine as part of a population-based HPV immunisation programme (as opposed to individuals receiving the HPV vaccine administered as part of an individual-based randomised trial).
Intervention	Any HPV immunisation programme. The programme may involve any formulation of the HPV vaccine and any dosing schedule.
Comparator	The comparator is the pre-vaccination period.
Outcomes	A reduction in HPV-related endpoints: 1. HPV infection 2. Anogenital warts 3. Histopathologically confirmed high-grade cervical lesions (cervical intraepithelial neoplasia [CIN] 2 or worse [CIN 2+]).
Study design	Observational studies with data available over two distinct time periods: pre-vaccination and post-vaccination.

Selection criteria

Studies were selected according to the following inclusion or exclusion criteria:

Inclusion criteria

1. Data were available on at least one endpoint:
    a. HPV infection
    b. Anogenital warts (AGW)
    c. Histopathologically confirmed high-grade cervical lesions (cervical intraepithelial neoplasia [CIN] 2 or worse [CIN 2+])

2. Assessment of the population-level effect was performed by comparing the frequency (for example, prevalence or incidence) of the endpoint between the pre-vaccination and post-vaccination periods (that is, time-trend studies)

3. Data from the pre-vaccination and post-vaccination periods were collected from the same population sources with use of the same recruitment methods.

Exclusion criteria

1. HPV vaccination was administered as part of an individual-based randomised trial (not population-level effect)

2. HPV vaccination effect was assessed by comparing the frequency of the endpoint between vaccinated and unvaccinated people during the post-vaccination period only (not time-trend studies)

3. Conference proceedings and abstracts whereby the full texts were unobtainable were excluded.

5.2.2 Search methods

Electronic searches

Electronic searches were conducted in Medline and Embase to identify population-based studies that investigated the impact or effect of HPV immunisation programmes on the incidence or prevalence of HPV-related infection or disease.

Search terms

Search terms (including Medical Subject Heading (MeSH) terms) were combined, with the Boolean operator word 'AND', related to:

1) the HPV vaccine,

2) HPV-related clinical outcomes and or endpoints, and

3) terms to signify a population-level programme (such as 'programme evaluation', 'population surveillance', 'sentinel surveillance', 'incidence' or 'prevalence').

A sample of the search strategy used in Embase and PubMed is included in Appendix 5A.

Searching other resources

To maximise efficiency, a decision was made to update an exisiting systematic review if a relevant, high-quality review could be identified. Searches were carried out for systematic reviews of the population-level effects of HPV immunisation

programmes. The quality and rigour of the identified systematic reviews were assessed using the AMSTAR 2 appraisal tool.[292] An updated search was undertaken for additional studies that emerged following the original review was published and the results were combined with those retrieved from the original review.

5.2.3 Data collection and analysis

Selection of studies

Citations were screened by one reviewer to eliminate clearly irrelevant studies. Two people independently reviewed the remaining citations per the inclusion criteria, with any disagreements being resolved by discussion or, if necessary, a third reviewer.

Data extraction and management

De novo data extraction was performed independently by two people with any disagreements being resolved by discussion or a third reviewer. As noted, the approach adopted was to update a previously published systematic review that had been assessed as being of high quality. Given satisfaction as to the quality and rigrour of this review, data extraction from the studies included therein was performed by one reviewer only.

Assessment of risk of bias in included studies

Assessment of the risk of bias followed the World Health Organization (WHO)'s *'Guidance For The Development Of Evidence-Based Vaccination related Recommendations'*.[293] Formulated by WHO's Scientific Advisory Group of Experts (SAGE), it provides recommendations on assessing the risk of bias in observational studies related to immunisation programmes. This was performed by two people independently, with disagreement resolved by discussion or a third party.

Measures of treatment effect and data synthesis

Where possible, for comparability, prevalence ratios or incidence rate ratios were used as the measure of effect for all HPV-related endpoints. These are referred to as relative risks (RRs) hereafter for ease of interpretation. In all cases, RRs were obtained by dividing the post-vaccination prevalence or incidence by the pre-vaccination prevalence or incidence. If not reported in individual studies, RRs were calculated using Review Manager Version 5.3 software.

Therefore, the primary outcomes of interest were the relative risks (RRs) comparing the pre-vaccination and post-vaccination periods of:

- Prevalence of HPV infection (with subgroups defined by the HPV types included in the 4- and 9-valent vaccines),

- Frequency (prevalence or incidence) of anogenital wart diagnosis, and
- Frequency (prevalence or incidence) of high-grade cervical lesions (CIN2+).

As documented in Chapter 2, the HPV vaccine was first licensed for use in 2006. Australia was the first country to implement a national programme in April 2007, and like the majority of programmes implemented internationally in the subsequent years, was initially aimed at girls aged 12 to 13 years of age. The analyses were therefore stratified by sex and age as younger girls (aged less than 20 years) were most likely to have received the HPV vaccine in study populations. Additionally, due to the expected wide variation in vaccine programmes, such as differences in vaccine coverage, it was decided *a priori* not to pool results from individual studies if high levels of heterogeneity were found.

Information about the immunisation programme characteristics, including vaccine coverage of the country or region of each study, was also collected.

Reporting guidelines

Reporting was in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[294]

5.3 Results

The search identifed a systematic review and meta-analysis published by Drolet et al. in 2015, entitled *Population-level impact and herd effects following human papillomavirus immunisation programmes: a systematic review and meta-analysis*.[295] A subsequent update to the review (also conducted by Drolet et al.) for the WHO's SAGE committee on vaccinations in July 2016 was identified, although only preliminary findings were presented and the final report is awaited.

The 2015 review by Drolet et al. was judged to be of sufficient quality (by AMSTAR 2 criteria, see Appendix 5B) and a decision was made to upate it rather than perform a *de novo* review.

The search by Drolet et al. ran from 1 January 2007 to 28 February 2014. From this systematic review, 16 original studies were identified and selected for inclusion. Conference abstracts and proceedings where full texts were unpublished were not included. A *de novo* search was performed to identify additional studies published between 28 February 2014 and 15 December 2017. A total of 1,159 studies were identified, 21 of which met the inclusion criteria. See Appendix 5C for the flow diagram of study selection.

This resulted in a total of 37 studies included in this review; 18 on HPV infection,[296-313] 16 on anogenital warts[314-329] and three on high-grade cervical lesions (CIN

2+).[330-332]

The studies were carried out in nine high-income countries (the USA, Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada and Germany). The population-level consequences of HPV vaccination were assessed in over 36,000 women and 129 men for HPV infection, over 63 million women and over 46 million men for anogenital warts, and almost 30 million women for high-grade cervical lesions. The very large number of individuals involved reflect the fact that anogenital warts are a notifiable disease in many jurisdictions and cervical lesions are identified through organised cervical screening programmes. Thus, large volume population-level data are available for these endpoints in many countries.

With the exception of two studies that included post-vaccination data from 2015,[299, 326] all studies reported on post-vaccination periods ranging from 2009 to 2014. Data therefore relates to the 2-valent and 4-valent vaccines, as the 9-valent vaccine did not become commercially available until authorised by the European Medicines Agency (EMA) in June 2015 (or by the Food and Drug Administration [FDA] in December 2014).

The vaccine used, vaccination strategy, delivery, and vaccine coverage varied substantially between countries. Tables 5.2 to 5.4 outline the key study characteristics of included studies. Appendix 5D details the Risk of bias assessment of included studies.

Across studies, substantial heterogeneity was noted. The most obvious source of heterogeneity was the variation in vaccine coverage in sampled populations, ranging from 25-30% (Skane region of Sweden between 2007 and 2010)[324] to 88-91% (Denmark, pre-2013)[317]. For this reason, a meta-analysis of study results was not performed.

Table 5.2: Study characteristics - HPV infection

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case (HPV testing methodology)	Outcome used in publication	Vaccine coverage *
Cameron, 2016[300]	2-valent	Scotland	Population based: Scottish Cervical Screening Call & Recall System	5,765 liquid-based cytology samples from women 20–21 years of age who underwent their first cervical smear testing during 2009–2013	Pre-: 2009–10; Post-: 2011–13	HPV+ Multimetrix HPV assay (Diamex, Heidelberg, Germany; 18 types)	Odds ratios of HPV prevalence (adjusted)	81%
Chow, 2015[298]	4-valent	Australia	Clinic-based	Women aged 25 years or younger who attended the Melbourne Sexual Health Centre (Melbourne, VIC, Australia) diagnosed with chlamydia	Pre-: 2004-2007; Post-: 2007-2014	PCR: HPV amplification and detection using the PapType high-risk HPV detection and genotyping kit	Frequency of infection, prevalence ratios (adjusted)	83%
Chow, 2017[299]	4-valent	Australia	Clinic-based	Heterosexual men aged 25 years or younger attending the Melbourne Sexual Health Centre between July 1, 2004, and June 30, 2015, who tested positive for chlamydia	Pre-: 2004-2005; Post-: 2014-2015 (boys' vaccine introduction was in 2013)	PCR (PapType assay [Genera Biosystems, Scoresby, VIC, Australia])	Frequency of infection, prevalence ratios (adjusted)	84%

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case (HPV testing methodology)	Outcome used in publication	Vaccine coverage*
Cummings, 2012[296]	4-valent	USA	Clinic based	Girls aged 14–17 years attending one of three urban primary care clinics in Indianapolis (IN, USA)	Pre-: 1999–2005; Post-: 2010	PCR Roche Linear Array test which detects 37 different HPV type]	Odds ratios of HPV prevalence (crude)	89%
Dunne, 2015[310]	4-valent	USA	Residual samples from cervical screening	Consecutive residual cervical specimens were retained from women aged 20–29 years at Kaiser Permanente Northwest	Pre-: 2007; Post-: 2012–2013	Research Use Only Linear Array (LA) HPV Genotyping Test (Roche Molecular Diagnostics) and HPV-52 quantitative polymerase chain reaction	Odds ratios of HPV prevalence (crude)	32%
Kahn, 2012[301]	4-valent	USA	Clinic based	Sexually experienced girls and women aged 13–26 years attending one hospital-based adolescent clinic and one community health centre in Cincinnati (OH, USA)	Pre-: 2006–07; Post-: 2009–10	HPV+ Roche Linear Array (Roche Molecular Systems, Alameda, CA, USA; 37 types)	HPV prevalence difference (adjusted)	77%

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case (HPV testing methodology)	Outcome used in publication	Vaccine coverage*
Kahn, 2016[302]	4-valent	USA	Clinic based	Sexually experienced girls and women aged 13–26 years attending one hospital-based adolescent clinic and one community health centre in Cincinnati (OH, USA)	Pre-: 2006–2007 (n = 371); Post-: 2009–2010 (n = 409) and Post-: 2013–2014 (n = 400)	HPV+ Roche Linear Array (Roche Molecular Systems, Alameda, CA, USA; 37 types)	HPV prevalence difference (adjusted)	71%
Kavanagh, 2014[309]	2-valent	Scotland	Population based: Scottish Cervical Screening Call & Recall System	Women aged 20–21 years participating in routine cervical screening in Scotland	Pre-: 2009–10; Post-: 2011–12	HPV+ Multimetrix HPV assay (Diamex, Heidelberg, Germany; 18 types)	HPV prevalence over time	60%
Markowitz, 2013[307]	4-valent	USA	Population based: NHANES study participants	Nationally representative sample of US girls and women aged 14–59 years	Pre-: 2003–06; Post-: 2007–10	HPV+ Roche Linear Array (Roche Diagnostics; 37 types)	Relative risk of HPV prevalence (crude)	34%

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case (HPV testing methodology)	Outcome used in publication	Vaccine coverage*
Markowitz, 2016	4-valent	USA	Population based: NHANES study participants	Nationally representative sample of US girls and women aged 14–59 years	Pre-: 2003–2006; Post-: 2009-2012	HPV+ Roche Linear Array (Roche Diagnostics; 37 types)	Relative Risk of HPV prevalence (crude)	34%
Mesher, 2013[306]	2-valent	England	Clinic based	Girls and women aged 16–24 years undergoing chlamydia screening in community sexual health services, general practice, youth clinics in 7 regions in England	Pre-: 2008; Post-: 2010–2012	2008: Hybrid Capture 2 and Roche Linear Array. 2010-2012: HPV+ In-house multiplex PCR and Luminex-based genotyping test (13 HPV types)	Odds Ratio of HPV prevalence (adjusted)	58%
Mesher, 2016[303]	2-valent	England	Clinic based	Girls and women aged 16–24 years undergoing chlamydia screening in community sexual health services, general practice, youth clinics in 7 regions in England	Pre-: 2008; Post-: 2010–2011 and 2012–2013	2008: Hybrid Capture 2 and Roche Linear Array. 2010-2013: HPV+ In-house multiplex PCR and Luminex-based genotyping test (HPV DNA to detect 13 HR types [HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68], five possible HR types [HPV26, 53, 70, 73 and 82] and two LR types [HPV6 and 11]	Odds Ratio of HPV prevalence (adjusted)	73%

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case (HPV testing methodology)	Outcome used in publication	Vaccine coverage*
Soderlund-Strand, 2014[311]	4-valent	Sweden	Clinic based	All samples collected for chlamydia screening in a defined region of Sweden (the Skane region in Southern Sweden with 1.27 million inhabitants).	Pre-: 2008; Post-: 2013	PCR with genotyping by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry. Secondary HPV DNA analysis on the Luminex platform	HPV prevalence over time	53 to 78% Overall coverage 7.5% (all women); vaccine coverage age 13 – 19 years ranged from 53.2 to 77.7% (average = 66%)
Sonnenberg, 2013[304]	2-valent	UK	Population based: NATSAL study participants	Nationally representative sample of men and women aged 16–74 years in Britain	Pre-: Natsal-1 (1990–1991) and Natsal-2 (1999–2001); Post-: between September 2010 and August 2012 (NATSAL 3).	HPV+ In-house Luminex-based genotyping assay (18 types) in urine samples	Odds Ratio of HPV prevalence (age-adjusted)	62%
Tabrizi, 2012[297]	4-valent	Australia	Clinic based	Women aged 18–24 years attending one of six family planning clinics in Sydney, Melbourne, and Perth (Australia)	Pre-: 2005–2007; Post-: 2010–2011	HPV+ Roche Linear Array (Roche Molecular Systems; 13 types)	Odds Ratio of HPV prevalence (adjusted)	88%

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case (HPV testing methodology)	Outcome used in publication	Vaccine coverage *
Tabrizi, 2014[313]	4-valent	Australia	Clinic based	Women aged 18–24 years attending one of six family planning clinics in Sydney, Melbourne, and Perth (Australia)	Pre-: October 2005 to July 2007; Post-: August 2010 to November 2012	AMPLICOR HPV test kit (Roche Molecular Systems Pleasanton, CA, USA) for HPV DNA positivity. Samples positive for HPV using any of these methods were genotyped using the LINEAR ARRAY HPV genotyping test (Roche).	Odds Ratio of HPV prevalence (adjusted)	74%
Tanton, 2017[305]	2-valent	UK	Population based: NATSAL study participants	Nationally representative sample of men and women aged 16–74 years in Britain	Pre-: NATSAL-1 (1990–1991) and NATSAL-2 (1999–2001); Post-: September 2010 to August 2012 (NATSAL 3)	Samples collected using FirstBurst urine collection device and tested for HPV using an in-house Luminex-based genotyping assay Note: Different to Sonnenberg 2013 as extended the analysis of NATSAL-3 data to include estimates of a wide range of HPV types, including HPV-6/11, HPV-31/33/45 and HPV-52/58.	Age-adjusted prevalence ratios comparing NATSAL-3 and-2	62%
Wilson, 2014[312]	4-valent	USA	Clinic-based	Data from patient test results archived in an electronic data warehouse; women who undergo regular gynecological screenings	Pre-: 2004-2006; Post-: 2011-2013. Vaccine introduced by 2007	Liquid-based endocervical samples. Acceptable sample types include Digene® Cervical Brushes, ThinPrep® PreservCyt® media, and SurePath™ preservative. Aggregated results for 13 high-risk HPV genotypes tested (genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68)	Raw positivity rates: high-risk hpv from pattern 1 (removal of ordering bias)	N/R

*Vaccine coverage refers to female coverage of at lease one dose. Individual-level vaccine coverage of the target population in the included study was extracted where possible. In studies where vaccine coverage was not reported, published national/regional vaccine uptake rates were obtained.
Key: DNA – deoxyribonucleic acid; HPV – human papillomavirus; NATSAL - National Survey of Sexual Attitudes and Lifestyles; NR – not reported; PCR – polymerase chain reaction.

Table 5.3: Study characteristics - anogenital wart diagnosis

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case	Outcome used in publication	Vaccine coverage*
Ali 2013[314]	4-valent	Australia	Clinic based	STI clinic attendees. New clients of eight sexual health centres across Australia aged 12 years and older	Pre-: 2005–2007; Post-: 2008–2012	Clinical diagnosis	Annual proportion of new clients with diagnosed AGW	Range from 52% (aged 20 to 26 years) to 83% (12 and 13 year olds)
Baandrup 2013[315]	4-valent	Denmark	Population based: Statistics Denmark, National Patient Registry	Entire population of Denmark aged 10 years and older	Pre-: 2007–2009; Post-: 2010–2011	ICD-10 code A63.0	Annual incidence rate of diagnosed AGW in the population	87% to 91% among 13-to 17-year olds up to 2013
Bauer, 2012[316]	4-valent	USA	Health provider/ insurance based: clinical encounters claims data of a health programme	Clients of the California Family Planning, Access, Care and Treatment (PACT) programme aged 10 years and older (87% are female clients)	Pre-: 2007; Post-: 2008–2010	ICD-9 codes 07 840, 07 811 OR prescription of imiquimod or podophyllotoxin	Annual proportion of PACT clients diagnosed with AGW	Unreported
Bollerup, 2016[317]	4-valent	Denmark	Danish National Patient Register and redemptions of prescription for podophyllo-toxin in the Danish National Prescription Registry	Entire Danish population	Pre-: 2008; Post-: 2013	ICD diagnostic code A63.0; for Podophyllin prescriptions: Anatomical Therapeutic Chemical code D06BB04	Annual incidence rate in the population	87% to 91% among 13- to 17-year olds up to 2013

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case	Outcome used in publication	Vaccine coverage *
Chow 2014[318]	4-valent	Australia	Clinic-based	New patients attending Melbourne Sexual Health Centre from July 2004 to June 2014	Pre-: 2004-2005; Post-: 2013/2014	Clinical diagnosis	Annual proportion of new clients with diagnosed AGW and adjusted ORs for diagnosis of AGW in postvaccination period	83% (aged 12 to 17 years)
Dominiak 2015[319]	4-valent	Belgium	Database (reimbursement database)	All women and men aged 16–59 years in Belgium	Pre-: 2006; Transitional: 2007–2008; Post-: 2009–2013.	First prescription of imiquimod with a level of reimbursement specific for AGWs	Incidence Rate Ratios and 95% CIs by age category	48%
Flagg 2013[320]	4-valent	USA	Health provider/ insurance-based	Enrollees in approximately 100 private health insurance plans across US	Pre-: 2004–2006; Post-: 2007–2010	ICD-9 codes associated with AGW OR ≥ 1 prescription for AGW treatment and therapeutic procedure or diagnosis of benign anogenital neoplasm	Annual proportion of insured individuals with diagnosed AGW	Unreported
Guerra 2016[321]	4-valent	Canada	Population-based: health administrative data	Entire population Ontario (13.3m) aged over 15	Pre-: 2004-2007; Post-: 2008-2013	Diagnostic and procedural codes from physician office visits that were combined into algorithms to generate a probable outcome definition for AGWs	Average annual incidence of diagnosed AGW (by physician office visits) and RR of anogenital warts (crude)	51-80%

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case	Outcome used in publication	Vaccine coverage *
Harrison 2014[322]	4-valent	Australia	Primary care	Nationally representative cross-sectional database of Australian general practice activity	Pre-: July 2002–June 2006; Post-: July 2008–June 2012	Genital warts were defined as ICPC 2 codes Y76 for males and X91 for females	Reduction in genital warts per 100,000 encounters	83% (aged 12 to 17 years)
Howell-Jones 2013[323]	2-valent	England	Genitourinary medicine (GUM) clinics database	Entire population of England aged 15–24 years	Pre-: 2006–2008; Post-: 2009–2011	Clinical diagnosis	Annual incidence rate of diagnosed anogenital warts in the population	80%
Leval 2012[324]	4-valent	Sweden	Population-based database	Entire Swedish population from Statistics Sweden	Pre-: 2006; Post-: 2007–2010	ICD-10 code A63 OR prescription of Imiquimod or Podophyllotoxin	Annual incidence rate of diagnosed AGW in the population	25-30% (one-dose, teenage girls)
Liu 2014[325]	4-valent	Australia	Survey	Australia-wide survey of women aged18–39 years (random-digit dialling mobile phone numbers in 2011 and compared to the same in 2001)	Pre-: 2001; Post-: 2011	Self-reported AGW diagnosis	Odds Ratio's from logistic regression adjusting for age, and other factors.	83% (aged 12 to 17 years)

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case	Outcome used in publication	Vaccine coverage*
Lurie 2017[326]	4-valent	Israel	Register-based population cohort study from publicly funded health-care provider	Entire Maccabi Healthcare Services population (one of four publicly funded insurance providers in Israel).	Pre-: 2006-2008, early post-: 2009-2012, late post-: 2013-2015	Diagnosis of AGW	Annual incidence rate of diagnosed AGW in the population	Unknown
Mikolajczyk 2013[327]	4-valent	Germany	Health provider/insurance based: German Pharmaco-epidemiological Research Database	Enrollees in one large health insurance company across Germany aged 10–79 years	Pre-: 2005–2007; Post-: 2008	ICD-10 code A63.0	Annual incidence rate of diagnosed AGW among insured individuals	35% of 17 year olds
Sando 2013[328]	4-valent	Denmark	Population based: Statistics Denmark, National Patient Registry, and Medical Products Statistics Registry	Entire population of Denmark aged 15–34 years	Pre-: 2007–2009; Post-: 2010–2011	ICD-10 code A63.0, OR prescription of podophyllotoxin	*see Baandrup, 2013	87% to 91% among 13-to 17-year olds up to 2013
Smith 2015[329]	4-valent	Australia	National population-based hospital database	National Hospital Morbidity Database (NHMD), a comprehensive data set of admissions to virtually all public and private hospitals in Australia	Pre-: 2006–2007; Post-: 2010–2011	ICD-10-AM code A63.0 (AGW)	EAPC AGW diagnosis (Poisson and negative binomial regression); crude frequency of AGW rate and rate per 100,000	83% (aged 12 to 17 years)

*The study by Sando et al. (2013) included the same data as those reported by Baandrup et al. (2013), so only the results from the Baandrup report are included in this review.
Key: AGW – anogenital warts; OR – odds ratio; STI – sexually transmitted infection.

Table 5.4: Study characteristics - Cervical intraepithelial Neoplasia (CIN 2+):

Study	Vaccine used	Country	Setting	Subjects included in the study	Pre- and post-vaccination periods	Definition of case	Outcome used in publication	Vaccine coverage*
Brotherton, 2011 (331)	4-valent	Australia	Health provider/ insurance based: cervical cancer screening programme registry	Girls and women younger than 69 years participating in the National Cervical Screening Program	Pre-: 2005–07; Post-: 2008–11	Histopathologically confirmed CIN 2+	Annual incidence of high-grade cervical lesions in screened girls and women; relative risk of high-grade lesion incidence (crude)	71 to 79%**
Ogilvie, 2015(330)	4-valent	Canada	Cervical Cancer Screening Programme database	Young women 15–22 years old	Linked to age of woman.¥	Histopathology abnormalities of CIN 2+	Incidence rate ratio (IRR)	58 to 62%
Baldur-Felskov, 2014(332)	4-valent	Denmark	Nationwide Pathology Data Bank	Girls and women over age 12	Pre-: 2000-2010; Post-: 2010-2013	Histopathologically confirmed CIN 2+	Estimated annual percentage change in CIN 2+	61 to 90%
Baldur-Felskov, 2015(333)	4-valent	Denmark	Nationwide Pathology Data Bank and Cancer Registry	Girls and women over age 12	Pre-: 1997-2009; Post-: 2010-2012	Histopathologically confirmed CIN2+ and cervical cancer	Estimated annual percentage change in CIN2+ and invasive cervical cancer	61 to 90%

**Vaccine coverage estimates from the National HPV Vaccination Program Register for the school programme in Victoria show a three-dose coverage of 79% in first-year high-school students and 71% in final-year high-school students.
¥ For young women 15 years old, unvaccinated calendar years were 2004–2009 and vaccinated calendar years were 2010–2012. Similarly, for young women 16 years old, unvaccinated calendar years were 2004–2010 and vaccinated years were 2011–2012. For 17 year old women, unvaccinated years were 2004–2011 and 2012 was the vaccinated year.

5.3.1 Outcome 1: HPV infection

Eighteen studies investigated the change in HPV infection following the introduction of a HPV vaccination programme.[296-313] All studies that investigated the change in HPV infection over time compared the prevalence of HPV infection (along with their respective 95% confidence intervals) between the pre-vaccination and post-vaccination eras. With the exception of three studies that included post-vaccination prevalence era data from 2014 and 2015,[298, 299, 302] all studies reported on post-vaccination eras that ranged from 2007 to 2013. No studies investigated the effect of the 9-valent vaccine.

Across studies, terms such as 'prevalence ratios', 'odds ratios' or 'risk ratios' were used to describe this change in prevalence following the introduction of a HPV vaccination programme. This is obtained by dividing the post-vaccination prevalence by the pre-vaccination prevalence. As mentioned previously, for simplicity, these will be referred to as relative risks (RRs) in this report. For example, if the prevalence of HPV infection halved between pre-vaccination and post-vaccination periods, this would be denoted by a RR of 0.5.

Where reported, adjusted RRs were extracted. The prevalence was often adjusted in studies to control for differences between the two periods, such as changes in sexual behaviour patterns (confounders). All studies investigated HPV infection patterns in women apart from the 2017 study by Chow et al., which investigated HPV prevalence in heterosexual males (under 25 years of age) attending sexually transmitted infection (STI) services in Australia.

In studies that reported the prevalence of HPV infection over time without calculating a ratio (post-vaccination divided by pre-vaccination prevalence), the RR was calculated using RevMan software. The resulting RRs and 95% confidence intervals compare the events (HPV infection) in the exposed (post-vaccination) group with the unexposed (pre-vaccination) group.

Subgroups were chosen *a priori* based upon age of participants and HPV type (as was done by Drolet et al.[295]). Firstly, studies were grouped into 'youngest' (less than age 20) and 'older' (aged 20 to 24) age groups. These age categories were selected because typically only those under 20 years of age were expected to have received the vaccine, and thus comprise our target age group. Older age groups are expected to have lower and varying levels of vaccine coverage, though they may have benefited from herd effects. However, due to varying reporting in the primary studies, these age categories were not precise and the age cut-off chosen between younger and older overlapped in some studies.

Secondly, studies were grouped by HPV type investigated: HPV types included in all vaccines (HPV 16 and 18) and the additional oncogenic types included in the 9-

valent vaccine (HPV 31, 33, 45, 52 and 58). Of note, none of the studies identified included the 9-valent vaccine as part of their immunisation programme; the 9-valent vaccine was first licensed by the European Medicines Agency (EMA) in 2015. The prevalence estimates indicate aggregate results, that is, for HPV 16 and 18 they indicate detection of HPV 16 or HPV 18 or both, and for HPV 31, 33, 45, 52 and 58, the detection of one of more of these five HPV types. Reductions in the prevalence of these five HPV types may indicate cross-protection from the 2-valent or 4-valent vaccine, while increases in prevalence could indicate type-replacement. No study examined the prevalence of HPV 6 and 11 infection. These types, which are associated for over 90% of anogenital warts, are included in the 4-valent and 9-valent vaccines.

Of note, the results of the 2014 study by Wilson et al. is not considered here as they only reported on the change in prevalence of 13 HPV types in aggregate form (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), so it was not possible to isolate HPV 16 or 18 or HPV 31, 33, 45, 52 and 58 specific outcomes.

HPV 16 and 18 in young men and women

Table 5.5 lists the RRs (adjusted for confounders where available) for HPV 16 and 18 infection comparing the pre-vaccination and post-vaccination periods for the youngest age group. A statistically significant reduction in HPV infection was documented in all but one study with point estimates ranging from 0.04 to 0.5, indicating a reduction in the prevalence of HPV 16 and 18 infection of between 50% to 96%. The strongest reduction (RR: 0.04 [95% CI 0.01-0.15]) was observed in a 2012 Australian study by Tabrizi et al. which compared HPV 16 and 18 prevalence in women aged less than 20 years for the period 2005 to 2007 with 2010 to 2011.[(297)] Vaccine coverage among participants was 88%.

A non-significant reduction (RR: 0.11 [0.01–2.09]) was observed in the 2017 Australian study by Chow et al. which compared HPV 16 and 18 prevalence in men aged less than 21 years for the period 2004 to 2005 with 2014 to 2015.[(299)] Vaccine coverage in women was 84%. The Australian HPV immunisation programme which commenced for females in 2007 was only extended to include 12 year old boys in 2013. Uptake of the vaccine among those attending the sexual health clinic is therefore anticipated to have been low and limited to individuals paying for HPV vaccination privately.

Table 5.5. Relative risk of prevalent HPV 16 and 18 infection in the youngest age group

Study (year)	Age group (yrs)	Study-specific vaccine coverage	RR (95% CI)*
Cameron. (2016)	1988 vs 1993 birth	72% (in 2013)	0.43 (0.26–0.67) (adjusted)
Chow (2015)	< 21	73%‡	0.13 (0.02–0.94) (crude, recalculated)
Chow (2017)**	< 21	84% (female coverage)	0.11 (0.01–2.09) (crude, recalculated)
Cummings. (2012)	< 20	89%	0.32 (0.12–0.89) (crude)
Kahn (2012)	< 20	77%	0.38 (0.25–0.58) (adjusted)
Kahn (2016)	13 – 26	71.3%	0.19 (0.12–0.31) (adjusted)
Markowitz (2013)	< 20	34%	0.50 (0.34–0.74) (crude)
Markowitz (2016)	< 20	51.4% (≥ 1 dose); 34.6% (all 3 doses)	0.37 (0.20–0.67) (adjusted)
Mesher (2013)	< 20	58%	0.47 (0.35–0.63) (adjusted)
Mesher (2016)	16 – 18	67.2%	0.3 (0.2–0.4) (adjusted)
Sonnenberg (2013)	< 20	62%	0.39 (0.19–0.79) (crude)
Tabrizi (2012)	< 20	88%	0.04 (0.01–0.15) (adjusted)
Tanton (2017)	18 – 20	58% (≥ 1 dose); 52.0% (all 3 doses)	0.48 (0.24–0.93) (adjusted)

Note: In all instances that the prevalence was recalculated using primary study data, Review Manager was used to calculate prevalence ratios.
*This RR is in fact the prevalence ratio (and 95% CI) comparing post- and pre-vaccination periods.
** Prevalence in males.
‡ Incomplete data, Australian-born only.

HPV 16 and 18 in older men and women

Table 5.6 lists the adjusted relative risk (RR) of prevalent HPV 16 and 18 infection comparing the pre-vaccination and post-vaccination periods for the next oldest age group (typical range 18 to 25). Point estimates ranged from 0.12 to 1.4 with 10 of the 13 studies reporting a reduction in the prevalence of HPV 16 and 18 infection, seven of which were statistically significant.

Only one of the 13 studies reported changes in the prevalence of HPV 16 and 18 in men. This Australian study by Chow et al. (2017) reported a non-significant reduction in prevalence (RR: 0.15 [0.02-1.24]) given a vaccine coverage of 84% in their female counterparts.[299] As noted previously, vaccine coverage in males was likely extremely low as it was not included as part of the national immunisation programme.

The reduction in HPV infection appeared to depend on the vaccine coverage in the post-vaccination period study group. When vaccine coverage exceeded 35%, a significant reduction in prevalence was seen in all studies (RR range: 0.12 [0.03–0.48] to 0.67 [0.61–0.74]) with greater reductions observed when coverage exceeded 80% (RR range: 0.12 [0.03–0.48] to 0.25 [0.17–0.36]). The latter represents a reduction of between 75% and 88% in the prevalence of HPV 16 and 18 in older women.

HPV 31, 33, 45, 52 and 58 in young men and women

While not included in the 2-valent or 4-valent vaccines, a change in prevalence of HPV types 31, 33, 45, 52 and 58 could indicate cross-protection or type replacement following the introduction of population-level immunisation. These are the five additional types included in the 9-valent vaccine. As noted earlier, no studies were retrieved that investigated the 9-valent vaccine.

Table 5.7 lists the RRs for HPV 31, 33, 45, 52 and 58 infection (in aggregate form) comparing the pre-vaccination and post-vaccination periods for the youngest age group (adjusted RRs, where reported). Vaccine coverage (2-valent or 4-valent vaccine) ranged from 34% to 88%. No difference in the prevalence of these HPV types was observed.

Table 5.6 Relative risk of HPV 16 and 18 infection in older age groups

Study	Age group (years)	Study-specific vaccine coverage	RR (95% CI)
Chow (2015)	≤ 25	73% (incomplete data, Australian born only)	**0.12 (0.03–0.48)** (crude, recalculated)
Chow (2017) *males	≤ 25	84% (female coverage)	0.15 (0.02–1.24) (crude, recalculated)
Dunne (2015)	20 – 24	31.9% (≥1 dose, 20.7% (all 3 doses)	**0.6 (0.5–0.7)** (crude)
Kahn (2012)	20 – 24	31%	0.70 (0.42–1.16) (adjusted)
Kavanagh (2014) (bivalent vaccine)	20 – 24	60%	**0.67 (0.61–0.74)** (crude)
Markowitz (2013)	20 – 24	18%	1.07 (0.74–1.56) (crude)
Markowitz (2016)	20 – 24	32.6% (≥1 dose), 18.1% (all 3 doses	**0.66 (0.45–0.97)** (adjusted)
Mesher (2013)	20 – 24	16%	1.09 (0.75–1.59) (adjusted)
Mesher (2016)	22 – 24	0.6%	1.1 (0.8–1.7) (adjusted)
Soderlund-Strand (2014)	All ages; most aged 18 – 23	35% coverage in ages 18 - 24	**0.49 (0.34–0.69)** (crude, recalculated)
Sonnenberg (2013)	20 – 24	16%	0.81 (0.48–1.38) (crude)
Tabrizi (2012)	20 – 24	83%	**0.25 (0.17–0.36)** (adjusted)
Tabrizi (2014)	18 – 24	86% (≥1 dose)	**0.22 (0.16–0.31)** (adjusted)

Note: In all instances that the prevalence was recalculated using primary study data, Review Manager was used to calculate prevalence ratios.
All statistically significant findings in **bold**.

Table 5.7 Relative risk of HPV 31, 33, 45, 52 and 58 infection in youngest age group

Study	Age group	Study-specific vaccine coverage	RR (95% CI)
Cameron (2016)	Comparing 1988 vs 1993 birth year	72% (3 doses, in 2013)	0.72 (0.42–1.20) (adjusted)*
Chow (2015)	< 21	73%*	0.77 (0.24–2.43) (crude, recalculated)
Chow (2017) **males	< 21	84% (female coverage)	1.62 (0.07–37.10) (crude, recalculated)
Cummings (2012)	< 20	89%	0.75 (0.37–1.52) (crude)
Kahn (2012)	< 20	77%	0.98 (0.72–1.34) (adjusted)
Markowitz (2013)	< 20	34%	0.73 (0.52–1.01) (crude)
Markowitz (2016)	< 20	Aged 14 to 19: 51.4% (≥1 dose); 34.6% all 3 doses	0.82 (0.53–1.28) (adjusted)
Mesher (2013)	< 20	58%	1.11 (0.87–1.40) (adjusted)
Mesher (2016)	16 – 18	67.2%	1.2 (0.9–1.7) (adjusted)
Sonnenberg (2013)	< 20	62%	1.30 (0.63–2.68) (crude)
Tanton (2017)	18 – 20	58% (≥1 dose); 52.0% all 3 doses	1.19 (0.69–2.05) (adjusted)
Tabrizi (2012)	< 20	88%	0.67 (0.28–1.59) (adjusted)

Note: In all instances that the prevalence was recalculated using primary study data, Review Manager was used to calculate prevalence ratios.
*The unadjusted odds ratio was significant, RR 0.41 (95% CI: 0.26–0.63)
**Incomplete data, Australian born only.

The 2016 study by Cameron et al.[300] was the only study to investigate the effects of the 2-valent vaccine. The adjusted odds ratio for the aggregate five HPV cross-protected types (31, 33, 45, 52 and 58), as reported in Table 5.7, did not achieve statistical significance in this study. The crude odds ratio, however, was significant (RR 0.41 [95% CI: 0.26–0.63]). As for the changes in prevalence of individual HPV types, significant decreases in HPV types 31, 33, and 45 (suggesting cross-protection), and a non-significant increase in HPV 51 was observed. Existing evidence from clinical trials suggests that cross-protective vaccine efficacy estimates against HPV types 31, 33, and 45 infection are higher for the 2-valent vaccine than for the 4-valent vaccine.[64]

HPV 31, 33, 45, 52 and 58 in older men and women

Table 5.8 lists the RRs for HPV 31, 33, 45, 52 and 58 infection comparing the pre-vaccination and post-vaccination periods for the older age groups. As with the younger cohort, no difference in prevalence of the five HPV types not included in the

2-valent or 4-valent HPV vaccines was found.

Table 5.8. Relative risk of HPV 31, 33, 45, 52 and 58 infection in older age groups (20+)

Study (year)	Age group (years)	Study-specific vaccine coverage	RR (95% CI)
Chow (2015)	≤25	73% (incomplete data, Australian born only)	1.23 (0.52–2.88) (crude, recalculated)
Chow (2017) *males	≤25	84% (female coverage)	0.74 (0.16–3.54) (crude, recalculated)
Dunne (2015)	20 – 24	31.9% at least one dose; 20.7% all 3 doses	1.1 (1.0–1.3) (crude)
Kahn (2012)	20 – 24	31%	1.42 (0.90–2.23) (adjusted)
Mesher (2016)	22 – 24	0.6%	1.3 (0.9 to 2.0) (adjusted)
Kavanagh (2014)	20 – 24	60%	0.91 (0.81–1.03) (crude)
Markowitz (2013)	20 – 24	18%	0.83 (0.60–1.13) (crude)
Markowitz (2016)	20 – 24	32.6% at least one dose; 18.1% all 3 doses	0.85 (0.51–1.41) (adjusted)
Mesher (2013)	20 – 24	16%	1.11 (0.81–1.51) (adjusted)
Sonnenberg (2013)	20 – 24	16%	1.11 (0.72–1.70) (crude)
Tabrizi (2012)	20 – 24	83%	0.95 (0.68–1.33) (adjusted)

Note: In all instances that the prevalence was recalculated using primary study data, Review Manager was used to calculate prevalence ratios.

5.3.2 Outcome 2: Anogenital warts

Sixteen studies investigated the effect of HPV vaccination on the incidence of anogential warts (AGWs),[314-329] 15 of which investigated the effect of the 4-valent vaccine. One UK-based study investigated evidence of cross-protection from the 2-valent vaccine. With the exception of one Australian-based study by Liu et al., which included females only, all studies investigated AGW incidence in both males and females. Any observed reduction in AGW in males was due to herd immunity, with the exception of the study by Lurie et al. (2017) where gender-neutral immunisation in Israel had been implemented in time to observe a direct effect on males. Similarly, any observed reduction in older age groups is likely a result of herd effects.

Two of the studies involved the entire Danish population over the same time period,[315, 328] and for this reason only results from the study by Baandrup et al. are presented here.

Table 5.9 summarises the key findings (incidence rate ratios comparing the pre-vaccination and post-vaccination period). All studies demonstrated a statistically significant reduction in AGW in young females, with the exception of a 2012 Swedish study where vaccine coverage was under 30%. The most striking reduction was observed in the country with the highest vaccine coverage: a 2016 Danish study by Bollerup et al. observed a RR of 0.08 (95% CI 0.07–0.10) in females aged 15 to 19 during a five-year period from 2008 to 2013 when vaccine coverage for this cohort was between 87% and 91%. A significant result was also observed in the older age group and in males. This would indicate a 92% reduction of AGW incidence in girls aged 15 to 19 in Denmark.

Across studies, no consistent trend was observed in older women (aged 20+) or in males. The 2017 Israeli study by Lurie et al. observed a statistically significant reduction in AGW in males (and females) following introduction of gender-neutral vaccination, with a relative risk of 0.59 (0.45–0.78) in boys aged less than 18 years.

Table 5.9: Results of studies investigating relative risk of incident AGWs

Study (year)	Country	Vaccine coverage in females*	Sex, (Age group [years])	RR (95% CI)**
Ali (2013)	Australia	52% (aged 20 to 26 years) to 83% (12 and 13 year olds)	Females (15 to 19)	**0.19 (0.15–0.24)**
			Females (20 to 39)	**0.51 (0.46–0.56)**
			Males (15 to 19)	**0.48 (0.35–0.66)**
			Males (20 to 39)	**0.73 (0.69–0.77)**
Baandrup (2013)	Denmark	87% to 91% among 13 to 17-year olds up to 2013	Females (15 to 19)	**0.54 (0.49–0.60)**
			Females (20 to 39)	**0.79 (0.74–0.83)**
			Males (15 to 19)	0.80 (0.63–1.01)
			Males (20 to 39)	**0.82 (0.77–0.87)**
Bauer (2012)	USA	56% Californian girls aged 13 to 17 years (1 dose)	Females (15 to 19)	**0.77 (0.73–0.80)**
			Females (20 to 39)	1.00 (0.98–1.03)
			Males (15 to 19)	**0.92 (0.85–0.99)**
			Males (20 to 39)	1.03 (1.00–1.05)
Bollerup (2016)	Denmark	87% to 91% among 13 to 17 to year olds up to 2013	Females (15 to 19)	**0.08 (0.07–0.10)**
			Females (20 to 39)	**0.66 (0.63–0.69)**
			Males (15 to 19)	**0.21 (0.18–0.25)**
			Males (20 to 39)	**0.80 (0.77–0.83)**
Chow (2014)	Australia	83% (aged 12 to 17 years)	Females (<21)	**0.27 (0.21–0.35)**
			Females (21 to 32)	**0.42 (0.37–0.49)**
			Males less than 21)	**0.51 (0.36–0.73)**
			Males (21 to 32)	**0.63 (0.57–0.70)**
Dominiak (2015)	Belgium	48%	Females (16 to 22)	**0.28 (0.22–0.35)**
Flagg (2013)	USA	53% of girls aged 13 to 17 years	Females (15 to 19)	**0.87 (0.83–0.90)**
			Females (20 to 39)	1.29 (1.27–1.32)
			Males (15 to 19)	1.34 (1.24–1.44)
			Males (20 to 39)	1.55 (1.51–1.58)
Guerra (2016)	Canada	51 to 80%	See below	
Harrison (2014)	Australia	83% (aged 12 to 17 years)	Females (15 to 27)	**0.39 (0.29, 0.51)**
			Females (28 to 49)	**0.64 (0.48, 0.85)**
			Males (15 to 27)	0.95 (0.72, 1.27)

			Males (28 to 49)	0.85 (0.66, 1.09)
Howell-Jones (2013); bivalent vaccine	UK	80% 3 dose coverage	Females (15 to 19)	**0.96 (0.94–0.97)**
			Females (20 to 39)	1.00 (0.98–1.01)
			Males (15 to 19)	1.03 (1.01–1.05)
			Males (20 to 39)	1.02 (1.00–1.03)
Leval (2012)	Sweden	25% of girls aged 13 to 20 years (min. 1 dose); >30% coverage by ≥1 dose among girls aged 15 to 18 years.	Females (15 to 19)	1.00 (0.95–1.05)
			Females (20 to 39)	0.98 (0.96–1.01)
			Males (15 to 19)	1.15 (1.06–1.25)
			Males (20 to 39)	1.06 (1.03–1.08)
Liu (2014)	Australia	83% (aged 12 to 17 years)	Females (18 to 30)	**0.58 (0.41–0.81)**
			Females (31 to 39)	1.35 (0.98, 1.87)
Lurie (2017)	Israel	Unreported	Females (18 or less)	0.48 (0.38–0.60)
			Females (19 to 34)	0.70 (0.67–0.74)
			Males (18 or less)	0.59 (0.45–0.78)
			Males (19 to 34)	0.91 (0.87–0.95)
Mikolajczyk (2013)	Germany	35% of 17 year olds	Females (15 to 19)	**0.78 (0.69–0.87)**
			Females (20 to 39)	1.10 (1.05–1.15)
			Males (15 to 19)	1.00 (0.82–1.21)
			Males (20 to 39)	1.19 (1.14–1.25)
Sando (2013)	Denmark	See Baandrup et al.; same sample studied.		
Smith (2015)	Australia	83% (aged 12 to 17 years)	Females (12 to 17)	**0.19 (0.13–0.28)**
			Females (18 to 30)	**0.43 (0.39–0.47)**
			Males (12 to 17)	1.57 (0.56–4.41)
			Males (18 to 30)	**0.76 (0.67–0.87)**

*Study-specific vaccine coverage if reported, otherwise published population-based estimates were used.
All significant findings in **bold.

A 2016 Canadian study by Guerra et al. reported on the estimated annual percentage change (from negative binomial models generated to analyse trends across time).[321] A statistically significant reduction in AGWs was only found in females aged 18 to 20 (-6.5%), while a statistically significant increase was noted in males aged 15 to 17 (+12%). The authors report that suboptimal coverage in the first several years of the programme may explain why evidence of herd effects in adolescent males was not found. The results of their model by sex and age category is provided in Appendix 5G.

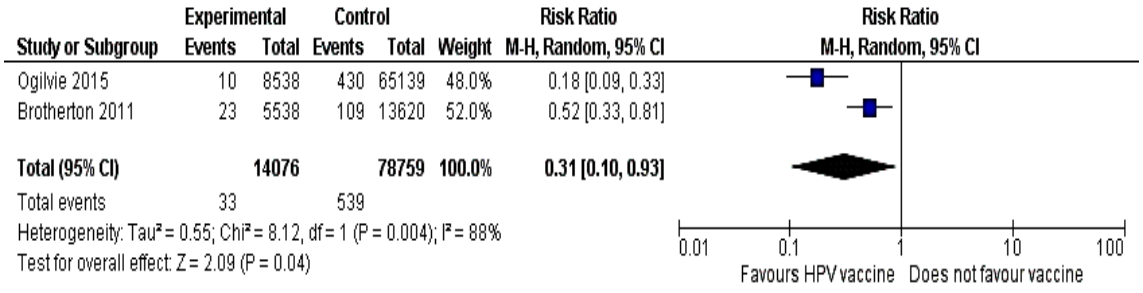
5.3.3 Outcome 3: High-grade cervical lesions

Four studies investigated the effect of HPV vaccination on the frequency (incidence or prevalence) of high-grade cervical lesions (cervical intraepithelial neoplasia [CIN] 2+). Information for two studies were retrieved from cervical screening programmes in Australia and Canada.[330, 331] Data for the remaining two studies were obtained from Denmark's Pathology Data Bank.[332, 333] This data bank contains information on all specimens from all Danish pathology departments, including cervical cytology (organised and opportunistic, normal and abnormal) and cervical biopsies and cones (normal and abnormal). As these two studies reported data from the entire Danish population with the same post-vaccination time period,[332, 333] only results from Baldur-Felskov et al. (2014) are reported here.[332]

Vaccine coverage in the post-vaccination period ranged from 58-62% (Australia)[331] to 72-79% (Canada).[330] All demonstrated a reduction in CIN 2+ in younger age groups; those most likely to have received the HPV vaccine.

Two studies report changes in the frequency of diagnosed CIN2+ between the pre-vaccine and post-vaccine era in girls aged less than 18 years.[330, 331] Figure 5.5 demonstrates the forest plot of these findings; both studies found a statistically significant reduction in CIN 2+, ranging from a RR of 0.18 (95% CI 0.09-0.33)[330] to 0.52 (95% CI 0.33-0.81).[331]

Figure 5.5. Forest plot of changes in CIN2+ (women< 18 years)



Using data from the national Pathology Data Bank, a third study reported on the estimated annual percentage change (EAPC) in CIN 2+ in Denmark from a Poisson regression model.[332] Table 5.11 lists their findings; again the effect is most evident in younger age groups.

Table 5.11. Change in annual incidence of CIN 2+ (Baldur-Felskov, 2014) compared with pre-vaccination era

Age	EAPC%	95% CI	p value
12-17 years	-41.8	-67.9 – 5.7	0.08
18-20 years	-14.8	-21.6 – (-7.5)	<0.01
21-23 years	-2.6	-6.9 – 1.9	0.25
24-30 years	1.3	-1 – 3.6	0.26
31-64 years	-1.8	-5.1 – 1.6	0.3
65+ years	-7.8	-18.7 – 4.6	0.21

* EAPC – estimated annual percentage chsnge

The 2011 study by Brotherton et al., also reported on older age groups; however, no similar temporal decline was noted.

5.4 Discussion

This systematic review of 37 individual studies, conducted in nine high-income countries and representing almost 140 million individual patient records, brings together a substantial volume of evidence regarding the changes that occurred in HPV-related disease following the introduction of population-based HPV immunisation programmes. Published between 2012 and 2017, these studies provide early evidence of the impact of population-based programmes, all of which initially targeted younger girls (typically aged 12 to 13 years). All data relates to programmes based on the 2-valent or 4-valent vaccines, prior to the introduction of the 9-valent vaccine.

Because mostly girls (less than 20 years of age) were vaccinated in the study populations, analyses were stratified *a priori* by age and sex. All studies that investigated changes in the prevalence of HPV 16 and 18 in young women (aged less than 20 years) demonstrated a statistically significant reduction regardless of vaccine coverage, ranging from a prevalence ratio of 0.04 (95% CI: 0.01-0.15)[(297)] to 0.50 (95% CI: 0.34-0.74).[(308)] This represents a reduction in the prevalence of HPV 16 and 18 infection of between 50% and 96%. The impact on HPV 16 and 18 infection appears to be correlated with vaccine coverage. A 50% reduction was observed in a population with 34% vaccine coverage, compared with a 96% reduction in a population with 88% vaccine coverage. Additionally, a statistically significant reduction in HPV 16 and 18 prevalence was observed in all studies involving older women (aged 20 to 24) when vaccine coverage exceeded 35%, indicating herd effects. When coverage exceeded 80%, prevalence ratios ranged from 0.12 (95% CI: 0.03–0.48)[(298)] to 0.25 (95% CI: 0.17–0.36),[(297)] suggesting a reduction in HPV 16 and 18 prevalence of 75% to 88%.

However, evidence of cross-protection or type replacement could not be concluded

from the data. No significant difference in the prevalence of HPV types 31, 33, 45, 52 and 58 (in aggregate form) was observed between pre-vaccination and post-vaccination periods in any study. The 2016 study by Cameron et al.[300] was the only study retrieved that investigated the effects of the 2-valent vaccine. While the adjusted odds ratio for the aggregate five HPV cross-protective types (31, 33, 45, 52 and 58) did not achieve statistical significance, the crude odds ratio was significant (RR 0.41 [95% CI: 0.26-0.63]). As for the changes in prevalence of individual HPV types, significant decreases in HPV types 31, 33, and 45 (suggesting cross-protection), and a non-significant increase in HPV 51 was observed. Existing evidence from clinical trials suggests that cross-protective vaccine efficacy estimates against HPV types 31, 33, and 45 infection are higher for the 2-valent vaccine than for the 4-valent vaccine.[64]

All studies demonstrated a statistically significant reduction in diagnoses of anogenital warts (AGWs) in young females following introduction of HPV vaccination, with the exception of a 2012 Swedish study, where vaccine coverage was less than 30%. The most striking reduction was observed in the country with the highest vaccine coverage: the 2016 Danish study by Bollerup et al. observed a 92% (95% CI: 90-93%) reduction in AGW diagnoses (RR: 0.08 [95% CI: 0.07-0.10]) in women aged 15 to 19 in a population where vaccine coverage was between 87% and 91%.[317] This study also noted statistically significant reductions in AGW in older females (RR: 0.66 [95% CI: 0.63-0.69]) and males (all age groups; RR: 0.82 [95% CI: 0.77-0.87]), with a more substantial reduction noted in males aged 15 to 19 (RR 0.21 [95% CI: 0.18–0.25]). An earlier Danish study demonstrated similar, but less dramatic, results.[315]

Similar reductions in AGWs were noted in other countries with high vaccination uptake such as Australia[314, 318, 322], whereas less pronounced or no effects were noted in countries with lower uptake of the 4-valent vaccine (Sweden, Germany, USA). No evidence of cross-protection from the 2-valent vaccine was observed in a UK-based study on which the the national immunisation programme was based until switching to the 4-valent vaccine in 2012. The most recent study, Lurie et al. (2017),[326] which originates from Israel where a gender-neutral programme was implemented in 2015, demonstrated a significant reduction in AGW in both males and females in all age categories.[326]

All three studies investigating the change in the incidence of high-grade cervical lesions (CIN 2+) following the introduction of a HPV immunisation programme demonstrated a statistically significant reduction in incidence in CIN 2+ in young women. Participants in all studies were women attending cervical screening and all were conducted in countries with high (over 50%) vaccine coverage. Estimates ranged from a RR of 0.18 (95% CI: 0.09-0.33)[330] to 0.52 (95% CI: 0.33-0.81).[331]

The studies identified in this review possess the strengths and limitations inherent in ecological studies. They provide a wealth of information about the effects of HPV vaccination using very large study populations. However, they are especially vulnerable to information bias and confounding. GRADE (Grading of Recommendations, Assessment, Development and Evaluations)[65] appraisal of the evidence was performed (Appendix 6F), whereby evidence for outcomes was deemed 'low' or 'very low' quality (this reflects the confidence in the evidence as opposed to the evidence being low quality). These GRADE findings are unsurprising, with downgrading occurring due to the sources of bias inherent in ecological studies.

The three most important potential sources of bias, however, are likely to underestimate the effect of vaccination in these studies. First, following the licensing of the HPV vaccines and the launch of HPV immunisation programmes, awareness of anogenital warts may have increased. The potential exists for confounding related to possible increases in health-seeking behaviours and information bias from increased diagnosis of anogenital warts over time. Second, most studies had insufficient information to adequately control for sexual activity, which might have changed over time, increasing or decreasing the risk of acquiring HPV infection. Third, information bias might be present as a consequence of masking by HPV type 16 and 18, especially in the pre-vaccine period.[334] As in, with a drop in vaccine-preventable types (HPV 16 and 18), there may be increased detection of previously 'masked' non-vaccine types in the post-vaccination period.[335]

Since CIN 2+ is the precursor of cervical cancer, a reduction in this intermediate outcome has been judged as an acceptable proxy for efficacy against cervical cancer by regulatory bodies worldwide.[43, 44, 336, 337] However, reductions in the incidence of CIN 2+ from screening databases as a proxy for cervical cancer presents difficulties as it might represent changes in screening recommendations and participation. Additionally, if vaccine uptake is higher in women who undergo screening, surveillance studies based on cervical screening registries could overestimate the effect of HPV vaccination.

All studies identifed were from high-income countries. Therefore, while these are likely applicable to Ireland, the results may not be directly applicable to low-income or middle-income countries. It has been demonstrated that substantial differences exist between high and low and middle-income countries in terms of HPV epidemiology,[338] sexual behaviour,[339] and potential co-factors of HPV infection and disease, such as high HIV prevalence.[340]

Finally, the time horizon of all studies was too short to examine waning of vaccine efficacy over time. However, randomised controlled trials (RCTs) have shown no signs of vaccine efficacy waning after nine years of follow up,[66] as indicated in Chapter 4 (Section 4.3.1).

Despite the limitations of time-trend analysis, this systematic review provides strong evidence that HPV vaccination is highly effective outside trial settings and reinforces the need for early vaccination and high vaccination coverage to maximise population-level effectiveness. Although causality cannot be concluded from time-trend ecological studies, the reductions in HPV types 16 and 18, anogenital warts, and high-grade cervical lesions were large and statistically significant in the target age groups for vaccination (girls less than 20 years of age). Additionally, the results showed consistency between countries with similar levels of vaccine coverage. The findings of the updated review are consistent with that of the original 2015 review by Drolet et al.[(295)] — significant reductions in HPV 16 and 18, anogenital warts and CIN 2+ were found in girls under 20 years of age. This original review also found that there was some evidence of cross-protection and herd effects in countries with high vaccine coverage (over 50%). While a meta-analysis of the data was not performed on data in this review (due to substantial heterogeneity), a reduction in HPV 16 and 18 in older women was noted when vaccine coverage exceeded 35%. The original review also noted a reduction in HPV types 31, 33, and 45, but not against types 52 or 58, when vaccine coverage was high. No significant change was noted in the data for the five aggregate non-vaccine types HPV 31, 33, 45, 52 and 58.

In conclusion, there is clear evidence of significant population-level effects of HPV immunisation programmes on HPV-related disease.

Key points

- The Evaluation Team updated a systematic review to investigate the real-world effect of HPV immunisation programmes. Studies were selected that investigated a change in HPV-related infection or disease on a population level, comparing pre-vaccination and post-vaccination periods.
- A total of 37 time-trend observational studies were identified; 18 on HPV infection, 16 on anogenital warts and three on high-grade cervical lesions. All studies were conducted in high-income countries and encompassed almost 140 million individual patient records.
- All immunisation programmes were based on the 2-valent or 4-valent HPV vaccines.
- All studies that investigated the prevalence of HPV 16 and or 18 infection in young women (aged less than 20 years) demonstrated a statistically significant reduction regardless of vaccine coverage, with prevalence ratios ranging from 0.04 (95% CI 0.01–0.15) to 0.50 (95% CI 0.34–0.74). This represents a reduction in the prevelance of HPV 16 and 18 infection of between 50% and 96% following the introduction of a HPV immunisation programme.
- A statistically significant reduction in HPV 16 and 18 was also demonstrated in older females (aged 20 to 24 years) when vaccine coverage was above 35%, indicating herd effects. When coverage exceeded 80%, prevalence ratios ranged from 0.12 (95% CI 0.03–0.48) to 0.25 (95% CI 0.17–0.36), that is a reduction in prevalence of HPV 16 and 18 infection of between 75% and 88%.
- Evidence of cross-protection could not be concluded from the data, as no reduction in the prevalence of HPV types 31, 33, 45, 52 and 58 (in aggregate form) was observed.
- All studies that investigated a change in anogenital warts demonstrated a statistically significant reduction in anogenital wart diagnoses in young females, with the exception of one study where vaccine coverage was under 30%.
- Although the majority of studies found that vaccinating younger women was associated with reduced anogenital wart diagnoses in males and older females, there was inconsistent evidence of herd effects.

- All three studies investigating the change in the incidence of high-grade cervical lesions following the introduction of a HPV immunisation programme demonstrated a statistically significant reduction in incidence in young women. Estimates ranged from a risk ratio of 0.18 (95% CI 0.09-0.33) to 0.52 (95% CI 0.33-0.81). This represents a reduction of between 48% and 82%.
- All studies demonstrated the strengths and limitations inherent in ecological studies. While they provided a substantial volume of population-level information, they were especially vulnerable to information bias and confounding. While causality cannot be concluded through time-trend analysis, the findings support the high efficacy reported in randomised controlled trials (Chapter 4).

6 Safety

6.1 Introduction

As with all medicines and vaccines, the safety of the human papillomavirus (HPV) vaccine was evaluated in large clinical trials prior to being licensed, and is monitored in post-marketing surveillance systems worldwide. In Ireland, the Health Products Regulatory Authority (HPRA) is responsible for monitoring adverse event reporting related to medicines and vaccines. Since its introduction, reported adverse events related to the HPV vaccine have been the subject of several high-profile case reports and considerable media interest.

Case reports occurring following vaccination imply a temporal relationship. However, it cannot be assumed that the vaccine is the cause, and epidemiological evidence of causality on a population level, with supporting biological plausibility, should be sought prior to attributing an adverse event to the HPV vaccine.[(341)]

As outlined in Section 2.7.1 of Chapter 2, the uptake of the HPV vaccine in Ireland's national immunisation programme declined to 51% in the 2016 to 2017 academic year. This decline has been attributed to concerns about HPV vaccine safety following high-profile negative publicity. Declines in vaccine uptake have also occurred countries such as Denmark and Japan. While uptake in Ireland has since increased to 62% in 2017 to 2018, reduced public confidence continues to be a barrier to high uptake in many jurisdictions leading to reduced protection against HPV-related disease.

This chapter provides a comprehensive assessment of the evidence on HPV vaccine safety. Evidence on HPV vaccine safety arising from a systematic review of the published literature is detailed in Section 6.2. Adverse event reporting in Ireland (HPRA data) is discussed in Section 6.3, along with a review of the evidence from other independent analyses, surveillance studies and expert narrative reviews in Section 6.4.

6.2 Systematic review of systematic reviews

6.2.1 Rationale and methodology

A scoping review of the literature was carried out in preparation for this project and a large body of evidence regarding the safety of the HPV vaccine was identified. This included multiple reviews and systematic reviews of varying quality and scope that evaluated a range of safety concerns related to the HPV vaccine. Based on the volume of literature available and project timelines, a 'systematic review of systematic reviews' was considered to be the most efficient method to assess the safety of the HPV vaccine.

'Systematic reviews of systematic reviews'(alternatively known as 'overviews of reviews', 'umbrella reviews', 'meta-reviews' or 'reviews of reviews') efficiently gather a large body of the best available evidence in a single source to provide broad, cumulative statements that summarise the current evidence related to an intervention.[342, 343] Systematic reviews of systematic reviews allow the findings of separate reviews to be compared and contrasted, thereby providing clinical decision-makers with the evidence they need. A systematic review of systematic reviews is limited to a summary of systematic reviews, that is, reviews that are prepared using a systematic approach, and is itself done according to the principles of systematic reviewing.

Published methodological guidance on the conduct of systematic reviews of systematic reviews include the 2011 paper by Smith et al.[342] and Chapter 22 of the Cochrane Handbook.[344] These resources were used in the design, data extraction, data analysis and reporting of this review.

6.2.2 Search strategy

A *de novo* search for systematic reviews evaluating the safety of HPV vaccines was conducted in PubMed, Embase and the Cochrane Library (Database of Abstracts of Reviews of Effects [DARE], Cochrane Database of Systematic Reviews [CDSR] and Health Technology Assessment Database [HTA]). No language restrictions were applied. Systematic reviews that included any study design (experimental or observational studies) were included. A search of reference lists of included systematic reviews was also performed.

Search terms that relate to safety were combined with terms that relate to the HPV vaccine. Search terms related to safety were guided by published literature.[345] Full details of the search strings used and the retrieved results are provided in Appendices 6A and 6B.

6.2.3 Selection of studies

The population, intervention, comparator, outcomes and study design (PICOS) criteria used for study selection are shown in Table 6.1.

Table 6.1 PICOS criteria for study eligibility

Population	Any population or individual receiving HPV vaccine
Intervention	Any HPV vaccine (1-, 2-, 4- or 9-valent)
Comparator	Any comparator (placebo, alternate vaccine or dosing schedule) or no comparator

Outcomes	Any safety data (serious adverse events, minor adverse events, mortality, any other safety endpoint)
Study design	Systematic reviews

Inclusion criteria

Studies were only included if they contained the following key characteristics of a systematic review:[346]

- a clearly stated set of objectives with an explicit, reproducible methodology
- a systematic search of at least two databases that attempts to identify all studies that would meet the eligibility criteria
- an assessment of the quality the included studies, for example through the assessment of risk of bias, and
- systematic presentation, and synthesis, of the characteristics and findings of the included studies.

