Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for overview of multiplex antigen near-patient tests for acute respiratory infections

Published 31 October 2023

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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1 Background

Respiratory tract infections (RTIs) are one of the most common illnesses among humans.[1, 2] RTIs can be caused by a range of pathogens including bacteria, fungi and viruses.[3-6] Some of the most common RTIs, which account for a large proportion of outbreaks annually, include SARS-CoV-2, influenza, and respiratory syncytial virus (RSV).[7-9] These can cause infections that present with very similar symptoms, making it difficult to clinically differentiate between them.[10] Differentiating between these respiratory viruses is important as early treatment with targeted antivirals, such as oseltamivir for influenza or nirmatrelvir-ritonavir or sotrovimab for SARS-CoV-2, is beneficial.[11, 12] Additionally, testing for multiple pathogens may be beneficial as positivity for one does not rule out infection with another, and co-infection by respiratory viruses may be associated with adverse clinical outcomes.[13] Therefore, multiplex tests that can simultaneously analyse a single sample to detect and differentiate between SARS-CoV-2, influenza, and RSV may have important implications for patient care.

Traditional testing methods, such as reverse transcription polymerase chain reaction (RT-PCR), for respiratory pathogens involve taking samples such as swabs from the oropharynx or nasopharynx or samples of sputum or blood and sending them to a laboratory for testing. However, more convenient methods for detecting respiratory pathogens have been developed, for example, near-patient tests (NPTs). NPTs are diagnostic devices that can be administered by a healthcare professional at the point and place of care. There are varied definitions of what constitutes "near-patient," though these tests are generally differentiated from self-testing and from conventional tests which are performed in dedicated laboratories by specialists; however, some NPTs may require some technical training.[14]

The focus of this overview is multiplex antigen NPTs. Antigen tests are a type of NPT that detect virus-specific antigens by using antibodies developed in a laboratory. They can detect the presence of infection during the acute stage of infection and typically have a faster turnaround time, and are easier to conduct relative to RT-PCR; however, they are typically less accurate.[15]

The Department of Health has requested an overview on the potential use of multiplex antigen NPTs for the diagnosis of SARS-CoV-2 and one or both of influenza and RSV in residential and primary care settings. The purpose of this protocol is to outline the process by which the Health Information and Quality Authority's (HIQA's) Health Technology Assessment Directorate will conduct this overview. The overview aims to:

- describe multiplex antigen NPTs
- provide an overview of how these tests are used in residential and primary care settings in Ireland and internationally

- provide an overview of the effectiveness, cost-effectiveness, advantages, and disadvantages of using multiplex antigen NPTs in residential and primary care settings.

The processes by which these aims will be addressed are detailed in the subsequent sections.

2 Description of technology

The description of technology chapter will consist of:

- a brief description of respiratory pathogens and their consequences (for example, treatment pathways and burden of disease), focusing on SARS-CoV-2, influenza, and RSV.
- an overview of diagnostic testing for respiratory pathogens, considering both molecular and antigen methods.
- a description of multiplex antigen NPTs for the diagnosis of SARS-CoV-2 and influenza and or RSV.

Types of multiplex antigen NPTs that claim to diagnose SARS-CoV-2 and either or both of influenza and RSV will be considered within scope. Provided they meet this criteria, multiplex antigen NPTs that can also detect other viruses, such as adenovirus, or bacteria, such as *Mycoplasma pneumoniae*, will be considered within scope. However, multiplex antigen tests used for self-testing will be considered out of scope.

This chapter will provide a high-level overview of multiplex antigen NPTs. As the purpose of the report is not to provide advice on specific tests, descriptions of individual tests will not be provided. This high-level overview will be informed by the WHO REASSURED framework for assessing diagnostic tests.[16] Information will be sourced from manufacturer websites and published literature to provide estimates, ranges, and high-level summaries on the following points:

- real-time connectivity
- ease of specimen collection
- cost
- effectiveness
- user-friendliness
- turnaround time
- throughput
- equipment required

- reagent storage and shelf life
- personnel required.

3 Use of multiplex antigen NPTs in Ireland and internationally

An overview of national and international guidance and or recommendations around the use of multiplex antigen NPTs in residential and primary care settings will be provided. Information will be identified primarily from government and health agency resources (for example, websites, reports and press releases). This information will be sought from a select number of countries and relevant guidance or recommendations on how multiplex antigen NPTs are or should be used in residential and primary care settings will be extracted and reviewed narratively. Representatives from key national-level organisations in Ireland will also be contacted, if required, to identify relevant case studies of the use of these tests within Ireland.

