Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Economic evaluation of repeat universal antenatal screening for HIV in the third trimester of pregnancy

April 2012

Safer Better Care

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Foreword

Published national guidelines for the management of HIV-1 in pregnancy have been available in Ireland since 2001. The guidelines include specific recommendations relating to antenatal screening for HIV, for which a national voluntary programme has been available since 1999. Antenatal diagnosis of HIV allows for effective interventions to be implemented, dramatically reducing the risk of HIV transmission from mother-to-child during pregnancy, delivery and in the postnatal period. It is recognised that the current HIV guidelines may not identify all women at ongoing risk. There may be a small group of women who initially test negative, but who go on to seroconvert during pregnancy and miss out on effective management during pregnancy and following childbirth.

The *Irish Guidelines for the Management of HIV-1 in Pregnancy* are due to be updated in 2012. In response to a request from the Guideline developers, the Authority agreed to undertake an economic evaluation of a potential new recommendation of repeat universal antenatal HIV screening in the third trimester. The purpose of this evaluation is to inform a recommendation and subsequent decision as to whether a change in the existing guidelines is warranted.

In addition to the specific issues related to the Guideline development, the Authority believed that the undertaking of this evaluation would provide an opportunity to demonstrate the utility of a 'mini-HTA'. Conducted in a shorter timeframe and with fewer resources than a full HTA, a mini-HTA pro forma could be used by decision makers when undertaking proportionate assessments relevant to their needs.

Work on this evaluation was undertaken by the HTA Directorate of the Health Information and Quality Authority (the Authority) supported by the Guideline developers, Dr Fiona Lyons, Department of Genitourinary Medicine, St James's Hospital, Dublin, and Professor Karina Butler, Our Lady's Children's Hospital, Crumlin, Dublin. The evaluation was informed and reviewed through a multidisciplinary advisory process.

The Authority would like to thank the Evaluation Team, the Guideline developers and all those who contributed to the expert advisory review process.

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Acknowledgements

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Individuals contributing to the multidisciplinary advisory process:

Deirdre Burke	Laboratory Manager, National Virus Reference Laboratory, Dublin
Prof Karina Butler	Consultant in Paediatrics and Paediatric Infectious Diseases, Our Lady's Children's Hospital, Crumlin, Dublin
Dr Jeff Connell	Assistant Director, National Virus Reference Laboratory, Dublin
Dr Cillian De Gascun	Registrar in Medical Virology, National Virus Reference Laboratory, Dublin
Dr Fiona Lyons	Consultant in HIV and Genitourinary Medicine, St James's Hospital, Dublin
Dr Michael O'Connell	Consultant Obstetrician, Coombe Women & Infants University Hospital, Dublin
Martina Ring	Chief Medical Scientist, Coombe Women & Infants University Hospital, Dublin

External Review:

Dr Pat Tookey	Senior Lecturer University College London Institute of Child Health; Principle Investigator National Study of HIV in Pregnancy and Childhood (UK)

Organisations that assisted the Authority in providing information, in writing or through meetings, included:

Coombe Women & Infants University Hospital, Dublin
National Virus Reference Laboratory, Dublin
Our Lady's Children's Hospital, Crumlin, Dublin

Members of the Evaluation Team:

Members of the Authority's Evaluation Team included Martin Flattery, Dr Patricia Harrington, Michelle O'Neill, Dr Conor Teljeur and Dr Máirín Ryan.

Conflicts of Interest:

None declared

Advice to the Health Service Executive

This economic evaluation examined the additional costs and health benefits associated with the introduction of repeat universal antenatal screening for HIV in the third trimester, together with the budget impact of such a policy. The purpose of the evaluation is to inform a recommendation as to whether a change in the existing *Irish Guidelines for Management of HIV-1 in Pregnancy* is warranted.