Additionally, the systematic review had to include at least one safety-related outcome (primary or secondary) related to the HPV vaccine.

Results were independently screened by two people to eliminate studies that were clearly irrelevant. Subsequently, the full texts of the remaining studies were assessed against the predefined inclusion criteria for identification of eligible systematic reviews. This was performed independently by two people. Any disagreements were resolved by discussion. A flow diagram of study selection is provided in Appendix 6B. A list of included studies is provided in Appendix 6C. Studies excluded from the review along with justification for their exclusion is provided in Appendix 6D.

6.2.4 Data extraction

The methods for data extraction and quality appraisal of included reviews were decided *a priori*. Data extraction was performed independently by two people with disagreements resolved by discussion. To adequately inform decisions in relation to the quantity and quality of evidence underpinning the findings of this assessment, quality appraisal of the systematic reviews was also undertaken. The approach adopted and the tools used are discussed the following subsections. The quality of the primary studies underpinning the systematic reviews were not directly evaluated. Instead, information was extracted from the systematic reviews on the quality of the primary evidence, where reported.

6.2.5 Quality appraisal

The methodological quality of the included systematic reviews was assessed using the AMSTAR 2 appraisal tool (AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both).[292] Further details of the AMSTAR 2 appraisal tool are provided in Appendix 6E.

It was decided *a priori* that, for the purposes of retrieving estimates to inform parameter values in the economic evaluation (Chapter 8), estimates from high-quality systematic reviews would be favoured over low-quality reviews. Systematic reviews of critically low quality would be deemed inappropriate for this purpose due to diminished confidence in reported estimates.

6.2.6 Quality of evidence assessment

If an included systematic review performed a quality of evidence assessment, this information was also collected during the data extraction process. Tools used included the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system criteria.[344] Further details of GRADE quality of evidence assessment are provided in Appendix 6F.

6.2.7 Results

6.2.7.1 Characteristics of included studies

In total, 10 systematic reviews were identified that met our inclusion criteria. Eight included only randomised controlled trials (RCTs)[347-354] and two included both RCTs and observational studies.[355, 356] The number of included studies in reviews ranged from three to 37 studies. Maximum follow up in any study was 10 years.[347] Only one review investigated the 9-valent vaccine[351] and only three reviews included males[349, 352, 356] in their analyses. The maximum number of trial participants was 74,628.[356] The main characteristics of included studies are given in Table 6.2.

Table 6.2 Characteristics of included studies

Study	Studies (participants)	Population	Intervention	Comparator	Follow up	Outcomes assessed
Adelaide HTA 2017 (Parsons et al.)[356]	26 RCTs and 11 observational studies (6 cohort and 5 self-controlled case series) (N=74,628 in trials; many million person years across observational studies)	Anyone receiving the HPV vaccine. Subgroups: age, sex, vaccine type	2- or 4-valent HPV vaccine	Any comparator vaccine or placebo	One month to 9 years in RCTs	Serious adverse events*, Grade 3-5, including death, and including but not limited to: 1. Guillain-Barré Syndrome 2. Autoimmune disease (including but not limited to multiple sclerosis, acute demyelinating encephalomyelitis, encephalitis, SLE, demyelinating disease) 3. Primary ovarian failure BUT excluding postural orthostatic tachycardia syndrome (POTS) and chronic regional pain syndrome (CRPS)
Arbyn et al. 2018[347]	26 RCTs of which 23 studies reported safety outcomes (N=73,428)	Females	1-, 2- or 4-valent HPV vaccine	Placebo (no active product or only the adjuvant of the HPV vaccine) or another non-HPV vaccine**	Vaccine safety was evaluated over a period of 6 months to 7 years in 23 studies. Maximum follow-up for mortality: 10 years	Safety/occurrence of adverse effects: a) local adverse effects (redness, swelling, pain, itching at the injection site); b) mild systemic effects; c) serious systemic effects; d) mortality; e) pregnancy outcomes

Coelho 2015[352]	14 RCTs	Males and females	4-valent HPV vaccine	Placebo or control vaccine	Unreported	Minor adverse events: pain, erythema, swelling and fever included in meta-analysis
Costa 2017[353]	3 RCTs (N=27,465)	Females	9-valent vaccine	4-valent vaccine	7 months	Local and systemic symptoms
Lu 2011[354]	13 publications representing 7 RCTs (N=43,283)	Females	1-, 2- or 4-valent HPV vaccine	Placebo or control vaccine	60 months	Adverse events, vaccine-related adverse events and serious adverse events
Medeiros 2009[350]	6 RCTs (N=47,236)	Females	1-, 2- or 4-valent vaccine	Placebo (adjuvant not mentioned in study details; Hep A vaccine was control in some cases)	48 months	Local, systemic and serious adverse events
Meggiolaro 2018[355]	1 RCT, 5 observational studies (2 case control studies and 3 cohort studies)	Males and females	2- or 4-valent vaccine	Not clearly stated	Range: 12 to 54 months in observational studies	Relative risk or odds ratio for Multiple Sclerosis (MS)
Ogawa 2017[351]	24 RCTs (N=59,081)	Females	2-, 4- or 9-valent vaccine	Placebo or control vaccine	48 months	Studies selected that evaluated solicited local symptoms, solicited systemic symptoms or unsolicited symptoms
Rambout 2007[348]	6 RCTs (n=40,323)	Females	Any HPV vaccine	Placebo (some in fact	3 years	Serious adverse events and death. Minor events additionally described. Definition

				were control vaccine)		of serious adverse event not given. One study reported on new-onset chronic disease
Setiawan 2017[349]	10 RCTs (n= 4,681)	Asian men and women (did not consider non-Asian populations)	Any HPV vaccine	Placebo or comparator vaccine	7 to 31 months	Adverse events - categorised as local or systemic

* All serious adverse events reported by the primary study authors, even if definition of serious was not given, were considered.
** In trials comparing 2-and 4-valent vaccines, 2-valent was the intervention and 4-valent was the comparator
Key: HPV – human papillomavirus; MS – multiple scleroisis; RCT – randomised controlled trial; SLE – systemic lupus erythematosis.

6.2.7.2 Quality appraisal

All systematic reviews were of **critically low quality** by the AMSTAR-2 quality appraisal tool, with the exception of the Cochrane Review by Arbyn et al. (high quality)[347] and the Health Technology Assessment by the Adelaide HTA group (low quality).[356] The most common critical flaws present across reviews included the lack of an *a priori* research design or protocol development prior to initiation of review, lack of detail given on excluded studies and a lack of consideration of publication bias. The full details of the AMSTAR 2 critical appraisal of each review are provided in Appendix 6G. Due to the fact that all but two studies were of 'critically low quality', which should be interpreted as '*should not be relied on to provide an accurate and comprehensive summary of the available studies*',[292] only results from the 2018 Cochrane Review by Arbyn et al. and the 2017 HTA by Parsons et al. are discussed in further significant detail.

In any case, significant overlap existed across systematic reviews; this was especially true of older systematic reviews of RCTs, whereby studies were either partly or wholly captured by later reviews. The Cochrane Review by Arbyn et al., published in May 2018, was the most recent systematic review identified and is therefore the most up-to-date review in addition to being the review of highest methodological quality.

6.2.7.3 Findings

For ease of reading, the evidence in relation to the safety of the HPV vaccines is presented in a number of seperate sections. A summary of conclusions across all 10 systematic reviews is presented in Table 6.3. Findings in relation to serious adverse events and deaths are presented in Section 6.2.7.3.1, with particular emphasis on the findings of the Cochrane review and the Adelaide HTA. Findings in relation to minor adverse events are presented in Section 6.2.7.3.2. Finally, data from observational studies included in the Adelaide HTA are presented in Section 6.2.7.3.3.

Table 6.3 presents the key findings from all 10 systematic reviews. While reviews differed in terms of the vaccines assessed (2-valent, 4-valent or 9-valent vaccine; alone or comparing two types), the population studied (three of 10 studies included males) and the adverse events assessed (all adverse events or limited to minor adverse events only or serious adverse events only), all reviews concluded that the HPV vaccine was safe for the comparison and population investigated.

Table 6.3 Summary of conclusions

Study	Main findings
Arbyn 2018[347]	▪ The risk of serious adverse events is similar in HPV and control vaccines (placebo or vaccine against another infection other than HPV); 669 per 10,000 in control group versus 656 per 10,000 in HPV vaccine group (RR 0.98; 95% CI: 0.92 to 1.05). ▪ The rate of death is similar overall (11 per 10,000 in control group, 14 per 10,000 in HPV vaccine group; RR: 0.98; 95% CI: 0.92 to 1.05). ▪ The number of deaths overall was low, although a higher number of deaths in older women was observed. ▪ No pattern in the cause or timing of deaths has been established.
Adelaide HTA 2017 (Parsons et al.)[356]	▪ There is no difference in the rate of serious adverse event between the: o 4-valent vaccine and placebo o 4-valent vaccine and a control vaccine o 2-valent vaccine and placebo o 2-valent vaccine and a control vaccine. ▪ There is no difference in the rate of new onset chronic disease between the: o 2-valent vaccine and placebo o 2-valent vaccine and a control vaccine ▪ There is no difference in the rate medically significant conditions between the: o 2-valent vaccine and placebo o 2-valent vaccine and a control vaccine. ▪ There is no difference in the rate of autoimmune diseases between people who have been vaccinated and people who have not. ▪ There is no difference in the rate of venous thromboembolism between people who have been vaccinated and people who have not. ▪ There is no difference in the rate of multiple sclerosis (MS) or other demyelinating diseases between people who have been vaccinated and people who have not.
Coelho 2015[352]	▪ The 4-valent vaccine is safe and well tolerated. ▪ The main adverse effects related to vaccination are pain (risk difference [RD] =11%, p<0.001), oedema (RD=8%, p<0.001), erythema (RD=5%, p<0.001) and fever (RD=2%, p<0.003).

Costa 2017[353]	▪ The 9-valent vaccine in female patients is as safe as the 4-valent vaccine. ▪ For injection site events, pain (OR: 1.72, 95% CI 1.62 to 1.82) and erythema (OR: 1.29, 95% CI 1.21 to 1.36) occur significantly more often in the 9-valent group. ▪ For systemic events, fever (OR 1.18; 95% CI 1.03 to 1.36), pruritis (OR: 1.44, 95% CI 1.26 to 1.15) and GI symptoms (OR: 1.72, 95% CI 1.09 to 1.42) occurred more commonly in the 9-valent group.
Lu 2011[354]	▪ The risk of serious adverse events (RR: 1.00; 95% CI: 0.91 to 1.09) or vaccine-related serious adverse events (RR: 1.82; 95% CI: 0.79 to 4.20) did not differ significantly between vaccine and control groups.
Medeiros 2009[350]	▪ Injection site events were more common in the 2-valent vaccine group compared with control groups (OR: 1.74, 95% CI: 1.27 to 2.4). ▪ Systemic events did not occur more commonly in the 2-valent vaccine group (OR: 1.18, 95% CI: 0.7 to 1.99).
Meggiolaro 2018[355]	▪ Authors concluded there is no significant association between HPV vaccination and multiple sclerosis (MS). ▪ Of five observational studies, four found no significant difference and one found a reduction in risk of MS following HPV vaccination. ▪ The RR of MS onset detected by cohort studies ranged from 1.37 (95% CI: 0.74 to 3.20) to 1.54 (95% CI: 0.04 to 8.59). In case-control studies, the odds ratio (OR) ranged from 0.3 (95% CI: 0.1 to 0.9) to 1.60 (95% CI: 0.79 to 3.25).
Ogawa 2017[351]	▪ A significantly higher incidence of solicited local symptoms was observed (2-valent or 4-valent vaccines) compared with placebo (RR for 2-valent: 1.25, 95% CI: 1.09 to 1.43, RR for 4-valent: 1.16, 95% CI: 1.11 to 1.20). ▪ The incidence of solicited systemic symptoms was not different between HPV vaccines and placebo (RR: 1.04, 95% CI: 0.99 to 1.09). ▪ The incidence of unsolicited symptoms was significantly higher for the 2-valent vaccine compared with placebo (RR: 1.28, 95% CI: 1.01 to 1.63), but was not significantly different between 2-valent and hepatitis B vaccines.
Rambout 2007[348]	▪ The majority of adverse events are minor. ▪ The incidence of serious adverse events and death were balanced between the vaccine and control groups.

Setiawan 2017[349]	■ HPV vaccination in Asian populations has a favourable safety profile. ■ A higher risk of local (RR: 1.89; 95% CI 1.65 to 2.17) and systemic (RR: 1.33; 95% CI 1.18 to 1.50) adverse events was observed in vaccinated individuals compared with controls.

RR=relative risk. OR=odds ratio. CI=confidence interval. RD=risk difference.

6.2.7.3.1 Serious adverse events and deaths

Five reviews provided a pooled estimate for serious adverse events; a statistically significant association was not found in any. The risk of serious adverse events ranged from RR 0.87 (95% CI 0.43, 1.78)[356] to OR 1.05 (0.91-1.21).[350]

A pooled estimate for mortality was provided in only two reviews (whereby no statistically significant association was found) and was not estimable in another (due to zero deaths found in both groups). Deaths were unreported in four reviews and a narrative description was provided in three (no deaths causally linked with HPV vaccination were found).

Appendix 6H provides estimates for serious adverse events and deaths across all included reviews. The remainder of this section will focus on the findings from the Cochrane review and the Adelaide HTA.

Serious adverse events and deaths: Cochrane review, 2018

As mentioned previously, the May 2018 Cochrane review by Arbyn et al. is the most up-to-date review identified and of the highest methodological quality.[347] This review evaluated the safety of the HPV vaccine (1-valent, 2-valent or 4-valent) in a total of 23 studies. The follow-up period for serious adverse events was six months to seven years, and for deaths was seven months to 10 years. All studies provided outcome data on serious adverse events and deaths (all-cause mortality), and most trials were judged to be at low risk of bias.

Table 6.4 outlines the serious adverse events and deaths observed across studies.

Table 6.4 Serious adverse events and deaths (Cochrane review, 2018)

	Anticipated absolute effects (95% CI)		Relative effect (95%CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with HPV vaccination	Risk with placebo			
Serious adverse events (Follow-up: 6 months to 7 years)	656 per 10,000 (616 to 703)	669 per 10,000	RR 0.98 (0.92 to 1.05)	71,597 (23 RCTs)	⨁⨁⨁⨁ HIGH
Deaths (Follow-up: 7 months to 10 years)	14 per 10,000 (9 to 22)	11 per 10,000	RR 1.29 (0.85 to 1.98)	71,176 (23 RCTs)	⨁⨁ LOW

The risk of serious adverse events was similar in those vaccinated and those who received placebo or control vaccine (RR 0.98, 95% CI 0.92 to 1.05; 71,597 participants; 23 RCTs; high-quality evidence). The absolute event rate was 656 per 10,000 in the vaccine group and 669 per 10,000 in placebo. The authors of the Cochrane review concluded that there was little or no difference in the adverse event rate between the different vaccines (1-valent, 2-valent or 4-valent [p=0.19]).

Restriction to data extracted only from publications in peer-reviewed journals yielded very similar results (RR 1.01, 95% CI 0.95 to 1.06; 71,452 participants; 22 RCTs) with very minor differences between the vaccine types (p=0.83).

Mortality during the study follow-up period was reported in 23 trials. Mortality was low: in absolute terms, the rate of deaths (any cause) in the control groups was 11 per 10,000 compared to 14 per 10,000 in the vaccine groups. Deaths occurred months to years after vaccination. No pattern in the causes of death was identified and study investigators did not establish a causal role of the HPV vaccines for any of the deaths. There was no difference in mortality between vaccinated and unvaccinated women (RR 1.29, 95% CI 0.85 to 1.98; 71,176 participants; 23 studies).

There was no difference in mortality between the 2-valent and 4-valent vaccines (p=0.62). Results were very similar when data extraction was restricted to peer-reviewed published reports (RR 1.31, 95% CI 0.84 to 2.05; 71,452 participants; 23 studies).

Study authors downgraded their appraisal of the quality of evidence for mortality to 'low'. This was due to imprecision from the wide confidence interval and inconsistency due to a statistically different risk between the two age cohorts; a higher risk of mortality in older women was observed. A rating of 'low quality' by GRADE criteria **should be interpreted as** '*further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate*'.[357]

A range of pregnancy outcomes were also investigated (normal infant, spontaneous abortion or miscarriage, elective termination or induced abortion, stillbirth, abnormal infant). No increased risk of these outcomes was found to be associated with the HPV vaccine.

Serious adverse events and deaths: Adelaide HTA, 2017

In 2017 the Adelaide Health Technology Assessment team, of the University of Adelaide, was contracted by the World Health Organization (WHO) to provide an independent assessment of serious adverse events associated with vaccination against HPV. Their aim was to provide the best available evidence to inform WHO's guidance on HPV vaccine safety.

Their primary study outcomes were as follows:

- Serious adverse events, Grade 3-5, including death, and including but not limited to:
    I. Guillain-Barré Syndrome
    II. Autoimmune disease (including but not limited to multiple sclerosis, acute demyelinating encephalomyelitis, encephalitis, SLE, demyelinating disease)
    III. Primary ovarian failure.

The review excluded postural orthostatic tachycardia syndrome (POTS) and chronic regional pain syndrome (CRPS). These were not specifically investigated as the WHO carried out independent analyses on these syndromes.

Both experimental (RCT) and observational (cohort or self-controlled case series) data were sought. All serious adverse events reported by the primary study authors were considered in their review (all events named as 'serious adverse events', even when definitions of what was considered 'serious' were not given, were included). Where studies assessed causality, this was reported. Otherwise, their assessment made no judgments on causality associated with the reported adverse events.

All RCTs reported outcomes related to 'serious adverse events', the primary study outcome of this review. Table 6.5 provides the absolute and relative differences between vaccine and control groups across studies, along with their conclusions and GRADE appraisal of the evidence. In summary, their extensive review concluded that HPV vaccination is not associated with an increased risk of serious adverse events compared to placebo or control vaccine.

Of note, the actual definition of 'serious' was not reported in most trials. While authors did not find any statistically significant association between vaccination and serious adverse events compared to control or placebo, the absolute adverse event rates varied widely. In the 2-valent vaccine versus control studies, for example, absolute rates ranged from 2% to 25% across trials. In absolute terms, the vaccine arm in the comparison 2-valent vaccine versus control experienced serious adverse event rates of 11,677 per 100,000. The vaccine arm in 4-valent vaccine versus control experienced a serious adverse event rate of 734 per 100,000. Authors concluded that variations in what constituted a serious adverse event in trials explained this difference, as no trial described how serious adverse events were identified or reported. Nonetheless, the wide variation in serious adverse event rate reporting did not alter study conclusions as serious adverse events did not occur more commonly in any vaccine comparison (vaccine versus placebo or vaccine versus control).

Authors also examined the difference in serious adverse events by gender. Each comparison was examined for studies comprising only males or only females. Only one small study for 2-valent vaccine included males; separating out this study did not affect the estimate. One good sized study of the 4-valent vaccine (n=3,895) comprised only males (along with two mixed-gender studies). Again, separating out studies by gender had little impact on the estimate for the 4-valent vaccine.

In the 4-valent vaccine trials, no deaths were considered related to the vaccine. In the 2-valent vaccine trials, two studies reported deaths. Causality was not assessed but the causes of death were reported: suicide, assault, car accidents, cancer, acute myocardial infarction, Crohn's disease, systemic lupus erythematosus and a HIV-related condition.

Table 6.5 Serious adverse event outcomes (Adelaide HTA), follow up of one month to nine years

Data size and source	Comparison of effects		Absolute event rate difference (per 100,000)	Relative difference	Conclusion	Certainty of the evidence (GRADE)
	Vaccine	Control				
4-valent vaccine versus placebo Based on data from 28,671 subjects in 7 RCTs	858.2 per 100,000	935.8 per 100,000	-77.6	RR 0.93 (95% CI 0.72 to 1.21)	There is no difference in the rate of serious adverse events between 4-valent vaccine and placebo	⨁⨁⨁⨁ HIGH
4-valent vaccine versus control Based on data from 3,810 subjects in 1 RCT	733.8 per 100,000	841.2 per 100,000	-107.4	RR 0.87 (95% CI 0.43 to 1.78)	There is no difference in the rate of serious adverse events between 4-valent vaccine and a control vaccine	⨁⨁⨁⨁ HIGH
2-valent vaccine versus placebo Based on data from 15,258 subjects in 10 RCTs	1,603.4 per 100,000	1,876.2 per 100,000	-272.8	RR 0.87 (95% CI 0.60 to 1.25)	There is no difference in the rate of serious adverse events between 2-valent vaccine ™ and placebo	⨁⨁⨁⨁ HIGH
2-valent vaccine versus control Based on data from 30,843 subjects in 8 RCTs	11,676.8 per 100,000	11,595.7 per 100,000	81.1	RR 1.01 (95% CI 0.95 to 1.07)	There is no difference in the rate of serious adverse events between 2-valent vaccine and a control vaccine	⨁⨁⨁⨁ HIGH

Additional outcomes assessed by Adelaide HTA included new onset chronic diseases and medically significant conditions (see Table 6.6). Only studies investigating the 2-valent vaccine reported on the outcome of new onset chronic diseases (a condition that had not been recorded in the participant's medical history before the trial). No difference was observed between 2-valent vaccine and placebo or control. Similarly, only the trials of 2-valent vaccine included the outcome of 'medically significant conditions' (events prompting emergency department or physician visit, not related to common diseases or visits for routine health issues). There was considerable variation in the reporting rate for this outcome, reflecting the differing definitions. For example, in the 2-valent vaccine versus control comparison, one study stated 35% of participants reporting medically significant conditions, whereas another trial had rates around 15%. No difference was shown between intervention and placebo or control for any comparison.

Table 6.6 Additional safety outcomes from RCTs (Adelaide HTA)

Outcome	Comparison	Data size and source	Comparison of effects		Certainty of the evidence (GRADE)
			Vaccine	Control	
New onset chronic disease **1 month – 9 years follow up**	**2-valent vaccine versus placebo**	Based on data from 9,511 subjects in 9 RCTs	1240.1 per 100,000	1306.6 per 100,000	⨁⨁⨁⨁ HIGH
			Absolute difference: -66.5 per 100,000 Relative difference: RR 0.83 (95% CI: 0.58 to 1.2)		
	2-valent vaccine versus control	Based on data from 30,349 subjects in 7 RCTs	4680.8 per 100,000	5079.9 per 100,000	⨁⨁⨁⨁ HIGH
			Absolute difference: -399.1 per 100,000 Relative difference: RR 0.93 (95% CI: 0.84 to 1.03)		
Medically significant conditions **1 month – 9 years follow up**	**2-valent vaccine versus placebo**	Based on data from 7,623 subjects in 6 RCTs	8201.4 per 100,000	6949.6 per 100,000	⨁⨁⨁⨁ HIGH
			Absolute difference: 1251.8 per 100,000 Relative difference: RR 1.15 (95% CI: 0.88 to 1.5)		
	2-valent vaccine versus control	Based on data from 28,498 subjects in 4 RCTs	29,372.9 per 100,000	30,069.4 per 100,000	⨁⨁⨁⨁ HIGH
			Absolute difference: -696.5 per 100,000 Relative difference: RR 0.98 (95% CI: 0.92 to 1.05)		

6.2.7.3.2 Minor adverse events

The Adelaide HTA did not consider minor adverse events and all other reviews were rated as being of critically low methodological quality. As such, only the 2018 Cochrane review by Arbyn et al. is considered here.

All vaccines were consistently associated with short-term local adverse effects in the Cochrane review. Local effects refer to the direct effect of vaccination that encompasses pain, redness and swelling. Overall, local adverse reactions were very common (absolute risk 8,080 per 10,000 in vaccine group [81%] and 6,847 per 10,000 in placebo [68%]). Local adverse reactions were significantly more common in the vaccine group (RR 1.18; 95% CI 1.16 to 1.20; 18,113 participants; 8 studies; moderate-quality evidence) than in the placebo group.

Table 6.7 compares the local injection-site reactions in HPV vaccine and placebo groups.

Table 6.7 Local reactions (Cochrane review, 2018)

Reaction	Absolute risk per 10,000		RR (95% CI)	No. participants	No. studies	Quality of evidence
	Vaccine	Placebo				
Pain	8782	6505	1.35 (1.23 to 1.49)	25,691	13	Moderate
Local swelling	2737	1582	1.73 (1.32 to 2.27)	22,106	9	Moderate
Redness	3333	1938	1.72 (1.50 to 1.97)	19,996	6	Moderate

Systemic events (such as fever or generally feeling unwell) with general mild symptoms occurred with similar frequencies in vaccinated recipients versus placebo or control vaccine recipients (RR 1.02, 95% CI 0.98 to 1.07; 18,191 participants; 8 studies; moderate-quality evidence).

6.2.7.3.4 Evidence from observational studies – Adelaide HTA 2017

Apart from the review on multiple sclerosis (MS) conducted by Meggiolaro et al.,[355] the HTA by Parsons et al. was the only review to include observational studies in their analysis of serious adverse events.[356] They included a total of six high-quality cohort studies and five self-controlled case series. Outcomes included autoimmune diseases, multiple sclerosis (MS) and other demyelinating diseases and venous thromboembolic diseases.

Six high-quality cohort studies were retrieved. Quality assessment was performed

using the AHRQ (Agency for Healthcare Research and Quality) item bank.[358] Certainty assessment by 'GRADE' criteria led to moderate-quality evidence, that is, '*further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate*'.[357] The studies were based on administrative data from Scandinavia (n=2), the Netherlands, the US (n=2) and the UK. The characteristics of the cohort studies, as described in the Adelaide HTA, are summarised in Table 6.8.

The two studies from Scandinavia used extensive linked administrative datasets to study large cohorts of girls for a range of relevant outcomes:

- one studied 53 predefined outcomes including a range of autoimmune conditions and venous thromboembolism (VTE)[359]
- and another studied multiple sclerosis and other demyelinating diseases.[360]

The cohort study in the Netherlands also used administrative data for migraine outcomes.[361] Two cohort studies were conducted in the US:

- one study investigated outcomes of Guillain–Barré Syndrome (GBS), stroke, VTE, appendicitis, anaphylaxis, seizure, syncope, and allergic reaction[362]
- and another investigated a range of autoimmune and neurological outcomes.[363]

A final study from the UK using general practice (GP) data investigated new-onset autoimmune disease.[364]

Table 6.8 Characteristics of cohort studies – Adelaide HTA 2017

Study	Data source	Population	Conditions	Associations found	Comment
Arnheim-Dahlstrom et al. 2013[359] **[Denmark and Sweden]**	Patient registers from hospital inpatients, outpatients and emergency departments	Nearly one million girls aged 10 to 17 years, of whom nearly a third had received at least one HPV vaccination (4-valent HPV vaccine predominantly used in Scandinavia)	Graves' disease, Hashimoto's thyroiditis, other hyperthyroidism, hypothyroidism, coeliac disease, Crohn's disease, ulcerative colitis, pancreatitis, ankylosing spondylitis, Behcet's syndrome, Henoch-Schonlein's purpura, juvenile arthritis, myositis, rheumatoid arthritis, systemic lupus erythematosis, vasculitis (unspecified), idipathic thrombocytopenic purpura, erythema nodosum, localised scleroderma, psoriasis, vitiligo, Raynaud's disease, Type 1 diabetes, Bell's palsy, epilepsy, narcolepsy, optical neuritis, and paralysis, VTE	1) Three outcomes were positively associated: Behcet's syndrome (rate ratio 3.37, 95% CI 1.05, 10.80), Raynaud's disease (1.67, 95% CI 1.14, 2.44) and type 1 diabetes (1.29, 95% CI 1.03, 1.62). 2) For two outcomes (epilepsy and paralysis), the incidence rate ratios were significantly decreased 3) No associations found for all other outcomes.	The authors investigated the strength of the signals for the three positive associations with a predefined analytical strategy. The rate ratios in the period starting at day 181 were similar to the rate ratios in the primary risk period, and the temporal pattern of cases was random. The authors concluded that no consistent evidence for a causal association was found with these three outcomes.
Chao et al. 2012[363] **[California, USA]**	Electronic health records of two managed care organisations	Women enrolled in two managed care organisations in California, nearly all aged between nine and 26 years	A range of autoimmune and neurological outcomes	No significantly elevated incidence rate ratios were found amongst all the outcomes considered, with the exception of Hashimoto's disease.	On investigating Hashimoto's disease, no consistent evidence for a safety signal was found.
Gee et al. 2011[362] **[USA]**	Administrative data from seven managed care organisations in several states in the US	The exposed cohort was formed from females aged 9-26 years who had received at leave one dose of 4-valent HPV vaccine. The	A range of outcomes: anaphylaxis, allergic reactions, appendicitis, Guillain-Barre syndrome (GBS), seizures, first ever seizures, stroke, syncope and VTE	▪ An apparent increased risk of appendicitis in youths was identified ▪ One case of GBS was identified and reviewed, and found not to be an incident	Analysis of data did not find any temporally-related clusters related to appendicitis, and the authors suspected a change

		cohort was matched to data from medical encounters in outpatients, emergency departments and hospitals, as well as immunisation data		▪ case ▪ No increased rates were seen for seizures, allergic reactions or syncope ▪ One vaccine-related confirmed case of anaphylaxis in a 26 year old was identified. This resulted in a rate of 1.7 cases per million doses (95% CI: 0.04 to 9.3)	in coding at one site may have affected the background rates.
Schurink-van't Klooster et al. 2011[(361)] **[The Netherlands]**	The Integrated Primary Care Information database: a longitudinal, observational database which contains medical patient records from general practitioners	All incident cases of migraine in 12-16 year old girls	Incident cases of migraine	▪ Only 22 girls with incident migraine were identified, with half of these vaccinated ▪ Incidence rate ratios for migraine in monthly periods following vaccination ranged between zero and three, with none statistically significant and none related to occurrence of vaccination	This study also embedded a self controlled case series within this cohort study, using a six-week high risk period post-vaccination as the exposed time. Although a raised relative risk in the high-risk time was observed, it was not statistically significant.
Scheller et al. 2015[(360)] **[Denmark/ Sweden]**	Cohort identified through centralised registries	3,983,824 women eligible for the cohort, of whom 789,082 were vaccinated. The study totalled 21,332,622 person-years	Multiple sclerosis (MS) and other demyelinating diseases	The authors concluded that the data did not support an association between HPV vaccination and MS (adjusted rate ratio 0.9 [95% CI: 0.7 to 1.15]) or other demyelinating diseases (adjusted rate ratio 1.00 [95% CI: 0.8 to 1.26])	

Willame et al. 2016[364] **[UK]**	Clinical Practice Research Datalink General Practice Online Database (CRPD GOLD), based on data from general practices, and some linked data to hospital episodes	Cohort of women aged 9-25 years with an age and sex- matched historical cohort (before the introduction of the vaccine), a concurrent age-matched male cohort and an historical age-matched male cohort. From the four eligible cohorts identified in the database, 65,000 were randomly chosen for each cohort for follow up, with a total of 259,876 in the final population for main analysis	Predefined new onset autoimmune disease with two co-primary endpoints: Neuroinflammatory/ ophthalmic diseases: multiple sclerosis, transverse myelitis, optic neuritis, Guillain-Barre syndrome, autoimmune uveitis and other demyelinating diseases; other autoimmune diseases: systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, Still's disease, psoriatic arthritis, ankylosing spondylitis, idiopathic thrombocytopenic purpura, autoimmune haemolytic anaemia, type 1 diabetes, autoimmune thyroiditis, Crohn's disease, ulcerative colitis and autoimmune hepatitis	Compared to the unexposed historical female cohort, a significant increased risk in the exposed cohort was found for autoimmune thyroiditis, no excess risk was found for Crohn's disease and a protective effect for type 1 diabetes was found	▪ The authors indicated that the incidence of autoimmune thyroiditis was still within the expected ranges for the age group ▪ Of note, the study and it was funded, designed, conducted, analysed and reported by GlaxoSmithKline.

Table 6.9 summarises these comparisons as assessed by Adelaide HTA. No safety signals for any of the four categories of outcomes assessed (venous thromboembolism, multiple sclerosis [MS], other demyelinating conditions, autoimmune diseases) were identified. Of note, one study also reported on the risk of anaphylaxis with HPV vaccination, noting an anaphylaxis rate of 1.7 cases per 1,000,000 doses (95% CI: 0.04 to 9.3).[362]

Table 6.9 Additional safety outcomes – observational studies (Adelaide HTA)

Outcome	Data size and source	Comparison of effects		Certainty of the evidence (GRADE)
		Vaccine	Control	
Venous thromboembolism	Data from 2 high-quality cohort studies	No difference in the rate of thromboembolism in those exposed to vaccine and those unexposed.		⊕⊕⊕⊖ Moderate
Multiple sclerosis	Data from 2 high-quality cohort studies	Between 3.4 and 6.1 per 100,000 person years	Between 2.5 and 21.5 per 100,000 person years	⊕⊕⊕⊖ Moderate
		IRR between 0.90 (95% CI 0.70 to 1.15) and 1.37 (95% CI 0.74 to 3.20)		
		No differences in rates of multiple sclerosis between those exposed to vaccine and those unexposed.		
Other demyelinating conditions	Data from 2 high-quality cohort studies	Between 1.1 and 7.5 per 100,000 person years	Between 1.6 and 16.1 per 100,000 person years	⊕⊕⊕⊖ Moderate
		IRR between 0.71 (95% CI 0.38 to 2.13) and 1.00 (95% CI 0.80 to 1.26)		
		No differences in rates of other demyelinating conditions between those exposed to vaccine and those unexposed.		
Autoimmune diseases	Data from 5 high-quality cohort studies	Pooled analysis of 2-valent vaccine versus comparator: RR 1.04 (95% CI: 0.62 to 1.74). No differences in rates of most autoimmune diseases between those exposed to vaccine and those unexposed.		⊕⊕⊕⊖ Moderate

IRR=incidence rate ratio

6.2.8 Discussion

Ten systematic reviews were retrieved from the scientific literature. The majority of reviews had multiple methodological flaws, and were deemed 'critically low quality' by AMSTAR 2 criteria, which diminished confidence in their estimates. Additionally, substantial overlap existed across reviews. Therefore, the systematic reviews that contributed most to this safety assessment were the two most recent and highest quality reviews identified: the 2018 Cochrane review by Arbyn et al. and the 2017 Health Technology Assessment by Parsons et al., commissioned by the WHO.

Across all 10 reviews, conclusions were consistent. As expected, minor adverse events that are transient in nature commonly occur following vaccination. The Cochrane review reported an absolute risk of any adverse event of 8,080 per 10,000 in the vaccine group (81%) compared with 6,847 per 10,000 in the placebo group (68%).

Across reviews, no safety issues were identified for a range of serious adverse events. Five reviews provided a pooled estimate for serious adverse events; a statistically significant association was not found in any. Due to the fact that the definition of 'serious' was not reported in most reviews (nor in the primary studies), the absolute adverse event rates varied widely. For example, the absolute rates ranged from 2% to 25% in individual studies in the 2-valent vaccine versus control comparison in the Adelaide HTA. Serious adverse event rates in the vaccine arms varied from 11,677 per 100,000 (2-valent vaccine versus control comparison) to 734 per 100,000 (4-valent vaccine versus control comparison). The Cochrane review reported an absolute rate of 656 per 10,000 in the vaccine arm of trials compared with 669 per 10,000 in the placebo group (resulting in a RR of 0.98, 95% CI 0.92 to 1.05; data from 71,597 participants in 23 RCTs; high-quality evidence).

Pooled values should be considered estimates as they were likely affected by the different definitions used. The comparisons between vaccine and placebo or control vaccine, however, should still be valid. The wide variation in serious adverse event rate reporting did not alter study conclusions, as serious adverse events did not occur more commonly in any vaccine comparison (vaccine versus placebo or control) in any review.

A pooled estimate for mortality was provided in only two reviews (with no statistically significant association found) and mortality was not estimable in another (due to zero deaths found in both groups). Deaths were unreported in four reviews and a narrative description was provided in three (no deaths causally linked with HPV vaccination was found). The Cochrane review reported a non-significant pooled relative risk estimate of 1.29 (95% CI: 0.85 to 1.98; data from 71,176 participants in 23 RCTs). Authors downgraded this estimate due to imprecision from wide confidence intervals and inconsistency due to a statistically different risk between

two age cohorts: a higher risk of mortality in older women was observed. The Adelaide HTA reported no deaths that were considered vaccine-related in 4-valent vaccine trials; two studies reported deaths in 2-valent vaccine trials, however causality was not assessed.

The Adelaide HTA team also investigated 'new-onset chronic disease' and 'medically significant conditions' in RCTs and did not find any associations. Furthermore, observational studies that included six large, good-quality cohort studies and five self-controlled case series were identified and no increased rates of the following conditions were found in vaccinated versus unvaccinated individuals: autoimmune disorders, venous thromboembolism, multiple sclerosis (MS) and other demyelinating conditions. Individual cohort studies also investigated a range of other conditions, such as Guillain–Barré syndrome, stroke, appendicitis, seizure, syncope and migraine. No observational studies concluded that a verifiable safety concern exists. A rate of 1.7 cases of anaphylaxis per million doses was noted.

In conclusion, this systematic review of systematic reviews retrieved 10 studies that included over 70,000 trial participants (and surveillance of many millions of individuals in cohort studies), and had a follow up of up to 10 years. The evidence from the systematic review of systematic reviews did not raise any safety concerns regarding HPV vaccines.

6.3 Safety data from Ireland

6.3.1 Introduction

Due to the relatively limited size of clinical trials, adverse events that are very rare may not be identified until a vaccine has been used wide-scale in large numbers of people. This applies to any new medicine or vaccine, and HPV vaccines are not unique in this regard.

Pharmacovigilance is the monitoring of the safety of medicines and includes all activities related to the detection, assessment, understanding and prevention of adverse effects and other possible drug-related problems. In Ireland, the Health Products Regulatory Authority (HPRA) is responsible for monitoring medicine safety through pharmacovigilance, including the operation of the national adverse reaction reporting system. Reporting of suspected adverse reactions is just one way of identifying possible new adverse reactions (often termed a 'signal') that may or may not have been identified in clinical trials.

6.3.2 Adverse event reporting to the HPRA

Between 1 January 2006 and 31 December 2017, the HPRA received 1,119 reports of suspected adverse reactions associated with the HPV 4-valent vaccine. During this time period, a total of 680,000 doses of 4-valent vaccine were administered as part

of the national immunisation programme, with 238,000 girls fully vaccinated.[365] The overall reporting rate is estimated to be approximately 1.7 reports per 1,000 doses. This compares to one report per 1,000 doses in the UK for the 2-valent vaccine.[366]

Enhanced surveillance is ongoing with proactive reporting to the HPRA. The HPRA actively encouraged reporting for the first year of the programme, including reports of expected non-serious reactions. Following this, reports of suspected serious adverse reactions were sought. The HPRA encouraged reporting through its Drug Safety Newsletter and interactions with healthcare professionals involved in the programme (for example, community health doctors and nurses). Adverse reaction reporting rates are influenced by many factors, including the seriousness of the event, their ease of recognition, the extent of use and publicity.

There are two important caveats to be cognisant of while interpreting reports of suspected adverse reactions to the HPRA.

1) Firstly, it is important to note that many of the reports received by the HPRA were not medically confirmed. Reports originated from a number of sources, including some directly from patients and family members. The HPRA reviews all data with duplicate cases reconciled under a unique identifying number where possible. The information typically contains variable levels of detail with regards to the nature and onset of symptoms, clinical assessment, investigations pursued and diagnoses received.

2) Secondly, it is important to note that reports submitted to the HPRA concern 'suspected' adverse reactions. This means that the effects experienced may represent side effects associated with the vaccine or the vaccination process, or may be coincidental in terms of timing, due to an underlying or previously undiagnosed condition that would have occurred in the absence of vaccination.

6.3.3 Reports by disease category

The majority of reports received by the HPRA were consistent with the expected pattern of adverse events for the vaccines, as described in the currently approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL), see Appendix 6I).

Events occurring at the time of vaccine administration, such as syncope (fainting), were among the most commonly reported events. Other commonly reported symptoms included gastrointestinal symptoms, malaise, headache, dizziness and injection site reactions. Reports of skin rashes, urticaria and flushing were also received, including isolated reports of more severe allergic or hypersensitivity-type reactions. There were also some reports describing chronic fatigue (18 reports as of

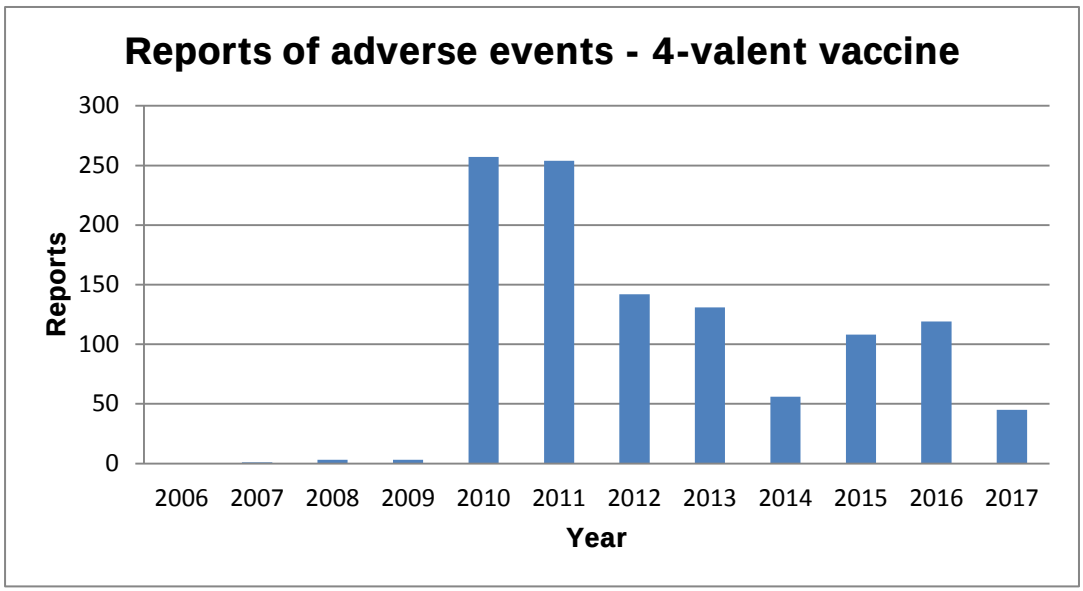
March 2017), generally with multiple other symptoms (for example headache, malaise, drowsiness, nausea, gastrointestinal upset, joint swelling, flu-like illness and menstrual disorders) following vaccination.

The full list of adverse reactions reported to the HPRA, by disease category, is provided in Appendix 6J. This summary listing presents reports by System-Organ-Class (SOC) format for those cases for which reports have been received from 1 January 2006 to 31 December 2017. At the end of the listing, background information on the national reporting system and guidance on interpretation of the data is provided.

6.3.4 Reports over time

Figure 6.1 represents the annual numbers of reports of suspected adverse reactions and or events received by the HPRA in association with the 4-valent vaccine. Very few reports were received prior to the introduction of the national school-based HPV immunisation programme in 2010. This likely reflects the very limited uptake of the vaccine in those paying out-of-pocket for the vaccine. The first two years (2010 and 2011) following introduction of the programme recorded the highest number of reports, due to HPRA request for all reports, with a decrease thereafter.

Figure 6.1 Reports to HPRA by year

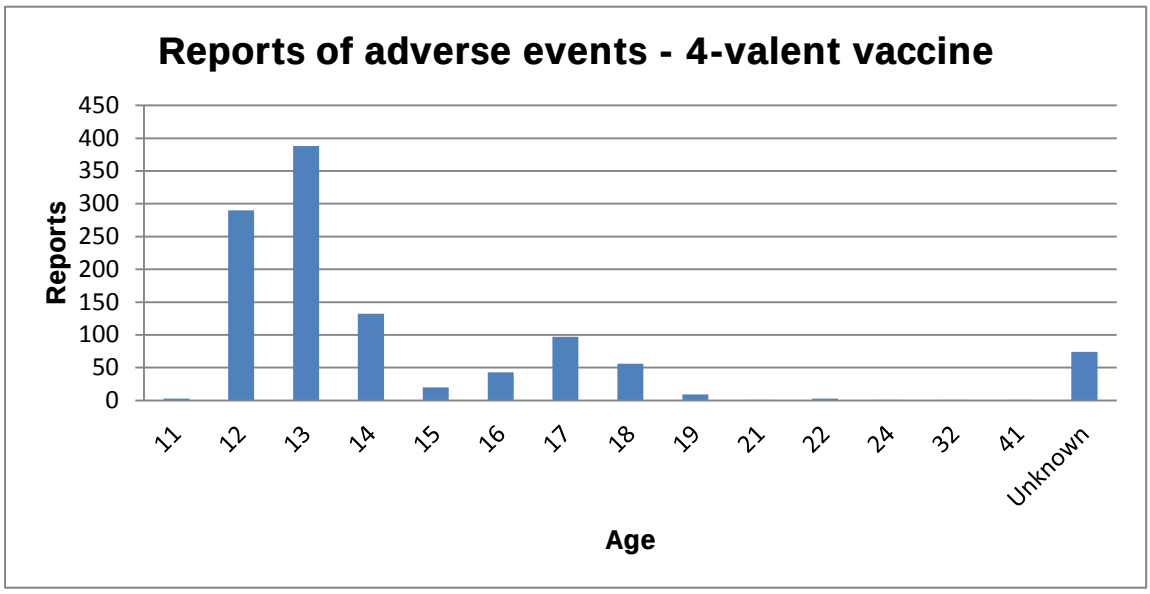


6.3.5 Reports by age

Figure 6.2 indicates the ages of patients provided in reports submitted. The majority of patients were aged between 12 and 14 years, as would be expected in accordance with the age at which adolescents are vaccinated as part of the national HPV immunisation programme (12 and 13 year old girls). As noted in Chapter 2, Section 2.7.1, a catch-up programme targeting girls in sixth year in second level

schools and for age-equivalent girls (date of birth 1 September 1993 to 31 August 1994) attending special schools, home schooled, Youthreach, and community training centres was provided from September 2011 and repeated for girls in sixth year in 2012 and 2013. This catch-up would therefore have primarily included girls aged 17 to 18 years of age.

Figure 6.2 Reports to HPRA by age of recipient



6.3.6 Source of suspected adverse drug reaction reports

Table 6.10 indicates the source of reports to the HPRA. The majority of reports were notified to the HPRA by healthcare professionals working in the national HPV immunisation programme. Of note, the HPRA occasionally receives reports from more than one source (for example, from a community doctor as well as directly from a patient or carer), hence the number of reports exceeds the total number of cases.

Table 6.10 Source of adverse event reports to HPRA

Source	Number of reports to the HPRA
Community care doctor	618
Community nurse	231
Community pharmacist	4
Pharmaceutical company	119
GP	76
Healthcare practitioner-other	7
Hospital doctor	35
Hospital nurse	17
Member of the Public	153
Media	12

Key: GP – general practitioner; HPRA – Health Products Regulatory Authority

6.3.7 Summary

In summary, the HPRA received 1,119 reports of suspected adverse reactions associated with the HPV 4-valent vaccine between 1 January 2006 and 31 December 2017. This represents a reporting rate of approximately 1.7 reports per 1,000 doses. Many of the reports were not medically confirmed, and all represent 'suspected' reactions.

The majority of reports were consistent with known adverse events associated with vaccination. The majority of suspected events occurred in 12 and 13 year olds from the year 2010 onwards, coinciding with the introduction of the school-based national immunisation programme. Most reports originated from community doctors and nurses, as expected. Continued reporting of adverse events to the HPRA and ongoing monitoring for suspected safety signals will remain a crucial component of the HPV immunisation programme.

6.4 Other expert reviews and independent analyses

Our systematic review of systematic reviews concurs with the assessments undertaken by the World Health Organization's (WHO's) Global Advisory Committee on Vaccine Safety (GACVS) and the European Medicines Agency (EMA) regarding the safety of the HPV vaccine. Both concluded that HPV vaccines are extremely safe. The WHO points to the potential for 'real harm' that can arise from the lack of use of safe and effective vaccines based on weak evidence.

The following sections outline the most recent key reviews conducted by the GACVS, the EMA, country-level regulatory agencies and expert narrative reviews not included in our systematic review of systematic reviews (Section 6.2).

6.4.1 World Health Organization's (WHO's) Global Advisory Committee on Vaccine Safety

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides the WHO with 'scientifically rigorous advice on vaccine safety issues of potential global importance'. The GACVS first reviewed the safety of HPV vaccines in 2007[(367)] and subsequently in 2008,[(368)] 2009,[(369)] 2013,[(370)] 2014,[(371)] 2015[(372)] and most recently in June 2017.[(373)]

Also in 2017, the WHO commissioned the systematic review of serious adverse events by the University of Adelaide, included in the systematic review of systematic reviews (Section 6.2).

Since 2006, the WHO reports that over 270 million doses of HPV vaccines have been distributed worldwide. The GACVS was aware of signals related to syncope and anaphylaxis from an early stage. Syncope was established as a common stress-related reaction to the injection. Anaphylaxis, on the other hand, is a serious allergic reaction that is rapid in onset and may result in death. The risk of anaphylaxis was characterised as approximately 1.7 cases per million doses. No other adverse reactions were identified and the GACVS considered HPV vaccination to be extremely safe.

In its most recent update, the GACVS reviewed the findings of a comprehensive literature review of further safety data that was generated from the UK, the US and Denmark. Among the new data were studies looking at Guillain-Barré syndrome (GBS), complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency, primary ovarian failure and venous thromboembolism. With large population-level data from several countries, the GACVS has maintained its assertion that there is insufficient evidence for a causal association between HPV vaccine and these conditions.

Guillain-Barré syndrome (GBS)

In 2015, the findings of a cohort study, carried out by the French Agency for the Safety of Health Products, were made public in an online report. A total of 14 autoimmune events were assessed. A signal of an association with GBS was noted at any time after the first dose of the vaccine (adjusted hazard ratio 4, 95% CI 1.84 to 8.69).[(319)] To investigate this finding, a large self-controlled case-series study was conducted in the UK based on 10.4 million doses of the vaccine.[(374)] This was the largest study to date to assess the risk of GBS following HPV vaccination, with 101 GBS episodes ascertained from a population given approximately 10.4 million HPV vaccine doses. Study authors found no significantly increased risk for GBS after any dose of the vaccine, in any of several risk periods assessed or for either vaccine brand. Additionally, based on the upper end of the 95% CI for the relative incidence

and the number of HPV vaccine doses given in England, the authors excluded a risk of about one case of GBS per million doses.

Furthermore, GBS was specifically selected as an outcome in studies from the US using the Vaccine Safety Datalink (VSD) and the Vaccine Adverse Events Reporting System (VAERS).[375] New data were presented to the GACVS pertaining to 60 million distributed doses from the VAERS and data on over 2.7 million doses administered until the end of 2015 from the VSD.[373] No association between HPV vaccination and GBS was identified. Based on these data, the GACVS similarly concluded that a risk of more than one case of GBS per million doses of the vaccine can be excluded.

Prior to this, seven large studies and one review by the Center for Disease Control and Prevention (CDC) in the US that investigated the association between HPV vaccination and GBS were published (two of these are included in the systematic review by Adelaide HTA).[359, 363, 376-380] The studies found no evidence of an increased risk of GBS with HPV vaccination.

CRPS and POTS

CRPS and POTS continue to be presented as case reports in association with HPV vaccines (in particular from Japan and Denmark). CRPS may be defined as continuing pain that is disproportionate to the inciting event (typically an episode of trauma or limb immobilisation), and associated with sensory, motor, pseudomotor and dystrophic changes.[381] It is usually confined to a single limb. Patients with POTS typically show abnormal increases in heart rate on standing, without orthostatic hypotension. These are accompanied by symptoms (for example, light-headedness, syncope, weakness, headaches, chronic aches and pains, gastrointestinal symptoms and fatigue).[381]

The GACVS investigated these syndromes in 2015 and again in 2017. As CRPS and POTS encompass a spectrum of diverse symptoms, their assessment using administrative health data posed significant challenges. The WHO comments on the following aspects of these syndromes that make assessment difficult:

- both disorders are of unclear and possibly heterogeneous etiology
- the epidemiology of both conditions is not well characterised
- the onset of both conditions is difficult to define
- POTS is possibly relatively common in young adolescents, yet infrequently diagnosed, and difficult to distinguish from the normal range of physiologic responses in this age group.

Despite these difficulties, reviews of data before and after the HPV vaccine was licensed provide no evidence that these syndromes are associated with HPV vaccination. Additionally, certain features of CRPS and POTS overlap with that of chronic fatigue syndrome for which a published observational study reported no association with HPV vaccines.[382]

In June 2017, new data from Japan were presented to the GACVS whereby cases with diverse symptoms, including pain and motor dysfunction, were assessed. Cases were identified from a nationwide epidemiological survey involving multiple hospital medical departments of various disciplines including pain, neurology, rheumatology, paediatrics, psychiatry and psychosomatic medicine. These complex syndromes manifested in both sexes, although were more common in girls, and occurred in both vaccinated and unvaccinated individuals.

The GACVS maintains its conclusion that there is still no evidence to suggest a causal association between HPV vaccine and CRPS or POTS.[373]

Other conditions

The GACVS also reviewed reports of an apparently heightened risk of coeliac disease from Denmark and Sweden (data relating to over three million women aged 18 to 44 years). Investigators considered that, most likely, this represented an unmasking of an existing condition during the vaccination visit. Overall, the study did not raise any other autoimmune safety issues of concern.

To date no safety concerns have arisen during the pre-licensure clinical trials or in post-license surveillance in pregnant women.[383] As the HPV vaccine is often administered during potential childbearing years, its safety profile during pregnancy is important to ascertain in the event that inadvertent exposure occurs. New data from the Vaccine Safety Datalink in the US for more than 92,000 eligible pregnancies were reviewed by the GACVS and no adverse obstetric, birth or structural abnormality outcomes were observed.[373] Additionally, a national cohort study from Denmark in 2017 that assessed 540,805 pregnancies found that the HPV vaccine was not associated with a significantly higher risk of adverse pregnancy outcomes.[384] Inadvertent administration of the HPV vaccine during pregnancy is therefore thought to be safe to mother and infant.

Summary

Safety studies encompassing millions of individuals and investigating a wide range of health outcomes led to the GACVS's conclusion that the HPV vaccine is safe.

Despite extensive data available on safety, attention continues to focus on sporadic case reports and allegations. The GACVS —

'continues to express concern that the ongoing unsubstantiated allegations have a demonstrable negative impact on vaccine coverage in a growing number of countries, and that this will result in real harm'.

6.4.2 European Medicines Agency (EMA) review of POTS and CRPS

HPV vaccines are authorised for marketing in Ireland through the European Commission. Following a recommendation from the European Medicines Agency (EMA), the European Commission granted marketing authorisation across the EU, Iceland, Norway and Liechtenstein. The EMA is a decentralised agency of the EU and is responsible for the scientific evaluation, supervision and safety monitoring of medicines. Market authorisation for the 4-valent vaccine was granted in September 2006, for the 2-valent vaccine in September 2007, and for 9-valent vaccine in June 2015. The European Public Assessment Report (EPAR) for 4-valent vaccine explains how the EMA assessed the medicine before granting a marketing authorisation and making its recommendations on the conditions of use for the 4-valent vaccine.[385]

As mentioned previously, routine surveillance of suspected adverse reaction reports raised questions on the potential association between the use of HPV vaccines and two syndromes, CRPS and POTS.

In November 2015, the EMA completed a review of the evidence surrounding CRPS and POTS in young women given the 2-valent, 4-valent or 9-valent HPV vaccines.[381] The initial review was conducted by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA. No causal link was found. The findings of the PRAC were passed to the EMA's Committee for Medicinal Products for Human Use (CHMP). The CHMP concurred that the available evidence does not support that CRPS and POTS are caused by HPV vaccines. It therefore did not recommend any changes to the terms of licensing or the product information for these medicines.

The review was based on analyses of clinical trial and post-marketing data and included a review of published literature, spontaneous reports of suspected adverse effects, reports submitted by member states as well as information from other countries and information submitted voluntarily by the public. The EMA also consulted a group of experts in these syndromes and in neurology, cardiology and pharmacoepidemiology.

The following conclusions and recommendations were made:

- Available estimates suggest that, in the general population, approximately 150 girls and young women per million aged 10 to 19 years may develop CRPS each year and at least 150 girls and young women per million may develop POTS each year.

- There is no evidence that the overall occurrence of these syndromes in vaccinated girls is different from that expected in these age groups.
- Even taking into account a variety of possible scenarios for underreporting, and reports that did not fully meet diagnostic criteria for these syndromes, there is no evidence for an increased occurrence.
- There are therefore no recommendations to amend the product information or to change the way HPV vaccines are used.

Of note, investigators across Europe have sought to explore health-seeking behaviour in this group. A case-control study in Denmark compared pre-vaccination health-seeking behaviour in HPV-vaccinated girls who had reported adverse events (cases) with matched cohorts of HPV-vaccinated girls who had not reported adverse events (controls).[386] The case group reported increased rates of health problems, that is, before receiving the first HPV vaccination, girls who suspected adverse reactions had symptoms and a healthcare-seeking pattern that is different from the matched population. Pre-vaccination morbidity should therefore be taken into account in the evaluation of vaccine safety signal.

A final point to note is that increasing trends in the background incidence of chronic fatigue syndrome, POTS and GBS must be taken into consideration in the interpretation of safety signals temporally linked to HPV vaccination. For example, a significant relative increase in the annual incidence of chronic fatigue syndrome (33% [95% CI; 3.0-70.3: p=0.029]) and POTS (16.5% [95% CI; 7.8-25.9: p<0.05]), but not in GBS (5.4% [95% CI; -8.4-21.3: p=0.460]), was observed in 12 to 15 year old girls in Finland in the decade before vaccination through assessment of hospital discharge records.[387] Pre-vaccination trends and variation in disease coding and healthcare-seeking behaviour over time may influence the interpretation of associations with HPV vaccination and must always be taken into consideration when investigating an apparent association.

6.4.3 Country-level surveillance activities

6.4.3.1 USA

Consistent with studies included in our review, as well as assessments undertaken by the GACVS and EMA, safety surveillance from the USA, following the granting of the vaccine license, has confirmed the general safety profile of the 4-valent vaccine. However, surveillance activities identified disproportionate reporting of syncope and venous thromboembolic events. No causal relation could be established, however.[388] Subsequent studies did not find an association with venous thromboembolic events.[389] One study identified in our systematic review of systematic reviews assessed new-onset autoimmune conditions related to

immunisation with the 4-valent vaccine at two healthcare organisations in California.[363] Significant associations were not found, with the exception of an apparently increased risk of Hashimoto thyroiditis (RR = 1.29, 95% CI 1.08 to 1.56). However, time relation and biological plausibility did not reveal evidence of causality.

In the US, the National Vaccine Injury Compensation Program accepts petitions that relate to various illnesses, disabilities or injuries that occur due to vaccination. Three conditions are covered that relate to HPV vaccination: anaphylaxis, shoulder injury related to vaccine administration, and vasovagal syncope.[22] As for time of onset, anaphylaxis must have first appeared within four hours of vaccine administration, shoulder injury within 48 hours and vasovagal syncope within one hour. Anaphylaxis, syncope and shoulder injury are known complications of HPV vaccine administration.

6.4.3.1 UK

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) set up a comprehensive pharmacovigilance study assessing the temporal association between chronic fatigue syndromes and the administration of the 2-valent HPV vaccine.[382] Despite the high coverage in girls and young women aged 12 to 20 years, no increased incidence of fatigue syndromes was observed after the introduction of HPV vaccination (incidence rate ratio: 0.94; 95% CI: 0.78 to 1.14). In addition, a detailed analysis of a self-controlled case series of 187 girls and young women did not reveal evidence that the HPV vaccine caused fatigue syndromes (incidence rate ratio: 1.07; 95% CI: 0.57 to 2).

6.4.3.1 Registries of Denmark and Sweden

As mentioned in the systematic review of systematic reviews, a large data linkage study that joined hospital records with HPV vaccine registries in Sweden and Denmark did not reveal associations between the administration of the 4-valent vaccine and most autoimmune, neurological or venous thromboembolic adverse events.[359] However, three autoimmune conditions were more common (Behcet's disease, Raynaud's disease and type 1 diabetes) and two neurological conditions were less common (epilepsy and paralysis) in vaccinated cohorts compared with non-vaccinated cohorts. However, on further assessment of the apparently increased incidence, the associations were weak and not temporally related to vaccine exposure. Furthermore, authors report that the findings need to be interpreted considering the multiple outcomes assessed.[359]

Since this data linkage study, investigators have concluded that no increased incidence of thromboembolism, multiple sclerosis or other demyelinating neurologic diseases after administration of the 4-valent vaccine was detected from the Danish-Swedish linkage studies.[360, 390]

6.4.4 Other narrative reviews

As the overview of reviews (Section 6.2) included data from systematic reviews only, key expert narrative reviews not discussed previously are considered here.

In 2013 Macartney et al. published an extensive review of 103 safety studies demonstrating a reassuring safety profile for the 2-valent and 4-valent HPV vaccines.[391] On 26 December 2017, the authors published an update to this review, identifying 109 new studies, encompassing 2.5 million vaccinated individuals, across six countries (Phillips et al. 2017).[392] A range of study designs were considered; 41 publications reported on a total of 81 clinical trials, 29 studies of surveillance systems were examined (including one pregnancy registry) along with 23 case reports or case series, and 16 population-based studies (several using multiple methods of analysis). The review included diverse populations, including those with underlying medical illnesses. Investigators also reviewed safety in males and assessed the safety of the 9-valent vaccine.

This comprehensive review confirmed previous reviews, concluding that all HPV vaccines demonstrate an acceptable safety profile. Injection-site reactions, however, were noted to be slightly more common for the 9-valent than 4-valent vaccine. Rates of anaphylaxis were in keeping with rates reported for other vaccines. Syncope continues to be reported, most commonly in younger females and males. It is now well-recognised that syncope is related to the population and the setting in which the HPV vaccine is administered and that practical measures, including a 15-minute observation period post-vaccination, should be taken to reduce the risk of syncopal seizure or falls following adolescent vaccination.[38]

Additional outcomes in specific populations were also assessed (adverse events of special interest, AESIs). Authors found no consistent evidence for an increased risk of any AESI, including demyelinating syndromes, venous thromboembolic events, autoimmune disorders or neurological conditions such as CRPS and POTS. No safety concerns were identified in specific populations, including males and those with underlying medical conditions.

This review also investigated the safety profile of the 9-valent HPV vaccine. Overall, data from clinical trials reported a similar safety profile for the 9-valent vaccine compared to the 4-valent vaccine.[249, 393, 394] However, injection-site reactions (including severe reactions) were slightly more frequent with the 9-valent vaccine. This is likely caused by the greater amount of adjuvant (500 versus 225 micrograms of aluminium). For example, in a multi-centre trial of more than 14,000 females aged 16 to 26 years, injection-site reactions and severe injection-site reactions were reported in 90.7% versus 84.9% and 4.3% versus 2.6% in 9-valent and 4-valent vaccine recipients, respectively.[393]

Another narrative review, conducted by the Centers for Disease Control and Prevention (CDC) in the US in 2016, concluded that there were no confirmed safety signals identified for the 4-valent HPV vaccine apart from syncope, which is preventable.[395] In this report, safety monitoring plans for the 9-valent HPV vaccine in the US are also discussed.