The below countries will be included in this review. These countries were selected based on a combination of geographical proximity to Ireland, population size, European Union membership and or availability of documents in English:

EU/EEA

- Austria
- Belgium
- Denmark
- Finland
- France
- Germany
- Italy
- Ireland
- Netherlands
- Norway
- Portugal
- Spain
- Sweden.

Non-EU

- Australia
- England
- Israel
- New Zealand
- Northern Ireland
- Scotland
- Wales.

Searches will be conducted in Google. Country and organisation websites that will be searched and associated search terms are detailed in Appendix 1. The first two hundred results from each search will be screened by one reviewer. The list of countries may be updated to include additional countries should this information be deemed relevant to the review. Additionally, the list of resources is not exhaustive and

will be expanded as necessary should relevant information be made available elsewhere.

4 Effectiveness of multiplex antigen NPTs

A non-systematic literature review to address the research questions detailed below will be conducted.

4.1 Research questions

The following key research questions were developed:

- What is known about the effectiveness of multiplex antigen NPTs to correctly classify a person as having SARS-CoV-2 and influenza and or RSV or not in residential and primary care settings?
- What are the advantages and disadvantages of using multiplex antigen NPTs for the diagnosis of SARS-CoV-2 and influenza and or RSV in residential and primary care settings (for example, turnaround time, appropriateness of patient treatment, or ability to subtype viruses)?
- What is known about the feasibility (cost and resource implications) of implementing multiplex antigen NPTs for the diagnosis of SARS-CoV-2 and influenza and or RSV in residential and primary care settings?

The applicability of each document will be considered in relation to the PICOS outlined in Table 1.

4.2 Literature search

As the purpose of this chapter is to provide an overview of what is known in relation to the research questions, rather than to provide a comprehensive review of all the literature on a topic, a non-systematic review will be performed. HTAs, systematic reviews, randomised controlled trials, non-randomised controlled trials, observational studies (but not case reports or case series) and other study designs (for example, qualitative or mixed-methods studies) that address any of the three research questions will be considered eligible for inclusion. Electronic searches will be conducted in Medline via EBSCOhost, Embase via Ovid, and CENTRAL via The Cochrane Library and Clinicaltrials.gov. The search strategy for Medline is presented in Appendix 2. Retrieved studies will be de-duplicated in Endnote and screened for relevance and inclusion in Covidence. Studies will be screened by one reviewer. Data relevant to the three research questions will be extracted by one member of the research team. Due to the expected variation in study types, study quality will be assessed without the use of formal tools.

4.3 Narrative review

Relevant studies identified in the literature search will be narratively reviewed. Where available, the review will focus on the strongest form of evidence, such as HTAs, systematic reviews and randomised controlled trials.

Table 1. Research question outlined in the PICOS format

Population	Adults with a suspected respiratory tract infection.
Intervention	Multiplex antigen NPTs to diagnose SARS-CoV-2 and one or both of influenza and RSV. **Exclusion criteria:** ▪ Self-testing: Tests conducted by patients or self-reported test results.
Comparator	Any or none. ▪ Potential comparators could include singleplex tests (that is, tests that detect only one pathogen), self-administered antigen tests, non-antigen tests designed to detect active infection (for example, molecular tests such as RT-PCR tests), or clinical judgement.
Outcomes	Outcomes relating to the performance of multiplex antigen NPTs as well as the potential impact on patient care. Examples include: ▪ test performance ○ test sensitivity and specificity ○ turnaround time ▪ cost and resource use ▪ impact on patient care ○ time to treatment ○ appropriate treatment with antibiotics/antivirals. **Exclusion criteria:** ▪ Outcomes related specifically to screening or monitoring and or surveillance.
Setting	Residential and primary care settings.

Key: NPT – near-patient test; RSV – respiratory syncytial virus; RT-PCR - reverse transcription polymerase chain reaction.

5 Quality assurance process

The review will be undertaken in accordance with HIQA's Quality Assurance Framework and led by an experienced member of staff. The report will be reviewed by two senior members of the team, to ensure processes are followed and quality maintained.