Based on the model assumptions and input parameters, the key findings of this economic evaluation, which precede and inform the Authority's advice below, are:

- Over a one-year period, in the absence of repeat universal antenatal screening for HIV in the third trimester in Ireland, five infants will be exposed to HIV and one of these infants will become HIV-positive.
- Introduction of repeat universal antenatal screening for HIV in the third trimester will, on average, prevent one infection a year with the estimated discounted life years gained being 14.4 years.
- The median incremental cost-effectiveness ratio is €66,278 (95% CI: €42,369 – €101,089) per life year gained.
- The five-year budget impact is estimated at €6 million with an average annual budget impact of €1.2 million, ranging from €1.25 million in the first year to €1.16 million by the fifth year.

Arising from the findings listed above, the Authority's advice to the Health Service Executive (HSE) is that the cost of introducing repeat universal antenatal HIV screening in the third trimester is high compared to the expected benefits. No change to the existing guidelines is therefore recommended at this time. That is, a single round of universal antenatal screening for HIV offered at the time of first booking for antenatal care with repeat testing offered throughout pregnancy to those with ongoing risk factors for acquisition of HIV. The number of HIV-infected children born to women not previously known to be HIV positive as well as the prevalence of HIV in pregnancy should continue to be monitored. In the context of a finite healthcare budget, consideration must be given to the existing services that may need to be displaced should a decision be made to introduce repeat testing at a cost of to €1.25 million per annum.

This study also has a secondary purpose of examining the utility of a mini-HTA pro forma as a decision-support tool. It demonstrates how the economic impact of guidelines under development can be carried out in a relatively short period of time. It provides an example of how a mini-HTA could be used and prepared in a short period of time, but still provide an appropriate evidence base to inform decision making.

Executive summary

There have been published national guidelines for the management of human immunodeficiency virus type 1 (HIV-1) in pregnancy in Ireland since 2001.[1;2] These describe a broad management approach for HIV in pregnancy. A revised document, *Irish Guidelines for Management of HIV-1 in Pregnancy*, has more recently been published on the website of the Society for the Study of Sexually Transmitted Disease in Ireland.[3]

One aspect of the guidelines relates to antenatal screening for HIV. It is recommended that all women booking for antenatal care receive a HIV test. Women with ongoing risk factors (for example, active injecting drug use, known HIV infected partner, partner from a high prevalence country or partner with identified risks for HIV infection and with an unknown HIV status), following an initial negative test, should be offered repeat testing throughout pregnancy.[3]

The HIV guidelines are due to be updated by 2012.[3] In relation to the antenatal HIV screening component of the guidelines specifically, it is recognised that the existing recommended practice may not identify all women at ongoing risk. There may be a small number of individuals who will initially test negative, but go on to seroconvert (develop detectable antibodies over a period of days, weeks or months after being newly infected) during pregnancy. The guidelines state that the mother-to-child transmission rate can be dramatically reduced by treatment of the mother and child, management of the delivery and the avoidance of breastfeeding.[3] Therefore, the opportunity to intervene and reduce the number of infants who become HIV infected may be missed in this small cohort.

The Guideline developers, Dr Fiona Lyons, Consultant in Genitourinary Medicine, St. James's Hospital, Dublin and Professor Karina Butler, Our Lady's Children's Hospital, Crumlin, Dublin requested the Authority to undertake an economic evaluation of a potential new recommendation to introduce a policy of repeat universal HIV testing of pregnant women in the third trimester of pregnancy. This test would be in addition to the test performed at antenatal booking. The evaluation was to include a cost-effectiveness analysis and a budget impact analysis. The purpose of the evaluation is to inform a recommendation and subsequent decision as to whether a change in the existing guidelines is warranted.

In this study, the additional costs and health benefits associated with the introduction of repeat universal antenatal screening for HIV in the third trimester were compared with the usual standard of care (i.e. universal screening at antenatal booking combined with opportunistic screening in the third trimester for those identified to have an ongoing risk of HIV-infection).

The economic evaluation was conducted using a model developed by the Health Information and Quality Authority.