Finally, a narrative review of published post-license safety data from active and passive surveillance was undertaken in 2015.[380] The post-license period included nine years of data from diverse populations around the world. The active safety surveillance from Denmark, Sweden and the US (Vaccine Safety Datalink and Kaiser Permanente) alone included more than 1.6 million doses of the 4-valent vaccine. Only syncope and possibly skin infections were associated with vaccination in the post-license setting. Serious adverse events, such as adverse pregnancy outcomes, autoimmune diseases (including Guillain-Barre Syndrome and multiple sclerosis), anaphylaxis, venous thromboembolism and stroke were extensively studied and no increase in the incidence of these events was found compared with background rates.

6.4.5 Manufacturer evaluations and the role of adjuvants

As illustrated in Table 2.1 of Chapter 2, the commercially available HPV vaccines differ in the adjuvant used in their formulation. The 2-valent vaccine uses a proprietary adjuvant system containing 500 µg of aluminum hydroxide and 50 µg of 3-O-desacyl-4-monophosphoryl lipid A (AS04). The 4-valent and 9-valent vaccines use an amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant, but differ in the quantity used (225 versus 500 µg).

It has been argued that the adjuvant may be associated with adverse events, and that vaccine trials that use a placebo that also contains the adjuvant as the comparator will not capture this effect. The manufacturer of the AS04-adjuvanted 2-valent HPV vaccine performed a pooled analysis of trials in 2008 investigating the occurrence of autoimmune events that are possibly associated with the use of AS04 adjuvanted vaccines (3-O-desacyl-4' monophosphoryl lipid A and aluminium salts).[396] The 2-valent HPV vaccine, herpes simplex virus and hepatitis B virus vaccines were analysed in an integrated analysis of individual data (N=68,512). A separate analysis of the 2-valent vaccine trials alone was also undertaken (N=39,160). Participants who received a non-adjuvanted control vaccine, aluminium adjuvanted vaccines or aluminium hydroxide alone were included in the control group. The average follow-up time was 21 months. Reporting rates of overall autoimmune events were around 0.5% and did not differ between the AS04 and control groups. The relative risk (AS04 versus control) of experiencing any autoimmune event was 0.98 (95% CI: 0.80 to 1.21) in the integrated analysis and 0.92 (95% CI: 0.70 to 1.22) in the 2-valent vaccine analysis.

Another manufacturer evaluation in 2014 of the AS04-adjuvanted 2-valent HPV vaccine consisted of a pooled analysis of safety data involving 31,173 adolescent girls and women who received the vaccine and 24,241 controls.[397] Controls included placebo aluminium hydroxide or a range of other vaccines, including Hepatitis A and B vaccines. Incidences of unsolicited adverse events reported within 30 days after any dose were similar between HPV and control groups (30.8% versus 29.7%). During the entire study period, reports of medically significant conditions (25.0% versus 28.3%) and serious adverse events (7.9% versus 9.3%) were also similarly distributed between groups. Deaths were rare and similarly distributed.

As the above studies demonstrate, difficulties arise in distinguishing potential adverse events that could be attributable to an adjuvant in RCTs when the 'control' groups receive a placebo that contains some or all elements of the vaccine adjuvant. While the above manufacturer evaluations did not raise any safety concerns, a proportion of individuals in 'control' groups received either aluminium-containing placebo or another vaccine. Nonetheless, population-based observational studies have concluded that vaccinated individuals do not experience a range of serious conditions more frequently than unvaccinated individuals, as previously discussed in Section 6.2.7.3.4.

6.5 Discussion and conclusion

Since licensure in 2006, over 270 million doses of HPV vaccines have been distributed globally.[373] A substantial volume of surveillance studies, post-license safety data and trial data (including over 70,000 participants in our systematic review of systematic reviews) has accumulated in the scientific literature comparing the risks for a wide range of adverse health outcomes in vaccinated compared with unvaccinated subjects.[373]

The Evaluation Team carried out a systematic review of systematic reviews and retrieved a large body of evidence relating to the safety of the HPV vaccine. Across all reviews, conclusions were consistent:

- no safety issues were identified for a range of serious adverse events.

The systematic reviews that contributed most to the safety assessment were the two most recent and of highest methodological quality retrieved: the 2018 Cochrane review by Arbyn et al. and the 2017 health technology assessment (HTA) by Parsons et al.. Other identified reviews suffered from multiple methodological flaws which diminished confidence in their estimates.

As expected, minor adverse events that are transient in nature commonly occur following vaccination. The Cochrane review reported an absolute risk of 8,080 minor events per 10,000 in the vaccine group (81%) compared to 6,847 per 10,000 in the

placebo group (68%).

The international literature consistenly found that there is no difference in the rate of serious adverse events or deaths between individuals who receive the HPV vaccine and participants who receive placebo or a control vaccine. However, it is of concern that the body of evidence related to serious adverse events lacks a standard definition of what constitutes a serious adverse event. The definition of 'serious' was not reported in most reviews (nor in the primary studies), and the absolute adverse event rates varied widely. For example, in the 2-valent vaccine versus control comparison in the Adelaide HTA, the absolute rates ranged from 2% to 25% in individual studies. Serious adverse event rates in the vaccine arms varied from 734 per 100,000 (4-valent vaccine versus control comparison) to 11,677 per 100,000 (2-valent vaccine versus control comparison). The Cochrane review reported an absolute rate of 656 per 10,000 in the vaccine arm of trials, compared to 669 per 10,000 in placebo (resulting in a RR of 0.98, 95% CI 0.92 to 1.05; data from 71,597 participants in 23 RCTs; high-quality evidence).

Pooled values should be considered estimates as they were likely affected by the different definitions used. The comparisons between vaccine and placebo or control vaccine, however, should still be valid. The wide variation in serious adverse event rate reporting did not alter study conclusions, as serious adverse events did not occur more commonly in any vaccine comparison (vaccine versus placebo or control) in any review.

No review reported deaths that were causally associated with the HPV vaccine. The Cochrane review reports a non-significant pooled relative risk (RR) estimate of 1.29 (95% CI: 0.85 to 1.98; data from 71,176 participants in 23 RCTs). Authors downgraded this estimate due to imprecision from wide confidence intervals and inconsistency due to a statistically different risk between two age cohorts: a higher risk of mortality in older women was observed. The Adelaide HTA reported no deaths that were considered vaccine-related in 4-valent vaccine trials. In 2-valent vaccine trials, two studies reported deaths, however causality was not assessed.

'New-onset chronic disease' and 'medically significant conditions' were also investigated in RCTs by the Adelaide HTA, and no associations were found. Furthermore, observational studies that included six large, good-quality cohort studies and five self-controlled case series were identified. In these studies, no increased rates of the following conditions were found in vaccinated versus unvaccinated individuals: autoimmune disorders, venous thromboembolism, multiple sclerosis (MS) and other demyelinating conditions. Individual cohort studies also investigated a range of other conditions, such as Guillain–Barré syndrome, stroke, appendicitis, seizure, syncope and migraine among many others. No observational studies concluded that a verifiable safety concern exists.

The overwhelming conclusion from this assessment of the literature is that a large volume of evidence demonstrates the overall safety of HPV vaccines. This review supports the position of the World Health Organization's (WHO's) Global Advisory Committee on Vaccine Safety (GACVS), the European Medicines Agency (EMA), multiple country-level regulatory agencies and other independent reviews and expert analyses that HPV vaccines are safe. In its most recent update, the GACVS maintained its assertion that HPV vaccines are not causally associated with Guillain-Barré syndrome, complex regional pain syndrome, postural orthostatic tachycardia syndrome, premature ovarian insufficiency, primary ovarian failure and venous thromboembolism. Similarly, country-level surveillance of the HPV vaccine in the US (including the CDC), UK, Denmark and Sweden do not point to safety signals associated with HPV vaccines.

However, despite extensive reassuring safety data available, media attention has continued to focus on occasional case reports. The WHO continues to express concern surrounding the continued allegations related to HPV vaccine safety, and cautions against the 'real harm' that ensues due to the negative impact on vaccine coverage in a growing number of countries. Ongoing surveillance, effective communication and a rapid response to concerns are required to maintain confidence in HPV immunisation programmes.

Key points

- No review reported deaths causally associated with the HPV vaccine. The Cochrane review reported a non-significant mortality relative risk of 1.29 (95% CI: 0.85 to 1.98; data from 71,176 participants in 23 RCTs; low-quality evidence).
- This review concurs with the assessments undertaken by WHO's Global Advisory Committee on Vaccine Safety (GACVS) and the European Medicines Agency (EMA) regarding the safety of the HPV vaccine. Both concluded that the HPV vaccine is safe. In its most recent update, the GACVS maintained its assertion that HPV vaccines are not causally associated with Guillain-Barré syndrome, complex regional pain syndrome, postural orthostatic tachycardia syndrome, premature ovarian insufficiency, primary ovarian failure or venous thromboembolism.

- Five reviews provided a pooled estimate for serious adverse events; no difference in the incidence of serious adverse events (between vaccine and placebo/control groups) was found in any. The Cochrane review reported an absolute rate of 656 per 10,000 in the vaccine arm of trials, compared to 669 per 10,000 in placebo (resulting in a RR of 0.98, 95% CI 0.92 to 1.05; data from 71,597 participants in 23 RCTs; high-quality evidence).
- The Adelaide HTA also investigated a range of other important outcomes and included observational data (six high-quality cohort studies and five self-controlled case series) related to safety endpoints. The HPV vaccine was not associated with an increased risk for the following conditions: 'new onset chronic disease', 'medically significant conditions', venous thromboembolism, multiple sclerosis, other demyelinating conditions or autoimmune diseases. Anaphylaxis occurred at a rate of 1.7 per 1,000,000 doses.

Systematic review of economic evaluations

This chapter reviews the existing international evidence on the cost-effectiveness of HPV immunisation programmes. The main areas of interest are: the cost-effectiveness of extending a girls-only programme (the current situation in Ireland) to include vaccination of adolescent boys, and the provision of gender-neutral HPV vaccination programmes compared with no vaccination.

7.1 Review methodology

A systematic review was undertaken to assess the available cost-effectiveness evidence on gender-neutral HPV immunisation and to inform a decision on a prospective extension of the Irish HPV immunisation programme to include boys.

7.1.1 Search strategy

A number of systematic reviews of the economic literature on HPV vaccination in boys have been published in recent years. However, none of these reviews were considered adequate to address the terms and reference for this HTA. For this reason, a new search was created rather than an update of existing reviews. A search was carried out to identify published economic analysis evaluating HPV vaccination in males. The search was carried out in Pubmed, EMBASE, EBSCOhost (CINAHL + EconLit), and the Cochrane Library. A search was also performed in Google Scholar to identify any additional studies that were not included in these databases. All searches were run until March 2017 (and subsequently updated in October 2017) and included terms for HPV vaccination and cost-effectiveness. Details of the search strategy can be found in Appendix 7A.

The two fundamental questions to be addressed by this review were:

1) What is the potential value of adding boys to the current girls-only HPV immunisation schedule?
2) What is the potential value of gender-neutral vaccination compared with no vaccination?

The PICO (Population, Intervention, Comparator, Outcomes) analysis used to formulate the search is presented in Table 7.1.

Table 7.1 PICO for systematic review of cost-effectiveness studies for the inclusion of boys in HPV immunisation programme

Population	Boys and girls ≥ 9 years of age
Intervention	HPV immunisation (two-dose/three-dose schedules) of girls and boys. 2-valent, 4-valent or 9-valent vaccine
Comparison	HPV immunisation (two-dose/three-dose schedules) of girls-only or no vaccination
Outcomes	Cost-effectiveness (Costs, QALYS, LYG, ICER, incremental benefits)

Key: HPV – human papillomavirus; ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYS – quality-adjusted life years.

Published cost-effectiveness literature was included if it examined the introduction of a:

- gender-neutral HPV immunisation programme compared with vaccination of girls only
- gender-neutral HPV immunisation programme compared with no vaccination
- or a male HPV immunisation programme compared with no vaccination.

Study types that were excluded from this review included:

- Burden of disease and cost of illness studies, as they only examine the costs and not the consequences of the intervention.
- Studies that focus on a well-defined subgroup of the population of interest, for example, immunocompromised children, men who have sex with men (MSM) population.

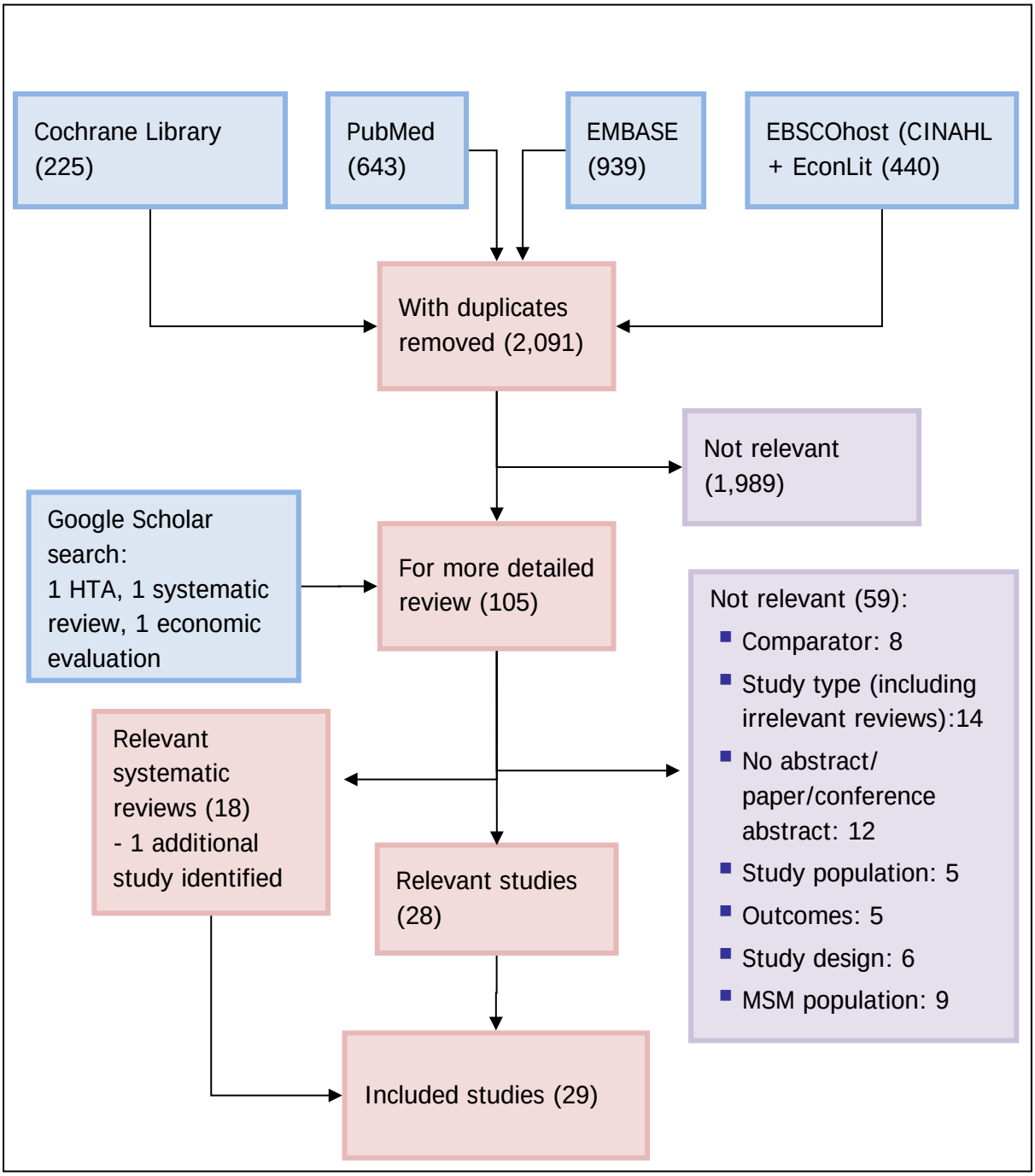
7.1.2 Study identification and data extraction

Preliminary screening of all returned results was undertaken by a single person to eliminate duplicates and studies that were clearly not relevant. Assessment of the eligibility of studies and identification of multiple reports from single studies was performed independently by two people, according to the inclusion criteria shown in Table 7.1. Disagreements were resolved by discussion.

Data extraction, assessment of quality and applicability to the Irish setting were carried out independently by two people, with any disagreements resolved by discussion. The quality of the modelled cost-effectiveness studies was assessed using the Philips checklist.[400] Transferability and applicability to the Irish setting were assessed using the ISPOR questionnaire.[401] Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes

measured and the overall study context. The credibility of the results were considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted and whether the authors had any conflicts of interest.

Figure 7.1 Cost-effectiveness literature search results



7.2 Results

The search identified 29[10, 402-430] relevant studies that met the inclusion criteria as per Table 7.1 and 18 relevant systematic reviews.[431-447] One of the included studies

had two papers published from the same study, [408, 409] therefore 30 papers were included representing 29 individual studies.

Each of the 18 systematic reviews was checked for additional relevant studies. One additional study Taira et al. 2004 was identified.[426] A flowchart of the results is shown in Figure 7.1.

7.2.1 Overview of study characteristics

Of the 29 studies included in this review:

- 14 studies were set in Europe (Austria,[10, 428] Denmark,[421, 422] Sweden,[430] Germany[406, 416, 419] Italy,[411, 420] Netherlands,[424] Norway,[403, 429] and the UK[413]),
- six in the United States,[402, 405, 407, 408, 415, 426]
- two in Canada,[410, 418]
- one in New Zealand,[423] Mexico,[412] Vietnam,[425] Australia,[417] Singapore[427] and Lao People's Democratic Republic (see Table 7.2).[404]

The majority of the studies conducted a cost-utility analysis,[10, 402-408, 410-413, 415, 417-423, 425-427, 429, 430] while three conducted a cost-effectiveness analysis[414, 424, 428] and one carried out a cost-benefit analysis.[416]

Nineteen studies related to the 4-valent vaccine, [10, 403, 405-408, 410-413, 415, 416, 418, 421-423, 425, 427, 429] while four considered the 2-valent vaccine, [404, 414, 426, 428] and three the 9-valent vaccine (see Table 7.3).[402, 419, 420] One study considered the 4-valent vaccine, but only modelled for HPV 16 and 18,[417] while another study modelled the 2-valent vaccine in their base case scenario, but modelled the 9-valent vaccine in a scenario analysis.[424] In the Swedish study, Wolff et al. modelled HPV 16 and 18, but considered the effect of HPV 6 and 11 in a scenario analysis.[430]

Assumptions about the vaccine in the studies included a coverage rate between 14% in boys[402] and 90% in girls and boys.[411, 414, 425] The duration of protection of the vaccine was assumed to be between 10 years and lifelong, and the efficacy of the vaccine was assumed to be between 41% and 100% depending on disease, HPV type and gender considered. Efficacy was sometimes lower when cross-protection to HPV types not included in the vaccine was considered (see Table 7.3); however, only four studies considered cross-protection in their model.[402, 406, 411, 418]

A number of studies considered the effect of not receiving the correct number of doses of the vaccine on efficacy. Some studies considered non-compliance to result in zero efficacy;[419, 420] while others considered a reduced efficacy for non-compliance.[10, 411] The effects of herd immunity was accounted for in most

studies,[10, 402-408, 411-415, 417, 418, 421, 422, 429, 430, 448] but was not accounted for in four studies.[410, 416, 419, 423]

Older studies considered a three-dose schedule for full vaccine efficacy, while a two-dose schedule was considered in seven studies (one from 2014,[418] one from 2015[416] and five from 2017.)[419, 420, 424, 427, 430] Most studies modelled vaccination in a pre-teen age group, most commonly nine to 12 years old, with only three studies considering vaccination in base case scenario for older age groups (12 to 26 years old[405, 407]and nine to 14 years old.)[419] However, a number of studies included scenarios with catch-up programmes in older age groups, most commonly in age groups up to the age of 30 years.[405, 408, 412, 413, 417-419, 421, 426, 427] One study modelled the cost-effectiveness of a catch-up programme up to the age of 75 years old.[404]

Table 7.2 Characteristics of included studies (setting and perspective)

Study	Country	Type of analysis	Perspective
Bresse (2014)	Austria	CUA	Public payer
Brisson (2016)	US	CUA	Societal
Burger (2014)	Norway	CUA	Societal
Chanthavilay (2016)	Lao PDR	CUA (DALYs)	Public payer
Chesson (2011)	US	CUA	Societal
Damm (2017)	Germany	CUA	Public payer and societal
Elbasha (2007)	US	CUA	US healthcare system
Elbasha (2010)	US	CUA	NR
Graham (2015)	Canada	CUA	Public payer
Haeussler (2015)	Italy	CUA	Unclear
Insinga (2007)	Mexico	CUA	NR
Jit (2008)	UK	CUA	Public payer
Kim (2007)	Brazil	CEA	Societal
Kim (2009)	US	CUA	Societal
Kotsopoulos (2015)	Germany	CBA	Public payer and societal
Kulsingam (2007)	Australia	CUA	Public payer
Laprise (2014)	Canada	CUA	Public payer
Largeron (2017)	Germany	CUA	Public payer
Mennini (2017)	Italy	CUA	Public payer
NOKC (2015)	Norway	CUA	Public payer and societal
Olsen (2010)	Denmark	CUA	Public payer
Olsen (2015)	Denmark	CUA	Public payer
Pearson (2014)	NZ	CUA	Public payer
Qendri (2017)	Netherlands	CEA	Public payer
Sharma (2015)	Vietnam	CUA	Societal
Taira (2004)	USA	CUA	Unclear
Tay (2017)	Singapore	CUA	Public payer
Wolff (2017)	Sweden	CUA	Public payer and societal
Zechmeister (2009)	Austria	CEA	Public payer

Key: CUA, cost-utility analysis; CEA, cost-effectiveness analysis; CBA, cost-benefit analysis; NR, not reported; DALY, disability-adjusted life year.

Table 7.3 Characteristics of included studies (programme details, coverage and vaccine)

Study	Age at vaccination (years)	Catch-up	Doses	Vaccine Coverage rate	Vaccine	Cross protection
Bresse (2014)	9	No	3	65% for both genders (80% compliance)	4-valent	No
Brisson (2016)	9	No	3	38% in girls and 14% in boys	9-valent	Yes
Burger (2014)	12	No	3	71% in girls and boys	4-valent	No
Chanthavilay (2016)	10	11-25 or 11-75 year olds	3	70%	2-valent	No
Chesson (2011)	12	Females: 13-26 year olds	3	30%, 20% and 75% in girls and boys	4-valent	No
Damm (2017)	12	No	3	50%	4-valent	Yes
Elbasha (2007)	12	12-24 years	3	70% (0 to 50% during first 5 years for catch-up)	4-valent	No
Elbasha (2010)	9-26	No	3	16% in girls and 9.6% in boys	4-valent	No
Graham (2015)	12	No	3	50%	4-valent	No
Haeussler (2015)	12	No	3	90.48%	4-valent	Yes
Insinga (2007)	12	Females: 12-24 year olds	3	70% in girls and boys	4-valent	No
Jit (2008)	12	Females: 15-25 years	3	80%	4-valent	No
Kim (2007)	12	No	3	0-90% in girls and boys	2-valent	No
Kim (2009)	12	No	3	75% in girls and boys	4-valent	No
Kotsopoulos (2015)	12	No	2	55%	4-valent	No
Kulsingam (2007)	12	Females: 14-26 years	3	80%	2-valent	No
Laprise (2014)	9	Females: 14 years old	2 and 3	80% in girls and boys	4-valent	Yes
Largeron (2017)	9-14	To age 17 years (unclear)	2	9-10 yrs - 16.3%; 11-12 yrs - 37.7%; 13 -14 yrs 45.6%; 15-17 yrs 55.6%	9-valent	No
Mennini (2017)	12	No	2	71.1% (with 90% compliance)	9-valent	No
NOKC (2015)	12	No	3	82% in girls and boys	4-valent	No
Olsen (2010)	12	Females: 13-26 years	3	70%	4-valent	No
Olsen (2015)	12	No	3	70% and 85%	4-valent	No

Table 7.3 continued (Characteristics of included studies (programme details, coverage and vaccine))

Study	Age at vaccination (years)	Catch-up	Doses	Vaccine Coverage rate	Vaccine	Cross protection
Pearson (2014)	12	No	3	Between 45% and 73% depending on scenario	4-valent	No
Qendri (2017)	12	No	2	60% for girls and 40% in boys	2-valent	No
Sharma (2015)	<12	No	3	Values tested: 25%, 50%, 75%, 90%	4-valent	No
Taira (2004)	12	24-30 year olds	3	70%	2-valent	No
Tay (2017)	11-12	Females: 13-17 year olds	2 and 3	80%; for catch-up: 50%	4-valent	No
Wolff (2017)	10	No	2	80% girls and boys	2-valent	No
Zechmeister (2009)*	12	No	3	65%	2-valent	No

* The Zechmeister study included a booster vaccination at 10 years after initial vaccination.

Note: some studies included both 4-valent and 9-valent vaccines in different scenarios.

Table 7.4 Characteristics of included studies (efficacy and duration of protection)

Study	Efficacy	Protection duration
Bresse (2014)¥	Disease, HPV-type and sex specific. Ranging from 41% to 100%.	Lifelong*
Brisson (2016)	95% against HPV 6/11/16/18. With cross protection: 46.2% for HPV 31, 28.7% for HPV 33, 7.8% for HPV 45, 18.4% for HPV 52, 5.5% for HPV 58. 95% against 16/18/6/11/31/33/45/52/58 for 9-valent vaccine.	Lifelong
Burger (2014)	100% in girls and 90% in boys	Lifetime
Chanthavilay (2016)	100%	Lifelong*
Chesson (2011)	95% in girls and 90% in boys	Lifetime
Damm (2017)	98% against HPV 16/18. 100% against HPV 6/11 for the 4-valent vaccine.	10 years, followed by 10% reduction per annum.
Elbasha (2007)	90% against HPV 6/11/16/18	Lifelong*
Elbasha (2010) ¥	98-100% females, 84-91% males (For females against HPV infection 76% to 96%, for males 85%.)	32 years (half-life)
Graham (2015)	83.80%	Unclear
Haeussler (2015) ¥	78% against cervical cancer, 70% against anal cancer, 50% against head & neck cancer	Lifelong
Insinga (2007)	95.2% cervical, 98.9%	Lifetime
Jit (2008)	100%	10 years to lifelong
Kim (2007)	100%	Lifetime
Kim (2009)	100% in girls and 85% in boys	Lifetime
Kotsopoulos (2015)	98% against CIN1, 98% against CIN2, 97% against CIN3, 100% against cervical cancer, 87% against anal cancer, 100% against vulvar cancer, 100% against vaginal cancer, 78-96% against head & neck cancer, 99% for females against genital warts, 89% for males against genital warts. Proportion cases attributable to HPV 6/11/16/18 is disease-specific.	Unclear
Kulsingam (2007)	100%	Lifelong*
Laprise (2014)	95%	three dose: 20 years to lifelong, two dose: 10 years - lifelong

Table 7.4 continued (Characteristics of included studies (efficacy and duration of protection))

Study	Efficacy	Protection duration
Largeron (2017) ¥	Disease, HPV-type and sex specific. Ranging from 41% to 100%. No protection against HPV16/18 related AIN/PIN/H&N neoplasia	Lifelong
Mennini (2017) ¥	Disease, HPV-type and sex specific. Ranging from 41% to 100%. No protection against HPV16/18 related AIN/PIN/H&N neoplasia	Lifelong*
NOKC (2015)	Persistent infection 6,11,16,18 RR 0.33 (95%CI 0.24,0.44) (boys);0.26 (0.16, 0.42) girls; CIN2/3 + cervical cancer RR 0.80 (95%CI 0.62, 1.02); VIN/VaIn2+ + vulvar cancer RR 0.49 (0.32, 0.76)	Lifetime
Olsen (2010)	100%	Lifelong
Olsen (2015)	100%	Lifetime
Pearson (2014)	99%	three dose: 20 years to lifelong
Qendri (2017)	98%	Lifelong*
Sharma (2015)	100% in girls and 85% in boys	Lifelong
Taira (2004)	90%	10 years
Tay (2017) ¥	95.2% against CIN; 98.9% against genital warts	Lifelong
Wolff (2017)	Vaccine 100% effective against HPV 16/18. Vaccine effectiveness based on proportion attributable to HPV 16/18: CIN 1 (26%), CIN 2 (43%), CIN 3 (61%), cervical cancer (70%), vaginal cancer (55%), vulvar cancer (54%), anal cancer (84%), oropharyngeal cancer (60%), penile cancer (48%)	Lifelong
Zechmeister (2009)	90%	Assumed waning efficacy and booster needed after 10 years.

¥ These studies made explicit assumptions about efficacy for individuals that were not compliant will the full dose schedule. These assumptions ranged from reduced efficacy to no efficacy.
* Shorter periods of protection were tested in sensitivity analyses.
Abbreviations: CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia; PIN, penile intraepithelial neoplasia; H&N, head & neck cancer; RR, relative risk.

Table 7.5 Characteristics of included studies (conditions included in model)

Study	CIN	Cervical cancer	VaIN	Vaginal cancer	VIN	Vulvar cancer	AIN	Anal cancer	PIN	Penile cancer	Head & neck cancer	Genital warts	RRP
Taira (2004)	x	x											
Kim (2007)	x	x											
Kulsingam (2007)	x	x											
Elbasha (2007)	x	x										x	
Insigna (2007)	x	x										x	
Jit (2008)	x	x										x	
Zechmeister (2009)	x	x											
Kim (2009)	?	x		x		x		x		x	x	x	x
Olsen (2010)	x	x										x	
Elbasha (2010)	x	x	x	x	x	x	x	x	x	x	x	x	x
Chesson (2011)	x	x		x		x		x		x	x	x	x
Pearson (2014)	x	x				x		x			x	x	
Burger (2014)		x		x		x		x		x	x	x	x
Laprise (2014)	x	x		x		x		x		x	x	x	
Bresse (2014)	x	x	x	x	?	x		x		x	x	x	?
Graham (2015)											x		
Sharma (2015)	x	x										x	
Kotsopoulos (2015)	x	x		x		x		x		x	O	x	
Olsen (2015)	x	x		x		x		x		x	x	x	
NOKC (2015)	x	x	O	O	x	x	O	O				x	
Haeussler (2015)	x	x	x	x	x	x	x	x		x	x	x	
Chanthavilay (2016)	x	x											
Brisson (2016)	x	x		x		x		x		x	x	x	

Table 7.5 continued (Characteristics of included studies (conditions included in model))

Study	CIN	Cervical cancer	VaIN	Vaginal cancer	VIN	Vulvar cancer	AIN	Anal cancer	PIN	Penile cancer	Head & Neck cancer	Genital warts	RRP
Damm (2017)	x	x										x	
Tay (2017)	x	x										x	
Qendri (2017)	?	x		x		x		x		x	x		
Largeron (2017)	x	x	x	x	x	x	?	x		O	O	x	O
Wolff (2017)	x	x		x		x		x		x	x	O	
Mennini (2017)	x	x	x	x	x	x	?	x		O	O	x	O

Notes: x, included; O, included in scenario analysis; ?, unclear if included.

The studies have been sorted by year to illustrate the trend for increasing number of conditions to be included in analyses.

Abbreviations: CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; AIN, anal intraepithelial neoplasia; PIN, penile intraepithelial neoplasia; H&N, head & neck cancer; RRP, recurrent respiratory papillomatosis.

Table 7.6 Cost-effectiveness findings of included studies

Study name	Study year	Country	Strategy reported	Assumptions	ICER
Taira	2004	US	FM v F	70% coverage	$442,039/QALY
				30% coverage in females	$40,865/QALY
Elbasha	2007	US	FM v F		FM strategy dominated
Insinga	2007	Mexico	FM v F		FM strategy dominated
Kim	2007	Brazil	FM v F	Vaccine cost of I$400/three doses	I$15,120/YLS for 50% coverage
					I$18,820/YLS for 75% coverage
Kulasingam	2007	Australia	FM v F		$33,644/QALY
Jit	2008	UK	FM v F+FCU	10 years of protection (80% girls coverage)	£113,846/QALY
				lifetime protection (80% girls coverage)	£520,255/QALY
Kim	2009	US	FM v F	All HPV disease included, screening every 2 years, efficacy <90%	>$100,000/QALY for all male and female cancers
				All HPV disease included, screening every 3 years, efficacy 90% in males, 100% females	$ 88,930/QALY
Zechmeister	2009	Austria	FM v F		€311,000 per LYG
Olsen	2010	Denmark	FM v screening only		€20,055/LYG, €18,677/QALY
Elbasha	2010	US	FM v F		$178,908/QALY for female cancers
					$25,664/QALY for all HPV diseases

Table 7.6 continued (Cost-effectiveness findings of included studies)

Study name	Study year	Country	Strategy reported	Assumptions	ICER
Chesson	2011	US	FM v F	Coverage 30%	$121,700/QALY for cervical cancer only
					$41,400/QALY for all HPV outcomes
Pearson	2014	New Zealand	FM v F		NZ$118,000/QALY
Burger	2014	Norway	FM v F	Vaccine price $75	$145,500/QALY for cervical cancer outcomes only
					$60,100/ QALY for all HPV outcomes
Laprise	2014	Canada	FM v F	2 dose	€86,214/QALY
				3 dose	>$100,000/QALY gained
Bresse	2014	Austria	FM v no vaccination		€26,701/QALY for cervical cancer only
					€10,033/QALY for all HPV disease
Graham	2015	Canada	M v no vaccination		Vaccination was cost saving relative to no vaccination and generated more QALYs
Sharma	2015	Vietnam	FM v F	at <I$25 for 3 doses	I$2800/QALY
Kotsopolous	2015	Germany	FM v no vaccination		Every €1 invested in HPV vaccination generates €1.70 in gross tax revenue over the lifetime of the cohort
Olsen	2015	Denmark	FM v F	2 dose	€28,031/QALY
				3 dose	€41,636/QALY
NOKC	2015	Norway	FM v F	3 doses	€155,550/QALY
Haeussler	2015	Italy	FM v F		€11,517/QALY

Table 7.6 continued (Cost-effectiveness findings of included studies)

Study name	Study year	Country	Strategy reported	Assumptions	ICER
Chanthavilay	2016	Lao PDR	FM v F		Not cost-effective - ICER >3GDP
Brisson	2016	US	MF v no vaccination	with cross protection	$5500/QALY
				without cross protection	$7300/QALY
Damm	2017	Germany	FM v F	3 dose +coverage ≥50% in girls and boys	>€50,000/QALY
				2 dose + 20% coverage in girls and 20-80% coverage in males	€37,985/QALY for 4-valent vaccine
Tay	2017	Singapore	FM v no vaccination	3 dose	S$27,837/QALY
				2 dose	S$22,574/QALY
Qendri	2017	Netherlands	FM v F	40% uptake in boys	€9134/LY
Largeron	2017	Germany	FM v F	9-valent FM v 4-valent F	€22,987/QALY
				9-valent FM v 9-valent F	€42,679/QALY
Wolff	2017	Sweden	FM v F	Societal perspective	€36,531/QALY
				Without inclusion of indirect costs	€38,999/QALY
				Inclusion of genital warts	€28,165/QALY
Mennini	2017	Italy	FM v F	9-valent F v 9-valent FM	€16,495/QALY
				4-valent F v 9-valent FM	€13,541/QALY

Notes: FM = vaccination of males and females, F = vaccination of females only, M = vaccination of males only, F+FCU = vaccination of females and a female catch up programme

A variety of HPV-related diseases were included in the analyses. With the exception of Graham et al. 2015,[410] all of the studies included cervical cancer in their models and most included CIN. Prior to 2009, only CIN, cervical cancer and sometimes genital warts were included in the models.[408, 412-414, 417, 426, 428] In more recent years, a number of studies also included cancer of the vagina, vulva, anus, and penis in their model and a smaller number of studies included the precancerous stages for each of these diseases (see Table 7.5). Although the HPV vaccine is not currently licensed for prevention of head and neck cancers, 13 studies included head and neck cancer in their model,[10, 402, 403, 405, 407, 410, 411, 415, 418, 422-424, 430] while another three studies included head and neck cancer in their sensitivity analysis.[416, 419, 420] RRP was only included in the base-case in four of the studies,[403, 405, 407, 415] but was included during sensitivity analysis in a further two studies.[419, 420] Elbasha et al. (2010)[409] developed the only model to include all HPV-related diseases, while nine studies included all HPV-related cancers and genital warts in their model.[10, 402, 403, 411, 415, 418-420, 422]

Of the 29 studies, 23 used models based on dynamic transmission modelling.[10, 402-408, 411-415, 417-422, 427-430] Two studies used hybrid models with dynamic transmission and a static disease progression model,[425, 426] while one study used a Markov macro-simulation static cohort model,[423] one used a static Markov state transmission model,[410] one used a Bayesian data synthesis framework,[424] and one used a prospective cohort model.[416] Dynamic models take into account the transmission of infection in the population, that is, susceptible persons have a lower risk of infection over time, even if they have not been vaccinated themselves; this is known as a herd effect. However, dynamic models require more information on sexual activity patterns within a population, as well as the natural history of HPV infection. Therefore, dynamic models require more assumptions and are associated with a greater level of uncertainty compared with static models.

Handling of parameter uncertainty is important as parameter values are typically known with imprecision, and appropriate methods should be used to assess the impact of that uncertainty on the outputs of an evaluation. In relation to HPV vaccination there are numerous parameters for which local data are often unavailable, particularly for elements of the dynamic transmission model. Due to the limited availability of data for certain parameters, some are defined within plausible ranges and then refined during model calibration. This process can result in a 'parameter set' that is known to result in plausible output values when the current standard of care is modelled. Some of the included CEAs used a single parameter set and then applied a deterministic approach to estimate cost-effectiveness, and then explored parameter uncertainty through a set of univariate sensitivity analyses or scenario analyses. A limited set of economic evaluations used either multiple parameter sets or a fully probabilistic model to estimate cost-effectiveness. A fully

probabilistic model is generally preferable as it facilitates a more in-depth exploration of decision uncertainty, which is particularly relevant given the limitations of the available data. However, it must be acknowledged that for some modelling approaches a fully probabilistic approach may incur a computational burden that is unreasonable, and therefore a deterministic approach may be acceptable. For most of the models that used a deterministic approach, it is unclear whether all parameters were subjected to a univariate sensitivity analysis or just the highly limited subset that were reported.

Most of the studies adapted existing models to estimate the costs and effectiveness of HPV vaccination. The model developed by Elbasha et al.[409] was used or adapted in seven studies;[10, 407, 408, 412, 419, 420, 427] the HPV Advise model[449] was used in two studies,[402, 418] and the Danish HTA model from 2007[450] was also used in two studies.[421, 422] Based on the previous work of others, Kim et al.[414, 415, 451] developed models which were used or adapted in two other studies.[403, 425]Models by Chesson et al.[405, 452] were used and or adapted in three of the studies.[405, 428, 429] One study[404] adapted the model used by Jit et al. in 2008,[413] while three studies developed a new model for their study.[410, 416, 430]

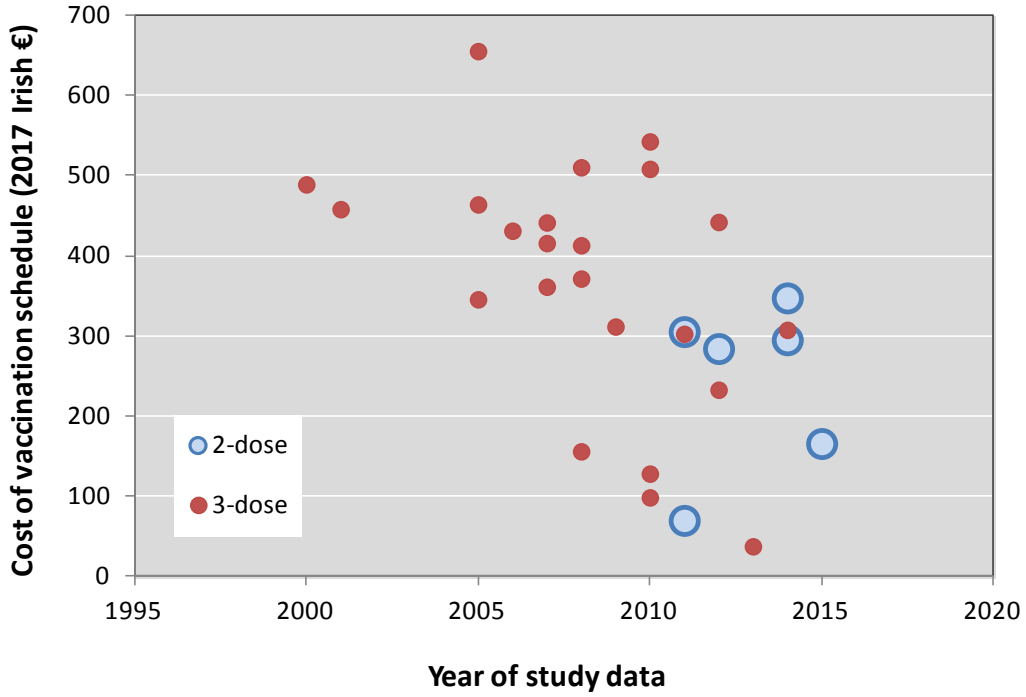
Perspective in health economic evaluations has implications for the interpretation of the results. For example an intervention may not appear to be cost-effective when the public payer perspective is considered, but if that intervention has benefits other than those born by the health sector, it may be cost-effective if the societal perspective is taken into account. The public payer perspective was adopted by 16 studies;[10, 404, 408, 410, 413, 417-424, 427-429] while six adopted a societal perspective[402, 403, 405, 414, 415, 425] and three did both.[406, 416, 430] It was not clearly stated what the perspective was for four studies.[407, 411, 412, 426]

The most suitable rate to apply for discounting costs and health outcomes in the future is often debated. This is particularly true when vaccines are concerned as often the health benefits occur in a different generation from the one paying for the vaccine.[453] However, in the base case scenarios of most of the studies, the costs and health outcomes where discounted at the same rate and the most common rates were 3%,[10, 402, 404-408, 411, 412, 414, 415, 418-425, 427, 430] or 5%.[410, 417, 428] Jit et al. used a discount rate of 3.5%,[413] Kotsopoulous et al. used a 1.4% discount rate,[416] and Burger et al. used a discount rate of 4%.[403] One model applied a variable discount rate of 4% between years 1 to 40, 3% from years 41 to 75 and 2% after year 75.[429]

In any assessment of a vaccination programme, the cost of the vaccine has the potential to be very influential on the estimated cost-effectiveness. This is because the cohort receiving vaccination may be very large, while the number benefiting from reduced morbidity and mortality may be relatively small. Vaccine costs are also

incurred at the outset and thus not impacted by discounting, while the health benefits may occur many years later and thus are subject to substantial discounting. The included CEAs were published between 2004 and 2017, but the included cost data span from 2000 to 2014. The reported cost of vaccination has decreased over time (Figure 7.2). The 9-valent vaccine is more costly than the 4-valent or 2-valent vaccine after having adjusted for year and number of doses. It should be noted that studies including a two-dose schedule used data from the 2011 to 2014 time period, during which there was no appreciable difference in price between a two and three-dose programme.

Figure 7.2 Reported cost of the vaccination schedule over time



For studies that tested the impact of varying the cost of vaccination, it did not generally change the interpretation of cost-effectiveness. This could, however, be a function of the narrowly defined bounds in those cases. It is typical in economic evaluations to vary costs by ±20%, and it is apparent from Figure 7.2 that average costs have declined by much more than 20% over the course of 15 years.

7.2.2 Quality of included studies

The quality of the modelled cost-effectiveness studies was assessed using the Philips checklist.[35] In general, the quality of the included studies was considered moderate to good, although there were a number of areas for which most if not all studies were considered poor quality.

A critical issue was the extent to which key parameters were based on a systematic synthesis of evidence. This issue was often evident within the efficacy data, which

could be based on expert opinion despite the availability of trial data. Another near-universal issue was the lack of quality assessment of key parameter data. Variables were often defined using data from evaluations published up to 10 years previously, with no indication of whether or not more up-to-date data were sought.

The approaches to parameter uncertainty were often inadequate, with the only evidence presented being a univariate analysis of a limited set of parameters. In many cases, the bounds selected for the parameter values in the sensitivity analysis were not justified or explained.

With the exception of one study, the identified studies were published in peer-reviewed journals and were therefore generally subject to word count and other formatting restrictions. While many provided additional detail in the form of supplementary appendices, the format does not lend itself to transparent reporting. Given the inherent complexity of dynamic transmission modelling, the brevity of the reporting gives rise to challenges in identifying how the work was done, and whether it was carried out to a high standard. As a number of the studies used previously published models, the model could be summarised with reference to the earlier study rather than any meaningful description of the model structure.

From a quality perspective, conflicts of interest should be taken into account as it may introduce bias. In the case of HPV vaccination evaluations, conflict of interest typically arose where the economic evaluation is undertaken by employees of the manufacturer or where the evaluation is sponsored by the manufacturer. Of the 29 identified studies, 16 reported a clear conflict of interest and in another two studies conflict of interest was unclear. Of the 11 studies where the authors were not considered to have a conflict of interest, four highlighted issues such as industry funding for unrelated work.

7.2.3 Applicability of included studies

The assessment of applicability is intended to determine the extent to which evaluation findings might apply in the setting relevant to the decision-maker. In this case, the decision-maker is interested in a school-based gender-neutral HPV vaccination programme using a two-dose schedule of the 9-valent vaccine. Studies based on a three-dose schedule may underestimate compliance and overestimate costs. A study based on the 2-valent or 4-valent vaccine may underestimate effectiveness. Studies that evaluate a gender-neutral relative to screening only and do not include a comparison with a girls-only programme are likely to generate biased estimates of cost-effectiveness and are therefore of limited applicability.

There were five studies based in developing countries (Brazil, Lao PDR, Mexico, Singapore and Vietnam). Much of the epidemiological data used in the models for aspects such as the transition probabilities came from earlier models constructed in

the context of developed countries. The vaccine costs used in the five developing world studies were also similar to those used in the remaining studies. However, other important elements such the costs of cancer screening and treatment are much lower than those that apply in Ireland. As such, the studies from developing nations are considered less applicable.

Transferability and applicability for the Irish setting was assessed using the ISPOR questionnaire.[36] Common issues across studies included the design of the model, inclusion of data not applicable to Ireland, and uncertainty regarding the face validity of the model. Many studies used a limited set of health outcomes, such as only CIN, cervical cancer and genital warts. Given the knowledge regarding a wider set of outcomes, studies with restricted outcomes are unlikely to generate estimates that are reflective of current knowledge of vaccine effectiveness.

7.2.4 Summary clinical effectiveness results

The majority of the studies (17 out of 29) reported on the effects of a switch to gender-neutral vaccination on cancer burden,[10, 402-406, 408, 413, 414, 416, 418, 419, 422, 425, 427, 429] with 10 studies also reporting on anogenital wart impact.[10, 403, 408, 413, 416, 418-420, 427, 429, 430] Other studies reported no clinical outcomes or reported them in a format that did not allow extraction of the effect on cancer burden of switching to a gender-neutral programme.

The most common reported clinical impact was on cervical cancer. Of those studies that reported the effect of introducing a gender-neutral programme on cervical cancer burden,[403-405, 408, 413, 418-420, 425, 429] reductions of 2.9%[418] to 24%[419] were reported in cervical cancer cases. The wide range of effect may be explained by the differing assumptions used in the studies regarding coverage and efficacy of the vaccine and using different models with different vaccination schedules. Largeron et al.[419] reported the largest decrease of 24% in the incidence of cervical cancer, however this figure compares the switch from the 4-valent vaccine for girls only to vaccinating girls and boys with the 9-valent vaccine, with an estimated 17% of the overall benefit being due to the change to the 9-valent from the 4-valent vaccine.

7.2.5 Summary cost-effectiveness results

Nineteen studies reported cost per quality-adjusted life year (QALY) gained for gender-neutral vaccination compared with girls-only programmes using a variety of assumptions on vaccine coverage, duration of vaccine effect and the number of doses delivered.[403, 405-408, 411-413, 415, 417-420, 422, 423, 425, 426, 429, 430] Three studies reported cost-effectiveness in terms of cost per life year saved or gained,[414, 424, 428] while one study reported cost per disability-adjusted life year[404] and another study reported in terms of a cost benefit ratio.[416] Four studies reported cost per QALY for gender-neutral vaccination compared with no vaccination[10, 402, 421, 427] and one study

reported the costs saved and QALYs gained per vaccinated male compared to no vaccination.[410]

Of the four studies that reported gender-neutral vaccination in comparison to no vaccination, all concluded that gender-neutral vaccination was cost-effective.[10, 402, 421, 427]

Of the 19 studies that compared gender-neutral vaccination with girls-only vaccination and reported costs per QALY, six studies concluded that compared with girls-only vaccination, a gender-neutral programme would be cost-effective,[407, 411, 417, 419, 420, 422] 12 concluded that it was either not cost-effective[413, 415, 418, 423] and or the optimal strategy would be to increase vaccine coverage in girls or introduce a catch-up programme in the girls-only programme,[403, 405, 412, 425, 429] or that it was only cost-effective when coverage in females was low.[406, 408, 426]

Two of the 19 cost-utility studies that compared gender-neutral vaccination with girls only vaccination were from developing countries — Mexico[412] and Vietnam[425] — and are therefore less applicable to the Irish setting. Jit et al. included a catch-up component in their comparison group, making a direct comparison to other studies difficult.[413] Table 7.7 shows the remaining studies with vaccine cost and ICER converted to 2017 Irish Euro and grouped by country.

Five of the studies are from the US;[405, 407, 408, 415, 426] despite the use of a similar vaccine cost (range €413 to €511), these studies have a wide range of ICERs reported (range €29,378/QALY to €675,293/QALY) (Table 7.7). Tiara et al. was the earliest study and reports the highest ICER value of all the studies (€675,293/QALY); however, this study assumed the vaccine only provided 10 years of protection and only included CIN and cervical cancer in their model which may partially explain the high ICER value. Two of the studies were from Norway;[403, 429] Burger et al. took the societal perspective and used a much lower vaccine cost than the NOKC study (€99 versus €308). The NOKC study took a health payer perspective, included fewer disease outcomes in their model and used a higher coverage, and reported a much higher ICER value than the study by Burger et al. (€39,808 versus €149,833).

Two of the studies were from Italy;[411, 420] both reported low ICERs compared to the rest of the studies (Table 7.7). Meninni et al. used a slightly higher vaccine cost (€295 versus €233), but modelled the two-dose schedule with the 9-valent vaccine and used a 100-year time horizon. Haeussler et al. modelled a three-dose schedule with the 4-valent vaccine and used a 55 year-time horizon. Although generating similar ICERs, Haessler had the lowest ICER at €14,258 per QALY while Mennini reported a higher ICER of €20,300 per QALY.

Two studies from Germany also reported similar ICERs (€45,692/QALY and €50,629/QALY),[406, 419] but differed in their assumptions. Damm et al. used a

substantially higher vaccine cost (€543) compared with Largeron et al. (€348); Largeron used a two-dose schedule for the 9-valent vaccine and assumed lifetime protection with the vaccine, while Damm modelled a three-dose schedule for the 4-valent vaccine and assumed 20 years of protection. Based on the lower vaccine cost, the two-dose schedule and the use of the 9-valent vaccine you would expect the ICER for the study by Largeron et al. to be lower than that generated by the model by Damm et al.; however, the former study did not account for herd immunity in the model.

Table 7.7 Reported incremental cost-effectiveness ratios

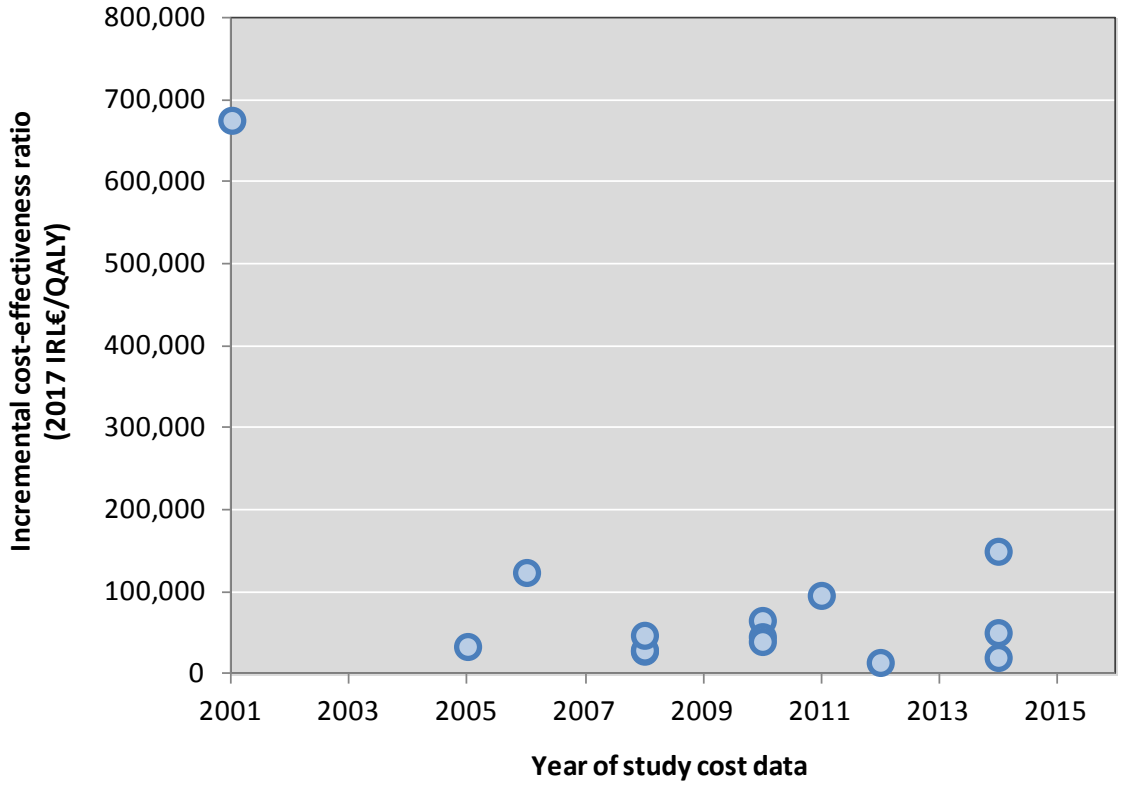
Study	Year	Country	ICER (€/QALY)	Cost of vaccine schedule €
Kulasingam (2007)	2005	Australia	33,722	346
Laprise (2014)	2010	Canada	65,467	128
Olsen (2015)	2008	Denmark	28,006	372
Damm (2017)	2010	Germany	45,692	543
Largeron (2017)	2014	Germany	50,629	348
Haeussler (2015)	2012	Italy	14,258	233
Mennini (2017)	2014	Italy	20,300	295
Pearson (2014)	2011	New Zealand	96,025	303
Burger (2014)	2010	Norway	39,808	99
NOKC (2015)	2014	Norway	149,833	308
Wolff (2017)	2015	Sweden	38,999	166
Taira (2004)	2001	US	675,293	458
Elbasha (2007)*	2005	US	Dominated	464
Kim (2009)	2006	US	123,959	431
Elbasha (2010)	2008	US	29,378	413
Chesson (2011)	2008	US	47,391	511

It is possible to define a subset of the most applicable studies based on several criteria: comparison of a gender-neutral programme with a girls-only programme; 4-valent or 9-valent vaccine; developed nation; and outcome reported as a cost-utility. Of the 15 studies meeting these criteria, some report multiple ICERs for different scenarios. In these cases, the comparison most applicable to the Irish setting was selected for that study. For one study, Elbasha *et al.*, a gender-neutral programme was dominated (that is, was more costly and less effective) by usual care. For the remaining 14 studies the ICERs ranged from €14,258 per QALY to €675,293 per QALY (see Figure 7.3). Six reported an ICER of less than €45,000 and QALY and one an ICER of less than €20,000/QALY. Only four of the 15 studies were not industry sponsored or supported, of which three estimated ICERs greater than €100,000/QALY.

Largeron et al. and Mennini et al. are the only studies that modelled the 9-valent vaccine and compared gender-neutral vaccination to a girls-only programme.[419, 420] Both of these studies are based on a two-dose schedule and have the same efficacy and lifelong duration of protection assumptions. Both models are based on Elbasha's models[407, 408] and in the base case they included cervical cancer, vaginal cancer, vulvar cancer and their precursors as well as anal cancer and genital warts. Penile cancer, head and neck cancer and RRP were included in the sensitivity analysis. Largeron et al. is a German study and they reported an ICER of €22,987 per QALY when comparing the 4-valent girls-only programme to a 9-valent gender-neutral programme. The ICER increases to €42,679 when a 9-valent girls-only programme is compared with a 9-valent gender-neutral programme. They concluded that the addition of boys to a girls-only programme was cost-effective. Mennini et al. is an Italian study and they reported an ICER of €13,541 per QALY when comparing the 4-valent girls-only programme with a 9-valent gender neutral programme and an ICER of €16,495 per QALY when comparing a 9-valent girls-only programme with a 9-valent gender-neutral programme. Mennini also concluded that a gender-neutral programme was cost-effective. However, both these studies were funded by the pharmaceutical industry providing a potential source of bias. Largeron et al. also did not allow for the effect of herd immunity in their model and therefore are likely to have underestimated the health benefits of vaccinating boys.

The number of diseases included in the model often differs between studies with studies reporting lower ICERs (that is, the intervention becomes more cost-effective) when additional diseases such as head and neck cancer are included in a scenario analysis. However, there is no direct correlation between the number of diseases included and the ICER value.

Figure 7.3 Reported incremental cost-effectiveness ratios by year in studies applicable to Ireland



7.3 Discussion

This systematic review identified 29 studies of economic evaluations of gender-neutral HPV vaccination programmes. The evidence of cost-effectiveness was equivocal, particularly relative to willingness-to-pay thresholds typically applied in Ireland. Numerous studies showed that the addition of boys to a girls-only HPV vaccination programme may only be cost-effective if current uptake of the HPV vaccine is low among girls and all potential health benefits (that is, including conditions for which the vaccines are not currently indicated) are included. Increasing vaccination coverage amongst girls was found to be a more efficient strategy than extending vaccination to boys. While studies noted that an increased vaccine coverage in girls should be strived for, achieving at least 90% coverage may be unrealistic given persistently low vaccine coverage among girls in some countries (for example the US, has remained fairly constant at 30% in the last five years).[405]

The efficiency of including boys in the vaccination programme was considered by most studies to be dependent on the vaccine price, coverage and the willingness-to-pay threshold. For example, Pearson et al.[11] found that regardless of how low vaccine or administration costs were set and bringing the discount rate to zero, extending vaccination to include boys still did not lead to the gender-neutral programmes being cost-effective compared with intensifying the girls-only

programmes — 73% vaccine coverage was shown to be equally effective and less costly than a gender-neutral programme where coverage remained at 47%. The authors noted, however, that the marginal costs to further increase girls-only coverage when the rate of coverage has reached a steady state may be significant. If the cost of increasing female coverage were included in an analysis, the vaccination of boys may become cost-effective when optimal scenarios of vaccine price and willingness-to-pay thresholds are considered. A German study by Damm et al. estimated a two-dose gender-neutral programme with male coverage of 20% or higher to be cost-effective only when coverage in girls was 20%.[(454)] At 50% coverage in girls it was not cost-effective to include boys in the programme.

The six evaluations published before 2009 were all restricted to outcomes of CIN, cervical cancer and genital warts. The only health benefit that could accrue to boys was therefore a reduction in the incidence of genital warts. Since 2009, 15 evaluations have included vaginal, vulvar, anal, penile and head and neck cancers. Six of those 14 evaluations also included the associated precancerous abnormalities (vaginal, vulvar, anal and penile intraepithelial neoplasia). The increased number of outcomes reflects the introduction of the 9-valent vaccine and the increasing evidence base in terms of efficacy of the vaccine. However, it should be noted that some of the earlier studies may have used optimistic estimates of efficacy based on expert opinion; subsequent trial evidence may be leading to more conservative estimates of efficacy. With longer follow-up trial data, a greater understanding of duration of protection is developing, with the assumption of lifelong protection becoming more plausible as longer follow-up data become available to support sustained immunity. Due to the evolving evidence base, the assumptions used in a study may be subsequently shown to be incorrect, and therefore the reported estimate of cost-effectiveness may no longer be supported.

In conjunction with the increasing evidence base for efficacy there has also been a downward trend for the cost of vaccination. Initially the vaccine was estimated to cost in excess of €450 for a three-dose schedule. Since 2009 the average cost has been less than €350. From the limited number studies reporting a two-dose schedule, it appears that costs are similar to those for a three-dose schedule. As stated previously, varying the cost of the vaccine did not tend to change the interpretation of the findings in evaluations that included a univariate sensitivity analysis. However, the lower bound tended to be 20% below the base-case cost. Due to the complex relationship between input parameters and the estimate of cost-effectiveness, it is not recommended to use a simple linear extrapolation to determine the likely cost-effectiveness for cost values outside what are reported in a study (for example, such as a 40% reduction in vaccine price).

Quality of evidence

The systematic review identified 29 studies. In many contexts this would be considered a substantial volume of economic evaluations on a single topic. However, given the large number of permutations regarding programme design, uptake, comparator, and so on, few of the studies provide evidence relevant to the specific circumstances of an Irish programme.

As stated previously, the nature of dynamic transmission modelling and the large number of clinical outcomes included mean that the models are necessarily complex. The majority of the reports provide limited detail on the model design and structure, or many of the decisions that were inevitably made in selecting data sources. As such, few of the studies could be considered 'reproducible' on the basis of the information provided. From a quality assessment perspective, it is challenging to identify what decisions were made and whether they were adequately justified. In terms of key parameters, efficacy was often based on an assumption rather than supported by any trial evidence – which was justified because in many cases trial evidence was not yet available. However, the results of those studies must be considered in terms of the evidence that is now available.

The conflicts of interest that are present for many of the studies are also worth highlighting. The large number of evaluations that were supported by industry are at increased risk of bias, and this can perhaps be seen in the lower ICERs reported in industry-supported studies.

Applicability

The included studies were assessed for applicability to the Irish setting. A number of factors may influence the applicability of cost-effectiveness evidence to a setting other than which it was intended for, such as the comparator, discount rate, disease burden and costs. The factors which have most influence on applicability are context specific. In the case of a HPV vaccination programme, the comparator should be a girls-only programme, preferably based on a two-dose schedule of the 9-valent vaccine and with an uptake rate of between 60% and 70%.

It is also important to understand the context of HTA methodology in Ireland. With the exception of a current agreement for pharmaceuticals at €45,000 per QALY,[(42)] there is no stated threshold below which a technology is automatically considered cost-effective in Ireland. A 5% discount rate is currently used in Ireland. Decreasing the discount rate in an evaluation of a vaccination programme typically lowers the incremental cost-effectiveness ratio (that is, the proposed intervention becomes more cost-effective).