An Expert Advisory Group (EAG) comprising representation from the Department of Health, patient representatives, and individuals with relevant expertise in diagnostics, microbiology, residential care and general practice will be convened. The EAG will review this protocol and the report and attend one virtual EAG meeting to inform interpretation of the evidence and development of the advice to the Department of Health.

References

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Appendices

Appendix 1 – Search strategy to identify information relevant to the use of multiplex antigen NPTs in Ireland and internationally

Country	Organisation	Sites	Search terms
International	BMJ Best Practice	bestpractice.bmj.com	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:bestpractice.bmj.com) 2020..2023
	CMA Infobase	joulecma.ca	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:joulecma.ca) 2020..2023
	ECDC	ecdc.europa.eu	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:ecdc.europa.eu) 2020..2023
	European Academy of Paediatrics	eapaediatrics.eu	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:eapaediatrics.eu) 2020..2023
	European Paediatric Association	epa-unepsa.eu	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:epa-unepsa.eu) 2020..2023
	European Society of Clinical Microbiology and Infectious Diseases	escmid.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:escmid.org) 2020..2023
	Guidelines International Network	g-i-n.net	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:g-i-n.net) 2020..2023
	INAHTA	inahta.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:inahta.org) 2020..2023

	Institute for Clinical Systems Improvement	icsi.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:icsi.org) 2020..2023
	WHO	who.int	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:who.int) 2020..2023
Ireland	Government	gov.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.ie) 2020..2023
	HIQA	hiqa.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:hiqa.ie) 2020..2023
	HPSC	hpsc.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:hpsc.ie) 2020..2023
	HSE	hse.ie	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:hse.ie) 2020..2023
Australia	Medical Services Advisory Committee	msac.gov.au	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:msac.gov.au) 2020..2023
	Department of Health	health.gov.au	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:health.gov.au) 2020..2023
	National Health and Medical Research Council	nhmrc.gov.au	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nhmrc.gov.au) 2020..2023
Israel	Government	gov.il	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.il) 2020..2023
New Zealand	Government	govt.nz	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:govt.nz) 2020..2023

Northern Ireland	Government services	nidirect.gov.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nidirect.gov.uk) 2020..2023
	Public Health Agency	publichealth.hscni.net	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:publichealth.hscni.net) 2020..2023
UK	Government	gov.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.uk) 2020..2023
	NHS	nhs.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nhs.uk) 2020..2023
	NICE	nice.org.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nice.org.uk) 2020..2023
	National Institute for Health and Care Research	nihr.ac.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nihr.ac.uk) 2020..2023
	Centre for Reviews and Dissemination	york.ac.uk/crd	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:york.ac.uk/crd) 2020..2023
Scotland	Scottish Medicines Consortium (HTA agency)	scottishmedicines.org.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:scottishmedicines.org.uk) 2020..2023
	Healthcare Improvement Scotland	healthcareimprovementscotland.org	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:healthcareimprovementscotland.org) 2020..2023
	Scottish Intercollegiate Guidelines Network	sign.ac.uk	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sign.ac.uk) 2020..2023
Singapore	Government	gov.sg	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.sg) 2020..2023

	National Centre for Infectious Diseases	ncid.sg	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:ncid.sg) 2020..2023
	Agency for Care Effectiveness (HTA agency)	ace-hta.gov.sg	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:ace-hta.gov.sg) 2020..2023
Wales	Government	gov.wales	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gov.wales) 2020..2023
	NHS	nhs.wales	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:nhs.wales) 2020..2023
Austria	Federal Ministry for Social Affairs, Health, Care and Consumer Protection	sozialministerium.at	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sozialministerium.at) 2020..2023
	Austrian Institute for HTA	aihta.at	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:aihta.at) 2020..2023
Denmark	Danish Health Authority	sst.dk/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sst.dk) 2020..2023
Finland	Ministry of Social Affairs and Health	stm.fi	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:stm.fi) 2020..2023
	Finnish institute for health and welfare	thl.fi/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:thl.fi) 2020..2023
	FinCCHTA (HTA agency)	oys.fi/fincchta/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:oys.fi/fincchta/en) 2020..2023
France	Government	gouv.fr	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:gouv.fr) 2020..2023