National guidelines for the economic evaluation of health technologies in Ireland, as published by the Authority, were applied.[4;5] In summary:

- a cost-effectiveness analysis was used
- the perspective of the evaluation was the publicly-funded health and social care system
- the study comparator was routine practice, that is, universal screening at antenatal booking combined with opportunistic screening in the third trimester for those identified to have an ongoing risk of HIV-infection
- life-time costs of treatment for infected infants was included with health outcomes modelled to full life expectancy for infected infants
- a standard discount rate of 4% was applied to both costs and benefits
- a range of data parameters (inputs) required to populate the model were agreed through a multidisciplinary expert advisory process.

A probabilistic sensitivity analysis was performed to allow the main parameters to vary within defined ranges, thereby allowing uncertainty to be encompassed in the model.

The costs used in the cost-effectiveness model related to the incremental cost of repeat universal antenatal screening for HIV in the third trimester, that is, added costs over and above the current operational costs. When estimating the marginal unit cost for the intervention, the costs of blood draws, HIV tests and treatment costs were included as appropriate. Cost data were provided by the National Virus Reference Laboratory (NVRL), Health Service Executive, St James's Hospital and the Coombe Women & Infants University Hospital. Cost savings related to the reduced consumption of existing resources due to a reduction in the number of infants infected with HIV at birth were also included.

In the absence of repeat universal antenatal screening for HIV in the third trimester in Ireland, it was estimated that annually there will be:

- 5 (range: 4-7) undiagnosed HIV-infected women giving birth
- 1 (range: 1-2) HIV-positive baby born to those undiagnosed.

With repeat universal antenatal screening for HIV in the third trimester there will be fewer than one HIV-positive baby born per year resulting in 14.4 discounted life years gained. The incremental cost-effectiveness ratio (ICER) associated with repeat universal antenatal screening for HIV in the third trimester was estimated at €66,278 per life year gained. Repeat universal antenatal screening for HIV in the third trimester is therefore not cost-effective by traditional standards for cost-effectiveness.

The cost-effectiveness model is subject to a number of limitations that may impact on the results or their interpretation. There is substantial uncertainty around both the suitable point estimates and the associated ranges of probable values for many of the key model parameters.

The costs considered were limited to the direct costs to the HSE. Costs to the individual (for example, out-of-pocket expenditure related to exclusive formula feeding or transport to appointments) or to society (for example, lost productivity in those women or their infants diagnosed with HIV) were not considered.

Over a five-year timeframe, the budget impact of implementing repeat antenatal screening for HIV was estimated at €6 million.

In conclusion, the cost of introducing repeat universal antenatal HIV screening in the third trimester is high compared to the expected benefits. In the context of a finite healthcare budget, consideration must be given to the existing services that may need to be displaced should a decision be made to introduce repeat testing at a cost of up to €1.25 million per annum.

List of abbreviations that appear in this report

BIA	budget impact analysis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CUA	cost-utility analysis
HAART	highly active anti-retroviral therapy
HIV	human immunodeficiency virus
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
LYG	life years gained
MTCT	mother-to-child-transmission
NVRL	National Virus Reference Laboratory
QALY	Quality-adjusted life year

1 Introduction

1.1 Background

There have been published national guidelines for the management of human immunodeficiency virus type 1(HIV-1) in pregnancy in Ireland since 2001. These describe a broad management approach for HIV in pregnancy.[1;2] A revised document, *Irish Guidelines for Management of HIV-1 in Pregnancy*, has more recently been published on the website of the Society for the Study of Sexually Transmitted Disease in Ireland.[3]

One aspect of the guidelines relate to antenatal screening for HIV. A HIV-infected mother can transmit the virus to her child during pregnancy, delivery or breastfeeding. It is recommended that all women booking for antenatal care receive a HIV test. Women with ongoing risk factors (active injecting drug use, known HIV infected partner, partner from a high prevalence country or partner with identified risks for HIV infection and an unknown HIV status) following an initial negative test should be offered repeat testing throughout pregnancy.[3] Almost all women attending for antenatal care in Ireland are tested with the latest available data reporting uptake rates of greater than 99% during 2007 and 2008.[6]