Only two studies reported vaccine costs that are similar to the anticipated cost in Ireland; one based on a two-dose schedule of a 2-valent vaccine,[(424)] and one based on a three-dose schedule of a 4-valent vaccine.[(403)] Of the 29 studies, 24 reported

vaccine costs that were at least twice the anticipated cost of vaccination in Ireland. Of the evaluations of the 9-valent vaccine, the lowest vaccine cost was three and a half to four times the expected cost of the vaccine in Ireland.[455]

Only three studies used the same 5% discount rate as applied in Ireland.[410, 417, 428] Two of those studies included only CIN and cervical cancer,[417, 428] while the third was restricted to only head and neck cancers.[410] Studies with discount rates lower than 5% are likely to underestimate the ICER in the Irish context. Most studies included a univariate sensitivity analysis in which the discount rate was varied and therefore, if the study was applicable to Ireland based on other factors, an approximation of the ICER at a discount rate of 5% could be interpolated.

Studies used a wide range of values for uptake rate in girls, and some used differing uptake rates for boys and girls. Coverage in Ireland has changed markedly in a short space of time from 87% uptake in the 2014 to 2015 academic year, to 51% in the 2016 to 2017 academic year. However, provisional data suggest that vaccine coverage is increasing. Given the fluctuations observed, it is unclear what steady state coverage will be for girls. It is also unclear what coverage might be achieved among boys. Coverage is critical: with low vaccination coverage, a gender-neutral vaccination programme appears more cost-effective as little benefit accrues from herd immunity; in scenario analyses, gender-neutral vaccination became less cost-effective at higher vaccination rates. Gender-neutral vaccination was also noted to be dominated (less effective and more costly) by intensified girls-only programmes where vaccine coverage was high. While offering the potential for further reductions in the total burden of HPV-related diseases, the feasibility of achieving such vaccine coverage rates has been questioned, particularly in countries with historically low vaccination rates (for example, the US) or where the vaccination rate has been seen to reach a steady state.

It was possible to restrict the available studies to those that most closely reflect the projected Irish context in terms of 9-valent vaccine, two-dose schedule, vaccine price, and coverage. The evaluation by Mennini et al. models a two-dose schedule of the 9-valent vaccine, and does not include head and neck cancer in the base case.[455] The uptake rate in girls is modelled as 71.1% with 90% compliance. However, the vaccine price, is three and a half to four times that anticipated in Ireland. That evaluation reports an ICER of €20,300 per QALY, although the figure would be likely to be higher if a discount rate of 5% had been used rather than the 3% included in the model. However, it is likely that the figure would be less than €45,000/QALY. A key issue with the Mennini *et al.* evaluation is the risk of bias due to industry support. It is difficult to determine the extent to which the reported ICER may over-estimate the cost-effectiveness.

Limitations

A number of the studies were limited in that they only represented heterosexual relationships, and therefore did not reflect HPV transmission risk among men who have sex with men (MSM). This omission likely overestimates the level of herd immunity conferred to males in a girls-only vaccination programme. However, the burden of disease estimates used to populate the models typically reflected cases among all individuals, and therefore include those occurring in the MSM population.[403]

Potential benefits for MSM were explored through scenario and sensitivity analysis by limiting the benefits of herd immunity cancer reduction benefits to the gender-neutral programme, and including MSM-attributable warts and cancers in the disease incidence data that populated the model. However, gender-neutral vaccination remained not cost-effective compared with a girls-only programme.[3] An MSM transmission rate of 3% in the base case analysis (that is, where 3% of the male population are exclusively MSM) was included in the study by Laprise et al. and tested through sensitivity analysis. However, even assuming an MSM transmission rate of 7%, a gender-neutral vaccination programme was dominated (more costly and less effective) by a girls-only programme.

In the study by Burger et al., based on Norwegian data, it was estimated the proportion of MSM to be 0.6% and 2.8% (age-dependent) and that prior to age 30 (when the majority of HPV transmission occurs), individuals typically identify with bisexual rather than exclusively homosexual behaviour. This assumed that herd-immunity benefits may continue to propagate within the MSM population. The study estimated that the herd immunity benefits in the girls-only programme would need to be overestimated by more than 15% (well above an at most 3% exclusively MSM population) in order for a gender-neutral programme to become cost-effective at a willingness-to-pay threshold of $50,000/QALY. It is noted that MSM have a higher HPV disease burden (increased risk of anal cancer and genital warts) and may realise a greater benefit from HPV vaccination. However, while targeted vaccination of MSM has been shown to be cost-effective in some settings, the targeted vaccination of a young MSM cohort prior to HPV exposure would be challenging and difficult to operationalise. [13;38]

7.4 Conclusion

A number of previous economic analyses show that if female HPV vaccine coverage is low and all potential health benefits are included, it may be cost-effective to include males in the vaccination schedule. However, cost-effectiveness was dependent on the vaccine price, coverage and the willingness-to-pay threshold. As expected, extending the benefit to include all HPV-related diseases was found to improve the cost-effectiveness of gender-neutral vaccination. The data on the effectiveness for preventing oropharyngeal disease are minimal despite a known

aetiological link with HPV infection, and none of the licensed vaccines are currently indicated for the prevention of HPV-related oropharyngeal disease. Some studies reported that increasing the uptake of vaccination in girls was a more efficient strategy, particularly if coverage was low. However, given the relatively high coverage in Ireland, the marginal costs of achieving increased female-only coverage may be substantial with limited additional benefit.

Female vaccination coverage in Ireland declined from in excess of 80% to approximately 50% in the 2016 to 2017 academic year, with early reports suggesting that coverage may be improving is some areas. Taking into account the coverage rate in females — when excluding head and neck cancers — the extension of the HPV vaccination schedule to include boys is unlikely to be cost-effective unless the vaccine price is substantially reduced relative to that reported in the studies reviewed in this chapter. An in-depth economic modelling exercise would be necessary to ascertain the vaccine price threshold levels and coverage rates at which gender-neutral HPV vaccination would be cost-effective.

Key Points

- A systematic review of published economic evaluations identified 29 evaluations.
- Three studies evaluated the cost-effectiveness of the 9-valent vaccine, 19 evaluated the 4-valent vaccine, and seven evaluated a 2-valent vaccine.
- Five studies evaluated a two-dose schedule, 22 evaluated a three-dose schedule, and two studies investigated both two and three-dose schedules.
- The cost of the full vaccine schedule ranged widely across studies from €38 to €655, with an average value of €348. There is a trend for decreasing vaccine cost over time.
- Sixteen of the studies were at risk of bias due to industry support.
- A number of published economic analyses show that if female HPV vaccine coverage is low and all potential health benefits are included, it may be cost-effective to include boys in the vaccination schedule.
- Few of the studies could be considered directly applicable to Ireland, as most used lower coverage and higher vaccine costs than would apply in Ireland.

8 Economic evaluation

8.1 Overview of the evaluation

The systematic review of cost-effectiveness studies of gender-neutral HPV immunisation programmes highlighted the variability in results. The estimated cost-effectiveness is influenced by a number of parameters that tend to be country specific, such as uptake rates and vaccine cost. As such, to determine the cost-effectiveness of a gender-neutral HPV immunisation programme in Ireland requires an economic model tailored to the Irish context. This chapter describes the economic model and the estimated cost-effectiveness and budget impact of a gender-neutral HPV immunisation programme in Ireland.

The objective of the economic evaluation is to aid decision-making by estimating the incremental costs and benefits of a gender-neutral HPV immunisation programme compared with those of the current girls-only programme and an alternative of no vaccination.

8.1.1 Study question

The study objective was to determine the cost-effectiveness and budget impact of extending the current school-based HPV immunisation programme for girls to include boys.

8.1.2 Type of economic evaluation

A cost-utility analysis was used, with benefits measured as quality-adjusted life years (QALYs) gained due to a HPV immunisation programme and compared to competing alternatives.

8.1.3 Study perspective

Costs and benefits were assessed from the perspective of the publicly-funded health and social care system. Only direct costs were included. Indirect costs such as productivity losses associated with morbidity and mortality as a result of a HPV-related disease were excluded.

National guidelines for the economic evaluation of health technologies in Ireland recommend that the perspective of the publicly-funded health and social care system in Ireland should be adopted when assessing costs.[456] For this intervention the majority of costs accrue to the health service, and hence it is appropriate to examine cost-effectiveness from the perspective of the publicly-funded health service only.

8.1.4 Technology

The technology being assessed is a schools-based gender neutral HPV immunisation programme. The aim of the intervention is to reduce HPV infection and thereby reduce HPV-attributable disease. A detailed description of the technology is provided in Chapter 2.

8.1.5 Choice of comparators

Two comparators were considered in the evaluation: the current girls-only immunisation programme, and no vaccination. The existing programme utilises a two-dose schedule of the 4-valent vaccine. The two active vaccination alternatives included in the evaluation (girls-only and gender-neutral) were modelled separately for the 4-valent and 9-valent vaccines. The schools-based programme is based on the academic years and is intended for children in first year of secondary school who are typically aged 12 to 13 years at the time of vaccination. From a modelling perspective, this has been simplified to 12 year olds on a calendar year. Consistent with recent implementation of other vaccines as part of the national immunisation programme, the inclusion of catch-up programmes was not considered. The full set of included strategies was:

- No vaccination
- Vaccination of 12 year old girls only with the 4-valent vaccine
- Vaccination of 12 year old girls only with the 9-valent vaccine
- Vaccination of 12 year old girls and boys with the 4-valent vaccine
- Vaccination of 12 year old girls and boys with the 9-valent vaccine

8.1.6 Target population

The target population of the HPV immunisation programme is all children in their first year of second-level school (12 to 13 years of age) and age-equivalent children in special schools or who are home-schooled in Ireland. The model followed consecutive cohorts to a maximum age of 99 years.

8.1.7 Time horizon

The total cost and clinical benefit for each of the HPV immunisation programmes was estimated by modelling consecutive cohorts over a 100 year time horizon.

8.1.8 Outcomes

Clinical benefit was measured using quality-adjusted life years (QALYs). Benefit could be gained through a reduction of HPV-attributable disease. Benefit could be lost through adverse events associated with vaccination. In the base case, HPV-attributable diseases included: anogenital warts, cervical intraepithelial neoplasia (CIN), cervical cancer, anal cancer, vulvar intraepithelial neoplasia (VIN), vulvar

cancer, vaginal intraepithelial neoplasia (VaIN), and recurrent respiratory papillomatosis (RRP). As treatment effect in terms of oropharyngeal and penile has not yet been demonstrated in the relevant target population, those cancers were only included in a scenario analysis.

8.1.9 Discounting

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Discounting facilitates comparison between costs and benefits that occur at different times. Costs and benefits were discounted at the rate of 5% as set out by the Department of Finance.[456] The discount rate was fixed in the main analysis and values of 0%, 4%, 6% and 10% were tested in the univariate sensitivity analysis.

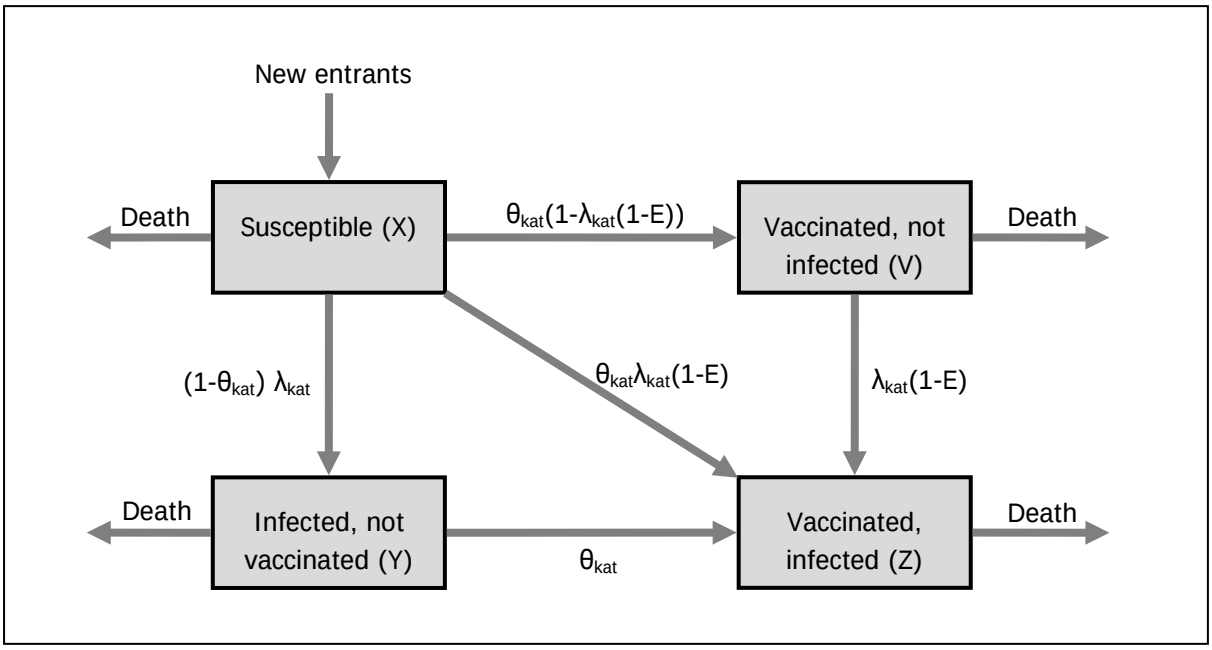
8.2 Description of the economic model

An economic model typically sets out to simulate a population and estimate the impact on costs and benefits of introducing, removing of altering an existing health intervention. In this case, the model was designed to estimate the impact of extending HPV vaccination to boys. The economic model used here was an adaptation of a dynamic population-based model developed by Chesson et al. originally used for an economic evaluation of the 4-valent vaccine in the US.[405]

8.2.1 Model structure

The model used a discrete time Markov approach. The population was allowed to move between five mutually exclusive states: susceptible; vaccinated and not infected; infected and not vaccinated; vaccinated and infected; and dead (Figure 8.1). Transition probabilities between states were governed by age and sex-specific characteristics including the annual probability of receiving HPV vaccination, the annual probability of acquiring HPV infection, and the vaccine efficacy against HPV infection. At any given time point, transition probabilities and hence the proportion population in each state were calculated using an iterative procedure. Full details of the model structure are provided by Chesson et al..[405] The impact of each of the vaccination strategies was estimated relative to each other and to a policy of no vaccination.

Figure 8.1 Model structure for estimating the cumulative lifetime probability of exposure to a given HPV type



Notes: θ, annual probability of receiving HPV vaccination; λ, annual probability of acquiring HPV infection; E, vaccine efficacy against HPV subtype; k, sex; a, age; t, year.

The model is calculated separately for each of the HPV subtypes for which the vaccine provides protection. Subtypes 6 and 11 were combined in the model, as were the five additional subtypes that the 9-valent vaccine protects against (31, 33, 45, 52 and 58).

The model was developed using a number of important simplifying assumptions:

- The model uses discrete time by modelling annual transitions between a limited set of mutually exclusive states. Other models have used a more exhaustive set of states and used a continuous time approach.
- Unlike the more complex dynamic transition models used elsewhere, the model here used a simplifying assumption regarding age-specific HPV acquisition probabilities.
- The model did not simulate the transition from HPV acquisition to HPV-associated outcomes. Instead the model estimated the reduction in HPV-associated outcomes as being proportional to the reduction in HPV infection. This simplification was based on the assumption that the percentage reduction in health outcomes attributable to a given HPV type (for a given year and age cohort) was directly proportional to the percentage reduction in the cumulative lifetime exposure to that HPV type (for the given year and age cohort).

- Cervical cancer screening did not need to be explicitly included in the model as it was reflected in the observed incidence of cervical intraepithelial neoplasia (CIN) and invasive cervical cancer as applied in the model.

- Individuals that do not complete the full dose schedule have no protection against HPV infection. Studies are being conducted to determine if children might acquire the same degree of protection from a single dose as from two doses.[457]
- The model assumes a heterosexual population and does not simulate the men who have sex with men (MSM) population. It is therefore assumed that the effects in the MSM population are identical to that in the heterosexual population and are a function of the effects in the female population.

These assumptions enable a more simplified modelling approach to be adopted that reduces the burden of data required for the model and also facilitates a more fully probabilistic approach due to lower computational demands. A review of HPV vaccination models found that the Chesson model gives similar results to full dynamic transmission models.[458] The model does not need calibration due to the assumption of reduced HPV-attributable disease incidence being proportional to reduced cumulative lifetime exposure to HPV infection. However, the model was developed and validated against outcomes from other more complex models designed for the US population. Some of the parameters in the model are not based on observed data, but were derived from the validation and calibration process applied to other models. These parameters include the annual acquisition probability of HPV infection and epsilon, a term used to reflect sexual mixing across age groups. In the absence of data to determine if these parameters apply in an Irish setting, it was assumed that they do and the impact of those assumptions was tested using sensitivity analyses.

The overall benefits and costs of competing HPV immunisation programmes were calculated by performing 10,000 model simulations. Randomly sampled individual parameter values were used in each simulation. Summarising across iterations provides an estimate of overall average costs and benefits, as well as the uncertainty associated with these values.

The original model was developed as a deterministic model in Microsoft Excel.[405] A probabilistic version of the model was developed as part of the Norwegian health technology assessment (HTA) on a gender-neutral HPV immunisation programme.[459] Some of the key parameters in the Norwegian adaptation were treated as fixed, such as uptake rate, and varied in sensitivity analyses. For this study, the model was constructed in R 3.4.2[460] and all parameters that were subject to uncertainty were allowed to vary in each simulation. The adapted code

was validated by using the Norwegian input data and then comparing the outputs of the R model with the original Excel version.

8.2.2 Epidemiological parameters

For modelling purposes, a variety of epidemiological parameters were required on the incidence of HPV-attributable disease, efficacy of HPV vaccination, and quality of life for those with HPV-attributable disease.

8.2.2.1 Target population

As stated previously, the true population is children in first year of secondary school, typically aged 12 to 13 years of age. The target population modelled was all 12 year old boys and girls in the State. The estimates for 2017 were 30,999 girls and 33,012 boys.[461] It was assumed that all 12 year old children in second-level and in special schools, home-schooled and out of school would be considered eligible for vaccination, and that they would represent 100% of 12 year old children in the State. In the model it is assumed that a steady state population applies: that is, each year another 30,999 12 year old girls and 33,012 12 year old boys become eligible for the HPV immunisation programme. The natural reduction in population with increasing age is achieved by applying age-specific all-cause mortality rates. The model does not incorporate migration or projected changes in birth rates.

8.2.2.2 Vaccine coverage

The model requires historical uptake rates as well as projected uptake rates for future cohorts. Historical data are published by the HSE-Health Protection Surveillance Centre (HPSC).[462] The historical data relate to girls only and include the catch-up programme for girls in sixth year of second-level schools that ran for three years from the academic years 2011-2012 to 2013-2014. Aggregated data for the pilot programme that ran in 2009 to 2010 and 2010 to 2011 suggested an average uptake of 81.9% across the two years. The model assumed that the average uptake applied to both years. The uptake rates in Table 8.1 are based on the percentage who received two doses of the vaccine. Prior to the 2014-2015 academic year, the programme was based on a three-dose schedule. The programme was changed to a two-dose schedule for those aged less than 15 years at the time of the first dose on the basis of evidence demonstrating non-inferiority of the immune response when compared with three doses in young adult women in whom efficacy has been proven. The model therefore assumed that those who completed two doses will have the same degree of protection against HPV infection as adults that received three doses.

Table 8.1 Historical uptake of HPV vaccine in Ireland

Year	Uptake in girls	
	12 year olds	17 year olds
2009	81.9%	0%
2010	81.9%	0%
2011	87.3%	74.1%
2012	86.3%	70.6%
2013	88.2%	46.8%
2014	86.9%	0%
2015	72.3%	0%
2016	51.0%	0%
2017*	56.4%	0%

* The uptake in 2017-2018 is the estimated uptake of the second dose. At present only the estimate for the first dose has been published (61.7%) and this HTA has conservatively assumed that the fall-off between first and second dose will be the same as observed in 2016-2017 (8.6%).

Future uptake rates were required for the model. It was assumed that uptake rates would continue to recover from the low of 51% in the academic year 2016-2017. Previous economic evaluations have found that gender-neutral immunisation programmes are more likely to be cost-effective if uptake rates among females are low. It is unclear to what extent the uptake rates will return to pre-2015 levels. For this model, it was assumed that the uptake rate for 12 year old girls will return to 63.2% in 2018 to 2019 and 70.0% (95% CI: 60.8% to 78.4%) by the academic year 2019 to 2020, with a constant uptake rate thereafter on the basis that a full recovery of uptake rates to 2013 levels seems unlikely. Given the results of other economic evaluations of gender-neutral HPV immunisation programmes and the relationship between uptake in girls and cost-effectiveness, a scenario analysis was used to investigate the impact of a return to an 88.2% uptake in girls, and also of uptake failing to recover and remaining at 55% in girls.

Based on a review of international data, it was assumed that the uptake rate in boys would be lower than for girls. A gender-neutral HPV immunisation programme was started in Australia in 2014. Coverage data for 2014 to 2016 show that uptake was consistently lower in boys than in girls, although the gap has narrowed over time.[463] Uptake in boys was 83.7% of the uptake in girls in 2014, 86.2% in 2015, and 92.8% in 2016. For the Irish model it was assumed that the average observed in Australia would apply: uptake in boys would be 87.7% (95% CI: 77.4% to 95.2%) of the uptake in girls. A sensitivity analysis was used to explore the impact of the uptake rate in boys being equal to that in girls.

The current Irish girls-only programme is based on a two-dose schedule, and it was assumed that this would continue. Based on the Irish uptake data, between 2011 and 2016, an average of 95.8% of girls who received the first dose of the vaccine completed the second dose. In the first four years of the programme the corresponding figure was 98.5%. The drop in uptake in 2015 to 2016 and 2016 to

2017 was associated with a reduced proportion completing the second dose. It was assumed that with a continued recovery of uptake rates there would also be an increase in the proportion completing the second dose, with an average of 97.1% (95% CI: 93.0% to 99.4%) of girls receiving the first dose would complete the two-dose schedule. It was assumed that completion would be marginally lower for boys: 94.2% (95% CI: 90.1% to 96.7%). The relevance of completion of the two-dose schedule is that all those receiving a dose incur a cost and are exposed to the risk of adverse events, irrespective of whether or not they complete the two-dose schedule and receive the protective effect of the vaccine.

8.2.2.3 Vaccine-related adverse events

Based on the findings of the review of HPV vaccine safety (Chapter 6), it is clear that there is a high rate of non-serious adverse events associated with the HPV vaccine. In relation to the 4-valent vaccine, approximately 69% of vaccine recipients will experience a non-serious adverse event such as pain at the injection site (Table 8.2). Based on a published meta-analysis, the rate of non-serious adverse events is higher in recipients of the 9-valent vaccine.[353]

Data on rates of serious adverse events were obtained from a variety of sources. The Health Products Regulatory Authority (HPRA) collects data on notified potential adverse reactions. The number of recorded potential adverse reactions was equivalent to 1.7 events per 1,000 vaccinations.[365] The severity of those events, and whether they have a confirmed association with the vaccine, is unclear. The rate of anaphylactic reactions was estimated at 1.7 per million vaccinations.[362] Given that in excess of 600,000 doses of HPV vaccine have been administered in Ireland to the end of the 2017-2018 academic year, the estimated incidence is equivalent to one case of anaphylaxis since the launch of the programme. There may be other causes of hospitalisation that would be considered serious adverse reactions.

The Norwegian HTA used local data to estimate a serious adverse event rate of 81 per million vaccine doses.[459] 'Serious' was defined as requiring hospital treatment. Applying that rate to the Irish programme, there would have been 50 cases requiring hospital care since the launch of the programme in 2010. The Norwegian incidence rate of serious adverse events was adopted for this study. The risk ratio between the 9-valent and 4-valent vaccines for non-serious adverse events was also applied to serious adverse events.

Table 8.2 Estimated incidence rate of vaccine-related adverse events

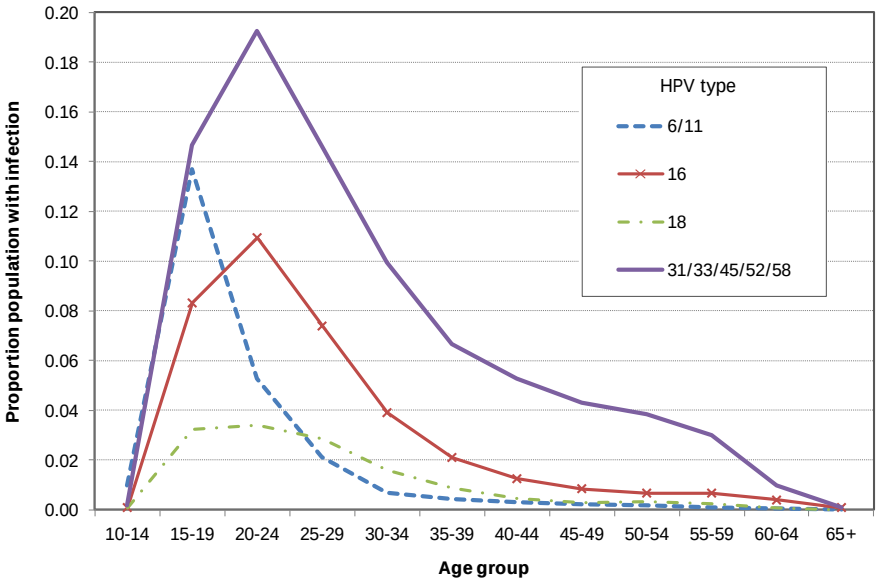
Vaccine	Non-serious/1,000		Serious/1,000,000	
	Mean	(95% CI)	Mean	(95% CI)
4-valent	691.8	(683.9 – 699.6)	80.8	(54.1 – 112.6)
9-valent	760.8	(683.8 – 841.2)	88.8	(58.6 – 125.6)

8.2.2.4 HPV infection and associated parameters

HPV infection was modelled using the annual probability of acquiring HPV infection for the first time in the absence of vaccination. Acquisition probabilities used in the original model by Chesson et al. were based on the outputs of several dynamic transmission models calibrated to the US population and then further adjusted to reflect HPV prevalence in the US.[405] The model was not designed to track HPV prevalence, but age-specific HPV prevalence could be calculated using assumptions about the annual probability of clearance and applying them to the annual probability of first-time acquisition of HPV infection in the absence of vaccination.

In the absence of comprehensive Irish data on the prevalence of HPV, the combined data from the UK[464, 465] and Denmark[466] was adapted to estimate the likely prevalence of HPV infection in Ireland by five-year age band (Figure 8.1). The prevalence of HPV 6 and 11 peaks in 15 to 19 year olds, while types 16, 18, 31, 33, 45, 52 and 58 peak in the 20 to 24 year old age band. The prevalence estimates were consistent with the available prevalence data generated by the Cerviva study in Ireland.

Figure 8.1 Estimated prevalence of HPV by age and HPV type

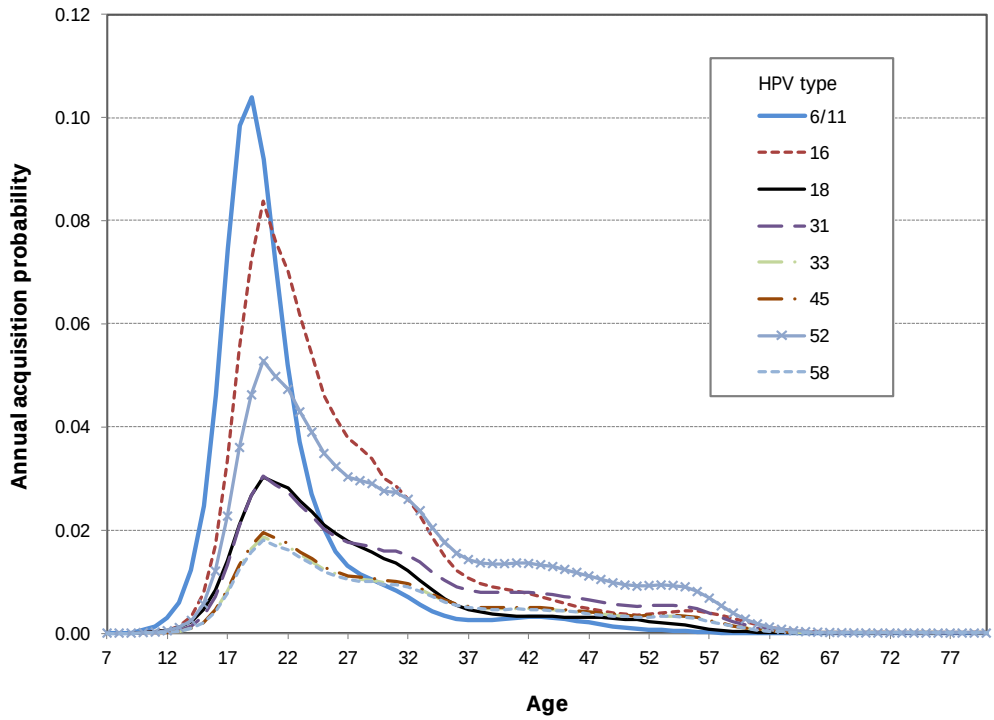


Having estimated the prevalence of HPV infection it was possible to adjust the US acquisition probabilities to generate plausible acquisition probabilities for Ireland. Annual clearance rates were applied of 0.79 for HPV 6 and 11, 0.46 for HPV 16, 0.64

for HPV 18, and 0.59 for HPV 31, 33, 45, 52 and 58.[467] The acquisition probabilities follow approximately the same shape as those used in the US study (Figure 8.2). In the absence of any clear evidence to support the estimation of different acquisition rates for males and females, the same probabilities were applied to both sexes.

The estimated acquisition probabilities were higher than were applied in the US and Norwegian evaluations. A scenario analysis was carried out to test the impact of using the lower US acquisition probabilities in the model.

Figure 8.2 Estimated annual acquisition probability by age and HPV type



8.2.2.5 Incidence of HPV-attributable disease

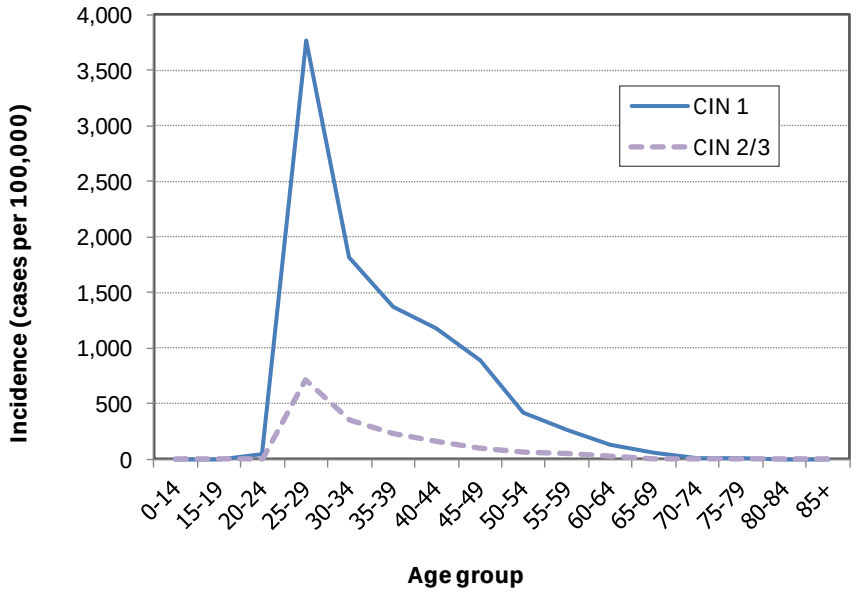
Based on the review of epidemiology (Chapter 3), evidence was identified regarding the proportion of disease incidence that can be directly attributed to persistent HPV infection. For most of the specified diseases, the largest proportion is attributable to HPV 16. With exception of anogenital warts and recurrent respiratory papillomatosis, the percentage of incidence of the specified diseases that is attributable to HPV 6 or 11 is less than 3%.

Oropharyngeal and penile cancers were not included in the base case analysis on the grounds that no treatment effect was incorporated. They were, however, included in a scenario analysis.

Where possible, the incidence of HPV-attributable disease was derived from Irish sources. However, due to the low incidence and associated small number of cases for some diseases, data was adapted from other settings. For cancers other than cervical cancer, as per the definitions outlined in Chapter 3, 'HPV-associated' refers to tumours that are of squamous cell carcinoma morphology and occur at an anatomic location known to be associated with HPV. For cervical cancer, 'HPV-associated' refers to carcinomas of any subtype.

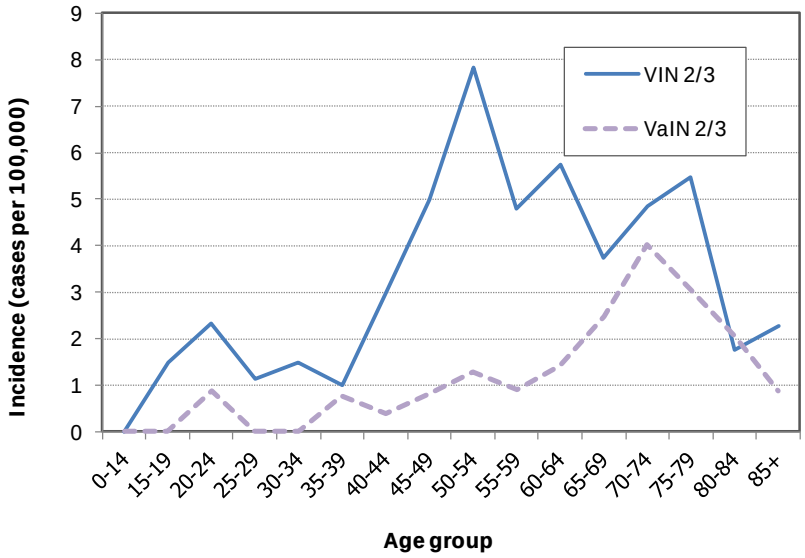
Data on the incidence of CIN 1 and CIN 2 and 3 were derived from CervicalCheck data as used previously in a HTA on cervical screening (Figure 8.3).[468]

Figure 8.3 Incidence of HPV-associated cervical intraepithelial neoplasia (CIN) by age (2015-2016)



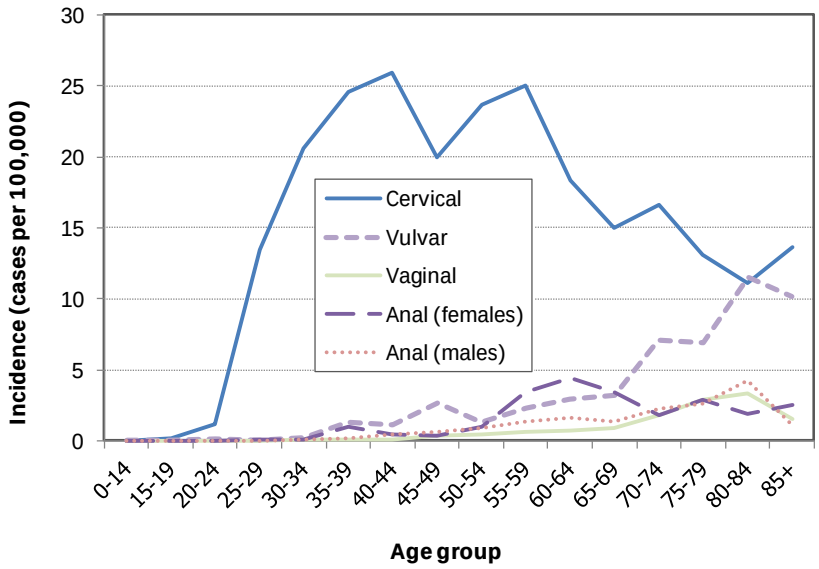
There were no Irish data available on the incidence of vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN). The incidence of invasive vulvar and vaginal cancer between Ireland and Norway was compared and although the profile of the incidence by age was found to be similar, the Norwegian data overestimated the incidence in Ireland by 70% for vulvar cancer and 48% for vaginal cancer. It was assumed that the Norwegian incidence of VIN 2 and VIN 3 and VaIN 2 and VaIN 3 would be an acceptable approximation of incidence in Ireland, subject to adjustment to account for the overestimation of the associated invasive cancers (Figure 8.4). The incidence of VIN peaks in women aged 50 to 54 years, while the incidence of VaIN peaks in women aged 70 to 74 years.

Figure 8.4 Incidence of HPV-associated vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VaIN) by age



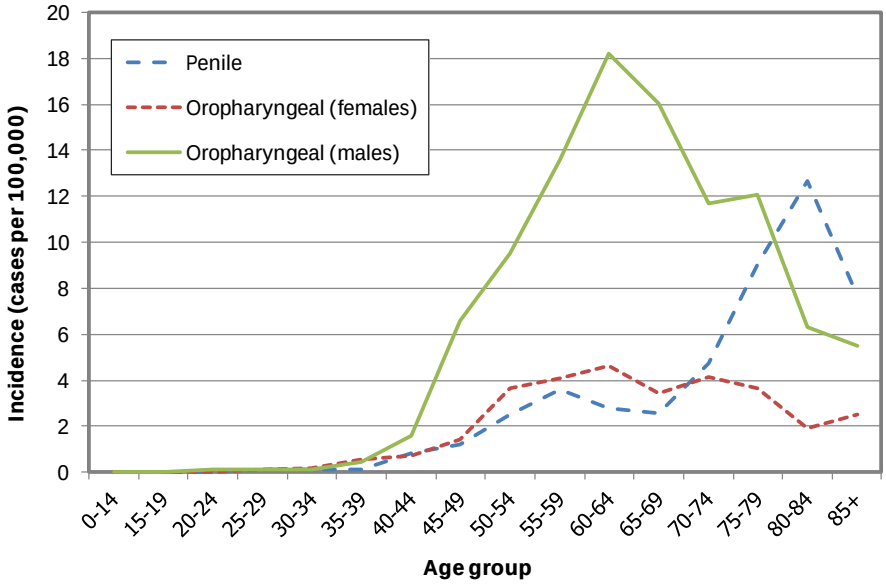
The incidence of HPV-attributable invasive cancers was obtained from the National Cancer Registry based on data for the years 2009 to 2013 (Figure 8.5). The data were extracted only for those cases that were considered associated with HPV. The highest incidence cancer was cervical cancer. Organised population-based cervical screening commenced in Ireland in 2008 with the establishment of CervicalCheck. The incidence data relate to a period when cervical screening was in place, but women vaccinated against HPV as part of the schools-based programme had not yet entered the screening cohort. The incidence of cervical cancer should therefore partly reflect the impact of cervical cancer screening, but not HPV vaccination. Peak incidence for cervical cancer is between the ages 40 and 59 whereas for the remaining HPV-associated cancers, incidence tends to increase with age.

Figure 8.5 Incidence of HPV-associated invasive cancers by age (2009-2013)



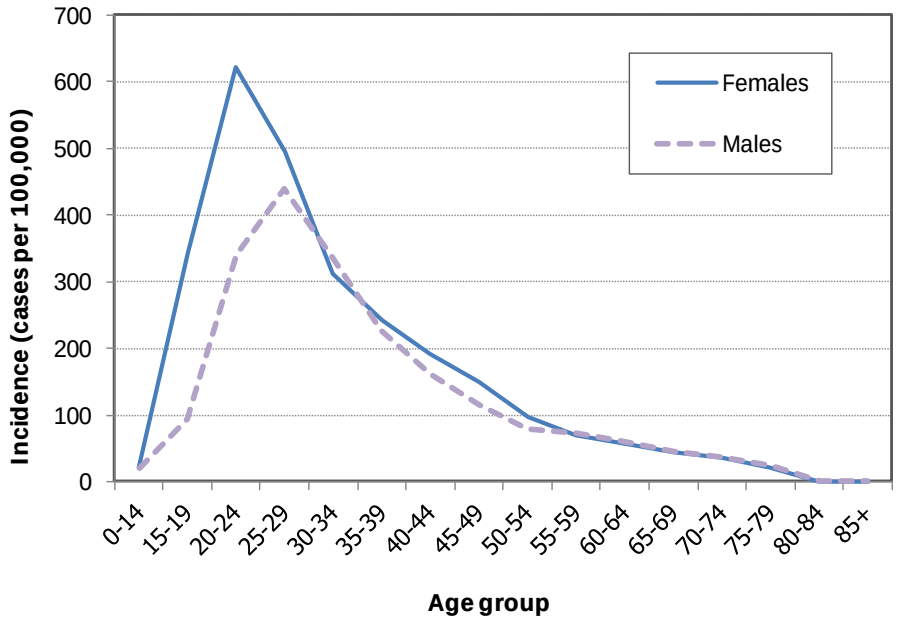
Although not included in the base case analysis, oropharyngeal and penile cancers were included in a scenario analysis. The incidence of both cancers increases with age (Figure 8.6). An important feature of oropharyngeal cancer is that a trend of increasing incidence over time has been observed, with one of the main drivers being the increasing prevalence of HPV infection.[469] In the United States, incidence increased by 57% between 1975 and 2014.[470] In tandem with increasing incidence, the average age of onset of oropharyngeal cancer is decreasing.

Figure 8.6 Incidence of HPV-associated oropharyngeal and penile cancers by age (2009-2013)



Although anogenital warts have been a notifiable disease in Ireland since 1985, the data on incidence in Ireland are an under-estimate due to several service providers not submitting data (see Chapter 3). In the absence of reliable Irish data, estimates of the incidence of anogenital warts were derived from a retrospective cohort study from Germany.[471] The data show a peak for females in the 20- to- 24 year old age band, while the peak for males is in the 25- to- 29 year old age group (Figure 8.7). A published systematic review of the incidence of anogenital warts found a similar profile for incidence across a range of countries.[472]

Figure 8.7 Incidence of anogenital warts by age and sex[471]



In the absence of Irish data, the incidence of recurrent respiratory papillomatosis (RRP) was estimated based on data from two US cities, Atlanta and Seattle.[473] The pooled incidence across the two sites was 0.97 per 100,000 (95% CI: 0.48 – 1.77).

8.2.2.6 HPV-attributable proportions

Not all of these tumours are directly caused by HPV, and hence the proportions attributable to HPV outlined in Table 8.2 were used to calculate the numbers of HPV-attributed cases. The proportions were derived from the analyses presented in Chapter 3.

HPV-attributable proportions of oropharyngeal and penile cancer were not included in the base case analysis on the grounds that no treatment effect was incorporated.

Table 8.2 Proportion disease attributable to persistent HPV infection

Clinical outcome	HPV type			
	6/11	16	18	31/33/45/52/58
CIN 1	0.001	0.205	0.035	0.250
CIN 2/3	0.001	0.467	0.079	0.307
Cervical cancer	0.001	0.623	0.105	0.162
Anal cancer	0.027	0.833	0.038	0.027
VaIN 2/3	0.010	0.580	0.061	0.135
Vaginal cancer	0.010	0.643	0.068	0.144
VIN 2/3	0.012	0.796	0.026	0.122
Vulvar cancer	0.012	0.712	0.024	0.104
Anogenital warts	0.900	0.000	0.000	0.000
RRP	0.900	0.000	0.000	0.000
Penile cancer	0.022	0.739	0.008	0.104
Oropharyngeal cancer (females)	0.001	0.470	0.009	0.018
Oropharyngeal cancer (males)	0.000	0.410	0.004	0.008

Notes: CIN, Cervical Intraepithelial Neoplasia; VIN, Vulvar Intraepithelial Neoplasia; VaIN, Vaginal Intraepithelial Neoplasia; RRP, recurrent respiratory papillomatosis.

8.2.2.7 Vaccine effect

The model required separate inputs for the vaccine effect against persistent HPV infection and effect against clinical outcomes. The data on vaccine effect were derived from the systematic review on vaccine efficacy (Chapter 4).

Data on vaccine efficacy against persistent infection were derived from trials of the 4-valent vaccine versus placebo and the 9-valent vaccine versus the 4-valent vaccine (Table 8.3). Trials of the latter comparison provided data on vaccine effect for HPV types 31, 33, 45, 52 and 58. The data reflect efficacy in the modified intention-to-treat population, that is, in those who were negative for the vaccine-related HPV types at baseline and who received at least one dose of the vaccine. Efficacy of the two-dose schedule in girls and boys aged 12 to 13 years is assumed based on non-inferiority of the immune response when compared with three doses of the HPV vaccine in young adult women and men in whom efficacy has been proven. It was assumed that the 4-valent vaccine offers no cross-protection against HPV types other than 6, 11, 16 and 18. Vaccine efficacy was incorporated into the model as relative risk reductions. For HPV types 6, 11, 16 and 18 it was assumed that the 4-valent and 9-valent vaccines were equally efficacious. Efficacy of the two dose schedule of the 9-valent vaccine against HPV types 31, 33, 45, 52 and 58 for boys and girls was assumed based on non-inferiority of the immune response when compared with three doses in young adult women and men in whom efficacy was proven.

Table 8.3 Relative risk of type-specific persistent HPV infection after vaccination

HPV type	Females			Males		
	Mean	(95% CI)		Mean	(95% CI)	
6/11	0.063	(0.006-0.270)	(250)	0.218	(0.095-0.430)	(237)
16	0.101	(0.026-0.271)	(250)	0.377	(0.242-0.561)	(237)
18	0.137	(0.012-0.582)	(250)	0.320	(0.165-0.570)	(237)
31/33/45/52/58*	0.062	(0.038-0.095)	(224)	0.062	(0.038-0.095)	(224)

* Reduction in persistent infection of HPV types 31, 33, 45, 52 and 58 only relates to 9-valent vaccine

Data on vaccine efficacy against clinical outcomes were primarily available for intraepithelial neoplasias (Table 8.4). It was assumed that the reduced risk of CIN 2+ was also applicable to cervical cancer, and that reductions in VIN 2+ and VaIN 2+ were applicable to vulvar and vaginal cancers. No evidence of a statistically significant reduction in penile or oropharyngeal cancers was found in the review of efficacy. Those outcomes were therefore excluded from the base case model. However, they were included in a scenario analysis to determine the impact of a treatment effect on the cost-effectiveness of the modelled vaccination strategies with a conservative assumed risk ratio of 0.5 (95% CI: 0.34 to 0.74). Evidence regarding a statistically significant reduction in AIN was restricted to the MSM population, and therefore excluded from the model.

Table 8.4 Relative risk of clinical outcomes after vaccination

Clinical outcome	Risk ratio		
	Mean	(95% CI)	
CIN 1	0.027	(0.007-0.071)	(9)
CIN 2/3, cervical cancer	0.009	(0.001-0.039)	(9)
VIN 2/3, VaIN 2/3, vaginal cancer, vulvar cancer	0.078	(0.007-0.331)	(9)
Anal cancer	0.476	(0.264-0.793)	(284)
Genital warts (females)	0.040	(0.015-0.088)	(9)
Genital warts (males)	0.220	(0.106-0.413)	(237)

Notes: CIN, Cervical Intraepithelial Neoplasia; VIN, Vulvar Intraepithelial Neoplasia; VaIN, Vaginal Intraepithelial Neoplasia.

The model is structured to calculate the reduction in cumulative acquisition of HPV infection by sex and HPV type. That reduction in acquisition is then converted into reductions in disease incidence using the following formula:

$$N_{k,a,t,lag,x} = R_{k,a} * P_{k,a,t} * A_{k,a,x} * C_{k,a-lag,t-lag,x} * AR$$

Where: $R_{k,a}$ = the incidence of a specific disease by sex *k*, age *a* and lag term *lag*

$P_{k,a,t}$ = population in sex category *k*, age *a* and time *t*

$A_{k,a,x}$ = the percentage of cases of the specific disease that are attributable to HPV type *x*

$C_{k,a,t,x}$ = the reduction in cumulative acquisition of HPV type *x* due to vaccination

AR_x = adjustment ratio which is the relative risk reduction (RRR) in the specific disease divided by the RRR for persistent infection of HPV type *x*. The RRR is defined as one minus the risk ratio.

lag = the lag term indicates the minimum time that must elapse between vaccination and when a given health outcome can be prevented. The lag term ranges from 1 year for CIN 1 to 5 years for the invasive cancers (Table 8.5).

The calculation is repeated for females and males separately for each HPV-attributable disease and each HPV type covered by the vaccine.

Table 8.5 Lag times for each outcome[405, 459]

Clinical outcome	Lag time (years)
CIN 1	1
CIN 2+	2
Cervical cancer	5
Anal cancer	5
VaIN 2/3	5
Vaginal cancer	5
VIN 2/3	5
Vulvar cancer	5
Anogenital warts	0
RRP	1
Penile cancer	5
Oropharyngeal cancer	5

Notes: CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; RRP, recurrent respiratory papillomatosis.

To test the impact on cost-effectiveness of the choice of lag times, scenario analyses were used in which the lag times for all outcomes were set to the extremes of zero and five years, respectively.

8.2.2.8 Health-related quality of life

As the model computes disease episodes avoided, those episodes must be quantified in terms of both costs avoided and quality-adjusted life years (QALYs) gained. The QALYs gained are age and sex-specific and it was assumed that the HPV immunisation programme reduces disease incidence, but not the stage distribution of cancers. QALYs were estimated to take into account the baseline health-related quality of life (HRQoL) in the population.[474]

In the original model and the Norwegian adaptation, the QALYs lost associated with each health outcome were calculated outside the model and then incorporated as statistical distributions. The disadvantage of that approach is that the discount rate is fixed and cannot be varied in relation to HRQoL data. In adapting the model, the structure was amended so that QALYs lost were recalculated in each simulation based on the associated stochastic parameters, thereby facilitating testing of other discount rates in sensitivity analyses.

Vaccine-related adverse events are assumed to impact on HRQoL in the form of a short-term disutility. It was assumed that non-serious adverse events would lead to a disutility of 0.02 (95% CI: 0.01 to 0.03) that would last an average of one week. The typical serious adverse event was assumed to be an anaphylactic reaction that would incur a disutility of 0.10 (95% CI: 0.05 to 0.17) which would last for four weeks. These are arguably conservative estimates that bias against vaccination.

There were a number of disease outcomes with no associated mortality and a short duration of treatment: CIN 1, CIN 2 and 3, Vin 2 and 3, VaIN 2 and 3, and anogenital warts. Mean disutilites ranging from 0.036 to 0.191 were applied as outlined in Table 8.6 with the disutility estimated to last for a mean of six months.[405, 459] The disutility represents both the disutility of treatment but also the related psychosocial impact of having a disease diagnosis. For anogenital warts and intraepithelial neoplasia it was assumed that the disutility would persist for 6 months (95% CI: 4.8 to 7.2).

Table 8.6 Impact of incidence of anogenital warts and HPV-attributable intraepithelial neoplasia on HRQoL

Disease	Disutility		
	Mean	(95% CI)	
CIN 1	0.090	(0.042-0.152)	[405]
CIN 2/3	0.130	(0.072-0.202)	[405]
VIN 2/3	0.191	(0.120-0.274)	
VaIN 2/3	0.191	(0.120-0.274)	
Anogenital warts	0.036	(0.025-0.048)	[475]

For invasive cancers, a wider set of parameters were required to account for stage distribution and survival. Cases of invasive cancer were modelled by age and stage at diagnosis. Incidence by age and stage at diagnosis were provided by the National Cancer Registry for the years 2009 to 2013. Due to the rare nature of some of the cancers and the small numbers involved, data for some of the table cells were suppressed. We used iterative proportional fitting to estimate incidence for cells with missing data.[476]

It was assumed that utilities differed for the treatment phase (Table 8.7) and the post-treatment period (Table 8.8). It was assumed that the disutility applied for one

year for stage I cancers and for two years for stage II, III, and IV cancers. Where stage-specific utility data were unavailable, an average was applied across stages. Based on Irish cancer survival data published by the NCRI, those who did not survive to five years were assumed to die on average after two years.

The same disutility values by stage at diagnosis were applied to cervical, vulvar and vaginal cancers. Data on disutility came from a range of sources and in some cases assumptions were made about the relative disutility of initial treatment.[405, 459, 475, 477-480]

Table 8.7 Disutility associated with initial treatment phase by cancer type and stage at diagnosis

Cancer	Stage at diagnosis			
	I	II	III	IV
Cervical[468]	0.29	0.37	0.45	0.45
Anal[477]	0.43	0.43	0.43	0.43
Vaginal	0.29	0.37	0.45	0.45
Vulvar	0.29	0.37	0.45	0.45
Oropharyngeal[479]	0.35	0.38	0.45	0.5
Penile[480]	0.29	0.37	0.45	0.45

Table 8.8 Disutility for survivors after treatment completion by cancer type and stage at diagnosis

Cancer	Stage at diagnosis			
	I	II	III	IV
Cervical	0.07	0.1	0.24	0.24
Anal[478]	0.18	0.18	0.18	0.18
Vaginal	0.07	0.1	0.24	0.24
Vulvar	0.07	0.1	0.24	0.24
Oropharyngeal	0.28	0.28	0.28	0.28
Penile	0.24	0.24	0.33	0.33

A disutility was applied for the final year of life for terminal cancer cases. It was assumed that the utility of the final year of life was 0.365 (95% CI: 0.27 to 0.46).[481]

8.2.3 Cost parameters

Costs were related to vaccination (vaccine, administration and adverse events) and to treatment of HPV-attributable disease. Where costs were derived from non-Irish studies, the cost data was inflated to 2017 values using the local consumer price index for health and then converted the costs to Irish values using purchasing power parities published by the OECD.[482]

8.2.3.1 Vaccine cost

The cost of the vaccine was a critical parameter in the model. It was apparent from the systematic review of economic evaluations (Chapter 7) that the vaccine price used across studies was highly heterogeneous, with an average cost of €341 (range: €38 to €655) for the full vaccination schedule.

The actual cost paid for the vaccine is subject to a competitive multi-annual tender and is classified as 'commercial in confidence'. For this study, the cost of vaccination was derived from the cost of the HPV immunisation programme, which covers the purchase of HPV vaccine, cold storage, information technology needs and provision of information materials and consent forms. Data on the cost of the programme were published for 2010 to 2016 (Table 8.9). In 2011, 92% of the total costs were used for vaccine procurement.[483] By conservatively assuming that 92% of the programme budget was used for the purchase of the HPV vaccine each year, it was possible to estimate an approximate cost per dose administered inclusive of VAT. The data for 2010 were not considered representative as the programme was in the pilot phase. The data for 2011 to 2013 related to the three-dose schedule while the subsequent data related to the two-dose schedule which was implemented in the schools-based programme starting in the 2014-2015 academic year. From 2011 to 2013 the approximate cost per dose was between €24 and €31.

In 2014, the cost per administered dose was estimated at €46.29. No cost was estimated for 2015 or 2016 as the available budget figures were projected rather than actual, and may over or under-estimate the true budget in those years. It is understood that the current contract for purchasing HPV vaccine is volume-based and therefore assumes a minimum ongoing annual uptake. Given the decline in vaccine coverage in recent years, since 2014 more vaccine doses were purchased than were used by the schools-based programme. Surplus vaccine has been used to vaccinate other groups at high-risk of HPV infection, for example HIV-positive individuals and MSM aged under 26 years of age.

Table 8.9 Historical budget for the HPV immunisation programme

Year	Programme cost (€)	HPV doses administered	Estimated average cost per dose administered
2009/10	3,785,000	146,907	23.70
2011	3,590,000	139,646	23.65
2012	4,410,000	132,925	30.52
2013	3,780,000	116,198	29.93
2014	2,835,000	55,121	47.32*

Note: data for 2015 and 2016 not included as only projected budget was available.
* The estimated average cost per dose administered in 2014 does not take into account surplus vaccine that may have been administered outside of the schools-based programme.

As the number of doses administered outside the schools-based programme in 2014 is unknown, we assumed that under a steady state the cost per dose of the vaccine

would be similar to that observed between 2011 and 2013. The price was increased by 20% to account for a combination of price increase and increased wastage under the assumption that surplus vaccine used outside the schools-based programme would not be used as efficiently. While it may be considered unlikely that there would be such a degree of wastage, we adopted a conservative estimate so as not to bias in favour of vaccination. The vaccine price was modelled at €27.20 (95% CI: 24.78 to 33.93) per dose, exclusive of VAT (value added tax). From a review of advertised vaccination fees, it was assumed that the 9-valent vaccine would cost 1.1 times (95% CI: 1.06 to 1.18) the price of the 4-valent vaccine.

8.2.3.2 Cost of administering vaccine

In 2010 the HSE received an additional €2.65 million to fund administration of the vaccine in the schools-based HPV immunisation programme. That funding is ongoing and also includes administration of Men C and Tdap booster vaccines offered to all students in first year of second-level school. HPV requires two doses whereas Men C and Tdap boosters both require a single dose. For girls, two visits are required with a recommendation that HPV and Tdap should be administered on the first visit, and HPV and Men C administered on the second visit six months later. At present, in the absence of a gender-neutral HPV immunisation programme, it is assumed that all boys receive both the Men C and Tdap booster doses on the same visit in both boys-only and mixed schools.

A 'visit' is defined here as the scheduled co-administration of two vaccines: visit one is assumed to include HPV (first dose) and Tdap for girls, and Tdap and Men C for boys; visit two includes HPV (second dose) and Men C for girls. A visit occurs to the school. The number of vaccination events each year was estimated; where an 'event' is where one or more vaccines are administered in a single visit and occurs at the level of the individual child (Table 8.10). The analysis was restricted to the years 2014 to 2016, as that period represents the two-dose schedule of the HPV vaccine; both the Men C and Tdap booster vaccinations are included. The uptake rates for Men C and Tdap booster doses are published annually by the HPSC, but are not provided by sex; we assumed the uptake rates are the same for boys and girls. We further assumed that the number of vaccination events in a visit is whichever uptake is higher of the two vaccines offered at that visit. As the budget of €2.65 million covers the cost of administering the three vaccines, the approximate cost per vaccination event is €31.84. Not all children receive the vaccine at school, such as those that are in special schools or are home-schooled. Depending on the age at vaccination, some children may require a third dose of the vaccine. Immunisation teams operate a policy of 'blitz and mop' to facilitate adherence to the recommended vaccination schedule , vaccination of the entire cohort, completion of the full vaccine course within a single academic year, and provision for school holidays and examination periods.[484] As such, not all vaccinations are completed according to a

simple two-visit school-based schedule. However, it is assumed that the two-visit schedule applies to the vast majority of vaccinations and the associated cost of administering is broadly accurate.

Table 8.10 Estimated cost of administering per vaccination event

Year	Girls Visit 1 HPV+	Tdap*	Visit 2 HPV+	Men C*	Boys Visit 1 Tdap*	Men C*	Total events	Cost per event
2014	27,668	27,107	26,799	26,801	28,868	28,541	83,336	31.80
2015	25,884	27,499	22,721	26,780	29,285	28,518	83,564	31.71
2016	17,926	27,218	16,372	26,570	28,986	28,296	82,774	32.01

Notes: a vaccination 'event' is where one or more vaccines are administered in a single session. HPV, human papillomavirus; Men C, meningococcal group C; Tdap, tetanus and low-dose diphtheria and acellular pertussis.
+ HPV figures do not include those vaccinated outside the cohort in second level and equivalent in special schools, home schooled and out of school.
* Approximate estimate of number of doses delivered.

With the introduction of a gender-neutral programme, a second visit will be required to vaccinate boys as per the existing programme for girls. For boys in co-educational or mixed schools, the immunisation team will already have a scheduled second visit on site to administer the second dose of the HPV vaccine to girls. For boys-only schools, it is assumed that only one visit by the immunisation team currently occurs; changing to gender-neutral vaccination would necessitate a second visit by the team. The cost per event of an additional visit may be higher in boys-only schools than in mixed schools where a second visit is already scheduled. Approximately one third of boys in their first year of second-level school are in boys-only schools, so the majority of boys will be vaccinated in schools where an economy of scale may apply.

For comparative purposes, the probable cost of vaccination was estimated based on a micro-costing exercise. It was assumed that, on average, an immunisation team comprises an average of four staff (senior medical officer, two registered nurses and a clerical officer) and took into account PRSI (pay-related social insurance), overheads and pension contributions as per the national guidelines. There are an estimated 603 girls-only or mixed second-level schools nationally. If approximately one in six pupils are in first year and an immunisation team can process up to 100 vaccinations per day with no more than one school visited per day, then immunisation would take approximately 612 days, equivalent to 2.76 full-time immunisation teams. This estimate was equivalent to €45.28 per vaccination event, or €22.63 per vaccine dose given co-administration. This is a very conservative estimate as it is possible that two small schools could be covered in a day if within a reasonable distance of each other. Although based on a number of assumptions, this estimate is higher than that based on the programme cost. Some immunisation teams may include more staff. It can be argued that teams may be able to cover two smaller schools in a day rather than only one location per day as this HTA was assumed. If, for example, teams could cover multiple schools in a day but only

complete 50 vaccinations in a day, then the estimated cost per vaccine dose given co-administration drops to €14.42.

As the HPV vaccine is co-administered with a second vaccine, the cost of a vaccination event was assumed to be shared equally across the two vaccines offered. A cost of €15.92 (95% CI: 13.88 to 18.26) to administer one dose of the HPV vaccine was applied. The cost of administration was included for all HPV vaccinations so that active immunisation programmes could be appropriately compared with a strategy of no vaccination.

8.2.3.3 Cost of vaccine-related adverse events

Vaccine-related adverse events were classified as non-serious and serious. Non-serious events were assumed to primarily relate to problems at the injection site such as pain, local swelling and redness. Although these adverse events are generally short-term and would be cared for by the immunisation team, it was assumed that some proportion of children affected would be brought to their general practitioner (GP). The Health Products Regulatory Authority (HPRA) reports 1.7 adverse events per 1,000 vaccinations, and so it was assumed that approximately 5% (95% CI: 1.7% to 10.1%) of those experiencing a non-serious adverse event would attend their GP. As this evaluation was carried out from the perspective of the HSE, the cost of GP attendance was only included as an opportunity cost associated with medical card patients. Based on medical card eligibility data from the Primary Care Reimbursement Service, 38.1% of 12 year old children are covered for GP care under the General Medical Care Scheme scheme. The opportunity cost of attending a GP was set at €55 (95% CI: 45 to 67). The cost of GP attendance was not incorporated into the budget impact analysis. No additional cost was included for adverse events managed by the immunisation team either on the day of vaccination or subsequently in the HSE clinics, as this cost is assumed to be included as part of the original €2.65 million budget allocated to the HSE for vaccine delivery.

In relation to serious adverse events, it was assumed that they would incur treatment costs similar to an anaphylactic reaction in terms of the level of medical care required – that is, treatment would typically involve an emergency admission and an associated short length of stay. The ICD-10AM code of T88.6 (anaphylactic reaction due to adverse effect of correct drug or medicament properly administered) was used to identify hospitalised cases of anaphylactic shock (not specifically vaccine related). The average cost per episode between 2012 and 2016 was €1,523 for inpatient episodes and €161 for day-case episodes. By restricting the analysis to emergency admissions, all day-case episodes were excluded and the average cost of an episode was €1,565.

8.2.3.4 Cost of treatment of HPV-attributable disease

Data on the cost of treating intraepithelial neoplasia were derived from HIQA's previously published HTA on cervical cancer screening.[468] Treatment costs were provided separately for CIN 1 and CIN 2/3. In the absence of suitable Irish data on the treatment of VIN 2/3 and VaIN 2/3, it was assumed that the treatment cost would be the same as for CIN 2/3.

To determine the cost of treating invasive cancers, data were extracted from the Hospital Inpatient Enquiry (HIPE) system, which records all inpatient and day-case episodes in public acute hospitals in Ireland. For each cancer type, all discharges from 2011 to 2016 were identified on the basis of primary diagnosis and the total cost of treatment extracted as estimated by the Diagnosis Related Groups (DRGs). The total treatment cost was then divided by the total cancer-specific incidence over the same period, as reported by the National Cancer Registry, to provide an estimate of the treatment cost per patient (Table 8.11) in relation only to inpatient and day-case care. Under the assumption that 10-15% of cases are treated in a purely private setting and would therefore not appear in the HIPE dataset, the incidence was multiplied by 0.875 to adjust the denominator.