	Haute Autorité de Santé (HTA agency)	has-sante.fr/jcms	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:has-sante.fr) 2020..2023
Germany	Government	bendesregierung.de/breg-en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:bendesregierung.de) 2020..2023
	Gemeinsamer Bundesausschuss (HTA agency)	g-ba.de/english	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:g-ba.de) 2020..2023
Italy	Ministry of Health	salute.gov.it	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:salute.gov.it) 2020..2023
	Ministry of Health	agenas.it	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:agenas.it) 2020..2023
	Healthcare and Social Innovation	assr.regione.emilia-romagna.it	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:assr.regione.emilia-romagna.it) 2020..2023
Netherlands	National Institute for Public Health and the Environment	rivm.nl/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:rivm.nl/en) 2020..2023
	Government	government.nl	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:government.nl) 2020..2023
	ZonMw (health research site)	zonmw.nl/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:zonmw.nl/en) 2020..2023
Norway	Norwegian Institute of Public Health	fhi.no/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:fhi.no) 2020..2023
Portugal	National Authority of Medicines and Health Products	infarmed.pt	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:infarmed.pt) 2020..2023

Spain	Ministry of Health	sanidad.gob.es/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sanidad.gob.es/en) 2020..2023
	Agencia de Evaluación de Tecnologías Sanitarias (HTA agency)	isciii.es	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:isciii.es) 2020..2023
Sweden	SBU (Swedish Agency for HTA)	sbu.se/en	("multiplex" AND "antigen") AND ("covid" OR "rsv" OR "influenza") AND (site:sbu.se) 2020..2023

Appendix 2 – Search strategy to identify information relevant to the effectiveness of multiplex antigen NPTs

Database Name	Medline Complete via Ebscohost
Date search was run	26/07/23

#	Query	Limiters/Expanders	Results
S23	S13 AND S17 AND S22	Limiters - Date of Publication: 20200101- Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	419
S22	S18 OR S19 OR S20 OR S21	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	549,027
S21	AB (antigen N3 (test* OR assay* OR immunoassay*)) OR TI (antigen N3(test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	34,466
S20	AB ("lateral flow" N3 (test* OR assay* OR immunoassay*)) OR TI ("lateral flow" N3(test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,994
S19	AB ((immunofluorescence OR immunochromatograph*) N3 (test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	25,967

	OR TI ((immunofluorescence OR immunochromatograph*) N3 (test* OR assay* OR immunoassay*))		
S18	(MH "Immunoassay+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	501,090
S17	S14 OR S15 OR S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	221,191
S16	AB (Sars-CoV-2 N1 (influenza OR flu OR RSV) N2 (test* OR assay* OR immunoassay*)) OR TI (Sars-CoV-2 N1 (influenza OR flu OR RSV) N2 (test* OR assay* OR immunoassay*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	51
S15	AB ((combo OR combin*) N2 (test* OR kit*)) OR TI ((combo OR combined) N2 (test* OR kit*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	24,684
S14	TX multiplex*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	197,045
S13	S7 OR S12	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	589,206

S12	S8 OR S9 OR S10 OR S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	364,688
S11	AB ((new or novel or “19” or “2019” or Wuhan or Hubei or China or Chinese) N3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)) OR TI ((new or novel or “19” or “2019” or Wuhan or Hubei or China or Chinese) N3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	73,981
S10	AB ((nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2)) OR TI ((nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	352,291

	Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2))		
S9	(MH "SARS-CoV-2")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	156,465
S8	(MH "COVID-19 Testing+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	11,365
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	244,966
S6	AB (Respiratory N3 (virus* OR illness* OR infection* OR pathogen*)) OR TI (Respiratory N3 (virus* OR illness* OR infection* OR pathogen*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	101,720
S5	AB (“Respiratory Syncytial Virus” OR RSV) OR TI (“Respiratory Syncytial Virus” OR RSV)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	21,324
S4	AB (flu or influenza*) OR TI (flu or influenza*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	146,886
S3	(MH "Respiratory Syncytial Viruses+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	10,608

S2	(MH "Influenza B virus") OR (MH "Influenza A virus+")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	50,439
S1	(MH "Influenza, Human")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	57,783

Published by the Health Information and Quality Authority (HIQA).

For further information please contact:

Health Information and Quality Authority

George's Court

George's Lane

Smithfield

Dublin 7

D07 E98Y

+353 (0)1 8147400

info@hiqa.ie

www.hiqa.ie