The guidelines document is due to be updated by 2012.[3] In relation to the antenatal HIV screening component of the guidelines specifically, it is recognised that the existing recommended practice may not identify all women at ongoing risk. There may be a small cohort of women who will initially test negative, but go on to seroconvert during pregnancy and miss out on effective management during pregnancy and following childbirth. The guidelines state that the mother-to-child transmission rate can be dramatically reduced by treatment of the mother and child, management of the delivery and the avoidance of breastfeeding.[3] Therefore, the opportunity to intervene and reduce the number of infants who become HIV infected may be missed in this smaller cohort. Between 2007 and 2009, there were four HIV-positive babies born in Ireland; three of these babies were born to women who had documented negative screening tests for HIV at the time of antenatal booking and did not receive any further testing.[7]

The prevalence of HIV-infection among pregnant women in Ireland has decreased from 3.2 and 3.3 per 1,000 in 2002 and 2003, respectively to 2.0 per 1,000 women tested in 2007 and 2008.[6] During this time period there has also been a reduction in the number of cases identified as a result of screening, with a 70% decrease in the number of women who were newly diagnosed as a result of antenatal screening.[6]

The guideline developers Dr Fiona Lyons (Consultant in Genitourinary Medicine, St. James's Hospital, Dublin) and Professor Karina Butler (Our Lady's Children's Hospital, Crumlin, Dublin) requested the Authority to undertake an economic evaluation of a potential new recommendation to introduce a policy of repeat universal HIV testing

of pregnant women in the third trimester, in addition to the test performed at antenatal booking. The evaluation was to include a cost-effectiveness analysis and a budget impact analysis. The purpose of the evaluation is to inform a recommendation and subsequent decision as to whether a change in the existing guidelines in respect of antenatal HIV screening of women is warranted.

Health technology assessment (HTA) is a relatively new discipline in Ireland. Its role in influencing health policy and the effective allocation of finite resources is expected to continue to grow in the coming years. The Authority has undertaken a number of projects since 2007, and the HSE, in its service plan for 2011, has committed to develop capacity in performing HTAs. The 'mini-HTA' is one such template for a HTA that could be used and adapted by the HSE when undertaking proportionate assessments that are relevant to their decision making needs. A mini-HTA has been described as a management and decision support tool that is based on the approach used in a HTA. Its purpose is to assist with decision making about the introduction or expansion of the use of technologies within a particular service setting or for a specific group of patients.[8] A mini-HTA is typically conducted in a much shorter timeframe with fewer resources and thus will have a lower level of detail included than a full HTA.

In addition to the specific issues related to the development of the guideline in this project, the Authority believed that the undertaking of an economic evaluation of repeat universal antenatal screening for HIV in the third trimester would provide an opportunity to demonstrate the utility of a mini-HTA. By populating the mini-HTA pro forma template with the required information, including details of the economic evaluation, a HTA could be produced in a relatively short period of time that was directly relevant to informing a decision as to whether antenatal screening should be expanded. The produced report might be seen as a good example of a relevant HTA prepared in a short period of time and aimed at a particular service setting. This mini-HTA pro forma is included as Appendix 1 to this report.

1.2 Cost-effectiveness analysis in HTA

Economic evaluation in HTA involves the comparative analysis of alternative courses of action. When comparing two or more technologies, the question that arises is: what is the additional cost involved for the additional benefit achieved? To answer this question, the incremental cost-effectiveness of the technology compared to the alternative is calculated, with the results presented as an incremental cost-effectiveness ratio (ICER).The ICER can be expressed as:

$$ICER = \frac{(Cost_A - Cost_B)}{(Effect_A - Effect_B)}$$

In this study, 'A' represents the costs and effects (health benefits) of introducing repeat universal antenatal screening for HIV in the third trimester in Ireland and 'B' represents the usual standard of care (i.e., the costs and health benefits of universal screening at antenatal booking combined with opportunistic screening in the third

trimester for those identified to have an ongoing risk of HIV-infection). The health benefits (effects) of antenatal screening for HIV in this study are defined as the impact of the technology on infant survival and are measured in life years gained (LYG).