Table 8.11 Cost of treating HPV-attributed cancers

Disease	Cost of treatment (€)	
	Mean	(95% CI)
CIN 1	353	(288-427)
CIN 2/3; VIN 2/3; VaIN 2/3	471	(386-572)
Cervical cancer	18,572	(15,240-22,377)
Anal cancer	26,327	(21,563-31,880)
Vaginal cancer	16,434	(13,459-19,991)
Vulvar cancer	13,054	(10,654-15,790)
Oropharyngeal cancer	29,453	(24,042-35,558)
Penile cancer	7,281	(5,934-8,841)

For HPV-associated invasive cancers treated in public hospitals, an average of 22% of the total length of stay is associated with patients that are considered 'private' in terms of health insurance status. The data specific to HPV-attributable cancers could not be extracted. For private patients, depending on the level of cover the patient has and type of room they were accommodated in, some portion of the treatment costs are recouped by the hospital after discharge. It was assumed that approximately half of the treatment costs for private patients would be recouped through health insurance, primarily through private accommodation charges.

In addition to inpatient and day-case care, patients will require follow-up outpatient appointments. It was assumed that intraepithelial neoplasia and anogenital warts would not incur outpatient appointments, but that 38% of CIN1 and 71% of CIN2+

cases would be HPV-positive and would result in an additional smear test at one year (at a cost of €79). The number of annual appointments was derived from a Swedish HTA of HPV vaccination and estimated as a weighted average by disease severity (Table 8.12).[430] Based on the HSE Ready Reckoner data and inflated to 2018 the cost of an outpatient visit was assumed to be €144.[485]

Table 8.12 Number of annual outpatient visits for patients with HPV-attributed invasive cancers

Disease	Outpatient visits per annum				
	Year 1	Year 2	Year 3	Year 4	Year 5
Cervical cancer	6.4	2.0	2.0	1.0	1.0
Anal cancer	8.0	3.5	2.0	2.0	2.0
Vaginal cancer	6.3	2.0	1.0	1.0	1.0
Vulvar cancer	6.5	2.0	1.0	1.0	1.0
Oropharyngeal cancer	11.4	4.0	2.5	2.5	2.5
Penile cancer	6.0	4.0	2.0	2.0	2.0

For those with HPV-attributed cancers who do not survive to five years, it was assumed that palliative care would be required in the last year of life. The cost of palliative care was set at €38,272 (95% CI: 31,371-46,346) for one year.[468]

The treatment of anogenital warts occurs in the primary care setting but may occur in one of a number of settings including sexually transmitted infection (STI) clinics and general practice (GP) surgeries (Table 8.13). Medicine costs were considered separately from equipment and staff costs to facilitate the inclusion of VAT in the budget impact analysis. The cost of treatment of anogenital warts in STI clinics has been estimated previously for Ireland.[486] The estimate of €330 for treatment was divided between clinical staff time and medication. The consumer price index for health was used to update the cost to 2017 values. For treatment in a GP setting, three main treatments options were considered: imiquimod, podophyllotoxin and cryotherapy. Finally, surgical excision was also considered.

Supporting data on the treatments were derived from a previously published UK economic evaluation of anogenital wart treatments.[200] As with the treatment of non-serious adverse events, GP costs were treated as an opportunity cost that only applied to patients with a medical card and as such were excluded from the budget impact analysis. Based on the age-sex distribution of incidence of anogenital warts, an estimated 29% of those treated would have medical cards. It was assumed that those not eligible for a medical card would pay out of pocket for treatment. It was assumed that episodes of anogenital warts that failed to clear with treatment would receive a second round of the same treatment. The average cost of treating anogenital warts was €229 (95% CI: 176 to 292).

Table 8.13 Number of annual outpatient visits for patients with HPV-attributed cancers

Treatment	% patients	Probability of treatment success	Resources per treatment		
			GP visits	Medicine (€)	Other costs (€)
STI clinic	50.0	1.00	0	32	323
Imiquimod	2.5	0.56	2	304	0
Podophyllotoxin	22.0	0.83	1	21	0
Surgical excision	1.0	0.85	0	0	179
Cryotherapy	24.5	0.71	4	0	20

Through the prevention of HPV infection it was assumed that there would be a reduction in recurrent respiratory papillomatosis (RRP) in children born to mothers with HPV infection. Treatment for RRP was estimated in the UK to be an average of £1,133 (€1,553) per episode, with an average of three episodes per year.[487] The mean age at diagnosis is four years and it was assumed that three treatment episodes a year would apply from age four to life expectancy. The average life expectancy for a four year old in Ireland is 76.9 years.[488] Taking into account discounting, the average lifetime cost of treating RRP was an estimated €78,316.

8.2.4 Model outputs

The outputs of the model included the total costs, QALYs gained and five-year budget impact for each of the alternatives modelled. Summary measures included the incremental cost-effectiveness ratio and plots of the cost-effectiveness plane and cost-effectiveness acceptability curves. Additional outputs such as the estimated reduction in incidence of cancer were also recorded. As the 4-valent girls-only programme represents the current standard of care, the results for vaccination strategies are presented relative to the current programme where relevant.

The incremental cost-effectiveness ratio (ICER) presents the additional costs divided by the additional benefits of one intervention in relation to another. The ICER is typically considered in the context of a willingness-to-pay (WTP) threshold, which represents the maximum a decision-maker is willing to pay for a unit benefit, such as a life year gained or a quality-adjusted life year. The WTP threshold reflects the monetary values that a stakeholder, in this case the HSE, is willing to pay for a specified outcome. In this study the outcome is QALYs. There is no stated universal willingness-to-pay threshold in Ireland below which an intervention is considered cost-effective. In previous evaluations in Ireland, willingness-to-pay thresholds of between €20,000 and €45,000 per QALY have typically been used as reference points. An international study generated estimates for Ireland suggesting that the WTP threshold is closer to €20,000 per QALY than €45,000 per QALY.[489] A 2016 framework agreement between the Irish Pharmaceutical Healthcare Association (IPHA) and the HSE for the supply and pricing of medicines sets out €20,000 per

QALY and €45,000 per QALY as reference points for decision-making in regards the reimbursement of medicines.[490] The agreement also sets out five-year budget impact thresholds for the level of HSE authority required in decision-making.

Cost-effectiveness acceptability curves (CEACs) are used as a method for summarising information on uncertainty in cost-effectiveness. A CEAC shows the probability that an intervention is cost-effective compared with the modelled alternatives for a range of willingness-to-pay thresholds.

8.2.5 Scenario and sensitivity analyses

A fully probabilistic model was used that explicitly takes into account the uncertainty in the model parameters. All of the key parameters were varied within plausible ranges of values. Where possible, ranges were derived from published evidence. As the structure of the economic model presented here is inherently stochastic, the outputs are equivalent to a multi-variate probabilistic sensitivity analysis.

Scenario analyses were also used to specifically look at the impact of a number of key assumptions in relation to parameter values. In each analysis, one or more parameters were set at alternative and potentially justifiable point estimates.

Univariate, or one-way, sensitivity analysis facilitates examination of the impact of each variable in the study by varying it across a plausible range of values while holding all other variables constant at their average value. The resulting difference provides some indication of how sensitive the results might be to changes in that parameter. Deterministic sensitivity analysis was used to examine this, where each parameter in turn was fixed at its upper and lower confidence bounds while all the other parameters were held at their average value.

The review of previously published cost-effectiveness studies, reported in Chapter 7, highlighted that the estimated cost-effectiveness of a gender-neutral programme was sensitive to the uptake rate in girls. A threshold analysis was used to examine the impact of varying the uptake rate separately in girls and boys.

8.3 Cost-effectiveness results

The model was run for 10,000 Monte Carlo simulations to estimate of the costs and consequences of each comparator in the economic model. To determine if the model had converged on a result, the mean Net Monetary Benefit (NMB) was monitored across simulations. After 5,000 simulations, the estimated mean NMB is within 1% of the estimated mean NMB after 10,000 simulations. After 3,000 simulations, the estimate was consistently within 4% of the final mean. Due to the computational burden of the model, for scenario analyses the model was only run for 3,000 simulations.

8.3.1 Base case cost-effectiveness results

Relative to the current girls-only 4-valent programme, a strategy of no vaccination is more costly and less effective (Table 8.14). The 9-valent girls-only programme is less costly and more effective than the current strategy, but less effective than the gender-neutral 9-valent immunisation strategy.

Table 8.14 Total costs and benefits of vaccination strategies (relative to the current girls-only 4-valent programme)

Strategy	Cost (€ millions)	Benefit (QALYs)
No vaccination	51.7	-10,462.8
Girls-only 4-valent	0.0	0.0
Gender-neutral 4-valent	26.4	418.9
Girls-only 9-valent	-14.7	2,012.0
Gender-neutral 9-valent	11.6	2,712.2

Note: QALY, quality-adjusted life year.

In terms of cost-effectiveness, the cost-effectiveness frontier comprises girls-only 9-valent vaccination and gender-neutral 9-valent vaccination (Table 8.15). The incremental cost-effectiveness of gender-neutral 9-valent vaccination is €37,593 per QALY relative to a girls-only 9-valent vaccination.

Table 8.15 Incremental costs and benefits of HPV vaccination strategies

Strategy	Cost (€ millions)		Benefit (QALYs)		ICER
	Total	Incremental	Total	Incremental	(€/QALY)
Girls-only 9-valent	-14.7	-	2,012.0	-	-
Gender-neutral 9-valent	11.6	26.3	2,712,2	700.2	37,593

Note: QALY, quality-adjusted life year.

The plot of the cost-effectiveness plane highlights the substantial uncertainty in the costs and benefits associated with the programmes, particularly in relation to the costs of the gender-neutral programmes (Figure 8.8). However, despite the uncertainty in the point estimates, there appears to be a relatively clear delineation between the included strategies.

At willingness-to-pay thresholds of €20,000 and €45,000 per QALY, the girls-only 9-valent strategy has a probability of 0.93 and 0.38, respectively, of being the most cost-effective option (Figure 8.9). Gender-neutral 9-valent vaccine is the only other strategy with a non-zero probability of being cost-effective at those thresholds, with probabilities of 0.07 and 0.62 of being the most cost-effective option.

Figure 8.8 Cost-effectiveness plane for HPV vaccination strategies

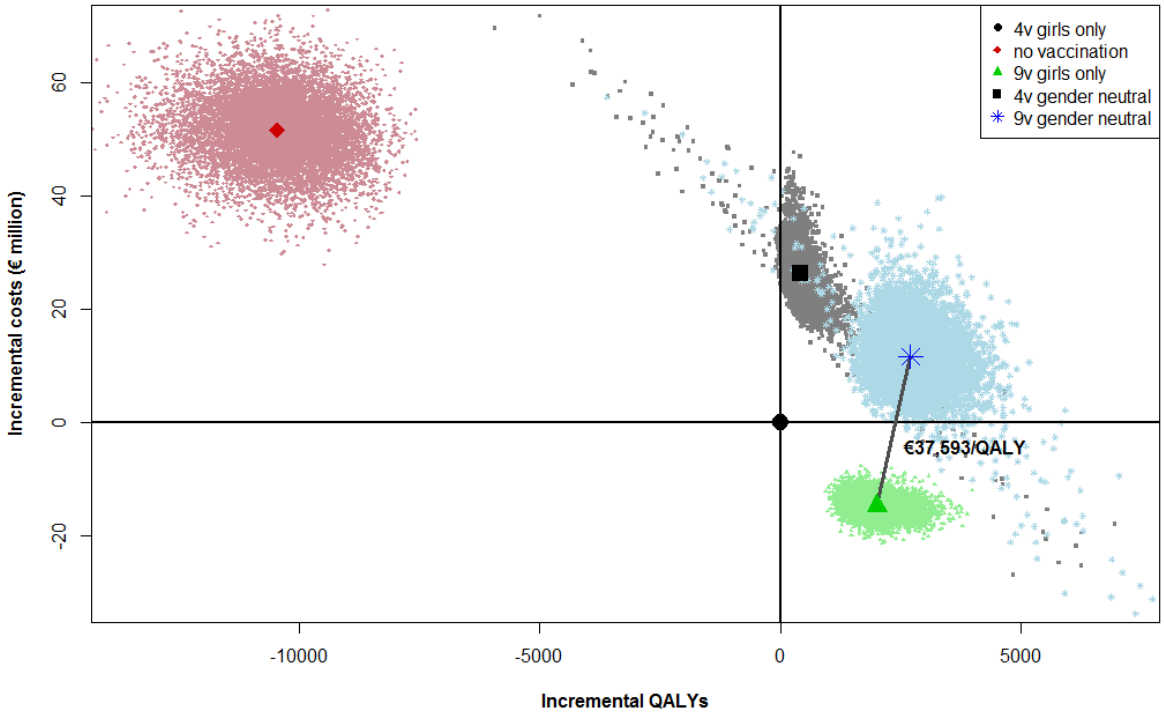
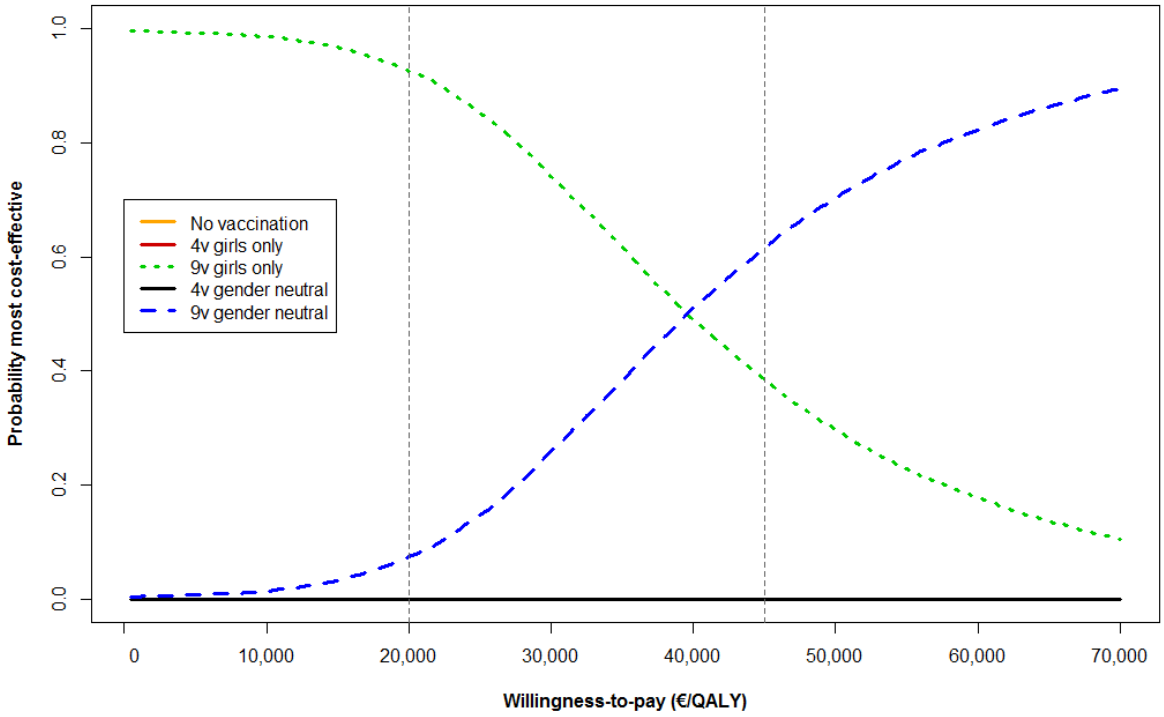


Figure 8.9 Cost-effectiveness acceptability curves for HPV vaccination strategies



The increased disease protection associated with the 9-valent vaccine and herd immunity associated with a gender-neutral immunisation programme lead to reduced incidence of HPV-attributed disease. An output of the model was the numbers of cancer and anogenital wart cases avoided by vaccination over and above what will be achieved by the existing girls-only 4-valent programme (Table 8.16).

The switch to a 9-valent vaccine is predicted to result in substantial reductions in cases of pre-cancerous lesions in the short to medium-term. The impact on invasive cancers will take longer to observe: 20 years after introduction it is expected that, relative to the existing girls-only 4-valent programme, there will be 10 fewer cases of cervical cancer per year with a girls-only 9-valent programme, and 15 fewer cases per year with a gender-neutral 9-valent vaccine.

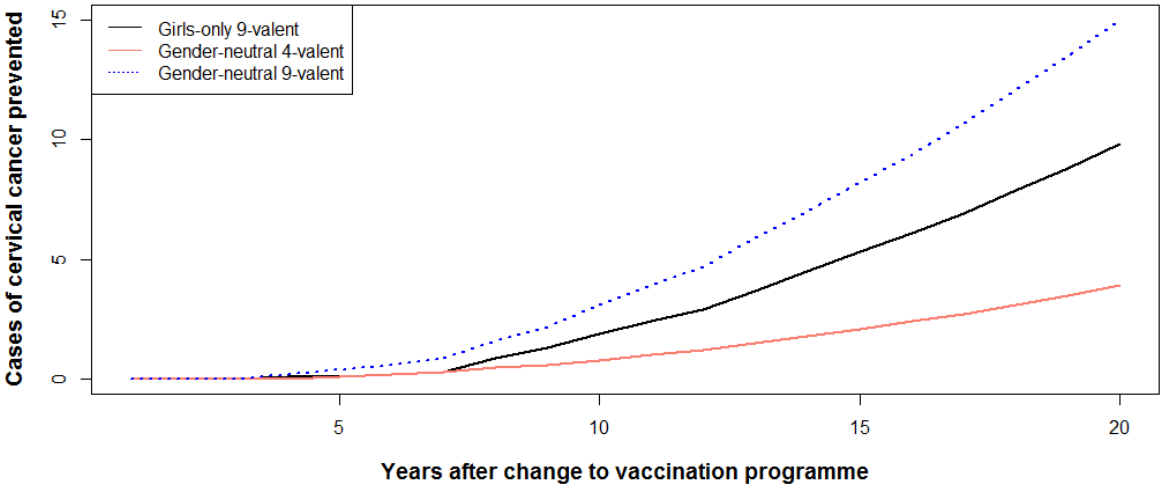
Table 8.16 Number of disease cases avoided each year after a change to the immunisation programme

Disease avoided	Cases prevented per year					
	Girls-only 9-valent			Gender-neutral 9-valent		
	10	20	30	10	20	30
Pre-cancerous lesions						
CIN 1	43.6	1,530.3	2,388.4	109.4	1,884.1	2,925.2
CIN 2+	15.2	396.4	562.7	45.7	513.7	726.4
VaIN 2/3	0.1	0.2	0.3	0.2	0.3	0.6
VIN 2/3	0.5	0.9	1.7	0.9	1.6	3.1
Invasive cancer						
Cervical cancer	1.9	9.8	19.1	3.1	15.0	29.5
Anal cancer	0.0	0.0	0.0	0.0	0.2	0.3
Vaginal cancer	0.0	0.0	0.1	0.0	0.1	0.2
Vulvar cancer	0.0	0.1	0.5	0.0	0.2	0.9
Other						
Anogenital warts	0.0	0.0	0.0	167.2	500.4	682.8

A girls-only 9-valent programme will not offer any greater protection than the existing programme against anogenital warts. This evaluation assumed that 90% of anogenital warts are due to HPV types 6 and 11; however, by extending vaccination to a gender-neutral programme, boys acquire protection against anogenital warts. After 20 years, it is anticipated that 500 additional episodes a year of anogenital warts will be prevented compared with the existing girls-only 4-valent HPV immunisation programme.

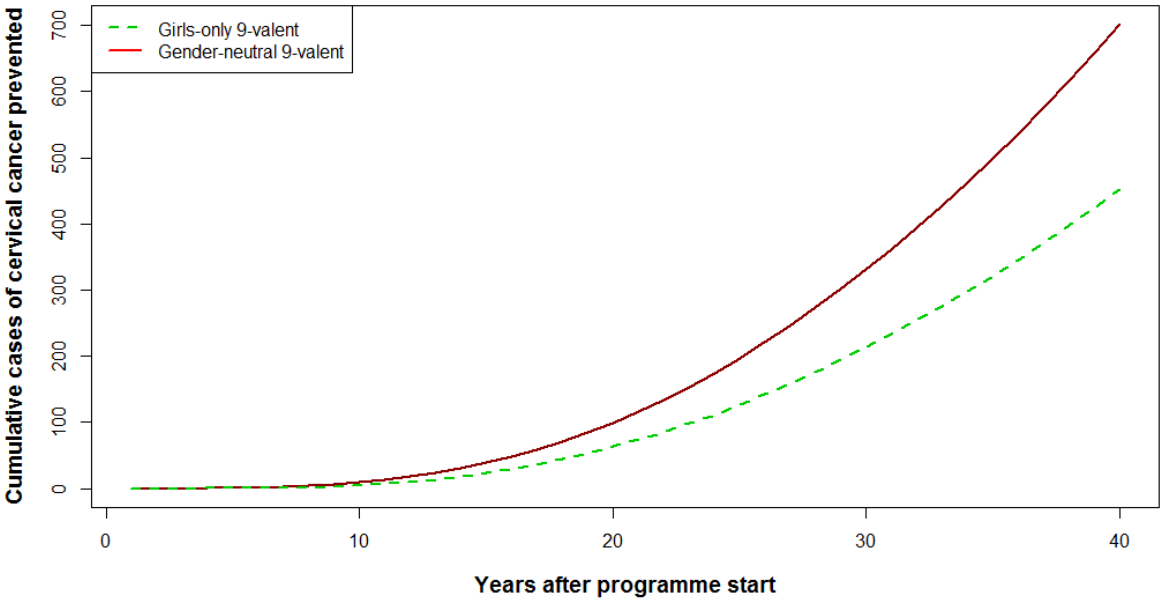
The reduction in incidence of cervical cancer is expected to take a number of years which is due to the age of the vaccinated cohort and the substantial lag before they become at risk of developing cervical cancer (Figure 8.10).

Figure 8.10 Number of cervical cancer cases avoided each year after a change to the immunisation programme



After 20 years, relative to the existing girls-only 4-valent programme, a girls-only 9-valent programme will have prevented an estimated 8,958 cases of CIN 1, 2,540 cases of CIN 2/3, and 63 cases of cervical cancer. Over the same time horizon, relative to the existing girls-only 4-valent programme, a gender-neutral 9-valent programme will have prevented 11,277 cases of CIN 1, 3,368 cases of CIN 2/3, and 99 cases of cervical cancer.

Figure 8.11 Cumulative number of cervical cancer cases avoided relative to the current girls-only 4-valent immunisation programme



8.3.2 Scenario analyses

In developing the model a number of important assumptions were made including the cost of the vaccine, future uptake rates, and the degree to which vaccination would protect against a number of cancers. The impact of these assumptions on

cost-effectiveness was tested in scenario analyses whereby plausible alternative parameter values or sets of parameter values were used.

8.3.2.1 Inclusion of oropharyngeal and penile cancer

Although it is accepted that a proportion of penile and oropharyngeal cancers can be attributed to HPV infection, it has not yet been demonstrated that HPV vaccination offers protection against these cancers. Both are cancers that would require substantial long-term follow up to detect an effect on the incidence of invasive cancers. While this has been partly addressed by monitoring pre-cancerous lesions for some cancers, in the case of oropharyngeal cancers there are no defined pre-cancerous lesions.

A scenario analysis was run, in which the vaccine was effective against penile and oropharyngeal cancers, with an average risk reduction of 50%. With this change in assumption the frontier still comprises girls-only 9-valent and gender-neutral 9-valent vaccination. The incremental cost-effectiveness ratio for gender-neutral 9-valent vaccination reduces to €29,089 per QALY compared to girls-only 9-valent vaccination. The probability of gender-neutral 9-valent vaccination being the most cost-effective option was 0.16 at €20,000 per QALY and 0.83 at €45,000 per QALY. These estimates are conservative as, in the absence of any supporting data, a low estimate of vaccine efficacy was used. If, for example, a vaccine efficacy similar to that for cervical cancer was used, then the ICER of a gender-neutral 9-valent programme would reduce further to €24,024 per QALY. These estimates are based on the incidence of oropharyngeal cancer from 2009 to 2013, and do not take into account the trend for increasing incidence.

8.3.2.2 Return to 2013 uptake rates

It is clear that two-dose uptake rates in the Irish HPV immunisation programme have fluctuated quite substantially from a high of 88.2% in 2013 to a low of 51% in 2016. It would appear that uptake rates are recovering but it is unclear whether they will return to the levels observed before 2015. As outlined in Chapter 7, previous economic evaluations have highlighted the association between the cost-effectiveness of a gender-neutral programme and the uptake rate in girls. The consistent finding has been that a high uptake rate in girls may render a gender-neutral programme not cost-effective. The base case analysis presented here assumed that a girls-only programme would achieve a stable uptake of 70%. A scenario analysis was used to assess the impact of uptake returning to 88.2% as per the 2013 figures. The higher uptake in girls, assuming the uptake in boys remains at 87.7% of the uptake rate in girls, results in an ICER of €125,632 per QALY for a gender-neutral 9-valent immunisation programme relative to girls-only 9-valent.

8.3.2.3 Equal uptake rates for girls and boys

The estimates of the relative uptake in boys in a gender-neutral programme were based on published data from the gender-neutral programme in place in Australia. An average from the first three years of the programme was used, although the data suggested a trend whereby uptake in boys is increasing and approaching the uptake in girls. In the event that uptake in boys is the same as that in girls (that is, an average of 70%), the ICER for a gender-neutral 9-valent immunisation programme relative to girls-only 9-valent would be essentially unchanged at €37,701 per QALY.

8.3.2.4 Fluctuating uptake rates

In the main analysis it was assumed that the uptake rate would be stable over time, so while the uptake rate was varied across simulations, it was fixed within each simulation. Uptake rates over the first eight years of the HPV immunisation programme have shown a marked fluctuation and raise questions over the resilience of uptake. An alternative scenario was explored in which the uptake rate was allowed to vary according to a cyclical pattern within each simulation based on an average uptake of 70% but varying between 50% and 90% over time according to a sine wave. The sine wave was defined with a ten year cycle between peaks of uptake. That is, it takes five years to go from a peak of high uptake to a low uptake, and a further five years to recover to a high uptake again. It was assumed that at the outset the uptake is increasing from the 2017 estimate of 56.4%. By incorporating a fluctuating uptake rate, the incremental cost-effectiveness ratio for a gender-neutral 9-valent programme reduced to €24,427 per QALY.

8.3.2.5 Alternate HPV acquisition probabilities

The acquisition probabilities used in the original model were based on data from US dynamic transmission models, and therefore reflect the prevalence of HPV infection in the US. For this evaluation the acquisition probabilities were adjusted to reflect the estimated prevalence of HPV infection in Ireland, which itself was based on UK and Danish data. The acquisition probabilities used in the model reflect a different profile to the US data and, as they were not generated as the output of a model calibration exercise, could skew the results. A scenario analysis was undertaken using the US data on acquisition probabilities. The incremental cost-effectiveness ratio increased from €37,593 per QALY to €41,125 per QALY. The effect of using the US data was therefore considered modest and would not change the interpretation of the results.

8.3.2.6 Equal cost of 4-valent and 9-valent vaccines

The base case model assumed that the 9-valent vaccine would, on average, cost 10% more than the 4-valent vaccine. This was based on data from private providers where a premium was being charged for the additional protection afforded by the 9-valent vaccine. In the event that the HSE is able to purchase the 9-valent vaccine at the same price as the 4-valent vaccine, the ICER for a gender-neutral 9-valent immunisation programme relative to girls-only 9-valent would drop to €31,705/QALY.

8.3.2.7 Waning efficacy

The base case analysis incorporated the assumption that vaccine efficacy is lifelong. That is, the effect of the vaccine does not diminish over time. Trial data suggest that there is no loss of efficacy after ten years, and this is often interpreted as being evidence of lifelong efficacy. An alternative approach is to assume that efficacy wanes after ten years and that after a number of years vaccine recipients may no longer have any protection from HPV infection. There are many ways in which waning efficacy can be modelled incorporating different rates of change, and whether those rates are linear over time or following some other function. It was assumed that full efficacy would be maintained from age 12 years to age 22 years and that efficacy would reduce by 5% per annum thereafter. By age 36 years, a vaccine recipient would have half the protection achieved at vaccination, and by age 53 years they would have 20% of the original efficacy. Under those conditions, the ICER for gender-neutral vaccination increases marginally to €38,447/QALY.

Applying more substantial reductions in efficacy further increases the ICER, such that a 20% per annum reduction in efficacy results in an ICER of €39,990 per QALY and a 50% reduction per annum gives an ICER of €40,944 per QALY.

8.3.2.8 Impact of non-serious adverse reactions

The base case analysis included a disutility for non-serious adverse reactions. Most previous economic evaluations have not included any disutility for that outcome, possibly on the grounds that the impact on health-related quality of life is so small as to not be measurable. In other words, the impact is not clinically significant. It was included in the base case here on the basis that for most people who experience a non-serious adverse reaction it might mean staying at home from school for a day or missing a sporting fixture or other activity due to a sore arm.

An alternative scenario analysis was undertaken in which the duration of disutility was reduced from the base case average of seven days down to two days. The incremental cost-effectiveness ratio reduced to €29,634 per QALY. Another scenario analysis was carried out in which no disutility was applied to non-serious adverse events, resulting in an incremental cost-effectiveness ratio of €27,387 per QALY.

8.3.2.9 Alternative length of survival for terminal cancer

In the base case analysis it was assumed that those who develop cancer but do not survive to five years will, on average, survive for two years after their initial cancer diagnosis. The assumption of two years was based on an analysis of summary survival data published by the National Cancer Registry and, due to the use of annual cycles in the model, the data were rounded to two years. The data were also not specific to HPV-attributable cancers, and they may be associated with shorter or longer survival relative to non-HPV-attributable cancers. Scenarios of an average of one year and three years of survival were used to test the impact of different assumptions. The incremental cost-effectiveness ratio reduced to €36,646 per QALY based on an average of one year of survival, and increased to €38,607 per QALY based on an average of three years of survival.

8.3.2.10 Alternative lag times to developing HPV-attributable disease

The model incorporates lag times for the development of HPV-attributable disease. The lag times acknowledge that it could take a number of years for invasive cancer to develop, for example, after HPV infection whereas anogenital warts could develop within a few months. Two scenarios were applied: one in which all lag times were set to zero years and one in which all were set to five years. When all lag times were set to zero years, the ICER reduced marginally to €36,472 per QALY, reflecting the fact that is invasive cancers can develop immediately then the impact of discounting is reduced. When all lag times were set to five years the ICER increased marginally to €38,529 per QALY.

8.3.3 Sensitivity analyses

A sensitivity analysis is an important step in identifying parameters for which parameter uncertainty has an important influence on decision uncertainty.

8.3.3.1 Univariate sensitivity analysis

In the univariate sensitivity analysis each stochastic parameter was set at its upper and lower 2.5 percentiles, respectively, while all other parameters were set at their mean values. Through this analysis the impact on decision uncertainty of uncertainty in individual parameters can be explored. For this analysis, we focused on the impact of the incremental cost-effectiveness ratio between the gender-neutral 9-valent versus girls-only 9-valent vaccination. In relation to the girls-only 9-valent strategy, there was no parameter for which setting the parameter at its bounds rendered the girls-only 9-valent strategy either less effective or more costly than the girls-only 4-valent strategy.

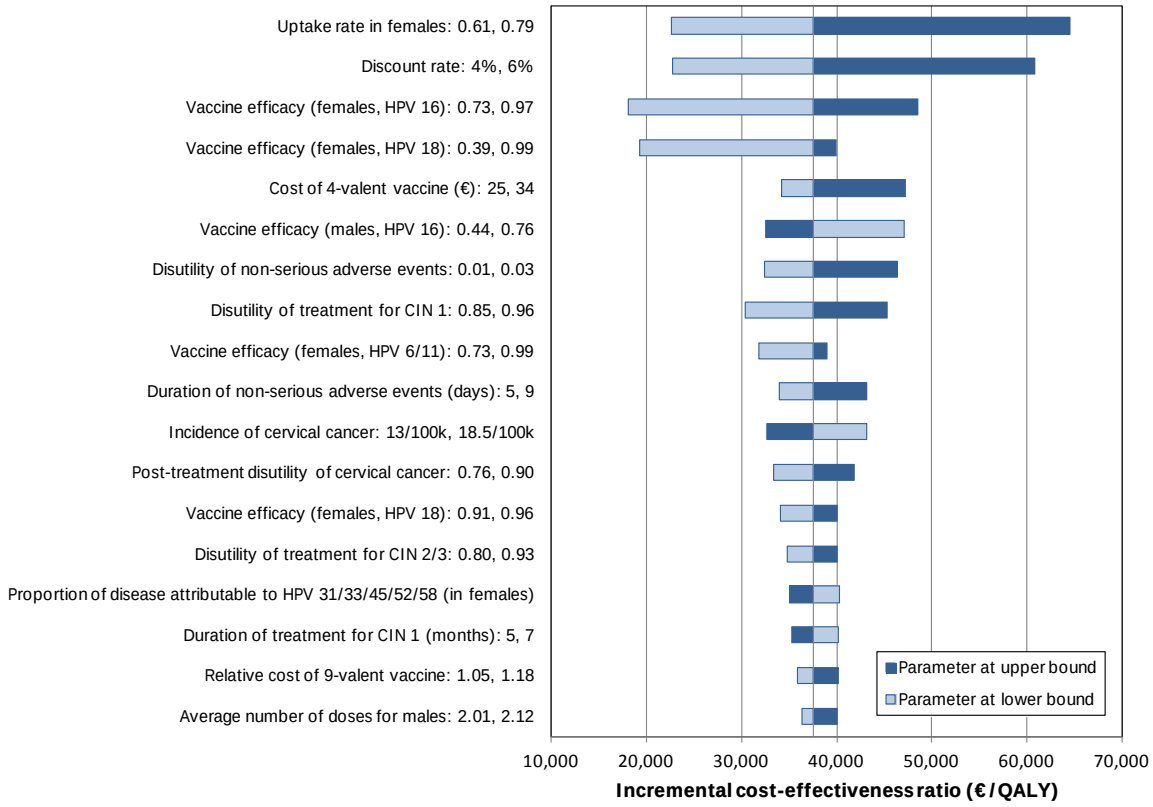
For the comparison of gender-neutral 9-valent versus girls-only 9-valent vaccination, setting the discount rate at alternate values (of 0%, 4%, 6% and 10%) had a substantial impact on the ICER (Figure 8.11). At a discount rate of 10%, the ICER increased to € 904,722 per QALY while at a discount rate of 0% the ICER was €2,698 per QALY (not shown in Figure 8.10). A high discount rate implies a strong time preference. For vaccines like the HPV vaccine, the cost of vaccination occurs years before health benefits are observed. As a result, benefits are valued less than if they were accrued immediately yet the costs have their full value. The discount rate used in the base case analysis is set by the Department of Finance. In the event of a discount rate change, historically the rate has changed by a single percentage point. At discount rates of 4% and 6% the ICER changed to €22,739 per QALY and €60,771 per QALY, respectively (Figure 8.10).

Uncertainty in the uptake rate in girls had a strong influence on the ICER: if the uptake rate in girls is 61% then the ICER drops to €22,686 per QALY, while if the uptake rate is 78% then the ICER increases to €64,563 per QALY. Vaccine efficacy in preventing persistent HPV 16 and 18 infection in girls is also an influential parameter. If efficacy in girls is lower than expected, expanding the programme to include boys is more likely to be cost-effective.

There were a number of parameters that, when set at their bounds, could result in an ICER of greater than €45,000 per QALY. To interpret the resulting tornado plot (Figure 8.12), it shows how much the ICER changes when a parameter has been set at its upper bound (dark blue bar) or lower bound (light blue bar) while all other parameters were set at their average values. For example, when the uptake rate in females was set at its upper bound (of 0.79) the ICER was approximately €64,000 per QALY. When the uptake rate in females was set at its upper bound (of 0.61) the ICER was approximately €24,000 per QALY.

All parameters that were defined by probability distributions were included in the univariate sensitivity analysis. In the interests of legibility, the tornado plot only includes parameters that, when set at their upper and lower bounds, resulted in a change in the ICER of at least 5%.

Figure 8.12 Tornado plot of univariate sensitivity analysis (incremental cost-effectiveness ratio of gender-neutral 9-valent versus girls-only 9-valent vaccination)



Notes: Discount rates of 0% and 10% are not included as it would obscure impact of other parameters. Only parameters shown where setting values at either upper or lower bound resulted in a change in ICER of greater than €1,880/QALY (i.e., 5% of the mean ICER). All stochastic parameters were varied for the analysis.

8.3.3.2 Varying vaccine price

If the vaccine cost is linked to the volume purchased, then the cost per dose could be lower for a gender-neutral programme than it is for the existing girls-only programme. The impact of vaccine price on cost-effectiveness was explored by testing 4-valent vaccine costs ranging from €10 to €100 per dose. The administration cost was left unchanged from the base case analysis. The relationship between incremental cost-effectiveness and vaccine cost was linear.

Below €15 per dose, a gender-neutral 9-valent immunisation programme becomes cost-effective at €20,000 per QALY. Above €32 per dose, the ICER of gender-neutral 9-valent vaccination was in excess of €45,000/QALY. At €100 per dose, the ICER increased to €140,652 per QALY.

8.3.3.3 Varying uptake rates

Two scenario analyses were carried out in relation to uptake rate:

1) the scenario where uptake in girls returned to the 2013 level of 88.2%,

2) and the scenario where uptake was the same in girls and boys.

The increased uptake in girls had a very marked impact on the ICER, while increasing the uptake in boys has a modest impact. A sensitivity analysis was carried out to test uptakes rates of 10% to 90% in girls and in boys to explore under which uptake conditions gender-neutral 9-valent vaccination might be cost-effective.

Varying the uptake in boys has a limited impact on cost-effectiveness, which is very sensitive to changes in uptake in girls. For all combinations of uptake in boys and girls, the cost-effectiveness frontier comprised either the gender-neutral 9-valent programme alone or both the girls-only and gender-neutral 9-vaent programmes. In this evaluation the focus has been on considering the incremental cost-effectiveness of the gender-neutral 9-valent programme relative to the girls-only 9-valent programme. The relationship between the ICER and uptake in girls is approximately exponential. If the uptake rate in girls is below 60%, a gender-neutral programme is likely to be cost-effective at a willingness-to-pay of €20,000/QALY. If the uptake rate in girls is 80% or lower, a gender-neutral programme is likely to be cost-effective at a willingness-to-pay of €45,000/QALY.

8.3.3.4 Additional benefit of including boys in the immunisation programme

The effectiveness of the different modelled programmes has been measured in terms of QALYs which are intended to capture both quantity and quality of life. In a girls-only programme, most of the benefits fall to females. In a gender-neutral programme, the benefits are estimated to increase for the population as a whole, with the share accruing to boys likely to increase. One way to compare the strategies of girls-only and gender-neutral 9-valent vaccination is to consider the increase in uptake required in the girls-only programme required to generate the same number of QALYs as is gained by switching to a gender-neutral programme.

If uptake in girls is at 70%, the girls-only 9-valent programme would generate an additional 2,014 QALYs relative to a girls-only 4-valent programme while the gender-neutral 9-valent programme would generate an additional 2,683 QALYs. For the girls-only 9-valent programme to generate an additional 2,683 QALYs the uptake would have to increase to 79.5%. In other words, in terms of QALYs generated, a girls-only 9-valent programme would need to increase uptake by almost 10% to achieve the same gain as realised by extending the programme to boys.

The relevance of this finding should be considered in the context of the additional cost of adding boys to the programme relative to the potential cost and feasibility of increasing uptake in a girls-only programme by 10%. The analysis also ignores how

those QALYs are distributed across males and females, assuming all QALYs to be equal.

Table 8.17 Impact of varying uptake rate on the incremental cost-effectiveness of gender-neutral 9-valent relative to girls-only 9-valent vaccination

Females \ Males	10%	20%	30%	40%	50%	60%	70%	80%	90%
10%	462	774	860	870	879	874	863	847	828
20%	2,417	2,518	2,496	2,386	2,373	2,339	2,284	2,255	2,226
30%	4,453	4,656	4,702	4,693	4,585	4,562	4,536	4,500	4,471
40%	7,593	7,639	7,815	7,857	7,915	7,925	7,953	7,957	7,962
50%	12,757	12,688	12,937	12,729	13,188	13,451	13,278	13,249	13,264
60%	20,244	21,008	21,429	21,596	21,685	22,044	22,029	21,952	21,958
70%	35,218	36,152	36,500	36,657	36,857	37,032	37,567	37,674	37,771
80%	66,598	67,983	68,477	69,032	69,473	70,775	70,865	71,095	72,269
90%	167,010	170,963	172,050	177,964	177,991	180,694	181,602	182,803	184,269

8.4 Budget impact results

Whereas an economic analysis addresses the additional health benefit gained from investment in a technology, such as the cost per QALY, budget impact analysis addresses the affordability of the technology. For example, it outlines the net annual financial cost of adopting the technology over five years. Although BIA and cost-effectiveness analysis have many similar data and methodological requirements, there are some important distinctions between the two approaches. Budget impact analysis:

- reports costs only
- reports the costs for each year in which they occur
- is concerned with costs over a short time horizon
- incorporates Value Added Tax (VAT) where it applies
- calculates costs for the entire patient population.

The nature of the cost-effectiveness model was that it included the entire eligible population, so adaptations to facilitate a budget impact analysis were relatively minor.

The budget impact is presented relative to the existing girls-only 4-valent HPV immunisation programme. This analysis focuses primarily on the girls-only 9-valent and gender-neutral 9-valent strategies because, from a cost-effectiveness perspective, they dominate the existing programme as well alternatives of no vaccination and a gender-neutral 4-valent programme. Over the first five years, a girls-only 9-valent HPV immunisation programme will incur an annual incremental budget impact of €0.15 million, equivalent to €0.76 million (96% CI: €0.38m to €1.35m) for the first five years (Table 8.18). A gender-neutral 9-valent HPV immunisation programme would have an annual incremental budget impact of €2.09 million in the first year, reducing to €2.06 million after five years for a total five-year budget impact of €10.40 million (95% CI: €8.4m to €13.2m).

Table 8.18 Estimated annual incremental budget impact relative to a girls-only 4-valent immunisation programme

Year	Incremental budget impact (€ millions)			
	Girls-only 9-valent		Gender-neutral 9-valent	
	Mean	(95% CI)	Mean	(95% CI)
1	0.16	(0.08,0.25)	2.09	(1.69,2.54)
2	0.16	(0.08,0.25)	2.09	(1.69,2.54)
3	0.15	(0.08,0.25)	2.08	(1.69,2.53)
4	0.15	(0.07,0.25)	2.07	(1.68,2.52)
5	0.15	(0.07,0.24)	2.06	(1.67,2.51)
Total	0.76	(0.38,1.35)	10.40	(8.42,13.16)

In the medium term, the girls-only 9-valent programme will be close to budget neutral relative to the girls-only 4-valent programme in year 10 (Figure 8.13). In year 10 the gender-neutral 9-valent programme would have a budget impact of €1.87 million (95% CI: €1.47m to €2.32m) relative to the current programme (Figure 8.14). The estimates reported here do not incorporate any additional expenditure in the first year that might be required as part of a public awareness or promotional campaign that may be associated with the extension of the programme to include boys.

Figure 8.13 Budget impact of girls-only 9-valent vaccine relative to existing girls-only 4-valent immunisation programme

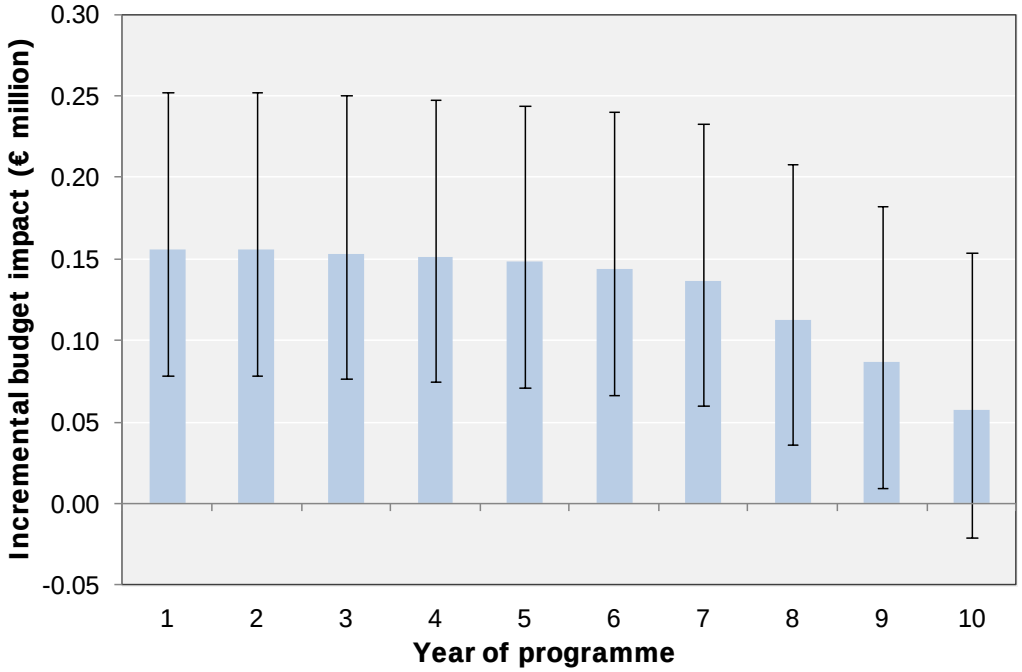
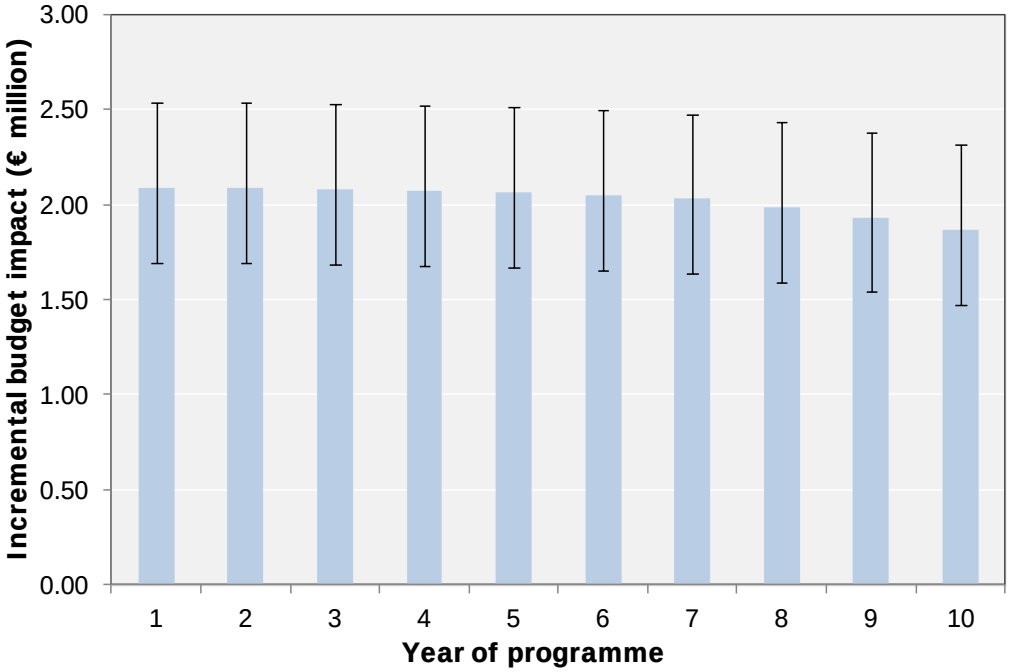


Figure 8.14 Budget impact of gender-neutral 9-valent vaccine relative to existing girls-only 4-valent immunisation programme



8.4.1 Scenario analysis

As with the cost-effectiveness analysis, an exploration of alternative scenarios can provide useful information about how modelling and parameter assumptions affect the estimated incremental budget impact. In these analyses, the focus has been on alternative assumptions that would affect costs in the short term, and hence impact on the estimated five-year budget impact. The results of the four scenario analyses are summarised in Table 8.19.

8.4.1.1 Return to 2013 uptake rates

Given the short-term nature of a budget impact analysis, the modelling assumptions that are most likely to alter the budget impact in this case are those that relate to the volume of vaccine used and the cost of the vaccine. Clearly, an increase in the uptake rate would increase the demand for vaccine. The incremental budget impact of the uptake rate in girls returning to the peak figure of 88.2% was estimated. Under those conditions, the five-year budget impact of a girls-only 9-valent programme increases from €0.76 million to €0.97 million (95% CI: €0.5m to €1.7m), and the gender-neutral 9-valent programme increases from €10.40 million to €12.72 million (95% CI: €10.5m to €16.0m).

8.4.1.2 Equal uptake for boys and girls

A scenario of equal uptake for girls and boys only impacts on the incremental budget impact of the gender-neutral programme, as it replicates the base case for the girls-

only programme. An average uptake rate of 70% in boys results in a five year incremental budget impact of €12.72 million (95% CI: €10.52m to €15.97m).

8.4.1.3 Equal uptake for boys and girls at 2013 levels

In the event that uptake rates in girls return to 2013 levels (88.2%) and that boys achieve the same uptake as girls, then this will lead to a maximum budget impact scenario. Under those conditions, the incremental five-year budget impact would be €0.97 million (95% CI: €0.5m to €1.7m) for a girls-only 9-valent programme, and €14.26 million (95% CI: €12.3m to €17.9m) for a gender-neutral 9-valent programme.

8.4.1.4 Equal cost of 4-valent and 9-valent vaccines

A final scenario analysis relates to the impact of the 9-valent vaccine being purchased at the same price as the 4-valent vaccine. For a girls-only 9-valent programme there would be no incremental budget impact for the first four years and in the fifth year a minor saving would be observed. For a gender-neutral 9-valent programme the five-year incremental budget impact budget impact would reduce to €8.9 million (95% CI: €7.4m to €11.1m).

Table 8.19 Estimated five year incremental budget impact relative to a girls-only 4-valent immunisation programme

Scenario	Five-year incremental budget impact			
	Girls-only 9-valent		Gender-neutral 9-valent	
	Mean	(95% CI)	Mean	(95% CI)
Base case	0.76	(0.38, 1.35)	10.40	(8.42, 13.16)
High uptake rate (88.2% in girls, 77.4% in boys)	0.97	(0.49, 1.70)	12.72	(10.52, 15.97)
Equal uptake rate in girls and boys (70%)	0.76	(0.38, 1.35)	11.71	(9.80, 14.60)
Equal high uptake rate in girls and boys (88.2%)	0.97	(0.49, 1.70)	14.26	(12.31, 17.88)
Equal price for 4-valent and 9-valent vaccines	-0.01	(-0.02, -0.01)	8.90	(7.42, 11.07)

8.4.2 Sensitivity analysis

As with the cost-effectiveness analysis, sensitivity analyses were used to identify parameters for which parameter uncertainty has an important influence on decision uncertainty in terms of budget impact.

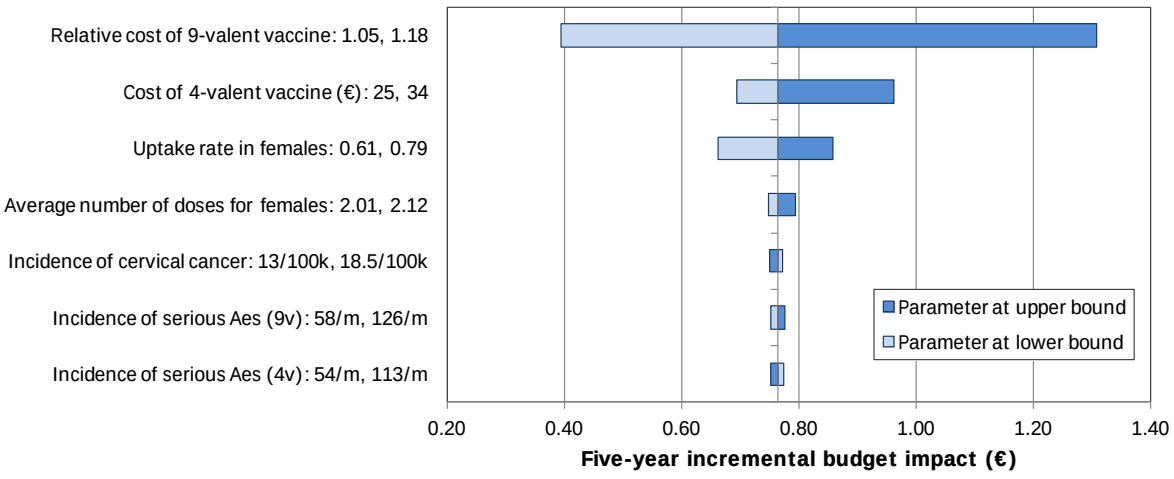
8.4.2.1 Univariate sensitivity analysis

A univariate sensitivity analysis was undertaken on the incremental five-year budget impact of both the girls-only and gender-neutral 9-valent strategies relative to the existing girls-only 4-valent HPV immunisation programme.

In relation to the girls-only 9-valent programme, uncertainty in the relative cost of the 9-valent vaccine resulted in substantial uncertainty in the incremental budget impact (Figure 8.15). The five-year budget impact was an estimated €0.4 million if the relative cost was 1.05 times and €1.31 million if the relative cost was 1.18 times the cost of the 4-valent vaccine. The cost of the 4-valent vaccine and the uptake in girls were also important parameters but their absolute effect on budget impact was minor.

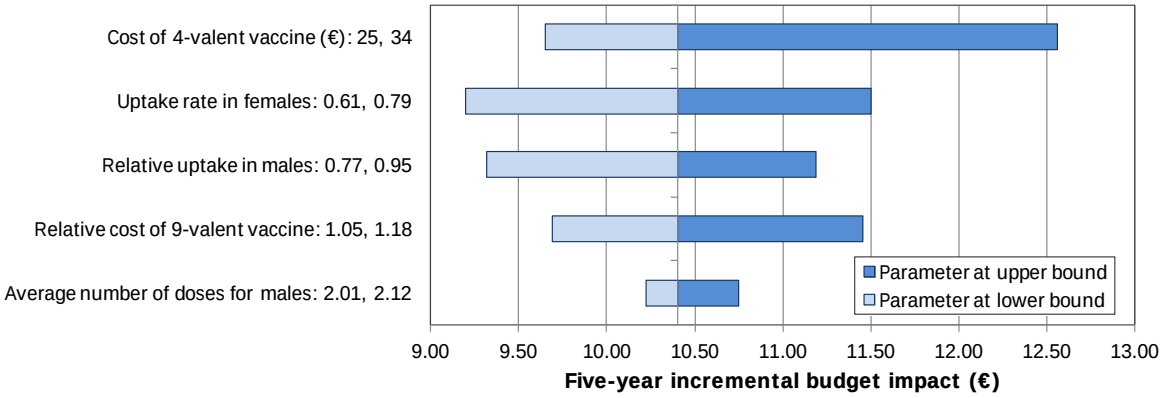
Regarding the gender-neutral 9-valent programme, the cost of the 4-valent vaccine and the uptake rates in girls and boys all influenced uncertainty in the incremental budget impact (Figure 8.16). When the cost of the 4-valent vaccine was at its upper bound, the five-year incremental budget impact of the gender-neutral 9-valent programme increased by €2.2 million. For gender-neutral 9-valent vaccination, the relative cost of the 9-valent vaccine had less impact on uncertainty in the budget impact than for the girls-only 9-valent strategy.

Figure 8.15 Tornado plot of univariate sensitivity analysis (five-year incremental budget impact of girls-only 9-valent versus girls-only 4-valent vaccination)



Note: all stochastic parameters were included in the analysis. Plot only includes parameters for which setting values at either upper or lower bound resulted in at least a 1% change in the average incremental budget impact.

Figure 8.16 Tornado plot of univariate sensitivity analysis (five-year incremental budget impact of gender-neutral 9-valent versus girls-only 4-valent vaccination)



Note: all stochastic parameters were included in the analysis. Plot only includes parameters for which setting values at either upper or lower bound resulted in at least a 1% change in the average incremental budget impact.

8.4.2.2 Vaccine price

In relation to vaccine price, the cost of the 4-valent vaccine was varied from €10 per dose to €100 per dose to test the impact on the incremental budget impact of the 9-valent girls-only and gender-neutral HPV immunisation programmes. The price of the 9-valent vaccine was set at 1.1 times the 4-valent price as per the base case assumption.

The incremental budget impact increased linearly with increasing vaccine price. When the 9-valent vaccine costs less than €20 per dose, the five-year incremental budget impact of the girls-only programme was less than €0.5 million. When the 9-valent vaccine costs more than €40 per dose, the five-year incremental budget impact of the girls-only programme was greater than €1.0 million. When the 9-valent vaccine costs less than €20 per dose, the five-year incremental budget impact of the girls-only programme was less than €8.0 million. When the 9-valent vaccine costs more than €40 per dose, the five-year incremental budget impact of the girls-only programme was greater than €13.0 million.

8.5 Discussion

The economic model presented in this chapter was used to estimate the cost-effectiveness of a number of school-based HPV immunisation programmes: girls-only 4-valent (the existing programme), girls-only 9-valent, gender-neutral 4-valent, and gender-neutral 9-valent. The alternative of no vaccination was also evaluated. The parameters used in the model were derived from a wide variety of sources based on Irish and international data. A discrete time Markov model that simulated a cohort from age 12 to 99 years was used to determine the impact of different vaccination strategies. Benefits were measured in terms of quality-adjusted life years (QALYs).

8.5.1 Main findings

In the cost-effectiveness analysis, the two 9-valent immunisation programmes were more effective than the 4-valent programmes and the alternative of no HPV vaccination. The girls-only 9-valent immunisation programme was estimated to be cost saving relative to, and more effective than, the existing girls-only 4-valent programme. Excluding oropharyngeal and penile cancers, a gender-neutral 9-valent programme was estimated to be more effective but more costly than the girls-only 9-valent alternative, with an incremental cost-effectiveness ratio of €37,593 per QALY. A gender-neutral 9-valent programme would therefore be considered not cost-effective at the modelled vaccine price compared to a threshold of €20,000 per QALY, but would be considered cost-effective at a threshold of €45,000 per QALY.

The potential impact of the different immunisation programmes on disease incidence was estimated. In terms of invasive cancers the primary impact in absolute terms is on the incidence of cervical cancer. Relative to the existing girls-only 4-valent programme, after 20 years of a girls-only 9-valent programme an estimated 63 cases of cervical cancer will have been prevented. After 20 years, a gender-neutral 9-valent programme will have prevented an estimated 99 cases of cervical cancer relative to the existing girls-only 4-valent programme. A more immediate impact of the gender-neutral immunisation programmes is that it would extend protection against anogenital warts to boys. As the prevalence of anogenital warts peaks in people in their 20s, the impact of the additional protection will start to become evident within 10 years of extending immunisation to boys.

The incremental budget impact of the girls-only 9-valent programme was €0.76 million (95% CI: €0.38m to €1.35m) over five years. By comparison, the five-year incremental budget impact of the gender-neutral 9-valent programme was €10.4 million (95% CI: €8.42m to €13.16m). Adopting a girls-only 9-valent programme incurs only the additional cost associated with a 9-valent vaccine and treatment costs associated with adverse events. The switch to a gender-neutral 9-valent programme incurs the cost of the vaccine and administration for boys as they are not currently part of the HPV immunisation programme.

Although there was substantial uncertainty around a number of the key parameters, the general finding is that a girls-only 9-valent programme is more effective and less costly than the existing girls-only 4-valent programme. The incremental cost-effectiveness of a gender-neutral 9-valent programme is sensitive to a number of parameters, most notably the long-term uptake rate in girls: an uptake rate of less than 60% in girls suggests an ICER of less than €20,000 per QALY, whereas an uptake rate in excess of 80% suggests an ICER of greater than €45,000 per QALY. The recent history of the HPV immunisation programme in Ireland is characterised by a marked and rapid drop in uptake followed by a partial recovery. It is unclear to

what extent the uptake will recover to the levels observed in the early years of the programme, and experiences in other countries may not be simply generalised to the Irish context.

As highlighted in Chapter 7, economic evaluations of gender-neutral HPV programmes, commonly find that cost-effectiveness is correlated with uptake in girls. When considered in terms of evaluations for which there was no identified conflict of interest, this HTA has one of the lowest published ICERs but also the lowest published cost for a completed vaccination schedule (Table 8.20). With the exception of the Swedish evaluation, studies that use high estimates of uptake tend to estimate large ICERs. The findings of this evaluation are therefore consistent with previously published evaluations. It should also be noted that oropharyngeal cancers were only included in the base case of two of the studies (Chesson et al. and Kim et al.), and the findings of this study indicate that their inclusion leads to a lower estimate of the incremental cost-effectiveness.

Table 8.20 Results of economic evaluations

Study	Country	Doses	Vaccine	Uptake	Vaccine cost per schedule (€)	ICER (€/QALY)
Taira (2004)	US	3	2-valent	70%	458	675,293
Kim (2009)	US	3	4-valent	75%	431	123,959
Chesson (2011)	US	3	4-valent	30%	511	47,391
NOKC (2015)	Norway	3	4-valent	82%	308	149,833
Damm (2017)	Germany	3	4-valent	50%	543	45,692
Wolff (2017)	Sweden	2	2-valent	80%	166	38,999
HIQA (2018)	Ireland	2	9-valent	70%	92	37,593

Notes: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

The previous Irish HTA on the girls-only HPV immunisation programme estimated an ICER of €17,383 per life-year gained.[491] This 2018 analysis has found that the 4-valent girls-only programme is cost saving relative to no vaccination. There are a number of factors that explain the difference in the findings. The earlier HTA only included the impact on cervical cancer through vaccine effect on HPV types 16 and 18. The cost of vaccine and administration was €390 to complete the immunisation schedule, compared with €86 in the present study (to complete a two dose schedule of the 4-valent vaccine). The addition of the impact on anogenital warts and other cancers related to HPV 6, 11, 16 and 18 results in the 4-valent vaccine being considered cost saving. It should also be noted that outcomes of life-years gained and QALYs are not equivalent, complicating comparison of the two results.

8.5.2 Scenario and sensitivity analyses

Scenario and sensitivity analyses were used to explore the impact of different assumptions in the model, particularly in relation to uncertainty. Scenario analyses facilitate the incorporation of an alternative set of assumptions to determine the impact on the estimated cost-effectiveness. For example, a key assumption in this evaluation was the long-term uptake rate in girls and there is limited evidence to support what the rate might be. Although a wide range of values can be used in the model, the estimated 'average' uptake will drive the summary estimate of cost-effectiveness. An important feature of scenario analyses is to consider whether the decision-maker has any control over the underlying assumption. For example, a decision-maker may be unable to influence the efficacy of a treatment, but they may be in a position to negotiate a lower price. As such, some scenario analyses illustrate the impact a different set of assumptions has on decision-making, while others may give practical guidance on the scope to improve the cost-effectiveness of a programme. Certain parameters were found to have a strong influence on the estimated cost-effectiveness of a HPV immunisation programme:

- Vaccination uptake rates

  Given the importance of uptake rates, scenarios where the uptake rate in girls returned to the peak observed in 2013 were evaluated, as well as a scenario where the uptake in boys equalled that in girls. An increased uptake in girls resulted in a substantially increased ICER for the gender-neutral 9-valent programme (€125,632/QALY). If the uptake in boys equalled that for girls, it would lower the ICER unchanged (€37,701/QALY). The decline in uptake rates observed after 2014 was attributed to parental concerns about vaccine safety that were spread by lobby groups established in 2015.[(492)] The HSE's National Immunisation Office, in conjunction with a wide range of organisations, has sought to promote the vaccine in Ireland with a view to improving the uptake rates. The objective of achieving a high uptake rate in girls should be pursued irrespective of how it impacts on the cost-effectiveness of a gender-neutral programme. A scenario analysis was used to explore the impact of fluctuating uptake rates, which demonstrated that the cost-effectiveness of a gender-neutral 9-valent programme improved under conditions of uptake increasing and decreasing cyclically. It may be considered unrealistic that uptake would cycle in such a regular manner, and that a more mature immunisation programme may be less susceptible to such frequent perturbations in uptake. However, this finding shows that a gender-neutral programme may improve the resilience of HPV immunisation over a girls-only programme.

  From a decision-making perspective, a high uptake rate in girls diminishes the added benefit of including boys in the HPV immunisation programme. Taking

into account the assumptions that underpin the evaluation, a gender-neutral programme is cost-effective at a threshold of €20,000 per QALY when the uptake rate in girls is below 60%, and is cost-effective at a threshold of €45,000 per QALY when the uptake rate in girls is below 80%.

- Impact on oropharyngeal and penile cancer

  Another important scenario to consider is whether the vaccine has an impact on the incidence of oropharyngeal and penile cancers. Based on the systematic review of efficacy, there are insufficient data available to determine if there is a treatment effect on these cancers. However, given the knowledge and understanding regarding attributable disease, it is plausible that a HPV immunisation programme would result in reduced incidence of oropharyngeal and penile cancers. If a modest treatment effect is assumed (relative risk reduction = 0.5) then the ICER reduces to €29,089. Due to the evident changes occurring in the incidence in oropharyngeal cancers, and taking into account the long time horizon used in the model, the incidence of oropharyngeal cancers used in the model was almost certainly a significant underestimate of the incidence that will be observed in the future. In the context of increasing incidence of oropharyngeal cancer, the analysis underestimates the impact of HPV immunisation. Over the coming years there may be sufficient data collected to determine whether or not there is a treatment effect on oropharyngeal and penile cancers but this may take some time.

- Relative cost of the 9-valent vaccine

  A further parameter to consider is the cost of the 9-valent vaccine in comparison to the 4-valent vaccine. This study assumed that the 9-valent vaccine would, on average, cost 10% more than the 4-valent equivalent. In the event that there was no difference in price, then the ICER for a gender-neutral 9-valent programme would drop to €31,705. The extent to which it may be possible to acquire the 9-valent vaccine at the same contract price as the 4-valent vaccine is unclear, but clearly has a bearing on the cost-effectiveness of a 9-valent programme. If a gender-neutral programme is selected, then it is possible that a lower price may be negotiated given the increase in volume of vaccine required to vaccine both boys and girls.

- Discount rate

The estimated cost-effectiveness was sensitive to the discount rate used. Changing the rate by ±1% had a substantial effect on the ICER (Figure 8.10). The discount rate reflects time preferences, specifically a societal preference for benefits to be realised in the present and costs to be experienced in the future. HPV vaccination, like many other immunisation programmes, incurs costs immediately while benefits are experienced much later. As such, immunisation programmes appear to be overly penalised by discounting, particularly given the high discount rate that applies in Ireland. Most other European countries have discount rates in the region of 3% to 4%, and it is possible that the discount rate in Ireland may change to reflect the changing economic circumstances. However, the results should be considered in terms of the discount rate that currently applies. Some countries have adopted hyperbolic discounting, whereby the discount rate changes over time. At the time of analysis, there was no published guidance for selecting suitable rates for hyperbolic discounting in Ireland.

- Non-serious adverse events

  The HPV vaccine is associated with a very high rate of non-serious adverse events, with the majority experiencing one at the time of vaccination. The impact of non-serious adverse events can be difficult to quantify, particularly when they are of such short duration. Furthermore they are in a population of children, and collecting quality of life data in that subgroup can be challenging as the underlying measurement tools are often designed for adult populations. In the base case analysis a disutility was included for non-serious adverse events that was assumed to last for an average of seven days. This could be considered a very conservative approach as it is quite possible that for the vast majority of children that experience a non-serious adverse event, the impact is potentially not measurable due to the limited impact and short duration. Scenario analyses were used to determine the impact of using a shorter duration or not including the disutility, both of which resulted in an increased probability that a gender-neutral 9-valent immunisation programme is cost-effective at a threshold of €20,000 per QALY. Another important aspect of the impact of non-serious adverse events is how it affects the benefits to harms balance in boys. If they are included as per the base case, the impact on quality of life of non-serious adverse events is to counter much of the additional benefits accruing to males through inclusion in the HPV immunisation programme. It is important to consider whether it is plausible for the immediate disutility of a non-serious adverse event can outweigh the longer-term benefits of a substantially reduced incidence of anogenital warts and anal cancer.

8.5.3 Limitations

The present study was subject to a number of limitations. As with any economic modelling exercise, the applicability of the findings is dependent on the quality of the parameter values used and the assumptions underpinning the model structure.

Some of the key parameters, such as vaccine efficacy and uptake rate, were either not based on Irish data or were based on a plausible estimate. Vaccine efficacy was derived from a systematic review of the evidence, but the applicability of the evidence was unclear for some of the outcomes. If vaccine efficacy in females is less than estimated, then a gender-neutral immunisation programme would be more likely to be considered cost-effective. Sensitivity and scenario analyses were used to test some of these assumptions; however, in most cases the uncertainty did not impact on the interpretation of the findings. In general, conservative values were adopted for parameters: that is, values that bias against gender-neutral or 9-valent programmes. It is therefore possible that the ICER may be lower than estimates here, although it is unlikely that the ICER is below €20,000/QALY.

There is a limited basis for determining what future uptake rates will be, as recent experience shows that uptake rates can decline substantially in a short space of time. Although uptake rates are recovering, it is unclear if they will recover fully or how long it will take before they stabilise again. That such change can occur so quickly points to limited vaccine resilience. The structure of the model incorporated a steady state uptake into the future. It may be possible to model the impact of perturbations to the vaccine uptake, such as occurred over the last four years in Ireland, to determine if a gender-neutral programme would provide greater vaccine resilience than a girls-only programme. However, the outcome of such an analysis would depend on assumptions about whether uptake in girls and boys was fully correlated (as was assumed in the model). If a reduction in uptake in girls did not automatically translate into a reduction in uptake among boys, then a gender-neutral programme might increase vaccine resilience.

As is generally the case for a health economic model, a steady state population was assumed. That is, the number of 12 year olds was constant each year for the next 100 years. In reality there are fluctuations in the birth rate and migration that impact on the true population size. However, changes to the population are unlikely to impact substantively on the cost-effectiveness analysis in this case unless it is assumed that those changes will also impact on other model parameters, such as the probability of acquiring HPV infection or incidence of cervical cancer. Disease incidence in particular changes over time due to shifts in behaviour and the exposure to risk factors. The very significant uncertainty associated with changes to those parameters would, if included in the model, dwarf the uncertainty in relation to our knowledge of the existing situation. In other words, the model reflects the best estimate of what is known currently rather than what might be known in the future.

Certain model parameters could be affected by migration, although that would be contingent on Irish rates being very different to those in migrants and for migrant numbers to be very substantial. A related issue regards assumptions around herd immunity and that those who are unvaccinated only acquire immunity while they remain in the herd. The movement of people in and out of the country and the mobility of the Irish population, particularly amongst those aged 20 to 30 years, mean that herd immunity may not exert a strong effect. However, for the loss of herd immunity to have a strong impact, the unvaccinated population would have to mix with a population with a much higher HPV prevalence than observed locally.

The model used in this evaluation was an adapted version of a model originally developed in the US and then adapted for use in Norway. Both the original model and the Norwegian adaptation were developed for a 4-valent vaccine model. This study extended the model to apply to a 9-valent vaccine. The additional five HPV strains were treated as a single block for computational simplicity and to account for the fact that there was no data on attributable proportions by individual types within the group. The study tested whether this simplification impacted on the model results by generating a version that treated the five types individually, and the generated outputs were the same. Unlike a number of the other published HPV models, the Chesson model is not a full dynamic transmission model. While this reduces the burden of data collection and computation, it may reduce the applicability of the findings. However, the lack of contemporary Irish data required to populate and calibrate a full dynamic transmission model mean that the assumptions required to utilise such a model may undermine any of the potential benefits. A potentially serious limitation is the underlying assumption that the reduction in health outcomes attributable to HPV infection is directly proportional to the percentage reduction in cumulative exposure to that HPV type. Other models have been designed that simulate the progression from HPV infection to HPV-attributable disease. A systematic review of HPV immunisation models found that the Chesson model generated similar results to other models, although it potentially overestimated the relative reduction in HPV prevalence at low uptake rates.[458] The findings of that systematic review suggest that the Chesson model may be biased towards generating lower ICERs than other HPV models using the same assumptions about uptake rates, although this bias maybe less evident at higher uptake rates, such as those assumed in this study.

The structure of the model was such that only those who completed the two-dose schedule were considered to have protection. In contrast, everyone receiving at least one dose was included in the estimation of costs and disutility associated with adverse events. There are ongoing studies investigating whether a single dose is sufficient to confer protection, suggesting that our assumptions were conservative. However, the impact is likely to be marginal as typically 97% of those who receive

the first dose go on to complete the schedule. The model incorporated the historic catch-up programme that ran for three years from 2011 to 2013. The study did not incorporate any informal catch-up that may be available when immunisation teams go to schools for the scheduled programme or where children may receive immunisation through their GP. It is likely that these assumptions have a limited impact on the results as the overwhelming majority who receive vaccination will do so through the scheduled programme when in first year of secondary school.

The MSM population was not explicitly included in the model, and therefore the results did not capture the benefits to that subgroup of the population. The current girls-only HPV immunisation programme is likely to have a negligible impact on HPV transmission in the MSM population. Extension of the programme to include boys would potentially, contingent on uptake rates, greatly improve protection against HPV infection and associated HPV-attributable disease.

There was substantial uncertainty regarding the interpretation of data on adverse events in terms of the cost of treatment, the disutility, and the incidence of serious adverse events. The intention was to incorporate data that reflected the adverse events associated directly with vaccination. Non-serious adverse events were primarily defined as effects such as pain or redness at the infection site. It was assumed that the effects would typically last one week which may be in excess of the typical experience. There was limited evidence for Ireland on serious adverse effects associated with vaccination. International data was relied on, which may have overestimated the incidence of serious adverse events in Ireland.

The main HPV-attributable diseases included in the model were cancers, which are noted for high treatment costs. If treatment costs continue to escalate then the benefit of reducing cancer cases through a HPV immunisation programme will improve cost savings, thereby reducing the incremental cost-effectiveness ratio.

In line with the national guidelines, this evaluation did not incorporate any indirect costs. Other evaluations have included indirect costs, particularly in relation to lost productivity due to mortality from invasive cancer. In the Irish setting, a societal perspective would also entail including out-of-pocket treatment costs that accrue to patients. Evaluations from Norway and Sweden applied both payer and societal perspectives, and in both cases the ICER from a societal perspective was approximately 7% to 10% lower than the ICER from a payer perspective.[430, 459]

8.6 Summary

Taking into account the model and data assumptions, 9-valent immunisation is more effective than 4-valent immunisation and the alternative of no HPV vaccination. A

girls-only 9-valent immunisation programme would be cost saving relative to, and more effective than, the existing girls-only 4-valent programme. A gender-neutral 9-valent programme would be more effective and more costly than the girls-only 9-valent alternative, with an incremental cost-effectiveness ratio of €37,593/QALY. A change to the HPV immunisation programme should include adoption of the 9-valent vaccine. At a willingness-to-pay threshold of €20,000 per QALY, a girls-only programme is most efficient while at €45,000 per QALY a gender-neutral programme is most efficient. The evaluation took a conservative approach in terms of a number of assumptions, such as the impact of non-serious adverse events and exclusion of oropharyngeal and penile cancers from the base case. It is therefore plausible that a gender-neutral 9-valent HPV immunisation programme is more cost-effective than estimated here.

The incremental budget impact of the girls-only 9-valent programme was €0.76 million (95% CI: €0.38m to €1.35m) over five years. By comparison, the five-year incremental budget impact of the gender-neutral 9-valent programme was €10.4 million (95% CI: €8.42m to €13.16m).

Consistent with previously published evaluations of gender-neutral HPV immunisation programmes, the cost-effectiveness is linked to the uptake rate in girls. If the uptake rate is above 80%, a gender-neutral programme is not cost-effective at a threshold of €45,000 per QALY; below 60%, it is cost-effective at a threshold of €20,000 per QALY.

Key points

- An economic model was adapted to estimate the cost-effectiveness of a number of school-based HPV immunisation programmes:
    - girls-only 4-valent (that is, the existing programme),
    - girls-only 9-valent,
    - gender-neutral 4-valent,
    - and gender-neutral 9-valent.
- A girls-only 9-valent immunisation programme was estimated to be cost saving relative to, and more effective than, the existing girls-only 4-valent programme.
- A gender-neutral 9-valent programme was estimated to be more effective and more costly than the girls-only 9-valent alternative, with an incremental cost-effectiveness ratio of €37,593 per quality-adjusted life year (QALY).
- After 20 years, relative to the existing girls-only 4-valent programme, a girls-only 9-valent programme will have prevented an estimated 8,958 cases of CIN 1, 2,540 cases of CIN 2/3, and 63 cases of cervical cancer. Over the same time horizon, relative to the existing girls-only 4-valent programme, a gender-neutral 9-valent programme will have prevented 11,277 cases of CIN 1, 3,368 cases of CIN 2/3, and 99 cases of cervical cancer.
- The incremental budget impact of the girls-only 9-valent programme was €0.76 million over five years (95% CI: €0.38m to €1.35m). By comparison, the five-year incremental budget impact of the gender-neutral 9-valent programme was €10.4 million (95% CI: €8.42m to €13.16m).
- Inclusion of oropharyngeal and penile cancers in the model resulted in an incremental cost-effectiveness ratio of €29,089 per QALY for a gender-neutral 9-valent HPV immunisation programme.
- Scenario analyses indicated that although alternative assumptions about model parameter values impacted on the estimate of incremental cost-effectiveness, there was a consistent finding that a gender-neutral 9-valent programme would be considered cost-effective at a threshold of €45,000 per QALY but would not be considered cost-effective at €20,000 per QALY, contingent on the uptake rate in girls stabilising at less than 80%.

9 Organisational issues

9.1 Introduction

This chapter outlines the expected organisational changes if the current HPV immunisation programme was extended to include boys. The current girls-only programme is described in Section 9.2. The potential increase in number of eligible participants (as in, 12 and 13 year old boys) and the increase in number of eligible schools (as in, boys-only schools) is quantified, along with logistical challenges that may be encountered in Section 9.3. A summary of international experiences in adopting gender-neutral vaccination is provided in Section 9.4 and, finally, the expected uptake rate for boys is described in Section 9.5.

9.2 Current HPV immunisation programme in Ireland

Ireland has a nationally funded, school-based, girls-only HPV immunisation programme (through the National Schools Immunisation Programme).[(493)] A pilot programme was first introduced in May 2010 in 20 Irish schools, with a national programme subsequently rolled out in September 2010. The vaccine is given by school vaccination teams from 32 local health offices around the country and is also provided to age-equivalent girls attending special schools and those who are home schooled. It is not available through general practitioners (GPs) except by private payment.

The programme first consisted of a three-dose schedule of the 4-valent vaccine (Gardasil®) for girls in first and second year of second level schools and age-equivalent girls attending special schools or who were home schooled. A catch-up programme targeting girls in sixth year (final year) in second level schools and for age-equivalent girls registered through other services (as above) was provided from September 2011 and repeated for girls in sixth year in 2012 and 2013. Since September 2014, the programme has targeted girls in first year only, and has moved to a two-dose schedule.

Every September schools send girls and their parents or guardians the HSE information packs, including the consent form which must be completed by the parent or guardian. For special schools, HPV vaccination is offered in September to girls who reach 12 years of age during the academic year. Parents of girls who are home-schooled must contact their local health office to make an appointment.

The current Irish national immunisation guidelines recommend a two-dose schedule for those aged nine to up to 15 years and three doses for those aged 15 years and older at the time of the first dose.[(494)] As outlined in Chapter 4, Section 4.3.6, this recommendation was based on demonstration of non-inferiority of the immune

response when compared with young adult women in whom efficacy has been proven. There are no data to support a two-dose schedule in girls or boys aged 15 years or older.

The first and second doses of the two-dose schedule are optimally administered six months apart. The National Immunisation Advisory Committee (NIAC) has set out the optimal and minimum intervals for HPV vaccines, as outlined in Table 9.1.[494]

Table 9.1: Optimal age and intervals for HPV vaccines

	Age* (Years)	Number of doses	Dose 1 to dose 2		Dose 2 to dose 3	
			Optimum interval	Minimum interval	Optimum interval	Minimum interval
4-valent HPV vaccine±	Aged 9 to 14 inclusive	2	6 months	24 weeks	N/A	N/A
	15 and older	3	2 months	4 weeks	4 months	12 weeks
9-valent HPV vaccine¥	Aged 9 to 14 inclusive	2	6 months	5-13 months	N/A	N/A
	15 and older	3	2 months	4 weeks	4 months	12 weeks

* Age at date of first dose

± If the second dose is administered earlier than 24 weeks less four days from the first, a third dose must be administered at least three months after the second dose.

¥ For those on a three-dose schedule, all three doses should be administered within 12 months.

Of note, if the HPV vaccination schedule is interrupted, it is possible to resume the vaccination without repeating the course, regardless of the time interval from the previous incomplete course.[495]

The HSE uses a comprehensive approach to HPV vaccination to enable adherence with the recommended vaccine schedule, its completion within one academic year (allowing for school holidays) and to enable vaccination of the entire eligible cohort. The goal is to administer the first dose of the HPV vaccine in a targeted five-week period between the end of September and the end of October. This is followed by a one-week period in which girls who missed their first dose in school are vaccinated in HSE clinics. Those attending special schools or who are home schooled may also be accommodated at this time. The second dose is administered in a period six months later (the exact timing may depend on the Easter holidays) which is again followed by sessions in the HSE clinics to facilitate those who missed the school visit or who are educated in other settings. Guidelines for school immunisation staff detailing these arrangements are published annually by the HSE.[495]

The schools immunisation programme is coordinated by the National Immunisation Office (NIO).[496] The HSE established the NIO in 2005 as a coordinating unit to ensure standardised implementation of all publicly funded immunisation programmes

(primary childhood, schools, seasonal influenza and others as required). In addition to the coordination of immunisation programmes, the NIO is also responsible for managing vaccine procurement and distribution and developing training and communication materials for health professionals and the public. Vaccine procurement accounts for over 90% of the NIO's budget and, since 2005, purchase of all vaccines for national programmes has been centralised and managed by the NIO.[(496)] Distribution of all vaccines under validated cold chain conditions (essential for vaccine potency) is provided by the HSE National Cold Chain Service with overall management, monitoring and control by the NIO.

In 2011 the NIO coordinated the implementation of the first national IT immunisation system which records HPV vaccinations. This system allows easier implementation and monitoring and enables timely delivery of data around vaccine uptake rates. Additionally, it allows vaccine status to be linked with cervical screening service records.

As noted, Ireland's current HPV immunisation programme is based on the 4-valent vaccine that protects against HPV types 16 and 18, thereby only protecting against approximately 70% of cervical cancer cases. Screening for cervical cancer is therefore still recommended for vaccinated cohorts.[(493)] The first cohort of vaccinated girls (that is, those vaccinated as part of the catch-up programme in 2011) became eligible for CervicalCheck – the National Cervical Screening Programme – in 2018 to 2019.

While adolescent boys are not included in Ireland's national HPV immunisation programme, since January 2017 men who have sex with men (MSM) aged 16 to 26 years may avail of HPV vaccination through publicly funded sexually transmitted infection (STI) clinics.[(50)] Additionally, both male and female patients who are HIV-positive (and under the age of 26) are offered HPV vaccination through HIV clinics.

9.3 Estimation of number of potentially eligible boys

If the decision is made to extend the immunisation schedule to include boys, it is anticipated that an invitation would be extended to all boys who are currently in first year of second level education similar to the approach currently used for the girls-only programme. It is assumed that it would be delivered by school vaccination teams from the 32 local health offices around the country and coordinated by the NIO. The same arrangements would be made for special schools (boys who turn 12 during the academic year would be offered the vaccine) and boys who are home-schooled (the parents or guardians should contact their local health office).

The total number of pupils in first year of second level education, along with the total number of second level schools, is provided in the Tables 9.2 and 9.3.[(497)] In total, based on Department of Education provisional data for the 2017 to 2018 academic

year, 30,065 boys would become eligible for vaccination, bringing the total number of individuals who would be offered the vaccine (males and females) to 59,671. HPV vaccination would then be offered in 111 additional schools (schools that are boys-only).

However, these data from the Department of Education vary from the full cohort of 12 year olds in Ireland as estimated by the CSO. the latter, which is the target population for the economic evaluation was estimated in 2017to be 30,999 girls and 33,012 boys, bringing the total cohort to 64,011.[461] While the legal requirement is to remain in school until 16 years of age, not all children aged 12 are in second level school, such as children who are still in primary school, those who are home schooled, attend special schools or who have otherwise not enrolled in second level school.

Table 9.2 Total number of boys and girls in first year*

	School type	Number of pupils in first year
Girls	Girls-only schools	12,189
	Co-education schools	17,417
	Total girls	**29,606**
Boys	Boys-only schools	10,095
	Co-education schools	19,970
	Total boys	**30,065**

*Source: Department of Education provisional 2017 to 2018 statistics

Table 9.3 Number of second level schools*

	School type	n
Girls	Girls-only schools	134
	Co-education schools	469
	Total girls	**603**
Boys	Boys-only schools	111
	Co-education schools	469
	Total boys	**580**

*Source: Department of Education provisional 2017 to 2018 statistics

Co-administration of the HPV vaccine with other vaccines is safe, including meningococcal conjugate, hepatitis A, hepatitis B, combined hepatitis A and B, tetanus, diphtheria, acellular pertussis, and inactivated poliovirus vaccines.[498] Currently, the HPV vaccine is co-administered with the tetanus, low dose diphtheria and low dose acellular pertussis (Tdap) booster, and with the meningococcal C (MenC) booster, to girls as part of the schools immunisation programme. Similar to

HPV vaccines, the low-dose boosters are also associated with frequent minor injection-site adverse events. For example, a 2018 study reported an adverse event rate of 85.6% for the Tdap booster (any solicited or unsolicited adverse event).[499] No serious adverse events were reported.

As per the guidelines issued to the schools immunisation teams, the first dose of the HPV vaccine is co-administered with Tdap in September and the second dose is co-administered with MenC six months later in girls.[495] The order in which these co-administered vaccines are administered is informed by HSE policy. Specificially, to extend protection against Meningococcal Group C infection until early adulthood (that is, including peak carriage at 15 to 19 years of age), HSE policy is to administer the MenC adolescent booster dose later in the academic year (that is, from January onwards, coinciding with the second or third term). Therefore, for girls, HSE policy is to administer the MenC booster with the second dose of the HPV vaccine.

Current practice is that the schools immunisation teams also administer the Tdap and MenC booster vaccines to boys in their first year of second level education. Again, the MenC booster is administered in the second or third term. In boys-only schools, the preferred option is to visit the school once only in the second or third term, and to co-administer the MenC and Tdap boosters at that time. In co-educational schools, where the immunisation team by necessity visits twice to facilitate administration of the two doses of the HPV vaccine, there is an option to administer the Tdap vaccine to the boys in the first semester and the MenC booster six months later when the immunisation team returns to the school (that is, two vaccination episodes). The alternative, more likely scenario is that the timing of the Tdap booster for boys is delayed and it is co-administered with the MenC booster on the immunisation team's return to the school (that is, a single vaccination episode).

Therefore, in cases where school immunisation teams visit boys-only or co-educational schools twice in the academic year to administer Tdap and MenC, no additional visits would be required if the immunisation schedule is extended to include HPV vaccination of boys. While this would result in fewer organisational changes in those schools, administration of an additional vaccine on both dates would place an additional burden on the immunisation team both in terms of vaccine delivery and the administrative burden associated with obtaining consent, dealing with queries and concerns, and recording the vaccine administration in the School Immunisation System. Additional staff may need to be deployed to the school during the immunisation session, or the session extended (and or delivered over two days, for example in very large schools).

For boys-only schools, extension of the HPV immunisation programme would mean that the immunisation team must visit the school on two occasions, six months apart. This will likely entail an additional school visit in addition to the resource implications

already listed associated with delivering two doses of the HPV vaccine. This additional visit could represent a significant logistical challenge for some immunisation teams given the relatively short academic year (September to May inclusive) and the need to work around vacation periods at midterm, Christmas and Easter as well as other events and activities scheduled at a school level. All schools would have to be visited in first term (typically starting in September through the end of October) and the second visit six months later. In the absence of a gender-neutral HPV immunisation programme, the option exists to visit boys-only schools in January or February, so that the work of the immunisation team is spread more evenly across the year.

Extending HPV immunisation to boys may necessitate additional staff in some areas or redeployment of staff from other public health activities onto the immunisation teams to provide extra capacity during the targeted periods. However, no other organisational or governance changes are anticipated to the schools-based programme.

An information campaign for parents of boys will be an important component of any change to the current programme, to educate parents and boys, allay any concerns regarding the safety or efficacy of the vaccine and enable informed consent. To support such a public awareness communication campaign, consideration would also need to be given to an educational programme for GPs, pharmacists and front line nursing staff given their important role both in vaccine administration and as a trusted information source for other childhood vaccines as part of the immunisation programme.

9.4 International experience of implementing male HPV immunisation programmes

9.4.1 Canada

Publicly-funded HPV immunisation programmes for females are available in all Canadian provinces and territories. In addition, most provinces (including Alberta, British Columbia, Ontario, Prince Edward Island, Nova Scotia, Newfoundland & Labrador and Saskatchewan) have publicly-funded HPV immunisation programmes for males in place, and those who do not are in the process of doing so in the near future. A systematic review and meta-analysis of uptake rates in Canada was published in 2017 to investigate differences in vaccine coverage.[500] A total of 12 papers were included, and the pooled analysis showed that HPV vaccine uptake in Canada is 55.91%. Females were 1.22 times (95% CI: 1.13 to 1.3) more likely to be vaccinated than males (female vaccine coverage: 57.2% [N=623,879] versus male vaccine coverage: 47% [N=725]). The small sample size for the male population reflects the fact that only two of the 12 studies included male participants.

Additionally, authors found that individuals participating in school-based programmes were 3.73 times more likely to be vaccinated against HPV compared with community-based programmes: 69.62% (95% CI 57.27 to 80.68) versus 18.66% (95% CI 6.66 to 34.92). These findings were similar to studies in other countries which show that school-based programmes have higher rates of vaccination uptake in Scotland, Australia, and the US.[501] The relative uptake of the HPV vaccine in a school-based gender-neutral programme for boys and girls was reported in one study (in Prince Edward Island) which noted uptake in boys was 93% of that in girls (79% in girls versus 85% in boys).

Following the introduction of male HPV vaccination in Canada, a policy analysis was conducted in 2016.[502] A number of obstacles to uptake of the HPV vaccine in boys were identified. They included:

- not receiving a recommendation from a doctor or healthcare provider
- lack of information about the HPV vaccine
- negative attitudes toward the HPV vaccine or other vaccines
- HPV being overidentified as a female disease
- cost and logistical challenges.

9.4.2 Australia

In 2007, the Australian government implemented their schools-based HPV immunisation programme, and extended this programme to include boys in 2013. A 2014 programme evaluation looked at all aspects of the programme, including implementation of the gender-neutral programme and factors that influenced its success.[503]

The process evaluation included surveys and interviews that covered stakeholders' experience of aspects of the programme implementation including communication and resources, programme planning and rollout, service delivery, data collection and reporting, strengths and challenges of the programme and recommendations for future national immunisation programmes. Respondents reported that the extension of the HPV vaccination programme to include adolescent males was less difficult to implement than the initial female programme.

Most programme managers and providers (n=14) observed that the male programme was well accepted. Reasons for acceptance included the establishment of the female programme on their National Immunisation Program, the expectation that

the vaccine would be extended to include males, greater knowledge of HPV and reduced parental concerns around a vaccine related to sexual health. Lessons learned from the female programme were also applied when extending the programme to males, including the development of comprehensive and accessible information resources and the establishment of enhanced surveillance activities for adverse events.

9.4.3 Europe

A pan-European cross-sectional survey investigated parental attitudes towards male HPV vaccination in 2015 (no countries had implemented gender-neutral vaccination at that time).[504] A literature study was carried out examining HPV vaccine acceptability to guide the construction of a questionnaire to be used in interviews with parents of sons in the UK, France, Germany and Italy. Approximately three out of four parents in the UK, Germany and Italy were in favour of giving the HPV vaccine to their sons. In France, only about half of parents were in favour.

Parents who favoured HPV vaccination for their sons wished to protect them from disease and found gender equality important. Parents in doubt about male HPV vaccination required more information about HPV diseases in men and male HPV vaccination. Parents who rejected the vaccine for their sons were generally sceptical of vaccines and feared adverse events associated with vaccination. Parents in countries with active vaccination policies (UK and Italy) tended to trust the importance of national immunisation programmes. Parents in countries with passive vaccination strategies (Germany and France) had greater need for information from healthcare professionals and public health authorities.

9.5 Anticipated vaccine uptake

9.5.1 Current uptake in Ireland

As described in Chapter 2 (Section 2.7.1), uptake of the vaccine was initially high in girls in Ireland at 86.9% for the two-dose schedule reported among girls in the first year of second level school (typically 12 to 13 years old) in the 2014 to 2015 academic year.[42] Subsequent two-dose vaccine uptake was 72.3% in 2015 to 2016, declining sharply to 51% in 2016 to 2017.

While not restored to pre-2015 levels, uptake in the most recent academic year (2017 to 2018) had increased substantially, with a first-dose uptake of 61.7% (two-dose uptake is awaited).[45] This first-dose uptake was significantly higher than the preliminary first-dose uptake seen in 2016 to 2017 (50%). Table 9.4 provides historical uptake rates of the first, second and third doses (prior to a change to two-dose schedule) of the HPV vaccine in girls in Ireland.

Table 8.1 Historical uptake of HPV vaccine in Ireland

Academic year	Uptake in girls		
	1st dose	2nd dose	3rd dose
2010/11	84.0%	82.1%	81.9%
2011/12	87.9%	87.3%	85.5%
2012/13	87.0%	86.3%	84.2%
2013/14	89.3%	88.2%	84.9%
2014/15	89.7%	86.9%	n/a
2015/16	82.4%	72.3%	n/a
2016/17	55.8%	51.0%	n/a
2017/18	61.7%	awaited	n/a

Source: *The Lancet* 2018: 391

9.5.2 Causes for, and response to, decline in uptake

The decline in vaccine uptake was due to parental concerns about vaccine safety.(45) Individuals and groups with HPV vaccine safety concerns developed a strong social media presence in 2015 in Ireland, with subsequent support from local and national media. A documentary followed, entitled *Cervical cancer vaccine—is it safe?*, which was broadcasted on Irish national television in December 2015. It contained footage from a similar Danish television documentary previously broadcasted.

In response, the NIO established a steering group of concerned organisations in early 2016 to encourage all key stakeholders to actively promote the vaccine. Focus groups on parental attitudes to HPV vaccination were held and the NIO intensively analysed social media. In light of the results of the focus group discussions and analysis of social media, the print and online materials were revised. This included videos on www.HPV.ie – an Irish WHO-accredited website.

Additionally, a comprehensive training programme was implemented for health professionals, enhanced by e-learning modules. In August 2017, the HPV Vaccination Alliance was launched.(27) The alliance consists of a group of over 35 different organisations working in areas that include health, child welfare and women's rights that are committed to raising awareness of HPV vaccination. In 2017 to 2018, a media campaign was launched featuring vaccinated girls, which was strongly supported by the HPV Vaccination Alliance in addition to senior politicians.

9.5.3 Importance of schools-based programmes

Many studies have demonstrated that school-based programmes have higher rates of vaccination uptake.(501) School immunisation programmes maximise uptake of vaccines since access to the cohort for vaccination is already established and should therefore minimise differences in HPV vaccination uptake between different sub-populations and the general population.(505)

Schools-based programmes also reduce inequality, particularly in disadvantaged and marginalised communities.[506] Vaccinating in the first year of second level school also maximises the likelihood that the child is still at school (although retention rates in second level schools are very high in Ireland,[507] unlike in some other countries).

9.5.4 Factors affecting uptake in adolescent boys

In certain jurisdictions where gender-neutral vaccination has been implemented, a lower uptake rate has been observed in males. In Australia, the national three-dose HPV vaccination coverage for females turning 15 years of age in 2016 was 78.6%, compared to 72.9% for males.[28] Coverage data for 2014 to 2016 show that uptake was consistently lower in boys than in girls, although the gap has been narrowing over time.[463] Uptake in boys was 83.7% of the uptake in girls in 2014, 86.2% in 2015, and 92.8% in 2016.

In Canada, as mentioned previously, a systematic review and meta-analysis reported a 57.2% female three-dose coverage versus 47% in males.[500]

A systematic review of factors that influence parents' attitudes to HPV vaccination of their sons was published in 2017.[508] Eighteen studies in total were included. Parental decisions were predominantly shaped by the perceived benefits of the vaccine, perceived risk of sons contracting HPV infection and recommendations from healthcare providers. Fear of adverse events due to vaccine administration and uncertainty about vaccine effectiveness were barriers to HPV vaccination. Other factors such as knowledge, parent-child dialogue and family characteristics appeared to be important when deciding whether to vaccinate boys.

9.6 Discussion

Ireland has a nationally funded, school-based, girls-only HPV immunisation programme (through the National Schools Immunisation Programme).[493] A pilot programme was first introduced in May 2010 in 20 Irish schools, with a subsequent national programme rolled out in September 2010. The programme is delivered by school vaccination teams from 32 local health offices around the country. The programme currently consists of a two-dose schedule of the 4-valent vaccine (Gardasil®) for girls in first year of second level schools and age-equivalent girls attending special schools or who were home schooled.

Currently, the first dose of the HPV vaccine is co-administered with the tetanus, diphtheria and acellular pertussis (Tdap) low-dose booster, and the second dose is co-administered with the meningococcal C (MenC) low-dose booster to girls as part of the schools immunisation programme. Boys similarly receive these booster vaccines in their first year of second level school. If HPV vaccination was offered to

boys in first year, 30,065 boys would become eligible, bringing the total number of individuals who would be offered the vaccine (girls and boys) in schools to 59,671. HPV vaccination would then be offered in 111 additional schools (schools that are boys-only). If the HPV vaccine is co-administered with booster vaccines, no additional visits would be required in schools that currently administer booster vaccines at two separate visits. An additional visit would be required in boys-only schools that currently co-administer Tdap and MenC at one visit.

In co-education schools, administration of an additional vaccine on both dates would place an additional burden on the immunisation team both in terms of vaccine delivery and the administrative burden associated with obtaining consent, dealing with queries and concerns, and recording the vaccine administration in the School Immunisation System. Additional staff may need to be deployed, or the session extended. For boys-only schools, extension of the HPV immunisation programme would mean that the immunisation team must visit the school on two occasions, six months apart, likely entailing an additional visit in addition to the resource implications already listed. This additional visit could represent a significant logistical challenge for some immunisation teams given the relatively short academic year that includes vacation periods and school events.

No other organisational or governance changes are anticipated to the schools-based programme, however. Consistent with the experience of the Australian immunisation programme, it is likely that extension of the HPV vaccination programme to include adolescent males would be less difficult to implement than the initial female programme.

As previously described, uptake of the vaccine was initially high in girls in Ireland with an 86.9% uptake for the two-dose schedule reported among girls in the first year of second level school (typically 12 to 13 years old) in the 2014 to 2015 academic year.[42] Subsequent two-dose vaccine uptake was 72.3% in 2015 to 2016, but then sharply declined to 51% in 2016 to 2017. The most recent academic year (2017 to 2018) experienced a significant increase; however, with a first-dose uptake of 61.7% (two-dose uptake is awaited).[45] In certain jurisdictions where gender-neutral vaccination has been implemented, a lower uptake rate has been observed in males. International evidence would suggest that uptake may be lower in boys, with the most recent data indicating an uptake rate of 93% of that achieved in girls.[28, 500]

While extending the HPV immunisation programme to include boys is likely to be easier than the initial girls-only programme, there will be a need to address the unique information needs of parents and boys in relation to the risk of acquiring HPV infection and the direct benefits of the vaccine for boys. An awareness campaign would be required to address these needs and to enable parents to provide informed consent. While international survey data suggest strong support for vaccination of

boys, as with HPV vaccination of girls, fear of adverse events and uncertainty around vaccine effectiveness are noted barriers to vaccine uptake.

Key points

- If the national immunisation programme is extended to include HPV vaccination of boys, an estimated 30,065 boys in their first year of second level school would become eligible (across 111 boys-only schools and 469 co-educational schools).
- As per current immunisation guidelines, the first dose of the HPV vaccine is co-administered with the tetanus, low dose diphtheria and low dose acellular pertussis (Tdap) booster vaccine in September or October and the second dose is co-administered with meningococcal group C (MenC) low-dose booster vaccine six months later in girls.
- Boys also receive these booster vaccines in their first year of second level school. School immunisation teams typically visit boys-only schools once (whereby Tdap and MenC are co-administered in the second or third term). Systems are therefore already in place to identify eligible students attending second level and special schools, obtain informed consent and to record vaccine administration.
- If the HPV vaccine were co-administered with Tdap or MenC to eligible boys, no increase in school visits would be anticipated in schools that are currently visited twice in the academic year. One additional visit would be required in schools that are currently visited once in the academic year.
- Additional resources will be required by immunisation teams if a gender-neutral HPV immunisation policy is adopted. Along with the increased administrative burden, an increase in staff time to deliver two additional vaccine doses to boys will be necessary and additional resources will be required to facilitate additional school visits in boys-only schools. Given the need to administer the vaccine at specified intervals within the academic year, this may pose logistical challenges within some areas with surge capacity necessary to reflect the time constraints within which the service must be provided.
- In certain jurisdictions where gender neutral vaccination has been implemented, a lower uptake rate has been observed in males. International evidence would suggest that uptake may be lower in boys, with the most recent data indicating an uptake rate of 93% of that achieved in girls.
- A 2014 programme evaluation from Australia noted that extension of the HPV vaccination programme to include adolescent males was less difficult to implement than rolling out the initial female programme.

- If gender-neutral vaccination is adopted, an awareness campaign will be required to include circulation of appropriate materials to address the information needs of parents and boys, as well as healthcare professionals, to enable informed consent to be provided. While international survey data suggest strong support for vaccination of boys, as with HPV vaccination of girls, fear of adverse events, lack of knowledge about male HPV issues and uncertainty around vaccine effectiveness are noted barriers to vaccine uptake.

10 Ethical considerations

10.1 Overview

This chapter discusses the ethical issues that should be considered in relation to the extension of the HPV immunisation programme to include HPV vaccination of boys. This chapter was developed broadly in line with the structure described in the European network of HTA (EUnetHTA) Core Model.[(1)] The ethical issues raised around a technology must be assessed in relation to the prevalent social and moral norms relevant to the technology. This section also examines the ethical issues related to the technology assessment itself.

While governments have an obligation to protect the health and wellbeing of citizens, this must be achieved in a way that is equitable, non-discriminatory, transparent, and, as far as possible, non-coercive. Vaccination of the population is one means by which governments achieve the objective of preventing the spread of infectious disease. Although it is reasonable for the State to aim for high vaccination rates, the balance of benefits and harms to individuals and the wider population must be continuously re-assessed. It must also be recognised that individuals have the right to opt-out of such programmes. As a result, there may be conflict between public and individual interests and a balance must be struck between competing values and principles.

In the context of this chapter, the technology is a schools-based HPV immunisation programme aimed primarily at 12 and 13 year old boys and girls. In order for a child to receive a vaccine, informed consent must be provided by a parent or guardian. For simplicity parents are referred to in the subsequent text, but this also refers to guardians.

10.2 Benefit-harm balance

When Ireland's girls-only HPV immunisation programme was introduced in 2010, the primary purpose of the programme was the prevention of cervical cancer. The decision to introduce this programme was informed by a HTA published by HIQA in 2008. Since the publication of the HTA, numerous studies have been undertaken to determine the efficacy and effectiveness of HPV vaccine against a range of cancers and in both females and males. The evidence generated by those studies was reviewed in Chapters 4 and 5. A wealth of data has also been gathered in relation to the safety of the vaccine, particularly following the roll-out of a number of national HPV immunisation programmes. This is reviewed in Chapter 6. In this section, the benefit-harm balance is considered from an ethical perspective.

In many vaccination programmes, all or almost all of the target population are offered vaccination in the knowledge that perhaps only a small proportion will benefit from the vaccination. In fact, the rubella vaccine programme was initially female only; subsequently a universal programme was implemented as it was shown to be more effective and equitable. Rubella elimination has since been achieved in Ireland.[509] In the case of HPV, the majority of the population will experience HPV infection at some point in their lives. HPV vaccination would prevent the majority of these infections. While there is no known treatment for HPV infection, approximately 90% of HPV infections resolve spontaneously. The clear benefit of HPV vaccination, however, is the prevention of persistent infection and its sequelae.

The benefit-harm balance must be considered not only at the population level but also at the individual level. The decision to be vaccinated is made by individuals, typically from the perspective of what the perceived benefit-harm balance is for them personally. The policy decision maker, on the other hand, must consider the benefit-harm balance at the population level.

10.2.1 Different benefit-harm balance for boys and girls

Based on current knowledge of HPV-attributable disease, it would appear that females benefit more from vaccination than boys, as currently the main contributor to the burden of HPV-attributable disease is cervical cancer. However, there is no evidence of a difference in harms between boys and girls in terms of vaccine-related adverse events. The balance of benefits and harms is therefore different for boys and girls, as girls are exposed to the same harms, but greater benefits.

The only harms that could be generated are due to vaccine-related adverse events. The vast majority of vaccine recipients who do experience an adverse event will experience a transient, non-serious reaction at the time of vaccination, such as soreness or redness at the injection site. A very small minority will experience what is described as a serious adverse event, such as an anaphylactic reaction. The rate of anaphylactic reactions is estimated by the World Health Organization (WHO) to be one in every 1.7 million vaccinations. Assuming an annual eligible cohort of 34,000 boys in Ireland at an uptake rate of 70% for a 2-dose schedule, it will take 37 years to reach 1.7 million administered doses in boys. As such, the risk of harm is primarily through exposure to non-serious, transient reactions, which at an individual level are likely to have a negligible impact on quality of life.

The benefits for boys have been modelled through a reduction in anogenital warts, anal cancer, penile cancer and oropharyngeal cancer. HPV is the most common viral sexually transmitted infection. As outlined in Chapter 3, it is estimated that between 3,000 and 4,000 cases of anogenital warts occur in women and between 3,500 and 4,500 occur in men each year in Ireland. Of these, 90% are attributable to vaccine-preventable HPV types (6 and 11). The incidence of anal cancer is relatively low with

approximately 13 HPV-attributable cases each year in males, with a five year survival for anal cancer of 70.5%. Penile cancer is very rare. Oropharyngeal cancer is the eighth most common invasive cancer in men in Ireland,[510] and rates are increasing rapidly. Oropharyngeal cancer occurs three to four times more commonly in men. While the HPV vaccines are not yet licensed for the prevention of penile or oropharyngeal cancers, HPV is accepted as the causative agent in many of these tumours. It is likely in the future that HPV vaccination will be shown to be effective in reducing incident cases of oropharyngeal cancers, similar to other HPV-attributable diseases.

As HPV is a contagious disease, vaccinating one sex confers benefits to both. If there was no benefit accruing directly to boys to balance against the very limited harms experienced, then there would be grounds to question a policy of gender-neutral vaccination on the ethical principle of respect for persons not being used solely as a means to an end. However, the potential benefits for males outweigh the potential harms.

While the benefit-harm balance differs between boys and girls, it also differs between vulnerable groups and the overall population. The incidence of anal cancer in men who have sex with men (MSM) is estimated to be similar to the rate of cervical cancer in an unscreened female population, and is even higher in MSM who are HIV-positive.[511] Although targeted vaccination strategies have been developed for MSM, this population has often been exposed to HPV infection prior to attending a sexual health clinic and will therefore benefit less than individuals who have been vaccinated prior to exposure. The MSM group do not benefit from girls-only vaccination.

While the benefits of herd effects in reducing transmission of HPV infection to boys may apply in a country with a high vaccine uptake rate in girls, these same benefits will not accrue to non-immunised males who travel to countries with substantially lower HPV immunisation rates and or a higher prevalence of HPV infection. Similiarly, the benefit-harm balance is altered for non-immunised girls that enter a population with low vaccine coverage. By vaccinating boys, their chances of encountering HPV from the native male population is substantially reduced in a society that vaccinates boys and girls.

Importantly, gender-neutral vaccination would also improve the resilience of the national HPV immunisation programme. Risks associated with fluctuations in vaccine uptake may be mitigated by ensuring a higher proportion of the population is directly protected.[512]

10.2.2 Adverse events

The review of safety (Chapter 6) found that minor, transient and non-serious adverse events are very common. Serious adverse events such as anaphylaxis, however, are extremely rare (approximately 1.7 per 1,000,000 doses).

Parents who provide consent for administration of the vaccine, and as such are responsible for deciding whether or not it is acceptable to expose their child to the risk of an adverse event, and for judging how serious that event could be. A robust informed consent process ensures that this decision is made on the basis of clear, relevant, up-to-date information about the benefits and risks associated with the vaccine. The provision of appropriate and adequate information to parents is even more important in light of the fact that anecdotal reports of harms can result in vaccine hesitancy and vaccine refusal.

Resilient immunisation programmes seek to maximise enablers to vaccination and minimise barriers by mitigating misperceptions and ensuring vaccine decisions are driven by evidence rather than fear. Co-occurrence of vaccination and a period of ill health may easily be perceived as being causally related, even though there may be no plausible mode of action to link the two events. The publication of a large volume of evidence refuting a link between the vaccine and a wide range of adverse events may be of little consolation to a parent who believes they have exposed their child to harm through vaccination. The concerns of parents who have worries about the safety of the vaccine should be addressed appropriately. It is critical that in cases in which a vaccine is perceived to have caused harm, these concerns are not dismissed. Parents may perceive that if a clinician dismisses the link between the vaccine and an adverse event, they are not accepting the occurrence or significance of the child's symptoms. Thus it is important that the seriousness of the child's presenting symptoms and how they are treated is not linked to the plausibility of a link to the vaccine. It is imperative to acknowledge the fact that parents who believe their child was harmed through vaccination are not inherently opposed to vaccination, as they consented to receiving the vaccine in the first place.

Finally, of note, there are studies being undertaken to determine if a single-dose schedule of the vaccine might achieve the same level of protection as a two-dose schedule. If a single-dose schedule was found to be non-inferior to the current two-dose schedule, then it would further reduce the exposure to potential harms of vaccination without impacting on the benefits.

10.2.3 Challenges in estimating benefits and harms

There are difficulties in collecting clinical outcome data for 12 year olds who receive the vaccine. Clinical outcome data largely comes from clinical trials of older

populations. Bridging studies using surrogate outcomes were used to determine whether the vaccine effect observed in 12 year olds corresponded to that in adults.

The time lag between vaccination and benefits observed presents difficulties in estimating future benefits (for some HPV-related tumours, onset is typically decades after vaccination). Following the implementation of a HPV immunisation programme, it could take many years before the impact on reduced cancer incidence is observed. However, the burden of anogenital warts and the effect on precancerous lesions (that could be identified during cervical screening) are early indicators of a population-level effect and have been observed in other jurisdictions. Due to the large number of confounders that would be present over a person's timespan, this means that it may never be possible to accurately determine the full benefits of vaccination. Non-serious adverse events, on the other hand, are typically of an acute onset and immediately follow the time of vaccination; the quantification of such harm is therefore more readily assessed.

It may be worth exploring how people differently interpret their immediate risk of a non-serious adverse event compared to their delayed risk of potentially developing invasive cancer (or more immediate risk, in the case of anogenital warts). Due to the time lag, it is important to stress the non-cancer benefits including international evidence of a decline in the incidence of anogenital warts in countries that have implemented HPV immunisation programmes. Similarly, while there is good evidence that cervical screening programmes reduce morbidity and mortality from invasive cervical cancer, as screening represents a secondary rather than a primary prevention strategy, the substantial health burden associated with the detection and treatment of pre-cancerous lesions should be stressed. As documented in Chapter 5, there is evidence of a decline in high grade pre-cancerous cervical lesions in young women in countries that have implemented HPV immunisation programmes.

Many of the clinical trials of HPV vaccines that monitored clinical outcomes focused on intraepithelial neoplasias, precursors to invasive cancer. Not all intraepithelial neoplasias develop into invasive cancers and typically they are not detected unless the individual attends screening. Precancerous cervical lesions (or CIN) are detected and treated by CervicalCheck, Ireland's national cervival screening programme. The lag time to developing invasive cancer can be quite substantial, and therefore a trial might need a follow up of 10 to 20 years to observe a direct effect on invasive cancers. The protective effect of the vaccine against invasive cancers can be estimated by the effect against intraepithelial neoplasias if it is assumed that all invasive HPV-related cancers, with the exception of oropharyngeal cancer, must develop from an intraepithelial neoplasia. A pre-invasive lesion has not yet been described for oropharygeal cancer and as such, screening for an oropharyngeal precursor lesion cannot be performed. Despite the clinical plausibility for a protective effect of HPV vaccination against oropharyngeal cancer, this will not be proven until

trials have followed participants in a manner that directly observes a protective effect due to vaccination.

Since current vaccines do not cover all HPV types, not all cases of cervical cancer can be prevented by vaccination (approximately 90% are targeted by the 9-valent vaccine). Vaccination is in itself, therefore, insufficient to guarantee the prevention of all cervical cancers. An important second tier of cancer prevention is cervical screening of women, whether vaccinated or not.

A futher difficulty regarding the vaccine's potential to cause an adverse event lies in the fact that the HPV vaccine is coadmininstered with another vaccine (Tdap and or MenC vaccines at visits one and two, respectively) as part of the school immunisation programme. Therefore, it is very challenging to disentangle the local or systemic effect of one vaccine from another (such as bruising and fever). In Ireland, suspected adverse reactions reported to the HPRA may relate to the HPV vaccine or to a coadministered vaccine, or indeed to both.

10.2.4 Impact of vaccination on behaviour

There may be a belief that vaccination will change later sexual behaviour patterns. Some parents may incorrectly hold the belief that vaccination may encourage their children to adopt more risky sexual behaviour on the grounds that HPV is a sexually transmitted disease. However, studies have refuted this claim.[(513)] Additionally, messaging in sexual education classes has not changed since introduction of the HPV vaccination; for example, while HPV vaccination confers protection against HPV, it does not confer any protection against any other STI. Messages that relate to the consistent and proper use of barrier protection, or delaying the initiation of sexual intercourse and the avoidance of risky sexual practices, have not changed as a result of the introduction of HPV vaccination.

HPV does not require the exchange of bodily fluids and may be inadvertently transmitted due to the fact it resides, and multiplies, in the superficial layers of human skin and mucosa. HPV is highly contagious and affects up to 90% of people at some point in their lives. Therefore, attempts at limiting the number of sexual encounters and avoidance of promiscuous partners provides no guarantee that an individual will not acquire HPV. The infection is asymptomatic and can occur after just one sexual encounter. From a public health perspective, HPV vaccination is key to prevent transmission.

10.2.5 Herd effects

The importance of herd effects on the benefit-harm balance was discussed in Section 10.2.1. Most vaccination programmes serve both an individual and a social purpose. A vaccinated individual protects themselves while also reducing the chance that

susceptible, or at risk, people in their social network would come into contact with an infectious person. However, while herd effects are important for those within the herd, they do not confer protection to all those 'outside the herd'. Examples of this include men who have sex with men (MSM) and migrants who leave or enter the herd.

Immunising all boys eliminates the difficulty in providing full coverage to the MSM group, who disproportionately suffer from the ill-effects of HPV infection compared to exclusively heterosexual males. Gender-neutral vaccination also provides direct protection to those males and females that move to countries with historically low HPV vaccine uptake rates and or high prevalence of HPV infection. Furthermore, people who enter the herd later in life (and who have not received the HPV vaccine themselves) will likely be indirectly protected if their sexual partners in society are vaccinated.

10.3 Autonomy and shared decision-making

Vaccination is provided to asymptomatic individuals to prevent the onset of illness and, as a result, its benefits may not be visible to the individuals who receive the vaccination. The herd effect that results from adequate coverage is often misunderstood as having a social, but not also an individual, benefit. As such, vaccination may be viewed as an intrusion on individual autonomy because even in situations where vaccination is not mandated, individuals, particularly parents, may feel under pressure to comply with vaccination requirements. While high rates of childhood vaccination coverage indicate that vaccination continues to be a widely accepted public health intervention, a number of individuals perceive it to be unnecessary. The interplay between autonomy, informed consent and shared decision-making are discussed in sections 10.3.1 and 10.3.2, below.

10.3.1 Informed consent

The elements of valid informed consent are capacity, understanding of information disclosed and voluntary agreement. As the proposed immunisation programme involves children who are too young to have the capacity to consent themselves, parents are requested to give consent on their behalf.

It is important to ensure that children and adolescents, whose autonomy is developing, but not yet fully developed, have an appropriate role in the process of deciding whether or not to get vaccinated. Given the age at vaccination, it may be appropriate to consider using a shared decision-making approach. To exercise autonomy, a child must be able to participate in each part of the informed consent process, even if alongside the parent.

Clear and comprehensible information is crucial to obtaining informed consent from parents for vaccination of their children. Informed consent materials must provide sufficient information in a form, manner and language that is comprehensible to parents. For example, in plain English. Additional resources may need to be made available for translation and for review by adult literacy services, such as the National Adult Literacy Agency (NALA). Sufficient time must also be afforded to parents and guardians to enable them to reflect on the choices available to them before making their decision. It is acknowledged that the girls-only HPV immunisation programme has been in place since 2010 and has developed information materials to support parents in deciding whether to consent to the vaccination of their daughter. In the event of a decision to extend the immunisation programme to include boys, materials and an awareness programme will be required that specifically address parents' needs in order to provide informed consent for the vaccination of their son.

While parents or legal guardians have the authority to consent to a medical intervention for children below the age of 16[11],(514) children exhibit a wide range of decision-making abilities and the views of minors considered to be mature (those who can understand and use the information provided to them as the basis for a decision) should be taken into consideration. Parents who have been given sufficient information and have consented to vaccination on the basis of an understanding of this information should also have obtained the assent of their children.

10.3.2 Shared decision-making

Given the age of children when the HPV vaccine is provided, it could be considered an important opportunity to initiate conversations between parents and children around their health, sexuality and sexual behaviour. Vaccination is a decision taken at age 12 or 13 years that has potentially lifelong consequences. It might be considered beneficial for there to be literature available that provides a framework for these conversations. Ideally, the type of information provided would be provided in the school setting and appropriately linked in with the school curriculum. Any divergence in the type of information delivered to children and parents must be justified. It can be challenging for parents to view their child as potentially a sexually active individual in a few years' time; some may prefer to defer such conversations. However, the age at which young Irish people are reaching sexual debut is slowly lowering and as a result the age at which sexual health education needs to be initiated is happening at a younger age.(515) Also, it is noteworthy that HPV vaccination triggers a better immune response in younger individuals. As evidenced in Chapter 4, a two-dose schedule in those aged less than 15 years provides comparable protection to a three-dose schedule in those aged 15 years and older.

[11] According to the National Consent Policy, seeking the consent of only one parent and or legal guardian is acceptable in health and social care practice.

Some, but not all, of the potential vaccine group (12 and 13 year old adolescents) have the ability to understand the benefits and harms of vaccination. Given the potentially long lag time between vaccination and health outcomes avoided, it is likely that children and parents will focus more on the immediate potential harms rather than the distant benefits. Overall, it is unlikely that a child of 12 or 13 will be able to fully comprehend the long-term impact of their choices. It may also be challenging for parents to make those choices on the child's behalf or to discuss the potential consequences of their choice with their child, particularly if they opt to refuse vaccination.

Inevitably, the situation will occasionally arise where parents and children disagree about receiving the vaccine. Most times, communication with parent and child resolves this issue. In resolving any disagreements between parents and minors, health professionals need to balance both the autonomy and the best interests of the child with a recognition of the parents' values and life plans for the child, while aiming to prevent excessive influence by parents.

10.3.3 Factors influencing access to the vaccine

For children who have high rates of non-attendance at school, it may be challenging to ensure they receive vaccination. Vaccination is offered in HSE clinics to those who were absent or unable to avail of vaccination during the visit by the immunisation team to their school, as well as for those who are home-schooled. It is important that the HSE continues to work with schools and parents to ensure that those who consent to vaccination receive it, and that barriers to access for disadvantaged groups are identified and minimised.

10.4 Respect for people

It is important to respect people's privacy during the vaccination process. School teams must ensure that children do not receive the vaccine in plain view of other pupils. This impacts the dignity and privacy of the child. Additionally, privacy during administration ensures minor adverse events, such as fainting, are not observed by other pupils.

Additionally, if a parent or child exercises their right to refuse the vaccine, they must not be questioned in front of others in a manner that can seem discriminatory or coercive. It should also not be readily identifiable which pupils who do not receive the vaccine, for fear of stigmatisation of those who exercise their right to refuse vaccination.

Children should ideally not be put in a situation where it is obvious to others whether or not the child has been vaccinated. However, it must be acknowledged that in practical terms this may be difficult to operationalise, particularly if a child is getting

neither of the vaccines being offered (in the event of co-administration). Practical steps can be taken by schools and immunisation teams to respect the privacy of individuals, such as not discussing consent forms in front of others. Similar to the opportunity to initiate shared decision-making, it provides a context for educating children on the importance of privacy in relation to healthcare, and the need to respect the decisions people make. As outlined in Chapter 9, the HSE has policies and procedures in place for school immunisation teams that address these issues.[516]

10.5 Justice and equity

Given that boys can benefit from vaccination, the existing girls-only programme may be viewed as discriminating against boys. When HPV vaccination was initially introduced, it was as a means to reduce the incidence of cervical cancer and hence seen as benefiting girls only. As documented in Chapters 4 and 5, there is now clear evidence that the vaccine can benefit boys too and therefore denying the vaccine to boys denies them access to that benefit.

The choice to vaccinate or not to vaccinate should consider not just the direct benefits and harms to the individual, but also the potential benefits and harms at a population level. Vaccination is often used as a mechanism to achieve benefits for the greater good, and many individuals experience a minor burden for the few who will experience a substantial benefit. In the case of HPV vaccination, the incidence of HPV-attributable disease is relatively high, and hence a large proportion of the population will experience some form of benefit, either directly or through a family member not contracting the disease.

10.7 Ethical consequences of HTA

The purpose of this section is to outline specific ethical issues that relate to the conduct of this HTA, including choice of outcomes, data sources and timing of the assessment.

10.7.1 Choice of outcomes

The economic evaluation was a cost-utility analysis where health states are valued based on the health-related quality of life in those states. For example, living with invasive cancer negatively impacts on quality of life. There are limited data available on quality of life for the different cancers included in the analysis. Although the use of cost-utility is recommended by many, some argue that one cannot combine quality and quantity of life. Had the evaluation used an outcome of life years gained, for example, then the only measure of outcome would have been survival. Given the burden of anogenital warts and intraepithelial neoplasia, both of which were assumed to have no impact on mortality, an analysis of life years gained would have only included benefits in terms of reductions in mortality from invasive cancer.

The base case analysis excluded oropharyngeal and penile cancers from the calculations on the grounds that efficacy has not yet been demonsrated, although it is entirely plausible. Excluding those cancers reduced the cost-effectiveness of the intervention. From an ethical perspective, the analysis therefore is likely to understate the benefits that will accrue to males from being included in the HPV immunisation programme.

10.7.2 Timing of assessment

The timing of the assessment is important, particularly in relation to the uptake rate in girls. Since the start of the HPV immunisation programme, the completed vaccine uptake rate went from a high of 86.9% in 2014/2015 to a low of 51% in 2016/2017. While there are signs of a recovery in uptake rates, it is unclear how that will evolve. Given the importance of uptake in the cost-effectiveness analysis, conducting the analysis at a time of uncertainty potentially has a bearing on decision-making. For example, if the assessment had been undertaken in 2014, it is likely that it would have concluded that a gender-neutral programme would not be cost-effective.

The timing of the assessment also affects the evidence base in terms of vaccine efficacy. It is possible that in another two to five years there will be a better understanding of the protective effect of the 9-valent vaccine. In accordance with accepted standards set by the WHO, the efficacy in children is inferred from non-inferiority bridging trials. Direct evidence of efficacy may emerge in the future through linkage of immunisation status with HPV-related outcomes. One important change that might be anticipated in the future is whether a single-dose schedule will be as efficacious as a two-dose schedule. Should a single-dose schedule be acceptable, there would be implications for both costs and exposure to adverse reactions.

To date, studies of vaccine efficacy have not suggested a decline in protection over time. However, the longest follow-up available is 10 years, and in theory the efficacy could wane after that. Vaccines that maintain protection to 10 years are generally considered to provide lifelong efficacy, and the base case analysis in the economic evaluation assumed lifelong efficacy. An analysis of the potential impact of waning efficacy after 10 years suggests that it had a limited impact on the cost-effectiveness of the intervention.

10.7.3 Data sources

The analyses relied on both Irish and international data. While high-quality data existed for invasive disease in Ireland, epidemiological evidence related to disease transmission were not readily available. Difficulties also arose in obtaining comprehensive data on the disutility of HPV-attributable diseases. There was also a

lack of clear data on the cost and consequences of non-serious adverse reactions. As is usual, some assumptions were also necessary in our model.

From an ethical standpoint, recommendations were made in the absence of complete Irish data; it is possible this would make a difference to the interpretation of the results. However, through extensive sensitivity analysis using alternative values, the results are relatively robust and hence it is believed that it should not greatly impact the conclusions from an ethical perspective.

10.8 Discussion

Ireland's current girls-only HPV immunisation programme was originally implemented due to consideration of its effectiveness and cost-effectiveness in preventing cervical cancer. As outlined in Chapter 4 and 5, there is now also evidence that vaccinating boys provides beneficial health impact to males, indirect herd protection to girls and has the ability to ensure vulnerable groups are included who do not benefit from herd effects (as in, men who have sex with men [MSM] and migrants who are 'outside the herd'). The economic evaluation reported in Chapter 8 demonstrated that a gender-neutral 9-valent HPV programme would only be considered cost-effective at willingness to pay thresholds of €20,000 and €45,000 per quality-adjusted life year (QALY) if uptake in girls is less than 60% and less than 80%, respectively. If cost-effectiveness is seen as a barrier, there are ethical reasons to justify extension of the current programme to gender-neutral vaccination on the basis of justice, non-discrimination and non-stigmatisation.

The healthcare budget is finite, however, and a switch to gender-neutral vaccination would require reallocation of resources. This could potentially impact the existing healthcare system by diverting resources from other effective treatments. Decisions about healthcare distribution should ensure that resources are allocated or reallocated fairly and that the opportunity cost (the value of the next best alternative forgone) of new investments are considered. This may prove difficult as there may be many competing claims requiring prioritisation of care. Ethical issues that may inform such decisions include issues of justice and equity with respect to a fair distribution of benefits and burdens.

Importantly, Ireland's girls-only HPV immunisation programme has been in place since 2010 and, as such, vaccinating an additional cohort of schoolchildren is not unprecedented. The initially high uptake rates indicated broad acceptance and the initial utility of the programme. Numerous examples of gender-neutral HPV immunisation programmes exist internationally. However, the drop in vaccine coverage experienced in Ireland highlights the need to maintain and protect public trust in any extension of the programme. This would ensure that the programme is resilient and has sufficient capacity, structure and mechanisms for a HPV-resilient

population.[512] This must be achieved through transparency and openness in terms of information (both the materials provided pre-vaccination but also in the monitoring and reporting of benefits and harms).

Many of the ethical concerns (for example, privacy and informed consent) apply equally to boys and girls. Where the difference lies between sexes is the fact that greater benefit is accrued to girls, due fully to the substantial burden of cervical cancer. Our estimates of the benefit to harm balance (in Chapter 8: Economic evaluation) are coloured, however, by two assumptions: the impact of the vaccine on non-serious adverse events and the exclusion of oropharyngeal and penile cancer (as the prevention of these cancers are not yet licensed indications for the vaccine).

10.9 Conclusion

Since the burden of HPV-related cancer is higher in females than in males, a female-only vaccination programme could be seen as equitable if the goal of health policy is to allocate resources in such a way as to prioritise those most affected by disease. However, for reasons of non-discrimination (due to the HPV-related health consequences that affect men), non-stigmatisation (falsely believing HPV-related disease is limited to girls) and the need to protect vulnerable groups (MSM and migrants from outside the 'herd'), there are important ethical reasons to recommend the inclusion of boys in the national HPV immunisation schedule, separate from arguments of efficiency (cost-effectiveness) alone.

Key points

- The main ethical issues associated with extending the national immunisation programme to include HPV vaccination of boys include equity of access, informed consent (particularly on the benefits and harms of vaccination) and fair allocation of resources.
- Based on current knowledge, females benefit more from HPV vaccination than males, as the main contributor to the burden of HPV-related disease is cervical cancer. However, vaccination of boys also confers real health benefits to males that greatly outweighs any potential harms associated with vaccination.
- However, the decision to invest in a gender neutral vaccination programme should consider not just the direct benefits and harms to the individual, but also the overall potential population-level benefits and harms.
- On a population level, HPV vaccination of boys provides direct protection against HPV related disease, indirect herd protection to girls, and ensures vulnerable groups are protected who do not benefit from these herd effects (as in, men who have sex with men [MSM] and migrants who are 'outside the herd').
- A robust informed consent process must be followed to ensure that the decision to vaccinate is made on the basis of clear, relevant, up-to-date information about the benefits and risks associated with the vaccine. This requires the provision of appropriate and adequate information to parents and children.
- For children who have high rates of non-attendance at school, it may be challenging to ensure they receive the HPV vaccine. It is important that the HSE continues to work closely with schools and parents to ensure these children do not miss vaccination for this reason.

- Gender-neutral vaccination may potentially improve vaccine resilience in the context of variable vaccine uptake at a local, national, and international level, thereby insulating our population from significant movements of individuals into and out of the country. It would also ensure our programme is resilient to future changes in female uptake rate.

- A gender-neutral 9-valent HPV programme would only be considered cost-effective at willingness to pay thresholds of €20,000 and €45,000 per QALY if uptake in girls is less than 60% and less than 80%, respectively.

- If cost-effectiveness is considered a barrier, there are ethical reasons to justify extending the current programme to gender-neutral vaccination on the basis of justice, non-discrimination and non-stigmatisation.

- Policy makers have a duty to ensure resources are allocated fairly. Reallocation of resources has the potential to affect the existing health care system as it may divert resources from other effective treatments provided within the overall healthcare fund.

11 Summary and conclusions

11.1 Key findings

11.1.1 Epidemiology and burden of disease

HPV is responsible for approximately 4.5% of the global cancer disease burden, with cervical cancer the most common cancer caused by HPV infection. HPV infection has a causal role in cancers of the anus, penis, oropharynx, vulva and vagina. HPV is also responsible for a range of precancerous lesions and anogenital warts in men and women. Three vaccines are licensed and marketed for use in Ireland to prevent HPV infections:

- the 2-valent vaccine Cervarix®, produced by GlaxoSmithKline which contains HPV 16 and 18 antigens;
- the 4-valent vaccine Gardasil®, produced by MSD which contains HPV 6, 11, 16 and 18 antigens;
- and the 9-valent vaccine Gardasil® 9, also produced by MSD which contains HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58 antigens.

The Evaluation Team accessed Irish data sources to estimate the burden of HPV-related disease, including data on invasive cancers from the National Cancer Registry Ireland (2009-2013) and precancerous cervical lesions from CervicalCheck (2015-2016). Prevalence estimates of HPV infection in women were provided by the Irish research collaboration CERVIVA, which estimated the prevalence of high-risk HPV in cervical specimens to be 14.6%. Estimates of the proportion of oropharyngeal cancers attributable to HPV (estimated by prevalence of the biomarker $p16^{INK4a}$) were provided by the NCRI and through an Irish clinical audit.

With the exception of the sources listed above, quantifying the burden of HPV-related disease in Ireland was difficult due to the paucity of Irish data. Firstly, no data are available on the overall prevalence of genital HPV infection in men in Ireland. A Danish study, however, reported a prevalence of oncogenic HPV types (hrHPV) of 30%. Secondly, data on precancerous lesions outside the cervix are not routinely collected in Ireland. Estimates were therefore retrieved from Scandinavian registry-based databases. Thirdly, while anogenital warts are a notifiable disease in Ireland, significant under-reporting takes place. Therefore, age-specific rates from large population-based studies in the UK and Germany were used. Finally, in the absence of relevant Irish data, the proportion of tumours directly attributable to specific HPV types were retrieved from the most applicable international population-based studies.

On average, 539 cases of HPV-associated cancers were diagnosed per year in Ireland during the period 2009 to 2013. These relate to tumours whose morphology and anatomic location are known to be associated with HPV infection. Of these, three out of four (405 or 75%) were in women and 134 (25%) in men. Cervical cancer was the most frequent, with on average 308 cases per year (76% of the female total and 57% of the overall total of HPV-associated cancers). The next most frequent were oropharyngeal squamous cell carcinomas (123 per year or 23% of the total) and squamous cell carcinomas of the vulva (37 per year or 7% of the total), penis (29 per year or 5% of the total), anus (28 per year or 5% of the total), vagina (eight per year or 1% of the total), and rectum (six per year or 1% of the total).

However, although associated with HPV, not all are a direct result of HPV infection. Across all HPV-related cancers, 383 cases per year were estimated to be directly attributable to HPV in Ireland. Of these, 285 are attributable to HPV 16 and 18 (covered by the 4-valent and 9-valent vaccines) and a further 55 cases are attributable to HPV 31, 33, 45, 52 and 58 (the additional benefit provided by the 9-valent vaccine). Cervical cancer is by far the most common HPV-attributable tumour in Ireland. The potential additional benefit of the 9-valent vaccine is clear, as an estimated 50 cervical cancer cases are attributable to HPV 31, 33, 45, 52 and 58 annually. The next most common tumour after cervical cancer is oropharyngeal cancer. It occurs in considerable numbers and accounts for 23% of all HPV-associated tumours. Overall, 48 cases of oropharyngeal cancer directly attributable to vaccine-preventable HPV types are estimated to occur in Ireland each year.

Overall rates of HPV-associated invasive cancers may be increasing. Between 1994 and 2014 there was a 2% increase in HPV-associated invasive cancers per year for both sexes in Ireland. By comparison, cancer rates as a whole in Ireland have increased more slowly over the same period. Oropharyngeal cancers increased significantly in females by 3.6% per year between 1994 and 2014, while male rates showed a significant 3.7% annual increase from 1999 to 2014. Mirroring international trends, oropharyngeal cancer cases have increased rapidly since 2014 in Ireland. A recent clinical audit on oropharyngeal cases diagnosed between 2014 and 2018 in Ireland found a 37% increase in cases compared with cases recorded by the NCRI between 2009 and 2013. Overall, 77.5% of all cases were in men, and approximately half are thought to be attributable to HPV.

In other countries, a much more rapid increase has been observed. One US study reported that the population-level incidence of HPV-positive oropharyngeal cancers has increased by 225% from 1988 to 2004. During the same period, the incidence of HPV-negative cancers declined by 50%. Investigators in the UK similarly noted a large increase in oropharyngeal cases, with a near doubling in the annual number of oropharyngeal squamous cell carcinomas diagnosed between 2002 and 2011 across the UK. However, the proportion of HPV positive cases remained static at

approximately 50%; authors concluded that the rapid increase in the UK cannot be solely attributable to the influence of HPV.

Beyond invasive cancers, a substantial number of pre-cancerous lesions (cervical, vulvar, vaginal, penile and anal) occur in Ireland each year. For all lesions, most result from infection with vaccine-preventable HPV types. The most significant pre-cancerous lesions are high grade cervical intraepithelial neoplasias (CIN) – CIN grade 2 and higher. Between September 2015 and August 2016 in Ireland, 8,885 new cases of high grade CIN were diagnosed. A reduction in the number of incidents of precancerous lesions through vaccination would have clear implications for Ireland's cervical screening service — with the potential to increase the screening interval as evidence emerges to support the long-term effectiveness of screening women vaccinated against HPV.

The burden of anogenital warts (warts in the anus or genital area) is substantial. Between 6,000 and 7,500 cases of anogenital warts causally associated with HPV types 6 or 11 are estimated to occur each year in Ireland, with comparable rates in males and females. Due to the high incidence of anogenital warts, there are resource implications for sexually transmitted infection (STI) and primary care services. HPV types 6 and 11 are also the causative agents in a rare condition known as recurrent respiratory papillomatosis. Both the 4-valent and 9-valent vaccines target HPV types 6 and 11.

11.1.2 Efficacy of HPV vaccines

The proposed gender-neutral HPV immunisation programme would apply to boys and girls in first year of second level school, generally aged 12 and 13 years. Due to the ethical and legal constraints of conducting such trials in pre and early adolescents who are not yet sexually active, clinical efficacy studies of HPV vaccines have not been conducted in adolescent girls and boys. HPV vaccines have therefore been approved by regulatory agencies for use in this population based upon 'bridging studies' that provide immunogenicity data to support the extrapolation of data on efficacy from adult cohorts to adolescent cohorts.

A systematic review was undertaken to identify evidence for the clinical efficacy and immunogenicity of 4-valent and 9-valent HPV vaccines from relevant published studies. The 4-valent HPV vaccine demonstrated a significant effect at reducing events associated with persistent HPV 6, 11, 16 or 18-related infections, anogenital warts, and HPV 6, 11, 16 and 18-related cervical intraepithelial neoplasia (CIN) 1, CIN 2, CIN 3, vulvar intraepithelial neoplasia (VIN)/vaginal intraepithelial neoplasia (VaIN) 1 and VIN/VaIN 2/3 in HPV-naïve adult women. The 4-valent HPV vaccine has also been shown to be effective at reducing events associated with persistent HPV 6, 11, 16 or 18-related infections and anogenital warts in HPV-naïve men.

In HPV-naïve adult females, no significant difference in clinical outcomes was observed for the HPV subtypes common to both the 9-valent and 4-valent vaccines (HPV 6, 11, 16 and 18). There was a significant reduction in the events associated with HPV 31, 33, 45, 52 and 58 type-related persistent infection (94%) and cervical, vaginal and vulvar diseases (98%) reported for the 9-valent compared with the 4-valent vaccine.

Of note, trials that investigated efficacy in the men who have sex with men (MSM) subgroup demonstrated a reduction in anal intraepithelial neoplasia (AIN), the precursor for invasive anal cancer and a licensed indication for HPV vaccine use. These trials were not specifically assessed in the systematic review due to the fact that our target population was 12 and 13 year old girls and boys. Additionally, it is worth noting that a reduction in penile intraepithelial neoplasia (PIN) was also observed; however, this reduction failed to reach statistical significance due to the very small numbers of absolute events in both intervention and placebo arms of trials.

The lack of waning of the immune response beyond 10 years contributed to an assumption of lifelong efficacy of the 4-valent HPV vaccine. The immunobridging studies demonstrated either superior or non-inferior immune responses for two-dose versus three-dose schedules for 4- and 9-valent HPV vaccines for all comparisons of girls versus women, girls versus girls and boys versus women at seven months. There are comparable immune responses between the two-dose schedules of the 9-valent HPV vaccine in boys and girls at seven months.

It is therefore reasonable to conclude that the efficacy against persistent HPV infection and HPV-related clinical outcomes observed in HPV-naïve adult women and men on a three-dose schedule will extend to 12 year old girls and boys on a two-dose schedule.

11.1.3 Effectiveness of HPV immunisation programmes

There is clear evidence of significant population-level effects of HPV immunisation programmes on HPV-related disease, as summarised by the systematic review of population-level effectiveness. In this review, 37 time-trend observational studies were retrieved that investigated the change in HPV-related disease comparing pre and post-vaccination periods.

Outcomes assessed consisted of HPV infection, anogenital warts and high-grade cervical intraepithelial lesions (CIN 2+), and analyses were stratified by age and sex. All studies that investigated changes in the prevalence of HPV types 16 or 18 in young women (aged less than 20 years) demonstrated a statistically significant reduction regardless of vaccine coverage, ranging from a prevalence ratio of 0.04 (95% CI: 0.01-0.15) to 0.50 (95% CI: 0.34-0.74). This represents a reduction in the

prevalence of HPV 16 and 18 infection of between 50% and 96%. Additionally, a statistically significant reduction in HPV 16 and 18 prevalence (the types all HPV vaccines cover) was observed in all studies involving older women (aged 20 to 24) when vaccine coverage exceeded 35% — this indicates a herd effect. Evidence of cross-protection or type replacement could not be concluded from the data, as no significant difference in the prevalence of HPV types 31, 33, 45, 52 and 58 (in aggregate form) was observed between pre and post-vaccination periods in any study.

All studies demonstrated a statistically significant reduction in diagnoses of anogenital warts in young females following introduction of HPV vaccination, with the exception of one study where vaccine coverage was less than 30%. The most striking reduction was observed in the country with the highest vaccine coverage: a 2016 Danish study observed a 92% (95% CI: 90-93%) reduction in anogenital wart diagnoses (RR: 0.08 [95% CI: 0.07-0.10]) in women aged 15 to 19 years in a population where vaccine coverage was between 87% and 91%. Herd effects were also noted: a statistically significant reduction in anogenital warts in older females (RR: 0.66 [95% CI: 0.63-0.69]) and males (all age groups; RR: 0.82 [95% CI: 0.77-0.87]) was observed, with a more substantial reduction noted in males aged 15 to 19 (RR 0.21 [95% CI: 0.18-0.25]).

All studies investigating the change in the incidence of high grade cervical lesions (CIN 2+) following the introduction of a HPV immunisation programme demonstrated a statistically significant reduction in incidence in CIN 2+ in young women. Participants in all studies were women attending cervical screening and all were conducted in countries with high (>50%) vaccine coverage. Estimates ranged from a RR of 0.18 (95% CI: 0.09-0.33) to 0.52 (95% CI: 0.33-0.81), corresponding with a 48 to 82% reduction in incidence of high-grade lesions.

All studies possessed the strengths and limitations inherent in ecological studies. While time-trend studies provide a wealth of information about the effects of HPV vaccination using very large study populations, they are especially vulnerable to information bias and confounding. Causality cannot be concluded from time-trend analysis alone. Nonetheless, the reductions in HPV types 16 and 18, anogenital warts, and high-grade cervical lesions were large and statistically significant in the target age groups for vaccination (girls less than 20 years of age).

11.1.4 Safety of HPV vaccines

To gather the best available evidence in relation to HPV vaccine safety, a systematic review of systematic reviews was undertaken in addition to retrieving Irish safety data (reported to the Health Products Regulatory Authority [HPRA]) and reviewing other key narrative reviews and independent expert analyses. The overwhelming

conclusion from the assessment of the literature was that a large volume of evidence demonstrates the overall safety of HPV vaccines.

The systematic review of systematic reviews retrieved 10 studies for analysis. Substantial overlap existed across reviews. Therefore, two studies contributed most to the safety assessment, the recent and high-quality Cochrane review by Arbyn et al. (2018) and the health technology assessment by the Adelaide HTA team (2017), commissioned by the World Health Organization (WHO). All other reviews suffered from multiple methodological weaknesses (by AMSTAR 2 criteria) which diminishes confidence in their estimates. Despite this, conclusions were consistent across all 10 reviews.

No safety issues were identified for a range of serious adverse events. No deaths causally associated with HPV vaccination were found. As expected, local injection site adverse events (pain, swelling or redness) that are transient in nature commonly occur following vaccination. The Cochrane review reported an absolute risk of 8,080 per 10,000 in the vaccine group (81%) compared with 6,847 per 10,000 in the placebo group (68%) across all trials.

Due to the fact that the definition of 'serious' was not reported in most reviews (nor in the primary studies), the absolute adverse event rates varied widely. For example, the absolute rates ranged from 2% to 25% in individual studies of the 2-valent vaccine and control arms in the Adelaide HTA. The Cochrane review reported an absolute rate of 656 per 10,000 in the vaccine arm of trials compared with 669 per 10,000 in the placebo group (resulting in a RR of 0.98, 95% CI 0.92 to 1.05; data from 71,597 participants in 23 RCTs; high-quality evidence). Pooled values should be considered estimates as they were likely affected by the different definitions used. However, the comparisons between vaccine and placebo or control vaccine should still be valid. The wide variation in serious adverse event rate reporting did not alter study conclusions, as serious adverse events did not occur more commonly in any vaccine comparison (vaccine versus placebo or control) in any review.

The Adelaide HTA team did not find any association between vaccination and 'new-onset chronic disease' or 'medically significant conditions' in randomised controlled trials (RCTs). Furthermore, observational studies that included six large, good-quality cohort studies and five self-controlled case series were identified and no increased rates of the following conditions were found in vaccinated versus unvaccinated individuals: autoimmune disorders, venous thromboembolism, multiple sclerosis and other demyelinating conditions. Individual cohort studies also investigated a range of other conditions, such as Guillain–Barré syndrome, stroke, appendicitis, seizure, syncope and migraine among many others. No observational study concluded that a verifiable safety concern exists. However, anaphylaxis may occur at a rate of 1.7 cases per 1,000,000 doses.

The review supports the position of the WHO's Global Advisory Committee on Vaccine Safety (GACVS), the European Medicines Agency (EMA), multiple country-level regulatory agencies and other independent reviews and expert analyses that state the HPV vaccines are safe. In its most recent update, the GACVS maintained its assertion that HPV vaccines are not causally associated with Guillain-Barré syndrome, complex regional pain syndrome, postural orthostatic tachycardia syndrome, premature ovarian insufficiency, primary ovarian failure and venous thromboembolism. Country-level surveillance of the HPV vaccine in the US (including the CDC), UK, Denmark and Sweden similarly do not point to safety signals associated with HPV vaccines.

10.1.5 Economic evaluation

A systematic review of published economic evaluations was undertaken, identifying 29 studies of which 16 were at risk of bias due to industry support. A number of the analyses show that if female HPV vaccine coverage is low and all potential health benefits are included, it may be cost-effective to include males in the vaccination schedule. Cost-effectiveness was particularly dependent on the vaccine price, coverage and the willingness-to-pay threshold. Where efficacy against oropharyngeal and penile cancer was included in evaluations, the cost-effectiveness of gender-neutral vaccination improved. Some studies reported that increasing the uptake of vaccination in girls was a more efficient strategy, particularly if coverage was low.

A previously developed economic model was adapted to the Irish setting. The cost-effectiveness of a range of HPV immunisation programmes was evaluated: girls-only 4-valent (that is to say, the existing programme), girls-only 9-valent, gender-neutral 4-valent and gender-neutral 9-valent, as well as the alternative of no vaccination.

The girls-only 9-valent immunisation programme was estimated to be cost saving relative to, and more effective than, the existing girls-only 4-valent programme. A gender-neutral 9-valent programme was estimated to be more effective and more costly than the girls-only 9-valent alternative, with an incremental cost-effectiveness ratio of €37,593 per quality-adjusted life year (QALY). A gender-neutral 9-valent programme would therefore be considered not cost-effective at the modeled vaccine price compared with a threshold of €20,000 per QALY. Willingness-to-pay thresholds of €20,000 and €45,000 per QALY have typically been used as reference points for decision-making regarding the reimbursement of medicines. A gender-neutral 9-valent programme would be considered cost-effective at a threshold of €45,000 per QALY, although this is contingent on the uptake rate of the vaccine in girls stabilising at 80% or lower.

The incremental budget impact of the girls-only 9-valent programme was €760,000 over five years. By comparison, the five-year incremental budget impact of the gender-neutral 9-valent programme was €10.4 million. When compared with the

current girls-only 4-valent programme, after 20 years, a girls-only 9-valent programme will prevent an estimated 63 additional cases of cervical cancer, and a gender-neutral 9-valent programme will prevent an estimated 99 additional cases of cervical cancer compared with the current girls-only 4-valent programme.

In line with the findings of previous evaluations, the estimated cost-effectiveness of a gender-neutral HPV immunisation programme is sensitive to the uptake rate in girls and to the price of the vaccine. The inclusion of oropharyngeal and penile cancers reduce the incremental cost-effectiveness ratio (that is, it becomes more cost-effective), although gender-neutral vaccination would still be considered not cost-effective at a threshold of €20,000 per QALY.

The economic model was subject to a number of limitations due to simplifying assumptions and the unavailability of data specific to the Irish setting. The use of scenario and sensitivity analyses demonstrated that overall the findings were relatively robust.

11.1.6 Organisational issues and resource implications

Ireland has a nationally funded, school-based, girls-only HPV immunisation programme (through the National Schools Immunisation Programme). If the national immunisation programme is extended to include HPV vaccination of boys, an estimated 30,065 boys in their first year of second level school would become eligible (across 111 boys-only schools and 469 co-educational schools).

As per current immunisation guidelines, the first dose of the HPV vaccine is co-administered with the tetanus, low dose diphtheria and low dose acellular pertussis (Tdap) booster vaccine in September or October and the second dose is co-administered with meningococcal group C (MenC) booster vaccine six months later in girls. Boys also receive these booster vaccines in their first year of second level school. If the HPV vaccine were co-administered with Tdap or MenC to eligible boys, no increase in school visits would be anticipated in schools that are currently visited twice in the academic year. One additional visit would be required in schools that are currently visited once in the academic year.

Additional resources would be required by immunisation teams if a gender-neutral HPV immunisation policy is adopted. Along with the increased administrative burden, an increase in staff time to deliver two additional vaccine doses to boys would be necessary and additional resources would be required to facilitate additional school visits in boys-only schools. Given the need to administer the vaccine at specified intervals within the academic year, this may pose logistical challenges within some areas with surge capacity necessary to reflect the time constraints within which the service must be provided.

Preliminary uptake of the first dose of vaccine in the most recent academic year (2017 to 2018) among girls was 61.7%. Figures for the two-dose uptake were not available at the time of this assessment. International evidence would suggest that uptake may be lower in boys; however, the most recent data indicates an uptake rate of 93% of that achieved in girls.

While extending the HPV immunisation programme to include boys is likely to be easier than rolling out the initial girls-only programme, there will be a need to address the unique information needs of parents and boys in relation to the risk of acquiring HPV infection and the direct benefits of the vaccine for boys. An awareness campaign would be required to address these needs and to enable parents to provide informed consent. While international survey data suggest strong support for vaccinating boys, as with HPV vaccination of girls, fear of adverse events and uncertainty around vaccine effectiveness are noted barriers to vaccine uptake. Extending the HPV immunisation programme to include boys would have to be accompanied by a public awareness campaign to ensure adequate knowledge among parents around the HPV vaccine and HPV-attributable disease to enable informed consent.

11.1.7 Ethical issues

Since the burden of HPV-related cancer is higher in females than in males, a girls-only vaccination programme could be seen as equitable if the goal of health policy is to allocate resources in such a way as to prioritise those most affected by disease. However, important factors, separate from arguments of cost-effectiveness, exist to recommend the inclusion of boys in the national HPV immunisation schedule; such as non-discrimination (due to the HPV-related health consequences that affect men), non-stigmatisation (falsely believing HPV-related disease is limited to girls) and protecting vulnerable groups (men who have sex with men and migrants from outside the 'herd').

Many ethical concerns (for example, privacy and informed consent) apply equally to boys and girls. As noted previously, where the difference lies between sexes is the fact that greater benefit is accrued to girls, due fully to the substantial burden of cervical cancer. Nonetheless, HPV vaccination provides a clear, beneficial health impact for males, indirect herd protection to girls and ensures vulnerable groups are not excluded (men who have sex with men).

Additionally, gender-neutral vaccination mitigates the negative effects of population movement between two jurisdictions with disparate HPV vaccine coverage. A final benefit is that gender neutral vaccination ensures the immunisation programme is resilient, mitigating the potential negative effects of future drops in vaccine coverage through directly protecting more individuals.

The healthcare budget is finite, however, and a switch to gender-neutral vaccination would require reallocation of resources. This could potentially impact the existing healthcare system by diverting resources from other effective treatments. Ethical issues that may strengthen such decisions include issues of justice and equity with respect to a fair distribution of benefits and burdens.

11.2 Summary

The burden of disease associated with persistent infection with HPV, the most common viral infection of the reproductive tract, is substantial and appears to be increasing in Ireland. HPV vaccines have proven efficacy in invoking a rigorous immune response against HPV infection. Additionally, observational studies support the high efficacy reported in trials, providing real-world evidence of the effectiveness of HPV immunisation programmes in reducing HPV-related disease. HPV vaccines also have a reassuring safety profile. With over 270 million doses distributed globally to date, regulatory bodies worldwide have not raised any verifiable safety concerns.

The Evaluation Team performed cost-effectiveness modeling on the vaccine programme. A girls-only 9-valent immunisation programme is estimated to be cost saving relative to, and more effective than, the existing girls-only 4-valent programme. A gender-neutral 9-valent programme was estimated to be more effective, but more costly, than a girls-only 9-valent alternative, with an incremental cost-effectiveness ratio of €37,593 per QALY. In line with the findings of previous evaluations, the estimated cost-effectiveness of a gender-neutral HPV immunisation programme is sensitive to the uptake rate in girls and to the price of the vaccine. Gender-neutral vaccination would be considered more cost-effective when oropharyngeal and penile cancers are included in the analysis. Extending the Irish schools immunisation programme to include boys would likely be easier than rolling out the initial girls-only programme, and a number of successful gender-neutral programmes have been implemented in other countries.

The ethical argument to extend the vaccination programme to include boys centres on issues of justice, equity, non-discrimination and non-stigmatisation. It would ensure the programme is resilient to future changes in female uptake rate and, as a dynamic population where people leave and enter the country, it would ensure individuals are directly protected as opposed to relying on herd protection. Finally, it would ensure men who have sex with men are protected as they do not benefit from the herd effects of female vaccination.

11.3 Conclusion

- Since 2010 there has been a national girls-only 4-valent HPV immunisation programme in place in Ireland.

- HPV infection is directly implicated in a number of cancers, including cervical, vaginal, vulvar, anal, penile and oropharygeal cancer. Additionally, HPV is the cause of anogenital warts.
- Across numerous studies, HPV vaccination has been demonstrated to be both safe and effective at preventing HPV infection in both girls and boys.
- A change to the HPV immunisation programme should include adoption of the 9-valent vaccine.
- At a threshold of €20,000 per QALY, a girls-only programme is the cost-effective option while at €45,000 per QALY a gender-neutral programme is the cost-effective option.
- The five-year incremental budget impact of the gender-neutral 9-valent programme is projected to be €10.4 million.
- Extending the HPV immunisation programme to include boys would need to be accompanied by a public awareness campaign to ensure adequate knowledge among parents around the HPV vaccine and HPV-attributable disease to enable informed consent.
- Gender-neutral vaccination may potentially improve vaccine resilience in the context of variable vaccine uptake at a local, national, and international level, thereby insulating our population from significant movements of individuals into and out of the country. It would provide protection to vulnerable groups not covered through the current girls-only programme, such as men who have sex with men. It would also ensure our programme is resilient to future changes in female uptake rate.
- The healthcare budget is finite, however, and a switch to gender-neutral vaccination would require reallocation of resources potentially impacting the existing healthcare system by diverting resources from other effective treatments.

References

1. de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. International Journal of Cancer. 2017;141(4):664-70.
2. Moscicki AB, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine. 2012;30 Suppl 5:F24-33.
3. Moreira ED, Jr., Giuliano AR, Palefsky J, Flores CA, Goldstone S, Ferris D, et al. Incidence, clearance, and disease progression of genital human papillomavirus infection in heterosexual men. The Journal of infectious diseases. 2014;210(2):192-9.
4. Veldhuijzen NJ, Snijders PJ, Reiss P, Meijer CJ, van de Wijgert JH. Factors affecting transmission of mucosal human papillomavirus. The Lancet Infectious diseases. 2010;10(12):862-74.
5. WHO. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017 Weekly epidemiological record. 12 May 2017. 2017.
6. Hartwig S, Baldauf J-J, Dominiak-Felden G, Simondon F, Alemany L, de Sanjosé S, et al. Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: Potential additional benefit of a nine-valent second generation HPV vaccine compared to first generation HPV vaccines. Papillomavirus Research. 2015;1:90-100.
7. Brian Buckley NH, Nicola Maayan et al. Anogenital warts: Incidence, prevalence, self-reported history & quality of life. Cochrane Response. 2016.
8. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED, Penny ME, Aranda C, et al. Efficacy of Quadrivalent HPV Vaccine against HPV Infection and Disease in Males. The New England journal of medicine. 2011;364(5):401-11.
9. Munoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. Journal of the National Cancer Institute. 2010;102(5):325-39.
10. Bresse X, Goergen C, Prager B, Joura E. Universal vaccination with the quadrivalent HPV vaccine in Austria: impact on virus circulation, public health and cost-effectiveness analysis. Expert review of pharmacoeconomics & outcomes research. 2014;14(2):269-81.
11. Center. IHPR. International Human Papillomavirus Reference Center. Human papillomavirus reference clones. Available at: http://www.hpvcenter.se/html/refclones.html. 2017.

12. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. Reviews in Medical Virology. 2015;25(Suppl Suppl 1):2-23.

13. Poljak M, Kocjan BJ, Ostrbenk A, Seme K. Commercially available molecular tests for human papillomaviruses (HPV): 2015 update. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2016;76 Suppl 1:S3-s13.

14. Munoz N, Bosch FX, De SS, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med. 2003;348(6):518-27.

15. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-23.

16. TL. Special Report: Policy A review of human carcinogens—Part B: biological agents. 2009.

17. IARC. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans: human papillomaviruses. Vol. 90. Lyon, IARC, 2007. Available at http://monographs.iarc.fr/ENG/Monographs/vol90/mono90.pdf. 2007.

18. IARC. International Agency for Research on Cancer. IARC Working Group Report: Primary End-Points for Prophylactic HPV Vaccine Trials. Vol 7. Lyon, IARC, 2014. Available at http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk7/Prophylactic_HPV_VaccineTrials.pdf. 2014.

19. Giuliano AR, Lee JH, Fulp W, Villa LL, Lazcano E, Papenfuss MR, et al. Incidence and clearance of genital human papillomavirus infection in men (HIM): a cohort study. Lancet (London, England). 2011;377(9769):932-40.

20. Rodriguez AC, Schiffman M, Herrero R, Hildesheim A, Bratti C, Sherman ME, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. Journal of the National Cancer Institute. 2010;102(5):315-24.

21. Munoz N, Mendez F, Posso H, Molano M, van den Brule AJ, Ronderos M, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. The Journal of infectious diseases. 2004;190(12):2077-87.

22. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. BMC Infectious Diseases. 2013;13:39-.

23. Arima Y, Winer RL, Feng Q, Hughes JP, Lee SK, Stern ME, et al. Development of genital warts after incident detection of human papillomavirus infection in young men. The Journal of infectious diseases. 2010;202(8):1181-4.

24. Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. The Journal of infectious diseases. 2009;199(6):805-14.

25. Larson DA, Derkay CS. Epidemiology of recurrent respiratory papillomatosis. APMIS : acta pathologica, microbiologica, et immunologica Scandinavica. 2010;118(6-7):450-4.

26. Stanley MA. Epithelial Cell Responses to Infection with Human Papillomavirus. Clinical Microbiology Reviews. 2012;25(2):215-22.

27. Kreimer AR, Pierce Campbell CM, Lin HY, Fulp W, Papenfuss MR, Abrahamsen M, et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. Lancet (London, England). 2013;382(9895):877-87.

28. al. SMe. Host responses to infection with human papillomavirus. JC Curr Probl Dermatol, 2014;45:58–74. 2014.

29. Villa LL DL. CHAPTER 7: Methods for detection of HPV infection and its clinical utility. International Journal of Gynecology and Obstetrics (2006) 94 (Supplement 1), S71---S80. 2006.

30. Dixit R, Bhavsar C, Marfatia YS. Laboratory diagnosis of human papillomavirus virus infection in female genital tract. Indian Journal of Sexually Transmitted Diseases. 2011;32(1):50-2.

31. Health Do. JCVI statement: extending the HPV vaccination programme. Evidence and considerations for extending the HPV vaccination programme to adolescent boys: interim statement from JCVI. UK. 2017.

32. FDA. Gardasil 9. Food and Drug Administration. Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf. 2017.

33. GlaxoSmithKline (Ireland) Ltd. Cervarix Suspension for Injection 1 dose - Summary of Product Characteristics2016 01/09/2016. Available from: http://www.medicines.ie/medicine/12544/SPC/Cervarix+Suspension+for+Injection+1+dose/.

34. Sanofi Pasteur MSD Limited. GARDASIL - Summary of Product Characteristics01/09/2016. Available from: http://www.medicines.ie/medicine/11524/SPC/GARDASIL.

35. Luckett R, Feldman S. Impact of 2-, 4- and 9-valent HPV vaccines on morbidity and mortality from cervical cancer. Human Vaccines & Immunotherapeutics. 2016;12(6):1332-42.

36. Health Service Executive. Immunisation Guidelines for Ireland. Human Papillomavirus Online [updated 01/09/2016. Available from: http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter10.pdf.

37. SPC. Cervarix. Summary of Product Characteristics. European Medicines Agency. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000721/WC500024632.pdf. 2017.

38. SPC. Gardasil. Summary of Product Characteristics. European Medicines Agency. Available at

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf. 2017.

39. SPC. Gardasil 9. Summary of Product Characteristics. European Medicines Agency. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003852/WC500189111.pdf. 2017.
40. Health Service Executive. Cervical cancer vaccination Online [Available from: http://www.hse.ie/eng/health/az/C/Cervical-cancer-vaccination/.
41. Committee NIA. Immunisation guidelines for Ireland - 2013 edition. Dublin, Ireland: 2013 2013. Report No.
42. Health Protection Surveillance Centre. HPV vaccine uptake in Ireland: 2014/2015 2016 28/08/2016. Available from: http://www.hpsc.ie/A-Z/VaccinePreventable/Vaccination/ImmunisationUptakeStatistics/HPVImmunisationUptakeStatistics/File,15781,en.pdf.
43. HPSC. Health Protection Surveillance Centre. HPV vaccine uptake in Ireland: 2015/2016. Publication date: 7 February 2017. 2017.
44. HPSC. HPV vaccine uptake in Ireland: 2016/2017. Available at: http://www.hpsc.ie/a-z/vaccinepreventable/vaccination/immunisationuptakestatistics/hpvimmunisationuptakestatistics/HPV%20Uptake%20Academic%20Year%202016%202017%20v1.1%2009012018.pdf. Accessed March 2017. 2017.
45. Corcoran B, Clarke A, Barrett T. Rapid response to HPV vaccination crisis in Ireland. The Lancet. 2018;391(10135):2103.
46. Authority DH. Sharp fall in HPV vaccination rate2016. Available from: https://sundhedsstyrelsen.dk/en/news/2016/Markant%20fald%20i%20tilslutningen%20til%20HPV-vaccinen.
47. Hanley SJB, Yoshioka E, Ito Y, Kishi R. HPV vaccination crisis in Japan. The Lancet.385(9987):2571.
48. Public Health Agency. Annual HPV vaccine coverage in Northern Ireland: 2016-17. Available at: http://www.publichealthagency.org/sites/default/files/directorates/files/HPV%202016-2017.pdf. Accessed May 2018. 2018.
49. Paul P, Fabio A. Literature review of HPV vaccine delivery strategies: considerations for school- and non-school based immunization program. Vaccine. 2014;32(3):320-6.
50. HSE. HPV Vaccine for people with HIV and MSM. Available at: http://www.hse.ie/eng/health/Immunisation/hcpinfo/OtherVaccines/hpvadults/. 2017.
51. Rehn M, Uhnoo I, Kühlmann-Berenzon S, Wallensten A, Sparén P, Netterlid E. Highest Vaccine Uptake after School-Based Delivery - A County-Level Evaluation of the Implementation Strategies for HPV Catch-Up Vaccination in Sweden. PLOS ONE. 2016;11(3):e0149857.

52. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: A systematic review of the literature. The Journal of infectious diseases. 2006;194(8):1044-57.

53. *Immunise Australia Program. Human Papillomavirus* [Online]. 2017. [Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv. Accessed on: 3 April 2017.

54. SSI. EPI NEWS. Report on the HPV vaccination coverage - status as per 4 September 2017. Available at: https://www.ssi.dk/English/News/EPI-NEWS/2017/No%2041%20-%202017.aspx. 2017.

55. NCRI. Personal communication with the National Cancer Registry Ireland (www.ncri.ie). 2017.

56. CERVIVA. Promoting quality research in HPV associated diseases (CERVIVA). www.cerviva.ie. 2017.

57. Preliminary analysis of P16 status for oropharyngeal squamous cell carcinomas registered by NCRI [unpublished data]. June, 2018. Provided by personal communication with Dr Paul Walsh, NCRI.

58. Irish Oropharyngeal Cancer Audit, 2014-2018 [unpublished data]. Provided by personal communication with Professor James Paul O'Neill, Beaumont Hospital (Dublin).

59. NCRI. Cancer trends: HPV-associated cancers. National Cancer Registry Ireland. 2017.

60. Giuliano AR, Nyitray AG, Kreimer AR, Pierce Campbell CM, Goodman MT, Sudenga SL, et al. EUROGIN 2014 Roadmap: Differences in HPV infection natural history, transmission, and HPV-related cancer incidence by gender and anatomic site of infection. International journal of cancer Journal international du cancer. 2015;136(12):2752-60.

61. Herrero R, Castle PE, Schiffman M, Bratti MC, Hildesheim A, Morales J, et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. The Journal of infectious diseases. 2005;191(11):1796-807.

62. Dunne EF, Unger ER, Sternberg M, McQuillan G, Swan DC, Patel SS, et al. Prevalence of HPV infection among females in the United States. Jama. 2007;297(8):813-9.

63. Giuliano AR, Lazcano-Ponce E, Villa LL, Flores R, Salmeron J, Lee JH, et al. The human papillomavirus infection in men study: human papillomavirus prevalence and type distribution among men residing in Brazil, Mexico, and the United States. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2008;17(8):2036-43.

64. Giuliano AR, Nielson CM, Flores R, Dunne EF, Abrahamsen M, Papenfuss MR, et al. The optimal anatomic sites for sampling heterosexual men for human

papillomavirus (HPV) detection: the HPV detection in men study. The Journal of infectious diseases. 2007;196(8):1146-52.

65. Barzon L, Militello V, Pagni S, Franchin E, Dal Bello F, Mengoli C, et al. Distribution of human papillomavirus types in the anogenital tract of females and males. Journal of medical virology. 2010;82(8):1424-30.

66. Smith JS, Gilbert PA, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of human papillomavirus infection in males: a global review. The Journal of adolescent health : official publication of the Society for Adolescent Medicine. 2011;48(6):540-52.

67. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in adults aged 18–69: United States, 2011–2014 NCHS data brief, no 280 Hyattsville, MD: National Center for Health Statistics. 2017.

68. Hebnes JB, Munk C, Nohr B, Nielsen A, Jorgensen HO, Iftner T, et al. Human Papillomavirus Infection Among 2460 Men in Denmark: Prevalence in Relation to Age Using 2 Human Papillomavirus DNA Testing Methods. Sexually transmitted diseases. 2015;42(8):463-7.

69. Hebnes JB, Olesen TB, Duun-Henriksen AK, Munk C, Norrild B, Kjaer SK. Prevalence of genital human papillomavirus among men in Europe: systematic review and meta-analysis. The journal of sexual medicine. 2014;11(11):2630-44.

70. Sonnenberg P, Clifton S, Beddows S, Field N, Soldan K, Tanton C, et al. Prevalence, risk factors, and uptake of interventions for sexually transmitted infections in Britain: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet (London, England). 2013;382(9907):1795-806.

71. C. M. Martin, White C, O`Leary JJ. CERVIVA HPV Screening study update. Dublin, Ireland: 2016.

72. CERVIVA. HPV Primary Screening Pilot Study: molecular testing of potential triage strategies for HPV-positive women Dublin 8, Ireland: Irish HPV Screening Research Consortium, Molecular Pathology, Coombe Women's Hospital 2016 [Available from: http://cerviva.ie/?q=projects/phase-iii-cerviva-carg/hpv-primary-screening-pilot-study-molecular-testing-potential-triage.

73. Martin CM, White C, O'Leary JJ. CERVIVA HPV primary screening study update. Dublin, Ireland2016.

74. Bruni L, Diaz M, Castellsagué X, Ferrer E, Bosch FX, Sanjosé Sd. Cervical Human Papillomavirus Prevalence in 5 Continents: Meta-Analysis of 1 Million Women with Normal Cytological Findings. The Journal of infectious diseases. 2010;202:1789 - 99.

75. Kjaer SK, Munk C, Junge J, Iftner T. Carcinogenic HPV prevalence and age-specific type distribution in 40,382 women with normal cervical cytology, ASCUS/LSIL, HSIL, or cervical cancer: what is the potential for prevention? Cancer causes & control : CCC. 2014;25(2):179-89.

76. Pierce Campbell CM KA, O'Keefe MT, Lin HY, Fulp W, Abrahamsen M, Villa LL, Lazcano-Ponce E, Trotti A, Kish JA, Caudell JJ, Giuliano AR. Oral HPV16

persistence among participants of the HPV Infeciton in Men (HIM) Study EUROGIN International Congress Florence, Italy. . 2013.

77. Nyitray A, Nielson CM, Harris RB, Flores R, Abrahamsen M, Dunne EF, et al. Prevalence of and risk factors for anal human papillomavirus infection in heterosexual men. The Journal of infectious diseases. 2008;197(12):1676-84.

78. Castro FA, Quint W, Gonzalez P, Katki HA, Herrero R, van Doorn LJ, et al. Prevalence of and risk factors for anal human papillomavirus infection among young healthy women in Costa Rica. The Journal of infectious diseases. 2012;206(7):1103-10.

79. Nyitray AG, Carvalho da Silva RJ, Baggio ML, Lu B, Smith D, Abrahamsen M, et al. Age-specific prevalence of and risk factors for anal human papillomavirus (HPV) among men who have sex with women and men who have sex with men: the HPV in men (HIM) study. The Journal of infectious diseases. 2011;203(1):49-57.

80. AG. N. Comparing and contrasting the natural history of anal HPV among women and men EUROGIN International Congress Florence, Italy. 2013.

81. Alvarez-Arguelles ME, Melon S, Junquera ML, Boga JA, Villa L, Perez-Castro S, et al. Human papillomavirus infection in a male population attending a sexually transmitted infection service. PLoS One. 2013;8(1):e54375.

82. Chin-Hong PV, Vittinghoff E, Cranston RD, Buchbinder S, Cohen D, Colfax G, et al. Age-Specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. The Journal of infectious diseases. 2004;190(12):2070-6.

83. Dona MG, Palamara G, Di Carlo A, Latini A, Vocaturo A, Benevolo M, et al. Prevalence, genotype diversity and determinants of anal HPV infection in HIV-uninfected men having sex with men. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2012;54(2):185-9.

84. Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. The Lancet Oncology. 2012;13(5):487-500.

85. Sadlier C, Rowley D, Morley D, Surah S, O'Dea S, Delamere S, et al. Prevalence of human papillomavirus in men who have sex with men in the era of an effective vaccine; a call to act. HIV medicine. 2014;15(8):499-504.

86. Hernandez BY, McDuffie K, Zhu X, Wilkens LR, Killeen J, Kessel B, et al. Anal human papillomavirus infection in women and its relationship with cervical infection. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005;14(11 Pt 1):2550-6.

87. Lu B VR, Villa LL, Lazcano-Ponce E, Salmeron J, da Silva RJ, Baggio ML, Quiterio M, Smith DC, Abrahamsen M, Papenfuss M, Giuliano AR. . Capsid antibody response to genital HPV 6, 11, 16, and 18 infection in healthy men

28th International Papillomavirus Conference San Juan, Puerto Rico; 2012. 2012.

88. Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, et al. Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. The Journal of infectious diseases. 2000;181(6):1911-9.

89. Carter JJ, Koutsky LA, Wipf GC, Christensen ND, Lee SK, Kuypers J, et al. The natural history of human papillomavirus type 16 capsid antibodies among a cohort of university women. The Journal of infectious diseases. 1996;174(5):927-36.

90. Ho GY, Studentsov Y, Hall CB, Bierman R, Beardsley L, Lempa M, et al. Risk factors for subsequent cervicovaginal human papillomavirus (HPV) infection and the protective role of antibodies to HPV-16 virus-like particles. The Journal of infectious diseases. 2002;186(6):737-42.

91. Viscidi RP, Schiffman M, Hildesheim A, Herrero R, Castle PE, Bratti MC, et al. Seroreactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection: results from a population-based study in Costa Rica. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2004;13(2):324-7.

92. Reiter PL, Pendergraft WF, 3rd, Brewer NT. Meta-analysis of human papillomavirus infection concordance. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010;19(11):2916-31.

93. Tota JE, Ramanakumar AV, Jiang M, Dillner J, Walter SD, Kaufman JS, et al. Epidemiologic approaches to evaluating the potential for human papillomavirus type replacement postvaccination. American journal of epidemiology. 2013;178(4):625-34.

94. Weinberger DM, Malley R, Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet (London, England). 2011;378(9807):1962-73.

95. Tota JE, Struyf F, Merikukka M, Gonzalez P, Kreimer AR, Bi D, et al. Evaluation of Type Replacement Following HPV16/18 Vaccination: Pooled Analysis of Two Randomized Trials. JNCI: Journal of the National Cancer Institute. 2017;109(7):djw300-djw.

96. National Cancer Registry Ireland. Cancer Trends: Cancers of the cervix and uterus. Cork, Ireland: NCRI, 2012.

97. National Cancer Registry Ireland. Cancer in Ireland 1994-2013: Annual report of the National Cancer Registry. Cork: NCRI, 2015.

98. International Agency for Research on Cancer. EUCAN - Cervical cancer factsheet http://eco.iarc.fr/EUCAN/CancerOne.aspx?Cancer=25&Gender=22012 [

99. Casey G, Morris B, Burnell M, Parberry A, Singh N, Rosenthal A. Celebrities and screening: a measurable impact on high-grade cervical neoplasia diagnosis from the "Jade Goody effect" in the UK. Br J Cancer. 2013;109(5):1192-7.

100. National Cancer Registry Ireland. Cancer projections 2015-2040. Cork, Ireland: NCRI, 2014.

101. CervicalCheck - The National Screening Service Programme. Programme Report 2015 to 2016. Available at: http://www.screeningservice.ie/publications/CervicalCheck-Programme-Report-2015-2016.pdf. Accessed 1/5/2018.

102. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. The Journal of pathology. 1999;189(1):12-9.

103. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. The Lancet Oncology. 2010;11(11):1048-56.

104. de Sanjose S, Quint WGV, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. The Lancet Oncology. 2010;11(11):1048-56.

105. Joura EA, Ault KA, Bosch FX, Brown D, Cuzick J, Ferris D, et al. Attribution of 12 High-Risk Human Papillomavirus Genotypes to Infection and Cervical Disease. Cancer Epidemiology Biomarkers & Prevention. 2014;23(10):1997.

106. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet (London, England). 2006;367(9509):489–98.

107. O'Connor M, O'Leary E, Waller J, Gallagher P, D'arcy T, Flannelly G, et al. Trends in, and predictors of, anxiety and specific worries following colposcopy: a 12-month longitudinal study. Psycho-Oncology. 2016;25(5):597-604.

108. Colombo N, Carinelli S, Colombo A, Marini C, Rollo D, Sessa C. Cervical Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23 Suppl 7:p.vii27-vii32.

109. Network SIG. Management of cervical cancer - a national clinical guideline. Edinburgh, Scotland: Scottish Intercollegiate Gudelines Network, 2008.

110. Chuang LT, Temin S, Berek JS. Management and Care of Women With Invasive Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline Summary. Journal of oncology practice / American Society of Clinical Oncology. 2016;12(7):693-6.

111. Pfaendler K, Wenzel L, Mechanic M, Penner K. Cervical cancer survivorship: long-term quality of life and social support. Clin Ther. 2015;37(1):39-48.

112. Wit E, Horenblas S. Urological complications after treatment of cervical cancer. Nat Rev Urol. 2014;11(2):110-7.

113. National Cancer Registry Ireland. Cancer Factsheet - Cervical Cancer http://www.ncri.ie/sites/ncri/files/factsheets/FACTSHEET_cervix_1.pdf20th March 2015 [

114. Sant M, Chirlaque L, Agresti R, Perez MS, Holleczek B, Bielska-Lasota M, et al. Survival of women with cancers of breast and genital organs in Europe 1999-2007: results of the EUROCARE-5 study. Eur J Cancer. 2015;51(15): 2191–205.

115. National Cancer Registry. Cancer Factsheet. Cervix. website [Internet]. 2013. Available from: http://www.ncri.ie/sites/ncri/files/factsheets/FACTSHEET_cervix.pdf.

116. Sant M, Chirlaque L, Agresti R, Perez MS, Holleczek B, Bielska-Lasota M. Survival of women with cacers of breast and genital organs in Europe 1999-2007: results of the EUROCARE-5 study. Eur J Cancer. 2015.

117. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. The Lancet Oncology. 2012;13(6):607-15.

118. ICO. Human Papillomavirus and Related Diseases Report. WORLD. Version posted at www.hpvcentre.net on 27 July 2017. 2017.

119. Moller B FH, Hakulinen T, Tryggvadottir L, Storm HH, et al. . Prediction of cancer incidence in the Nordic countries up to the year 2020. Eur J Cancer Prev 11 Suppl 1: S1–96. 2002.

120. Larsen IK SM, Johannesen TB, Langmark F, Parkin DM, et al. . Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 45: 1218–1231. 2009.

121. Nygard M, Hansen BT, Dillner J, Munk C, Oddsson K, Tryggvadottir L, et al. Targeting human papillomavirus to reduce the burden of cervical, vulvar and vaginal cancer and pre-invasive neoplasia: establishing the baseline for surveillance. PLoS One. 2014;9(2):e88323.

122. Hartwig S, Baldauf J-J, Dominiak-Felden G, Simondon F, Alemany L, de Sanjosé S, et al. Estimation of the epidemiological burden of HPV-related anogenital cancers, precancerous lesions, and genital warts in women and men in Europe: Potential additional benefit of a nine-valent second generation HPV vaccine compared to first generation HPV vaccines. Data retrieved from Appendix - available online at https://www.sciencedirect.com/science/article/pii/S2405852115000099#s3095 . . Papillomavirus Research. 2015;1:90-100.

123. de Sanjose S, Alemany L, Ordi J, Tous S, Alejo M, Bigby SM, et al. Worldwide human papillomavirus genotype attribution in over 2000 cases of intraepithelial and invasive lesions of the vulva. Eur J Cancer. 2013;49(16):3450-61.

124. Alemany L, Saunier M, Tinoco L, Quiros B, Alvarado-Cabrero I, Alejo M, et al. Large contribution of human papillomavirus in vaginal neoplastic lesions: a worldwide study in 597 samples. Eur J Cancer. 2014;50(16):2846-54.

125. Sankaranarayanan R, Ferlay J. Worldwide burden of gynaecological cancer: the size of the problem. Best practice & research Clinical obstetrics & gynaecology. 2006;20(2):207-25.

126. Grulich AE, Poynten IM, Machalek DA, Jin F, Templeton DJ, Hillman RJ. The epidemiology of anal cancer. Sexual health. 2012;9(6):504-8.

127. van der Zee RP, Richel O, de Vries HJ, Prins JM. The increasing incidence of anal cancer: can it be explained by trends in risk groups? The Netherlands journal of medicine. 2013;71(8):401-11.

128. Silverberg MJ, Lau B, Justice AC, Engels E, Gill MJ, Goedert JJ, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2012;54(7):1026-34.

129. Diamond C, Taylor TH, Aboumrad T, Bringman D, Anton-Culver H. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. Sexually transmitted diseases. 2005;32(5):314-20.

130. Roberts JR, Siekas LL, Kaz AM. Anal intraepithelial neoplasia: A review of diagnosis and management. World Journal of Gastrointestinal Oncology. 2017;9(2):50-61.

131. Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. ANZ journal of surgery. 2006;76(8):715-7.

132. Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. The British journal of surgery. 2005;92(9):1133-6.

133. Durante AJ WA, Da CM, Darragh TM, Khoshnood K, Palefsky JM. Incidence of anal cytological abnormalities in a cohort of human immunodeficiency virus-infected women. Cancer Epidemiol Biomarkers Prev 2003;12:638–42. 2003.

134. Chin-Hong PV VE, Cranston RD, Browne L, Buchbinder S, Colfax G, Da CM, Darragh T, Benet DJ, Judson F, Koblin B, Mayer KH, et al. . Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study. J Natl Cancer Inst 2005;97:896–905. 2005.

135. Li AH PN, Sahasrabuddhe VV, Chaithongwongwatthana S, Vermund SH, Jenkins CA, Shepherd BE, Teeratakulpisarn N, van der LJ, Avihingsanon A, Ruxrungtham K, Shikuma C, et al. . Anal squamous intraepithelial lesions among HIV positive and HIV negative men who have sex with men in Thailand. Sex Transm Infect 2009;85:503–7. 2009.

136. Palefsky JM HE, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIVnegative homosexual and bisexual men. AIDS 1998;12:495–503. 1998.

137. Nielsen A, Munk C, Kjaer SK. Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978-2008. Int J Cancer. 2012;130(5):1168-73.

138. Alemany L, Saunier M, Alvarado-Cabrero I, Quiros B, Salmeron J, Shin HR, et al. Human papillomavirus DNA prevalence and type distribution in anal carcinomas worldwide. Int J Cancer. 2015;136(1):98-107.

139. Corazziari I QM, Capocaccia R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer 1990 2004; 40 :2307–16. doi:10.1016/j.ejca.2004.07.002. 2004.

140. M.C. Bleeker DAH, P.J. Snijders, S. Horenblas, J. Dillner, C.J. Meijer. Penile cancer: epidemiology, pathogenesis and prevention World J Urol, 27, pp. 141-150. 2009.

141. Ziada M, Bunker CB, Muneer A. Premalignant penile lesions. Journal of Clinical Urology. 2016;9(4):216-22.

142. IARC. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Biological Agents: A Review of Human Carcinogens, vol 100B. International Agency for Research on Cancer, Lyon, France 2009.

143. G. Albero XC, A.R. Giuliano, F.X. Bosch. Male circumcision and genital human papillomavirus: a systematic review and meta-analysis. Sex Transm Dis, 39 , pp. 104-113. 2012.

144. Baldur-Felskov B, Hannibal CG, Munk C, Kjaer SK. Increased incidence of penile cancer and high-grade penile intraepithelial neoplasia in Denmark 1978-2008: a nationwide population-based study. Cancer causes & control : CCC. 2012;23(2):273-80.

145. Alemany L, Cubilla A, Halec G, Kasamatsu E, Quiros B, Masferrer E, et al. Role of Human Papillomavirus in Penile Carcinomas Worldwide. European urology. 2016;69(5):953-61.

146. Aldalwg MAH, Brestovac B. Human Papillomavirus Associated Cancers of the Head and Neck: An Australian Perspective. Head and Neck Pathology. 2017;11(3):377-84.

147. Abogunrin S, Di Tanna GL, Keeping S, Carroll S, Iheanacho I. Prevalence of human papillomavirus in head and neck cancers in European populations: a meta-analysis. BMC cancer. 2014;14:968.

148. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.

149. BÁEz A. Genetic and Environmental Factors in Head and Neck Cancer Genesis. Journal of Environmental Science and Health, Part C. 2008;26(2):174-200.

150. Langevin SM, McClean MD, Michaud DS, Eliot M, Nelson HH, Kelsey KT. Occupational dust exposure and head and neck squamous cell carcinoma risk in a population-based case-control study conducted in the greater Boston area. Cancer medicine. 2013;2(6):978-86.

151. Benson E, Li R, Eisele D, Fakhry C. The clinical impact of HPV tumor status upon head and neck squamous cell carcinomas. Oral oncology. 2014;50(6):565-74.

152. Mountzios G, Psyrri A. Molecular Features and Treatment Modalities of "Classic" Versus Human Papilloma Virus-Associated Head and Neck Cancer. In: Burtness B, Golemis EA, editors. Molecular Determinants of Head and Neck Cancer. New York, NY: Springer New York; 2014. p. 7-21.

153. Palma DA NA. Human papillomavirus in head and neck cancer. Can Med Assoc J. 2014;186(5):370. 2014.

154. Deng Z, Hasegawa M, Kiyuna A, Matayoshi S, Uehara T, Agena S, et al. Viral load, physical status, and E6/E7 mRNA expression of human papillomavirus in head and neck squamous cell carcinoma. Head & neck. 2013;35(6):800-8.

155. Maxwell JH, Grandis JR, Ferris RL. HPV-Associated Head and Neck Cancer: Unique Features of Epidemiology and Clinical Management. Annual review of medicine. 2016;67:91-101.

156. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. The Lancet Oncology. 2010;11(8):781-9.

157. Bose P, Brockton NT, Dort JC. Head and neck cancer: from anatomy to biology. Int J Cancer. 2013;133(9):2013-23.

158. Hocking JS, Stein A, Conway EL, Regan D, Grulich A, Law M, et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. Br J Cancer. 2011;104(5):886-91.

159. Gillison ML AL, Snijders PJ et al Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine. 30(Suppl 5):F34–F54. 2012.

160. Herrero R CX, Pawlita M et al IARC Multicenter Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 95(23):1772–1783. 2003.

161. Holzinger D SM, Dyckhoff G et al Viral RNA patterns and high viral load reliably define oropharynx carcinomas with active HPV16 involvement. Cancer Res 72(19):4993–5003. 2012.

162. Castellsagué X AL, Quer M et al HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. J Natl Cancer Inst 108(6):djv403. 2016.

163. Gillison ML, Koch WM, Capone RB, Spafford M, Westra WH, Wu L, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. Journal of the National Cancer Institute. 2000;92(9):709-20.

164. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. Preventive Medicine. 2011;53(Suppl 1):S5-S11.

165. Hobbs CG, Sterne JA, Bailey M, Heyderman RS, Birchall MA, Thomas SJ. Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2006;31(4):259-66.

166. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005;14(2):467-75.

167. Pytynia KB, Dahlstrom KR, Sturgis EM. Epidemiology of HPV-associated oropharyngeal cancer. Oral oncology. 2014;50(5):380-6.

168. Mena M, Taberna M, Tous S, Marquez S, Clavero O, Quiros B, et al. Double positivity for HPV-DNA/p16ink4a is the biomarker with strongest diagnostic accuracy and prognostic value for human papillomavirus related oropharyngeal cancer patients. Oral oncology. 2018;78:137-44.

169. Viens LJ HS, Watson M, et al. . Human Papillomavirus–Associated Cancers — United States, 2008–2012. MMWR Morb Mortal Wkly Rep 2016;65:661–666. DOI: http://dx.doi.org/10.15585/mmwr.mm6526a1. 2016.

170. Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW, et al. US Assessment of HPV Types in Cancers: Implications for Current and 9-Valent HPV Vaccines. JNCI Journal of the National Cancer Institute. 2015;107(6):djv086.

171. Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsague X, Laporte L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. The Lancet Oncology. 2014;15(12):1319-31.

172. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363(1):24-35.

173. Chaturvedi AK, Engels EA, Pfeiffer RM. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol. 2011;29.

174. Schache AG, Powell NG, Cuschieri KS, Robinson M, Leary S, Mehanna H, et al. HPV-Related Oropharynx Cancer in the United Kingdom: An Evolution in the Understanding of Disease Etiology. Cancer research. 2016;76(22):6598-606.

175. Coughlin AM, Qiu S, Underbrink MP. Management of human papillomavirus-related head and neck cancer. Current problems in dermatology. 2014;45:236-51.

176. Burtness B GE. Overview: the pathobiology of head and neck cancer. New York: Springer. 2014.

177. NICE. National Collaborating Centre for Cancer: Upper aerodigestive tract cancer. Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over. NICE Guideline 36, February 2016. Available at:

https://www.nice.org.uk/guidance/ng36/evidence/full-guideline-pdf-2307980269 Accessed: August 2017. 2016.

178. Ghanem CCT. Cancer of the Oropharynx: Risk Factors, Diagnosis, Treatment, and Outcomes. AHNS Education Committee. American Head & Neck Society. 2017.

179. Fundakowski CE, Lango M. Considerations in surgical versus non-surgical management of HPV positive oropharyngeal cancer. Cancers of the Head & Neck. 2016;1(1):6.

180. Sheahan P. Changing Paradigms for Oropharynx Cancer: Swinging of Pendulum Back Towards Surgery. Irish medical journal. 2015;108(7):197-8.

181. Parsons JT, Mendenhall WM, Stringer SP, Amdur RJ, Hinerman RW, Villaret DB, et al. Squamous cell carcinoma of the oropharynx: surgery, radiation therapy, or both. Cancer. 2002;94(11):2967-80.

182. Haughey BH, Hinni ML, Salassa JR. Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. Head & neck. 2011;33.

183. Weinstein GS, O'Malley BW, Jr., Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma. Archives of otolaryngology--head & neck surgery. 2010;136(11):1079-85.

184. Calais G AM, Bardet E, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Oudinot P, Bertrand P. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 1999; 91:2081. 1999.

185. Denis F GP, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G. . Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004; 22:69-76. 2004.

186. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al. [Stage III and IV cancers of the oropharynx: results of a randomized study of Gortec comparing radiotherapy alone with concomitant chemotherapy]. Bulletin du cancer. 2000;87 Spec No:48-53.

187. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. Journal of the National Cancer Institute. 2008;100(4):261-9.

188. Kostareli E, Holzinger D, Bogatyrova O, Hielscher T, Wichmann G, Keck M, et al. HPV-related methylation signature predicts survival in oropharyngeal squamous cell carcinomas. The Journal of Clinical Investigation. 2013;123(6):2488-501.

189. Kimple RJ, Harari PM. The prognostic value of HPV in head and neck cancer patients undergoing postoperative chemoradiotherapy. Annals of Translational Medicine. 2015;3(Suppl 1):S14.

190. Mirghani H, Blanchard P. Treatment de-escalation for HPV-driven oropharyngeal cancer: Where do we stand? Clinical and Translational Radiation Oncology. 2018;8:4-11.

191. Rischin D, Young RJ, Fisher R, Fox SB, Le QT, Peters LJ, et al. Prognostic significance of p16INK4A and human papillomavirus in patients with oropharyngeal cancer treated on TROG 02.02 phase III trial. J Clin Oncol. 2010;28(27):4142-8.

192. Lassen P, Overgaard J, Eriksen JG. Expression of EGFR and HPV-associated p16 in oropharyngeal carcinoma: correlation and influence on prognosis after radiotherapy in the randomized DAHANCA 5 and 7 trials. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2013;108(3):489-94.

193. Harari PM, Harris J, Kies MS, Myers JN, Jordan RC, Gillison ML, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. J Clin Oncol. 2014;32(23):2486-95.

194. Yanofsky VR, Patel RV, Goldenberg G. Genital Warts: A Comprehensive Review. The Journal of Clinical and Aesthetic Dermatology. 2012;5(6):25-36.

195. C J N Lacey SCW, A Wikstrom and J Ross3. 2011 European Guideline for the Management of Anogenital Warts. IUSTI 2011 GW guidelines V7 130911. Available at: http://www.iusti.org/regions/europe/pdf/2012/Euro_HPV_guidelines.pdf Accessed August 2017. 2011.

196. JD. O. Natural history of genital warts. Br J Vener Dis 1971;47:1–13. 1971.

197. HPSC. Ano-genital warts in Ireland, 2015. Health Protection Surveillance Centre. . 2016.

198. S. Desai SW, S.C. Woodhall, L. Peters, G. Hughes, K. Soldan. Genital warts and cost of care in EnglandSex. Transm. Infect., 87 (2011), pp. 464-468. 2011.

199. A.A. Kraut TS, R. Schulze-Rath, R.T. Mikolajczyk, E. Garbe. Incidence of anogenital warts in Germany: a population-based cohort study BMC Infect. Dis., 10 (2010), p. 360. 2010.

200. Thurgar E, Barton S, Karner C, Edwards SJ. Clinical effectiveness and cost-effectiveness of interventions for the treatment of anogenital warts: systematic review and economic evaluation. Health technology assessment (Winchester, England). 2016;20(24):v-vi, 1-486.

201. BASHH. British Association for Sexual Health and HIV. United Kingdom National Guideline on the Management of Anogenital Warts. 2007. Available at: www.bashh.org/documents/86/86.pdf Accessed August 2017. 2007.

202. Donne AJ, Keltie K, Cole H, Sims AJ, Patrick H, Powell S. Prevalence and management of recurrent respiratory papillomatosis (RRP) in the UK: cross-sectional study. Clinical otolaryngology : official journal of ENT-UK ; official

journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery. 2017;42(1):86-91.

203. NCRI. National Cancer Registry. Cancer in Ireland 1994-2014: Annual Report of the National Cancer Registry. 2016. NCR, Cork. 2016.

204. World Health Organsiation (WHO). Human papillomavirus vaccines: WHO position paper, May 2017 Weekly epidemiological record. . 2017.

205. European Medicines Agency (EMA). Summary of the European public assessment report (EPAR) for Gardasil. 2008.

206. European Medicines Agency (EMA). Summary of the European public assessment report (EPAR) for Gardasil 9

2015.

207. IARC HPV Working Group. Primary end-points for prophylactic HPV vaccine trials: International Agency for Research on Cancer; 2014.

208. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.

209. Cochrane Response. Randomised controlled trials of human papillomavirus (HPV) vaccines: Systematic reviews. WHO Strategic Advisory Group of Experts (SAGE) on Immunization, 2016 June 2016. Report No.

210. D'Addario M, Redmond S, Scott P, Egli-Gany D, Riveros-Balta AX, Restrepo AMH, et al. Two-dose schedules for human papillomavirus vaccine: Systematic review and meta-analysis. Vaccine. 2017;35(22):2892-901.

211. Higgins J, Altman DG. Assessing risk of bias in included studies. Cochrane handbook for systematic reviews of interventions: Cochrane book series. 2008:187-241.

212. WHO Strategic Advisory Group of Experts (SAGE) on Immunization. Guidance for the development of evidence-based vaccination- related recommendations. WHO, 2017 31st January 2017. Report No.: 8.0.

213. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical epidemiology. 2011;64(4):401-6.

214. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. Journal of clinical epidemiology. 2011;64(4):383-94.

215. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ (Clinical research ed). 2008;336(7650):924-6.

216. Deeks JJ, Higgins JP. Statistical algorithms in review manager 5. Statistical Methods Group of The Cochrane Collaboration. 2010:1-11.

217. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine. 2002;21(11):1539-58.

218. Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. Jama. 2013;309(17):1793-802.

219. Ferris D, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Reisinger KS, et al. Long-term study of a quadrivalent human papillomavirus vaccine. Pediatrics. 2014;134(3):e657-65.

220. Ferris DG, Samakoses R, Block SL, Lazcano-Ponce E, Restrepo JA, Mehlsen J, et al. 4-Valent Human Papillomavirus (4vHPV) Vaccine in Preadolescents and Adolescents After 10 Years. Pediatrics. 2017:e20163947.

221. Hernandez-Avila M, Torres-Ibarra L, Stanley M, Salmeron J, Cruz-Valdez A, Munoz N, et al. Evaluation of the immunogenicity of the quadrivalent HPV vaccine using 2 versus 3 doses at month 21: An epidemiological surveillance mechanism for alternate vaccination schemes. Hum Vaccin Immunother. 2016;12(1):30-8.

222. Huh W. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16–26 years: a randomised, double-blind trial. The Lancet. 2017.

223. Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E, Chokephaibulkit K, et al. Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. Jama. 2016;316(22):2411-21.

224. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med. 2015;372(8):711-23.

225. Nygard M, Saah A, Munk C, Tryggvadottir L, Enerly E, Hortlund M, et al. Evaluation of the Long-Term Anti-Human Papillomavirus 6 (HPV6), 11, 16, and 18 Immune Responses Generated by the Quadrivalent HPV Vaccine. Clinical and vaccine immunology : CVI. 2015;22(8):943-8.

226. Vesikari T, Van Damme P, Lindblad N, Pfletschinger U, Radley D, Ryan D, et al. An open-label, randomized, multicenter study of the safety, tolerability, and immunogenicity of quadrivalent human papillomavirus (types 6/11/16/18) vaccine given concomitantly with diphtheria, tetanus, pertussis, and poliomyelitis vaccine in healthy adolescents 11 to 17 years of age. The Pediatric infectious disease journal. 2010;29(4):314-8.

227. Reisinger KS, Block SL, Collins-Ogle M, Marchant C, Catlett M, Radley D, et al. Safety, tolerability, and immunogenicity of gardasil given concomitantly with Menactra and Adacel. Pediatrics. 2010;125(6):1142-51.

228. Kosalaraksa P, Mehlsen J, Vesikari T, Forsten A, Helm K, Van Damme P, et al. An open-label, randomized study of a 9-valent human papillomavirus vaccine given concomitantly with diphtheria, tetanus, pertussis and poliomyelitis vaccines to healthy adolescents 11-15 years of age. The Pediatric infectious disease journal. 2015;34(6):627-34.

229. Schilling A, Parra MM, Gutierrez M, Restrepo J, Ucros S, Herrera T, et al. Coadministration of a 9-Valent Human Papillomavirus Vaccine With Meningococcal and Tdap Vaccines. Pediatrics. 2015;136(3):e563-72.

230. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet (London, England). 2007;369(9576):1861-8.

231. Block SL. Comparison of the Immunogenicity and Reactogenicity of a Prophylactic Quadrivalent Human Papillomavirus (Types 6, 11, 16, and 18) L1 Virus-Like Particle Vaccine in Male and Female Adolescents and Young Adult Women. Paediatrics Volume 118, Number 5, November 2006. 2006.

232. Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. The Journal of infectious diseases. 2009;199(7):926-35.

233. Castellsagué X. Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine 33 (2015) 6892–6901. 2015.

234. Dillner J, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, Hernandez-Avila M, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. Bmj. 2010;341:c3493.

235. Group FIS. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356(19):1915-27.

236. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007;356(19):1928-43.

237. Giuliano AR, Palefsky JM, Goldstone S, Moreira ED, Jr., Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med. 2011;364(5):401-11.

238. Goldstone SE, Jessen H, Palefsky JM, Giuliano AR, Moreira ED, Jr., Vardas E, et al. Quadrivalent HPV vaccine efficacy against disease related to vaccine and non-vaccine HPV types in males. Vaccine. 2013;31(37):3849-55.

239. Hillman RJ, Giuliano AR, Palefsky JM, Goldstone S, Moreira ED, Jr., Vardas E, et al. Immunogenicity of the quadrivalent human papillomavirus (type 6/11/16/18) vaccine in males 16 to 26 years old. Clinical and vaccine immunology : CVI. 2012;19(2):261-7.

240. Joura EA, Leodolter S, Hernandez-Avila M, Wheeler CM, Perez G, Koutsky LA, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. Lancet (London, England). 2007;369(9574):1693-702.

241. Joura EA, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, Hernandez-Avila M, et al. HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine. Vaccine. 2008;26(52):6844-51.

242. Kang S, Kim KH, Kim YT, Kim YT, Kim JH, Song YS, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, placebo-controlled trial in 176 Korean subjects. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2008;18(5):1013-9.

243. Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (Types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. Cancer prevention research (Philadelphia, Pa). 2009;2(10):868-78.

244. Li R, Li Y, Radley D, Liu Y, Huang T, Sings HL, et al. Safety and immunogenicity of a vaccine targeting human papillomavirus types 6, 11, 16 and 18: a randomized, double-blind, placebo-controlled trial in Chinese males and females. Vaccine. 2012;30(28):4284-91.

245. Majewski S, Bosch FX, Dillner J, Iversen OE, Kjaer SK, Munoz N, et al. The impact of a quadrivalent human papillomavirus (types 6, 11, 16, 18) virus-like particle vaccine in European women aged 16 to 24. Journal of the European Academy of Dermatology and Venereology : JEADV. 2009;23(10):1147-55.

246. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. The Pediatric infectious disease journal. 2007;26(3):201-9.

247. Van Damme P, Olsson SE, Block S, Castellsague X, Gray GE, Herrera T, et al. Immunogenicity and Safety of a 9-Valent HPV Vaccine. Pediatrics. 2015;136(1):e28-39.

248. Van Damme P, Meijer CJLM, Kieninger D, Schuyleman A, Thomas S, Luxembourg A, et al. A phase III clinical study to compare the immunogenicity and safety of the 9-valent and quadrivalent HPV vaccines in men. Vaccine. 2016;34(35):4205-12.

249. Vesikari T, Brodszki N, van Damme P, Diez-Domingo J, Icardi G, Petersen LK, et al. A Randomized, Double-Blind, Phase III Study of the Immunogenicity and Safety of a 9-Valent Human Papillomavirus L1 Virus-Like Particle Vaccine (V503) Versus Gardasil(R) in 9-15-Year-Old Girls. The Pediatric infectious disease journal. 2015;34(9):992-8.

250. Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer. 2006;95(11):1459-66.

251. Yoshikawa H, Ebihara K, Tanaka Y, Noda K. Efficacy of quadrivalent human papillomavirus (types 6, 11, 16 and 18) vaccine (GARDASIL) in Japanese women aged 18-26 years. Cancer science. 2013;104(4):465-72.

252. European Medicines Agency (EMA). Note for guidance on the clinical evaluation of vaccines 2009.

253. Herrero R. Human papillomavirus (HPV) vaccines: limited cross-protection against additional HPV types. The Journal of infectious diseases. 2009;199(7):919-22.

254. Arbyn M XL, Simoens C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane database of Systematic Reviews. 2018.

255. Deleré Y, Wichmann O, Klug SJ, van der Sande M, Terhardt M, Zepp F, et al. The efficacy and duration of vaccine protection against human papillomavirus: a systematic review and meta-analysis. Deutsches Ärzteblatt International. 2014;111(35-36):584.

256. Signorelli Cea. Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence. Epidemiol Infect, .Page 1 of 21.

257. Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine. 2012;30:F123-F38.

258. Health Service Executive. Public Information on the Second Level School Immunisation Programme 2017 [updated 23rd November 2017.

259. Noronha AS, Markowitz LE, Dunne EF. Systematic review of human papillomavirus vaccine coadministration. Vaccine. 2014;32(23):2670-4.

260. Ault KA, Joura EA, Kjaer SK, Iversen OE, Wheeler CM, Perez G, et al. Adenocarcinoma in situ and associated human papillomavirus type distribution observed in two clinical trials of a quadrivalent human papillomavirus vaccine. Int J Cancer. 2011;128(6):1344-53.

261. Barr E, Gause CK, Bautista OM, Railkar RA, Lupinacci LC, Insinga RP, et al. Impact of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like particle vaccine in a sexually active population of North American women. American journal of obstetrics and gynecology. 2008;198(3):261.e1-11.

262. Draper E, Bissett SL, Howell-Jones R, Waight P, Soldan K, Jit M, et al. A randomized, observer-blinded immunogenicity trial of Cervarix((R)) and Gardasil((R)) Human Papillomavirus vaccines in 12-15 year old girls. PLoS One. 2013;8(5):e61825.

263. Einstein MH, Baron M, Levin MJ, Chatterjee A, Edwards RP, Zepp F, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18-45 years. Human vaccines. 2009;5(10):705-19.

264. Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18

vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12-24 in a Phase III randomized study of healthy women aged 18-45 years. Human vaccines. 2011;7(12):1343-58.

265. Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18-45 years. Human vaccines. 2011;7(12):1359-73.

266. Einstein MH, Levin MJ, Chatterjee A, Chakhtoura N, Takacs P, Catteau G, et al. Comparative humoral and cellular immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: follow-up through Month 48 in a Phase III randomized study. Hum Vaccin Immunother. 2014;10(12):3455-65.

267. Einstein MH, Takacs P, Chatterjee A, Sperling RS, Chakhtoura N, Blatter MM, et al. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: end-of-study analysis of a Phase III randomized trial. Hum Vaccin Immunother. 2014;10(12):3435-45.

268. Group FIS. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. The Journal of infectious diseases. 2007;196(10):1438-46.

269. Garland SM, Cheung TH, McNeill S, Petersen LK, Romaguera J, Vazquez-Narvaez J, et al. Safety and immunogenicity of a 9-valent HPV vaccine in females 12-26 years of age who previously received the quadrivalent HPV vaccine. Vaccine. 2015;33(48):6855-64.

270. Gilca V, Sauvageau C, Boulianne N, De Serres G, Crajden M, Ouakki M, et al. The effect of a booster dose of quadrivalent or bivalent HPV vaccine when administered to girls previously vaccinated with two doses of quadrivalent HPV vaccine. Hum Vaccin Immunother. 2015;11(3):732-8.

271. Joura EA, Garland SM, Paavonen J, Ferris DG, Perez G, Ault KA, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. Bmj. 2012;344:e1401.

272. Joura EA. Clinical efficacy and immunogenicity of the nonavalent HPV Vaccine. Acta Cytologica. 2016;60:35-6.

273. Krajden M, Cook D, Yu A, Chow R, Mei W, McNeil S, et al. Human papillomavirus 16 (HPV 16) and HPV 18 antibody responses measured by pseudovirus neutralization and competitive Luminex assays in a two- versus three-dose HPV vaccine trial. Clinical and vaccine immunology : CVI. 2011;18(3):418-23.

274. Krajden M, Cook D, Yu A, Chow R, Su Q, Mei W, et al. Assessment of HPV 16 and HPV 18 antibody responses by pseudovirus neutralization, Merck cLIA and Merck total IgG LIA immunoassays in a reduced dosage quadrivalent HPV vaccine trial. Vaccine. 2014;32(5):624-30.

275. Leung TF, Liu AP, Lim FS, Thollot F, Oh HM, Lee BW, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9-14 years: Results to month 12 from a randomized trial. Hum Vaccin Immunother. 2015;11(7):1689-702.

276. Luna J, Plata M, Gonzalez M, Correa A, Maldonado I, Nossa C, et al. Long-term follow-up observation of the safety, immunogenicity, and effectiveness of Gardasil in adult women. PLoS One. 2013;8(12):e83431.

277. Luxembourg A, Moreira ED, Jr., Samakoses R, Kim KH, Sun X, Maansson R, et al. Phase III, randomized controlled trial in girls 9-15 years old to evaluate lot consistency of a novel nine-valent human papillomavirus L1 virus-like particle vaccine. Hum Vaccin Immunother. 2015;11(6):1306-12.

278. Luxembourg A, Brown D, Bouchard C, Giuliano AR, Iversen OE, Joura EA, et al. Phase II studies to select the formulation of a multivalent HPV L1 virus-like particle (VLP) vaccine. Hum Vaccin Immunother. 2015;11(6):1313-22.

279. Munoz N, Manalastas R, Jr., Pitisuttithum P, Tresukosol D, Monsonego J, Ault K, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine in women aged 24-45 years: a randomised, double-blind trial. Lancet (London, England). 2009;373(9679):1949-57.

280. Ogilvie G, Sauvageau C, Dionne M, McNeil S, Krajden M, Money D, et al. Immunogenicity of 2 vs 3 Doses of the Quadrivalent Human Papillomavirus Vaccine in Girls Aged 9 to 13 Years After 60 Months. Jama. 2017;317(16):1687-8.

281. Olsson SE, Villa LL, Costa RL, Petta CA, Andrade RP, Malm C, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine. 2007;25(26):4931-9.

282. Olsson SE, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Human vaccines. 2009;5(10):696-704.

283. Paavonen J. Efficacy of a prophylactic human papillomavirus vaccine against high-grade vulval and vaginal intraepithelial neoplasia. Therapy. 2008;5(3):325-8.

284. Palefsky JM, Giuliano AR, Goldstone S, Moreira ED, Jr., Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576-85.

285. Perez G, Lazcano-Ponce E, Hernandez-Avila M, Garcia PJ, Munoz N, Villa LL, et al. Safety, immunogenicity, and efficacy of quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 virus-like-particle vaccine in Latin American women. Int J Cancer. 2008;122(6):1311-8.

286. Petersen LK. Impact of baseline covariates on the immunogenicity of the 9-valent HPV vaccine – A combined analysis of five phase III clinical trials. Papillomavirus Research 3 (2017) 105–115. 2017.

287. Sankaranarayanan R, Prabhu PR, Pawlita M, Gheit T, Bhatla N, Muwonge R, et al. Immunogenicity and HPV infection after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre prospective cohort study. The Lancet Oncology. 2016;17(1):67-77.

288. Villa LL. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005; 6: 271–78. 2005.

289. Wheeler CM, Bautista OM, Tomassini JE, Nelson M, Sattler CA, Barr E. Safety and immunogenicity of co-administered quadrivalent human papillomavirus (HPV)-6/11/16/18 L1 virus-like particle (VLP) and hepatitis B (HBV) vaccines. Vaccine. 2008;26(5):686-96.

290. Wheeler CM, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. The Journal of infectious diseases. 2009;199(7):936-44.

291. Merck Sharpe & Dohme. A Phase III Study of a 2-dose Regimen of a Multivalent Human Papillomavirus (HPV) Vaccine (V503), Administered to 9 to 14 Year-olds and Compared to Young Women, 16 to 26 Years Old. Protocol V503-010. 2016.

292. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358.

293. WHO. World Health Organization Guidance For The Development Of Evidence-Based Vaccinationrelated Recommendations. Available at: http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf Accessed May 2018. 31 January 2017.

294. PRISMA. Transparent Reporting of SYSTEMATIC REVIEWS and META-ANALYSES. Available at: http://www.prisma-statement.org/. 2018.

295. Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. The Lancet Infectious diseases. 2015;15(5):565-80.

296. Cummings T, Zimet GD, Brown D, Tu W, Yang Z, Fortenberry JD, et al. Reduction of HPV infections through vaccination among at-risk urban adolescents. Vaccine. 2012;30(37):5496-9.

297. Tabrizi SN, Brotherton JM, Kaldor JM, Skinner SR, Cummins E, Liu B, et al. Fall in human papillomavirus prevalence following a national vaccination program. The Journal of infectious diseases. 2012;206(11):1645-51.

298. Chow EPF, Danielewski JA, Fehler G, Tabrizi SN, Law MG, Bradshaw CS, et al. Human papillomavirus in young women with Chlamydia trachomatis infection 7 years after the Australian human papillomavirus vaccination programme: A cross-sectional study. The Lancet Infectious Diseases. 2015;15(11):1314-23.

299. Chow EPF, Machalek DA, Tabrizi SN, Danielewski JA, Fehler G, Bradshaw CS, et al. Quadrivalent vaccine-targeted human papillomavirus genotypes in heterosexual men after the Australian female human papillomavirus vaccination programme: a retrospective observational study. The Lancet Infectious Diseases. 2017;17(1):68-77.

300. Cameron RL, Kavanagh K, Pan J, Love J, Cuschieri K, Robertson C, et al. Human papillomavirus prevalence and herd immunity after introduction of vaccination program, Scotland, 2009–2013. Emerging Infectious Diseases. 2016;22(1):56-64.

301. Kahn JA, Brown DR, Ding L, Widdice LE, Shew ML, Glynn S, et al. Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. Pediatrics. 2012;130(2):e249-56.

302. Kahn JA, Widdice LE, Ding L, Huang B, Brown DR, Franco EL, et al. Substantial Decline in Vaccine-Type Human Papillomavirus (HPV) among Vaccinated Young Women during the First 8 Years after HPV Vaccine Introduction in a Community. Clinical Infectious Diseases. 2016;63(10):1281-7.

303. Mesher D, Panwar K, Thomas SL, Beddows S, Soldan K. Continuing reductions in HPV 16/18 in a population with high coverage of bivalent HPV vaccination in England: An ongoing cross-sectional study. BMJ Open. 2016;6(2).

304. Sonnenberg P, Clifton S, Beddows S, Field N, Soldan K, Tanton C, et al. Prevalence, risk factors, and uptake of interventions for sexually transmitted infections in Britain: findings from the National Surveys of Sexual Attitudes and Lifestyles (Natsal). Lancet (London, England). 2013;382(9907):1795-806.

305. Tanton C, Mesher D, Beddows S, Soldan K, Clifton S, Panwar K, et al. Human papillomavirus (HPV) in young women in Britain: Population-based evidence of the effectiveness of the bivalent immunisation programme and burden of quadrivalent and 9-valent vaccine types. Papillomavirus research (Amsterdam, Netherlands). 2017;3:36-41.

306. Mesher D, Soldan K, Howell-Jones R, Panwar K, Manyenga P, Jit M, et al. Reduction in HPV 16/18 prevalence in sexually active young women following the introduction of HPV immunisation in England. Vaccine. 2013;32(1):26-32.

307. Markowitz LE LG, Hariri S, Steinau M, Dunne EF, Unger ER. . Prevalence of HPV After Introduction of the Vaccination Program in the United States. Pediatrics 2016; 137(3): e20151968. . 2016.

308. Markowitz LE, Hariri S, Lin C, Dunne EF, Steinau M, McQuillan G, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. The Journal of infectious diseases. 2013;208(3):385-93.

309. Kavanagh K, Pollock KG, Potts A, Love J, Cuschieri K, Cubie H, et al. Introduction and sustained high coverage of the HPV bivalent vaccine leads to a reduction in prevalence of HPV 16/18 and closely related HPV types. Br J Cancer. 2014;110(11):2804-11.

310. Dunne EF, Naleway A, Smith N, Crane B, Weinmann S, Braxton J, et al. Reduction in human papillomavirus vaccine type prevalence among young women screened for cervical cancer in an integrated US healthcare delivery system in 2007 and 2012-2013. Journal of Infectious Diseases. 2015;212(12):1970-5.

311. Söderlund-Strand A, Uhnoo I, Dillner J. Change in population prevalences of human papillomavirus after initiation of vaccination: The high-throughput HPV monitoring study. Cancer Epidemiology Biomarkers and Prevention. 2014;23(12):2757-64.

312. Wilson AR, Welch RJ, Hashibe M, Greenwood J, Jackson B, She RC. Surveillance of human papilloma virus using reference laboratory data for the purpose of evaluating vaccine impact. Online journal of public health informatics. 2014;6(3):e194.

313. Tabrizi SN, Brotherton JML, Kaldor JM, Skinner SR, Liu B, Bateson D, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: A repeat cross-sectional study. The Lancet Infectious Diseases. 2014;14(10):958-66.

314. Ali H, Donovan B, Wand H, Read TR, Regan DG, Grulich AE, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. Bmj. 2013;346:f2032.

315. Baandrup L, Blomberg M, Dehlendorff C, Sand C, Andersen KK, Kjaer SK. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. Sexually transmitted diseases. 2013;40(2):130-5.

316. Bauer HM, Wright G, Chow J. Evidence of human papillomavirus vaccine effectiveness in reducing genital warts: an analysis of California public family planning administrative claims data, 2007-2010. American journal of public health. 2012;102(5):833-5.

317. Bollerup S, Baldur-Felskov B, Blomberg M, Baandrup L, Dehlendorff C, Kjaer SK. Significant reduction in the incidence of genital warts in young men 5 years into the danish human papillomavirus vaccination program for girls and women. Sexually transmitted diseases. 2016;43(4):238-42.

318. Chow EP, Read TR, Wigan R, Donovan B, Chen MY, Bradshaw CS, et al. Ongoing decline in genital warts among young heterosexuals 7 years after the Australian human papillomavirus (HPV) vaccination programme. Sexually transmitted infections. 2015;91(3):214-9.

319. Dominiak-Felden G, Gobbo C, Simondon F. Evaluating the early benefit of quadrivalent HPV vaccine on genital warts in Belgium: A cohort study. PLoS ONE. 2015;10(7).

320. Flagg EW, Schwartz R, Weinstock H. Prevalence of anogenital warts among participants in private health plans in the United States, 2003-2010: potential impact of human papillomavirus vaccination. American journal of public health. 2013;103(8):1428-35.

321. Guerra FM, Rosella LC, Dunn S, Wilson SE, Chen C, Deeks SL. Early impact of Ontario's human papillomavirus (HPV) vaccination program on anogenital warts (AGWs): A population-based assessment. 2016;34(39):4678-83.

322. Harrison C, Britt H, Garland S, Conway L, Stein A, Pirotta M, et al. Decreased management of genital warts in young women in Australian general practice post introduction of national HPV vaccination program: results from a nationally representative cross-sectional general practice study. PLoS One. 2014;9(9):e105967.

323. Howell-Jones R, Soldan K, Wetten S, Mesher D, Williams T, Gill ON, et al. Declining genital Warts in young women in england associated with HPV 16/18 vaccination: an ecological study. The Journal of infectious diseases. 2013;208(9):1397-403.

324. Leval A, Herweijer E, Arnheim-Dahlstrom L, Walum H, Frans E, Sparen P, et al. Incidence of genital warts in Sweden before and after quadrivalent human papillomavirus vaccine availability. The Journal of infectious diseases. 2012;206(6):860-6.

325. Liu B, Donovan B, Brotherton JM, Saville M, Kaldor JM. Genital warts and chlamydia in Australian women: comparison of national population-based surveys in 2001 and 2011. Sexually transmitted infections. 2014;90(7):532-7.

326. Lurie S, Mizrachi Y, Chodick G, Katz R, Schejter E. Impact of quadrivalent human papillomavirus vaccine on genital warts in an opportunistic vaccination structure. Gynecologic Oncology. 2017;146(2):299-304.

327. Mikolajczyk RT, Kraut AA, Horn J, Schulze-Rath R, Garbe E. Changes in incidence of anogenital warts diagnoses after the introduction of human papillomavirus vaccination in Germany-an ecologic study. Sexually transmitted diseases. 2013;40(1):28-31.

328. Sando N, Kofoed K, Zachariae C, Fouchard J. A reduced national incidence of anogenital warts in young Danish men and women after introduction of a national quadrivalent human papillomavirus vaccination programme for young women--an ecological study. Acta dermato-venereologica. 2014;94(3):288-92.

329. Smith MA, Liu B, McIntyre P, Menzies R, Dey A, Canfell K. Fall in genital warts diagnoses in the general and indigenous Australian population following implementation of a national human papillomavirus vaccination program: analysis of routinely collected national hospital data. The Journal of infectious diseases. 2015;211(1):91-9.

330. Ogilvie GS, Naus M, Money DM, Dobson SR, Miller D, Krajden M, et al. Reduction in cervical intraepithelial neoplasia in young women in British Columbia after introduction of the HPV vaccine: An ecological analysis. International Journal of Cancer. 2015;137(8):1931-7.

331. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. Lancet (London, England). 2011;377(9783):2085-92.

332. Baldur-Felskov B, Dehlendorff C, Junge J, Munk C, Kjaer SK. Incidence of cervical lesions in Danish women before and after implementation of a national HPV vaccination program. Cancer Causes and Control. 2014;25(7):915-22.

333. Baldur-Felskov B, Munk C, Nielsen TS, Dehlendorff C, Kirschner B, Junge J, et al. Trends in the incidence of cervical cancer and severe precancerous lesions in Denmark, 1997-2012. Cancer causes & control : CCC. 2015;26(8):1105-16.

334. Mori S, Nakao S, Kukimoto I, Kusumoto-Matsuo R, Kondo K, Kanda T. Biased amplification of human papillomavirus DNA in specimens containing multiple human papillomavirus types by PCR with consensus primers. Cancer science. 2011;102(6):1223-7.

335. Tota JE, Ramanakumar AV, Villa LL, Richardson H, Burchell AN, Koushik A, et al. Evaluation of Human Papillomavirus Type Replacement Post-vaccination Must Account for Diagnostic Artifacts: Masking of HPV52 by HPV16 in Anogenital Specimens. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2015;24(1):286-90.

336. Pagliusi SR, Teresa Aguado M. Efficacy and other milestones for human papillomavirus vaccine introduction. Vaccine. 2004;23(5):569-78.

337. Statement on human papillomavirus vaccine. An Advisory Committee Statement (ACS). Canada communicable disease report = Releve des maladies transmissibles au Canada. 2007;33(Acs-2):1-31.

338. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. The Journal of infectious diseases. 2010;202(12):1789-99.

339. Wellings K, Collumbien M, Slaymaker E, Singh S, Hodges Z, Patel D, et al. Sexual behaviour in context: a global perspective. Lancet (London, England). 2006;368(9548):1706-28.

340. Adler DH, Kakinami L, Modisenyane T, Tshabangu N, Mohapi L, De Bruyn G, et al. Increased regression and decreased incidence of human papillomavirus-related cervical lesions among HIV-infected women on HAART. AIDS (London, England). 2012;26(13):1645-52.

341. WHO. Causality assessment of an adverse event following immunisation (AEFI): user manual for the revised WHO classification. World Health Organization. Geneva: WHO; January 2018. Available at: http://www.who.int/vaccine_safety/publications/gvs_aefi/en/. Accessed May 2018.

342. Smith V, Devane D, Begley CM, Clarke M. Methodology in conducting a systematic review of systematic reviews of healthcare interventions. BMC Medical Research Methodology. 2011;11(1):15.

343. Oxman LABaAD. Chapter 22: Overviews of reviews. The Cochrane Handbook. Available at: http://handbook-5-1.cochrane.org/chapter_22/22_overviews_of_reviews.htm. Accessed April 2018.

344. Guyatt GH OA, Schunemann HJ, Tugwell P, Knottnerus A. . GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011; 64(4): pp.380-2.

345. Golder S, Loke Y. Search strategies to identify information on adverse effects: a systematic review. Journal of the Medical Library Association : JMLA. 2009;97(2):84-92.

346. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLOS Medicine. 2009;6(7):e1000100.

347. Arbyn M, Xu L, Simoens C, Martin-Hirsch PPL. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors. Cochrane Database of Systematic Reviews. 2018(5).

348. Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: A systematic review of randomized controlled trials. CMAJ. 2007;177(5):469-79.

349. Setiawan D, Luttjeboer J, Pouwels KB, Wilschut JC, Postma MJ. Immunogenicity and safety of human papillomavirus (HPV) vaccination in Asian populations from six countries: A meta-analysis. Japanese Journal of Clinical Oncology. 2017;47(3):265-76.

350. Medeiros LR, Rosa DD, Da Rosa MI, Bozzetti MC, Zanini RR. Efficacy of human papillomavirus vaccines a systematic quantitative review. International Journal of Gynecological Cancer. 2009;19(7):1166-76.

351. Ogawa Y, Takei H, Ogawa R, Mihara K. Safety of human papillomavirus vaccines in healthy young women: a meta-analysis of 24 controlled studies. Journal of pharmaceutical health care and sciences. 2017;3:18.

352. Coelho PLS, Da Silva Calestini GL, Alvo FS, De Moura Freitas JM, Castro PMV, Konstantyner T. Safety of human papillomavirus 6, 11, 16 and 18 (recombinant): Systematic review and meta-analysis. Revista Paulista de Pediatria. 2015;33(4):474-82.

353. Costa APF, Cobucci RNO, Da Silva JM, Da Costa Lima PH, Giraldo PC, Gonçalves AK. Safety of human papillomavirus 9-valent vaccine: A meta-analysis of randomized trials. Journal of Immunology Research. 2017;2017.

354. Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among

Women: A Systematic Review & Meta-Analysis. BMC Infectious Diseases. 2011;11.

355. Meggiolaro A, Migliara G, La Torre G. Association between Human Papilloma Virus (HPV) vaccination and risk of Multiple Sclerosis: A systematic review. Hum Vaccin Immunother. 2018:1-9.

356. Jacqueline Parsons PTM, Prof Michael Gold. Serious adverse events associated with HPV vaccination. Adelaide Health Technology Assessment, University of Adelaide. 2017.

357. Group GW. Grading quality of evidence and strength of recommendations. BMJ : British Medical Journal. 2004;328(7454):1490-.

358. Viswanathan M BN, Dryden DM, et al. . Assessing Risk of Bias and Confounding in Observational Studies of Interventions or Exposures: Further Development of the RTI Item Bank [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Aug. Appendix C, Item Bank for Assessing Risk of Bias and Confounding for Observational Studies of Interventions or Exposures. Available from: https://www.ncbi.nlm.nih.gov/books/NBK154460/. 2013.

359. Arnheim-Dahlström L, Pasternak B, Svanström H, Sparén P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ : British Medical Journal. 2013;347.

360. Scheller NM, Svanstrom H, Pasternak B, Arnheim-Dahlstrom L, Sundstrom K, Fink K, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. Jama. 2015;313(1):54-61.

361. Schurink-Van't Klooster TM, de Ridder MA, Kemmeren JM, van der Lei J, Dekker F, Sturkenboom M, et al. Examining a possible association between human papilloma virus (HPV) vaccination and migraine: results of a cohort study in the Netherlands. European journal of pediatrics. 2015;174(5):641-9.

362. Gee J, Naleway A, Shui I, Baggs J, Yin R, Li R, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine. 2011;29(46):8279-84.

363. Chao C, Klein NP, Velicer CM, Sy LS, Slezak JM, Takhar H, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. Journal of internal medicine. 2012;271(2):193-203.

364. Willame C, Rosillon D, Zima J, Angelo MG, Stuurman AL, Vroling H, et al. Risk of new onset autoimmune disease in 9- to 25-year-old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. Hum Vaccin Immunother. 2016;12(11):2862-71.

365. NIO. National Immunisation News: The Newsletter of the HSE National Immunisation Office, March 2018. Available at:

https://www.hse.ie/eng/health/immunisation/infomaterials/newsletter/newsletter28.pdf. Accessed 31 May 2018. 2018.

366. MHRA. MHRA PUBLIC ASSESSMENT REPORT Cervarix (HPV vaccine): Update on UK safety covering the first two years of the HPV immunisation programme. October 2010.

367. WHO. World Health Organization. Weekly epidemiological record. Nos. 28/29, 2007, 82, 245–260. Available at: http://www.who.int/wer.

368. WHO. World Health Organization. Weekly epidemiological record. No. 5, 2009, pp. 37–40. Available at: http://www.who.int/wer.

369. WHO. World Health Organization. Weekly epidemiological record. No. 32, 2009, pp. 325–332. Available at: http://www.who.int/wer.

370. WHO. World Health Organization. Weekly epidemiological record. No. 29, 2013, pp. 301–312. Available at: http://www.who.int/wer.

371. WHO. World Health Organization. Weekly epidemiological record. No. 7, 2014, pp. 53–60. Available at: http://www.who.int/wer.

372. WHO. World Health Organization. Weekly epidemiological record. No. 3, 2016, pp. 21–32. Available at: http://www.who.int/wer.

373. WHO. World Health Organisation. Weekly Epidemiological Record, 14 July 2017, vol. 92, 28 (pp. 393–404). Available at: http://www.who.int/wer/2017/wer9228/en/.

374. Andrews N, Stowe J, Miller E. No increased risk of Guillain-Barre syndrome after human papilloma virus vaccine: A self-controlled case-series study in England. Vaccine. 2017;35(13):1729-32.

375. Flagg EW, Torrone E, Weinstock H. Prevalence of low-and high-grade cervical intraepithelial lesions among female participants in private health plans in the United States, 2007-2013: Ecologic evidence of population effectiveness of human papillomavirus vaccination. Sexually transmitted infections. 2015;91:A167-A8.

376. Sukumaran L. Advisory Committee on Immunization Practices - Immunization Safety Office - Centers for Disease Control and Prevention (CDC, Atlanta). Human Papillomavirus Vaccine Safety Update. 2015.

377. Gee J, Sukumaran L, Weintraub E. Risk of Guillain-Barre Syndrome following quadrivalent human papillomavirus vaccine in the Vaccine Safety Datalink. Vaccine. 2017;35(43):5756-8.

378. Grimaldi-Bensouda L, Guillemot D, Godeau B, Benichou J, Lebrun-Frenay C, Papeix C, et al. Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. Journal of internal medicine. 2014;275(4):398-408.

379. Ojha RP, Jackson BE, Tota JE, Offutt-Powell TN, Singh KP, Bae S. Guillain-Barre syndrome following quadrivalent human papillomavirus vaccination among vaccine-eligible individuals in the United States. Hum Vaccin Immunother. 2014;10(1):232-7.

380. Vichnin M, Bonanni P, Klein NP, Garland SM, Block SL, Kjaer SK, et al. An Overview of Quadrivalent Human Papillomavirus Vaccine Safety: 2006 to 2015. The Pediatric infectious disease journal. 2015;34(9):983-91.

381. EMA. HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS. 20 November 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/11/WC500196762.pdf. Accessed May 2018. 2015.

382. Donegan K, Beau-Lejdstrom R, King B, Seabroke S, Thomson A, Bryan P. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine. 2013;31(43):4961-7.

383. Bonde U, Joergensen JS, Lamont RF, Mogensen O. Is HPV vaccination in pregnancy safe? Human Vaccines & Immunotherapeutics. 2016;12(8):1960-4.

384. Scheller NM, Pasternak B, Molgaard-Nielsen D, Svanstrom H, Hviid A. Quadrivalent HPV Vaccination and the Risk of Adverse Pregnancy Outcomes. N Engl J Med. 2017;376(13):1223-33.

385. EMA. European Medicines Agency. European public assessment report (EPAR) for Gardasil. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000703/human_med_000805.jsp&mid=WC0b01ac058001d124. Accessed May 2018.

386. Mølbak K, Hansen ND, Valentiner-Branth P. Pre-Vaccination Care-Seeking in Females Reporting Severe Adverse Reactions to HPV Vaccine. A Registry Based Case-Control Study. PLOS ONE. 2016;11(9):e0162520.

387. Skufca J, Ollgren J, Ruokokoski E, Lyytikainen O, Nohynek H. Incidence rates of Guillain Barre (GBS), chronic fatigue/systemic exertion intolerance disease (CFS/SEID) and postural orthostatic tachycardia syndrome (POTS) prior to introduction of human papilloma virus (HPV) vaccination among adolescent girls in Finland, 2002-2012. Papillomavirus research (Amsterdam, Netherlands). 2017;3:91-6.

388. Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. Jama. 2009;302(7):750-7.

389. Naleway AL, Crane B, Smith N, Daley MF, Donahue J, Gee J, et al. Absence of venous thromboembolism risk following quadrivalent human papillomavirus vaccination, Vaccine Safety Datalink, 2008-2011. Vaccine. 2016;34(1):167-71.

390. Scheller N, Pasternak B, Svanström H, Hviid A. Quadrivalent human papillomavirus vaccine and the risk of venous thromboembolism. Jama. 2014;312(2):187-8.

391. Macartney KK, Chiu C, Georgousakis M, Brotherton JM. Safety of human papillomavirus vaccines: a review. Drug safety. 2013;36(6):393-412.

392. Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of Human Papillomavirus Vaccines: An Updated Review. Drug safety. 2018;41(4):329-46.

393. Joura EA, Giuliano AR, Iversen O-E, Bouchard C, Mao C, Mehlsen J, et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. New England Journal of Medicine. 2015;372(8):711-23.

394. Moreira ED, Jr., Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, et al. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. Pediatrics. 2016;138(2).

395. Gee J, Weinbaum C, Sukumaran L, Markowitz LE. Quadrivalent HPV vaccine safety review and safety monitoring plans for nine-valent HPV vaccine in the United States. Hum Vaccin Immunother. 2016;12(6):1406-17.

396. Verstraeten T, Descamps D, David MP, Zahaf T, Hardt K, Izurieta P, et al. Analysis of adverse events of potential autoimmune aetiology in a large integrated safety database of AS04 adjuvanted vaccines. Vaccine. 2008;26(51):6630-8.

397. Angelo MG, David MP, Zima J, Baril L, Dubin G, Arellano F, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. Pharmacoepidemiology and drug safety. 2014;23(5):466-79.

398. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(1):10.

399. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. Journal of Clinical Epidemiology. 2009;62(10):1013-20.

400. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health technology assessment (Winchester, England). 2004;8(36):iii-iv, ix-xi, 1-158.

401. Jaime Caro J, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, et al. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014;17(2):174-82.

402. Brisson M, Laprise JF, Chesson HW, Drolet M, Malagon T, Boily MC, et al. Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. Journal of the National Cancer Institute [Internet]. 2016; 108(1) (no pagination). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/574/CN-01141574/frame.html.

403. Burger EA, Sy S, Nygard M, Kristiansen IS, Kim JJ. Prevention of HPV-related cancers in Norway: cost-effectiveness of expanding the HPV vaccination program to include pre-adolescent boys. PLoS One. 2014;9(3):e89974.

404. Chanthavilay P, Reinharz D, Mayxay M, Phongsavan K, Marsden DE, Moore L, et al. The economic evaluation of human papillomavirus vaccination strategies against cervical cancer in women in Lao PDR: a mathematical modelling approach. BMC health services research. 2016;16(1):418.

405. Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The cost-effectiveness of male HPV vaccination in the United States. Vaccine. 2011;29(46):8443-50.

406. Damm O, Horn J, Ultsch B, Scholz S, Mikolajczyk R, Wiese-Posselt M, et al. Cost-effectiveness of additional vaccination of boys against HPV in Germany. Value in Health. 2017;20(9):A411.

407. Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. Vaccine. 2010;28(42):6858-67.

408. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis. 2007;13(1):28-41.

409. Elbasha EH, Dasbach EJ, Insinga RP. A multi-type HPV transmission model. Bulletin of mathematical biology. 2008;70(8):2126-76.

410. Graham DM, Isaranuwatchai W, Habbous S, de Oliveira C, Liu G, Siu LL, et al. A cost-effectiveness analysis of human papillomavirus vaccination of boys for the prevention of oropharyngeal cancer. Cancer. 2015;121(11):1785-92.

411. Haeussler K, Marcellusi A, Mennini FS, Favato G, Picardo M, Garganese G, et al. Cost-Effectiveness Analysis of Universal Human Papillomavirus Vaccination Using a Dynamic Bayesian Methodology: The BEST II Study. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2015;18(8):956-68.

412. Insinga RP, Dasbach EJ, Elbasha EH, Puig A, Reynales-Shigematsu LM. Cost-effectiveness of quadrivalent human papillomavirus (HPV) vaccination in Mexico: a transmission dynamic model-based evaluation. Vaccine. 2007;26(1):128-39.

413. Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. Bmj. 2008;337:a769.

414. Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. Br J Cancer. 2007;97(9):1322-8.

415. Kim JJ, Goldie SJ. Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States. Bmj. 2009;339:b3884.

416. Kotsopoulos N, Connolly MP, Remy V. Quantifying the broader economic consequences of quadrivalent human papillomavirus (HPV) vaccination in Germany applying a government perspective framework. Health economics review. 2015;5(1):54.

417. Kulasingam S, Connelly L, Conway E, Hocking JS, Myers E, Regan DG, et al. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the

Australian National Cervical Cancer Screening Program. Sexual health. 2007;4(3):165-75.

418. Laprise JF, Drolet M, Boily MC, Jit M, Sauvageau C, Franco EL, et al. Comparing the cost-effectiveness of two- and three-dose schedules of human papillomavirus vaccination: a transmission-dynamic modelling study. Vaccine. 2014;32(44):5845-53.

419. Largeron N, Petry KU, Jacob J, Bianic F, Anger D, Uhart M. An estimate of the public health impact and cost-effectiveness of universal vaccination with a 9-valent HPV vaccine in Germany. Expert review of pharmacoeconomics & outcomes research. 2017;17(1):85-98.

420. Mennini FS, Bonanni P, Bianic F, de Waure C, Baio G, Plazzotta G, et al. Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. Cost effectiveness and resource allocation : C/E. 2017;15:11.

421. Olsen J, Jepsen MR. Human papillomavirus transmission and cost-effectiveness of introducing quadrivalent HPV vaccination in Denmark. International journal of technology assessment in health care. 2010;26(2):183-91.

422. Olsen J, Jørgensen TR. Revisiting the cost-effectiveness of universal HPV-vaccination in Denmark accounting for all potentially vaccine preventable HPV-related diseases in males and females. Cost Effectiveness and Resource Allocation. 2015;13(1).

423. Pearson AL, Kvizhinadze G, Wilson N, Smith M, Canfell K, Blakely T. Is expanding HPV vaccination programs to include school-aged boys likely to be value-for-money: a cost-utility analysis in a country with an existing school-girl program. BMC Infect Dis. 2014;14:351.

424. Qendri V, Bogaards JA, Berkhof J. Health and Economic Impact of a Tender-Based, Sex-Neutral Human Papillomavirus 16/18 Vaccination Program in the Netherlands. Journal of Infectious Diseases. 2017;216(2):210-9.

425. Sharma M, Sy S, Kim JJ. The value of male human papillomavirus vaccination in preventing cervical cancer and genital warts in a low-resource setting. BJOG : an international journal of obstetrics and gynaecology. 2016;123(6):917-26.

426. Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis. 2004;10(11):1915-23.

427. Tay SK, Hsu TY, Shcheprov A, Walia A, Kulkarni AS. The clinical and economic benefits of school-based quadrivalent HPV vaccination in Singapore. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2017.

428. Zechmeister I, Blasio BF, Garnett G, Neilson AR, Siebert U. Cost-effectiveness analysis of human papillomavirus-vaccination programs to prevent cervical cancer in Austria. Vaccine. 2009;27(37):5133-41.

429. Jimenez E, Torkilseng EB, Klemp M. Cost-Effectiveness of HPV-Vaccination of Boys Aged 12 in a Norwegian Setting. Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)

430. Wolff E, Public Health Agency of Sweden. Health economic evaluation of universal HPV vaccination within the Swedish national vaccination programme for children. Sweden: Public Health Agency of Sweden, 2017.

431. Ben Hadj Yahia MB, Jouin-Bortolotti A, Dervaux B. Extending the Human Papillomavirus Vaccination Programme to Include Males in High-Income Countries: A Systematic Review of the Cost-Effectiveness Studies. Clinical drug investigation. 2015;35(8):471-85.

432. Brisson M, Van de Velde N, Boily MC. Economic evaluation of human papillomavirus vaccination in developed countries. Public health genomics. 2009;12(5-6):343-51.

433. CADTH. HPV vaccination in men: review of clinical effectiveness, cost effectiveness and guidelines. Canada: 2017.

434. Favato G, Easton T, Vecchiato R, Noikokyris E. Ecological validity of cost-effectiveness models of universal HPV vaccination: A systematic literature review. Vaccine. 2017.

435. Fesenfeld M, Hutubessy R, Jit M. Cost-effectiveness of human papillomavirus vaccination in low and middle income countries: a systematic review. Vaccine. 2013;31(37):3786-804.

436. Fonseca AJ, de Lima Ferreira LC. Systematic review of the cost-effectiveness of the vaccination against HPV in Brazil. Hum Vaccin Immunother. 2014;10(12):3484-90.

437. Jiang Y, Gauthier A, Preaud E, Largeron N. Critical review of cost-effectiveness analyses of human papillomavirus vaccine in boys. Value in Health. 2012;15(7):A396.

438. Khatibi M, Rasekh HR. Applying a Simple Model of Cost Effectiveness Study of HPV Vaccine for Iran. Iranian journal of pharmaceutical research : IJPR. 2015;14(2):635-49.

439. Koleva D, De Compadri P, Padula A, Garattini L. Economic evaluation of human papilloma virus vaccination in the European Union: a critical review. Internal and emergency medicine. 2011;6(2):163-74.

440. Marra F, Cloutier K, Oteng B, Marra C, Ogilvie G. Effectiveness and cost effectiveness of human papillomavirus vaccine: a systematic review. PharmacoEconomics. 2009;27(2):127-47.

441. Marsh K, Chapman R, Baggaley RF, Largeron N, Bresse X. Mind the gaps: what's missing from current economic evaluations of universal HPV vaccination? Vaccine. 2014;32(30):3732-9.

442. Newall AT, Beutels P, Wood JG, Edmunds WJ, MacIntyre CR. Cost-effectiveness analyses of human papillomavirus vaccination. The Lancet Infectious diseases. 2007;7(4):289-96.

443. Setiawan D, Oktora MP, Hutubessy R, Riewpaiboon A, Postma MJ. The health-economic studies of HPV vaccination in Southeast Asian countries: a systematic review. Expert review of vaccines. 2017;16(9):933-43.

444. Sinisgalli E, Bellini I, Indiani L, Sala A, Bechini A, Bonanni P, et al. HPV vaccination for boys? A systematic review of economic studies. Epidemiologia e prevenzione. 2015;39(4 Suppl 1):51-8.

445. Song X, Mao F, Zhou Z, Zhao Q, Fang Y. [Health economic evaluation of human papillomavirus vaccines in the developing countries: systematic reviews]. Zhonghua yu fang yi xue za zhi [Chinese journal of preventive medicine]. 2016;50(1):85-90.

446. Suijkerbuijk AW, Donken R, Lugner AK, de Wit GA, Meijer CJ, de Melker HE, et al. The whole story: a systematic review of economic evaluations of HPV vaccination including non-cervical HPV-associated diseases. Expert review of vaccines. 2017;16(4):361-75.

447. Techakehakij W, Feldman RD. Cost-effectiveness of HPV vaccination compared with Pap smear screening on a national scale: a literature review. Vaccine. 2008;26(49):6258-65.

448. Mennini FS, Bianic F, Baio G, Largeron N, Plazzotta G, Rinaldi A, et al. Estimating the cost-effectiveness profile of a vaccination programme with a nine-valent HPV vaccine in Italy. Value in Health. 2015;18(7):A457.

449. Brisson M, Laprise JF, Drolet M, Van de Velde N, Franco EL, Kliewer EV, et al. Comparative cost-effectiveness of the quadrivalent and bivalent human papillomavirus vaccines: a transmission-dynamic modeling study. Vaccine. 2013;31(37):3863-71.

450. National Board of Health. Danish Centre for for Health Technology Assessment. Reduction in the risk of cervical cancer by vaccination against human papillomavirus (HPV)- a Health Technology Assessment. Copenhagan: National Board for Health, Danish Centre for Health Technology Assessment 2007.

451. Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. N Engl J Med. 2008;359(8):821-32.

452. Chesson HW, Ekwueme DU, Saraiya M, Markowitz LE. Cost-effectiveness of human papillomavirus vaccination in the United States. Emerg Infect Dis. 2008;14(2):244-51.

453. Jit M, Mibei W. Discounting in the evaluation of the cost-effectiveness of a vaccination programme: A critical review. Vaccine. 2015;33(32):3788-94.

454. Damm O, Horn J, Mikolajczyk RT, Kretzschmar MEE, Kaufmann AM, Deleré Y, et al. Cost-effectiveness of human papillomavirus vaccination in Germany. Cost Effectiveness and Resource Allocation. 2017;15(1).

455. Mennini FS, Bonanni P, Bianic F, Waure C, Baio G, Plazzotta G, et al. Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. Cost Effectiveness and Resource Allocation. 2017;15(1).

456. Health Information and Quality Authority. Guidelines for the economic evaluation of health technologies in Ireland. Dublin, Ireland: HIQA, 2018.

457. Sankaranarayanan R, Joshi S, Muwonge R, Esmy PO, Basu P, Prabhu P, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. Vaccine. 2018.

458. Brisson M, Benard E, Drolet M, Bogaards JA, Baussano I, Vanska S, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. The Lancet Public health. 2016;1(1):e8-e17.

459. Jiménez E, Torkilseng EB, Klemp M. Cost-effectiveness of HPV-vaccination of boys aged 12 in a Norwegian setting. Oslo: Norwegian Knowledge Centre for the Health Services (NOKC), 2015.

460. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2017.

461. PEA11: Population estimates from 1926 by Single Year of Age, Sex and Year [Internet]. CSO. 2018 [cited 27/04/2018].

462. Health Protection Surveillance Centre. HPV Immunisation Uptake Statistics Dublin, Ireland2018 [Available from: http://www.hpsc.ie/a-z/vaccinepreventable/vaccination/immunisationuptakestatistics/hpvimmunisationuptakestatistics/.

463. National HPV Vaccination Programme Register. Coverage data Melbourne: HPV Register, Australia; 2018 [Available from: http://www.hpvregister.org.au/research/coverage-data.

464. Kitchener HC, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A, et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. Br J Cancer. 2006;95(1):56-61.

465. Sargent A, Bailey A, Almonte M, Turner A, Thomson C, Peto J, et al. Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial. Br J Cancer. 2008;98(10):1704-9.

466. Kjaer SK, Breugelmans G, Munk C, Junge J, Watson M, Iftner T. Population-based prevalence, type- and age-specific distribution of HPV in women before introduction of an HPV-vaccination program in Denmark. Int J Cancer. 2008;123(8):1864-70.

467. Ramanakumar AV, Naud P, Roteli-Martins CM, de Carvalho NS, de Borba PC, Teixeira JC, et al. Incidence and duration of type-specific human papillomavirus infection in high-risk HPV-naive women: results from the control arm of a phase II HPV-16/18 vaccine trial. BMJ Open. 2016;6(8):e011371.

468. Health Information and Quality Authority. Health technology assessment of human papillomavirus testing as the primary screening method for prevention of cervical cancer. Dublin, Ireland: HIQA, 2017.

469. Berman TA, Schiller JT. Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases. Cancer. 2017;123(12):2219-29.

470. Osazuwa-Peters N, Simpson MC, Massa ST, Adjei Boakye E, Antisdel JL, Varvares MA. 40-year incidence trends for oropharyngeal squamous cell carcinoma in the United States. Oral oncology. 2017;74:90-7.

471. Kraut AA, Schink T, Schulze-Rath R, Mikolajczyk RT, Garbe E. Incidence of anogenital warts in Germany: a population-based cohort study BMC Infect. Dis., 10 (2010), p. 360. 2010.

472. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. BMC infectious diseases. 2013;13:39.

473. Armstrong LR, Preston EJ, Reichert M, Phillips DL, Nisenbaum R, Todd NW, et al. Incidence and prevalence of recurrent respiratory papillomatosis among children in Atlanta and Seattle. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2000;31(1):107-9.

474. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(5):509-18.

475. Woodhall SC, Jit M, Soldan K, Kinghorn G, Gilson R, Nathan M, et al. The impact of genital warts: loss of quality of life and cost of treatment in eight sexual health clinics in the UK. Sexually transmitted infections. 2011;87(6):458-63.

476. Norman P. Putting Iterative Proportional Fitting on the researcher's desk. Leeds: School of Geography, University of Leeds, 1999.

477. Conway EL, Farmer KC, Lynch WJ, Rees GL, Wain G, Adams J. Quality of life valuations of HPV-associated cancer health states by the general population. Sexually transmitted infections. 2012;88(7):517-21.

478. Cromwell I, Gaudet M, Peacock SJ, Aquino-Parsons C. Cost-effectiveness analysis of anal cancer screening in women with cervical neoplasia in British Columbia, Canada. BMC health services research. 2016;16:206.

479. Meregaglia M, Cairns J. A systematic literature review of health state utility values in head and neck cancer. Health and quality of life outcomes. 2017;15(1):174.

480. Sosnowski R, Wolski JK, Kulpa M, Zietalewicz U, Kosowicz M, Kalinowski T, et al. Assessment of quality of life in patients surgically treated for penile cancer: Impact of aggressiveness in surgery. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2017;31:1-5.

481. de Kok IMCM, Korfage IJ, van den Hout WB, Helmerhorst TJM, Habbema JDF, Essink-Bot ML, et al. Quality of life assumptions determine which cervical cancer screening strategies are cost-effective. Int J Cancer. 2018;142(11):2383-93.

482. Organisation for Economic Co-operation and Development. Prices and purchasing power parities (PPP). Paris: OECD; 2018.

483. National Immunisation Office. Driving Change in Immunisation: The Role of the National Immunisation Office 2005–2011. Dublin, Ireland: HSE National Immunisation Office, 2012.

484. National Immunisation Group. Guidelines for Staff: School Immunisation Programme. Dublin, Ireland: Health Service Executive, 2018.

485. National Casemix Programme. Ready Reckoner 2012. Dublin, Ireland: HSE, 2012.

486. Dee A, Howell F, O'Connor C, Cremin S, Hunter K. Determining the cost of genital warts: a study from Ireland. Sexually transmitted infections. 2009;85(5):402-3.

487. Donne AJ, Clarke R. Recurrent respiratory papillomatosis: an uncommon but potentially devastating effect of human papillomavirus in children. International journal of STD & AIDS. 2010;21(6):381-5.

488. Central Statistics Office. Irish Life Tables: 2010-2012. Cork, Ireland: CSO, 2015.

489. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2016;19(8):929-35.

490. Irish Pharmaceutical Healthcare Association and Health Service Executive. Framework Agreement on the Supply of Medicines to the Health Services 2016-2020. Dublin, Ireland: IPHA and HSE, 2016.

491. Health Information and Quality Authority. The role of human papillomavirus vaccines in reducing the risk of cervical cancer in Ireland. Dublin, Ireland: HIQA, 2008.

492. Corcoran B, Clarke A, Barrett T. Rapid response to HPV vaccination crisis in Ireland. Lancet (London, England). 2018;391(10135):2103.

493. HSE. HPV Vaccination Programme - Health Service Executive. Available at: https://www.hse.ie/eng/health/immunisation/pubinfo/schoolprog/hpv/hpv-vaccination-programme/. Last updated: May 2018. Accessed June 2018. 2018.

494. HSE. Immunisation Guidelines for Ireland (National Immunisation Advisory Committee). Chapter 10: Human papillomavirus. Available at: https://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/. Accessed June 2018. 2016.

495. HSE. Guidelines for Staff: School Immunisation Programme 2017/2018. 2017.

496. HSE. The Role of the National Immunisation Office 2005–2011. Driving Change in Immunisation.

497. DOE. Department of Education. Post-primary schools lists 2017-2018 provisional data. Available at:

https://www.education.ie/en/Publications/Statistics/Data-on-Individual-Schools/post-primary-school-lists-2017-2018-provisional.xlsx. Accessed June 2018. 2018.

498. Noronha AS, Markowitz LE, Dunne EF. Systematic review of human papillomavirus vaccine coadministration. Vaccine. 2014;32(23):2670-4.

499. Kovac M, Kostanyan L, Mesaros N, Kuriyakose S, Varman M. Immunogenicity and safety of a second booster dose of an acellular pertussis vaccine combined with reduced antigen content diphtheria-tetanus toxoids 10 years after a first booster in adolescence: An open, phase III, non-randomized, multi-center study. Human Vaccines & Immunotherapeutics. 2018:1-10.

500. Bird Y, Obidiya O, Mahmood R, Nwankwo C, Moraros J. Human Papillomavirus Vaccination Uptake in Canada: A Systematic Review and Meta-analysis. International journal of preventive medicine. 2017;8:71.

501. Hopkins TG, Wood N. Female human papillomavirus (HPV) vaccination: global uptake and the impact of attitudes. Vaccine. 2013;31(13):1673-9.

502. Shapiro GK, Perez S, Rosberger Z. Including males in Canadian human papillomavirus vaccination programs: a policy analysis. Cmaj. 2016;188(12):881-6.

503. NCIRS. National Centre for Immunisation Research and Surveillance. Evaluation of the National Human Papillomavirus Vaccination Program (Australia). 2014.

504. Lee Mortensen G, Adam M, Idtaleb L. Parental attitudes towards male human papillomavirus vaccination: a pan-European cross-sectional survey. BMC Public Health. 2015;15(1):624.

505. Hofstetter AM, Rosenthal SL. Factors impacting HPV vaccination: lessons for health care professionals. Expert review of vaccines. 2014;13(8):1013-26.

506. Poole T, Goodyear-Smith F, Petousis-Harris H, Desmond N, Exeter D, Pointon L, et al. Human papillomavirus vaccination in Auckland: Reducing ethnic and socioeconomic inequities. Vaccine. 2012;31(1):84-8.

507. DOE. Retention Rates of Pupils in Second-Level Schools 2010 Entry Cohort. Available at: https://www.education.ie/en/Publications/Statistics/Statistical-Reports/retention-rates-of-pupils-in-second-level-schools-2010-entry-cohort.pdf. 2017.

508. Radisic G, Chapman J, Flight I, Wilson C. Factors associated with parents' attitudes to the HPV vaccination of their adolescent sons : A systematic review. Prev Med. 2017;95:26-37.

509. HPSC. Notifiable disease: Rubella. Available at: http://www.hpsc.ie/a-z/vaccinepreventable/rubella/. Accessed July 2018. 2018.

510. NCRI. World Head and Neck Cancer Day infographic 2015. Oropharyngeal cancer: Ireland. Available at: https://ncri.ie/publications/infographics/world-head-and-neck-cancer-day-2015. Accessed July 2018. 2015.

511. Schim van der Loeff MF, Mooij SH, Richel O, de Vries HJ, Prins JM. HPV and anal cancer in HIV-infected individuals: a review. Current HIV/AIDS reports. 2014;11(3):250-62.

512. WHO. Immunization Demand team, Division of Health Emergencies and Communicable Diseases (DEC). Vaccine-preventable Diseases programme (VPI). WHO Regional Office for Europe 2016 progress report. Available at: http://www.who.int/immunization/sage/meetings/2017/april/8_VPI_Demand_team_2016_report.pdf. Accessed July 2018. 2016.

513. Smith LM, Kaufman JS, Strumpf EC, Lévesque LE. Effect of human papillomavirus (HPV) vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario Grade 8 HPV Vaccine Cohort Study. CMAJ : Canadian Medical Association Journal. 2015;187(2):E74-E81.

514. Kuther T. "Medical decision-making and minors: issues of consent and assent". Adolescence 38: 150, 343-357. 2003.

515. Layte R, McGee H, Quail A, Rundle K, Cousins G, Donnelly C, et al. The Irish Study of Sexual Health and Relationships Summary Report2018.

516. HSE. Guidelines for Staff: School Immunisation Programme (2017/2018). 2018.

Published by the Health Information and Quality Authority.

For further information please contact:

Health Information and Quality Authority
Dublin Regional Office
George's Court, George's Lane
Smithfield, Dublin 7
D07 E98Y

Phone: +353 (0) 1 814 7400
URL: www.hiqa.ie