One of the implications of making comparisons between the cost-effectiveness of different technologies is that there is a threshold ratio above which a technology may be considered not cost-effective. In practice, there is no fixed threshold above which an ICER would be considered not cost-effective or below which it would. However, in order for decision makers to interpret the ICER of an intervention, it is usual to examine whether it compares favourably with other healthcare interventions in the same setting.

In Ireland, most interventions with an ICER less than €20,000/QALY have been recommended for reimbursement. At ICERs above this guideline threshold, other factors have been taken in to consideration in judging cost-effectiveness of the intervention. Some economic evaluations of other interventions in an Irish setting include:

- An evaluation on the role of vaccination against human papillomavirus in reducing the risk of cervical cancer, demonstrated that a vaccination programme was cost-effective, with an ICER of €17,383/LYG.[9] The vaccination programme was implemented.
- A recent economic evaluation of the gene-expression profiling assay, Oncotype DX®, in lymph-node negative, oestrogen-receptor positive early stage breast cancer found the ICER under the base case assumptions was €25,615/QALY. This was considered not cost-effective and was not recommended for reimbursement at the submitted price.[10] However, following commercial negotiations led by the National Cancer Control Programme a reduction in the cost was obtained and Oncotype DX® was recommended for reimbursement.[11]
- The cost-effectiveness of implementing a programme of universal infant pneumococcal conjugate vaccination compared to an existing policy of no organised vaccination was evaluated. A decision analytic model was constructed and resulted in a base case ICER of €98,279/LYG. However, when the model accounted for the transmission of infection in the population (i.e., the effect of herd immunity) the ICER decreased to €5,997/LYG. This latter result was, therefore, considered cost-effective in the Irish healthcare setting and the vaccination programme was subsequently reimbursed.[12]

If a technology has an ICER that is significantly higher than that of other healthcare technologies that are reimbursed, other factors such as the innovative nature of the technology or the wider costs and benefits to patients and society may be taken into consideration.

1.3 Antenatal HIV screening – review of economic literature

A systematic review was undertaken to identify existing literature on the economic evaluation of antenatal screening for HIV to reduce the risk of mother-to-child-transmission (MTCT). The purpose of the review was to identify and evaluate the methodological and modelling methods used by other groups to assess their relevance, and to set the findings of this economic evaluation in the context of those from other antenatal HIV screening programmes.

The search was performed in June 2011. Detailed descriptions of the literature search terms and study characteristics are provided in Appendix 2.
Eighteen economic evaluations of antenatal screening for HIV were identified during the literature search (see Appendix 2 for further details).

These included four studies, summarised below, which looked at repeat screening in late pregnancy.[13-16] All studies found rescreening to be cost-effective or even cost saving. The estimated prevalence of HIV in pregnancy in each of the four studies was, however, considerably higher (range 0.3%-29.5%) than that estimated in Ireland (0.2%).[6]

- Postma et al. (UK, 2000) [13] concluded that if test costs were between £4 and £40 then an expanded antenatal screening would be cost-effective in London, which has a high prevalence of HIV (0.3%) relative to the rest of the UK. The additional benefits to both the mother and partner of earlier diagnosis of HIV were also included in this study.[13]
- Sansom et al. (US, 2003) [14] found that a repeat universal screening test was cost-effective only when the prevalence was greater than 1.2 per 1,000.
- Soorapanth et al. (South Africa, 2006) [15] found rescreening to be cost saving, but the incidence of HIV during pregnancy was estimated at 2.3% and that rescreening would only be cost saving if there was at least 3 to 18 weeks between tests.
- Teerawattananon et al. (Thailand, 2005) [16] estimated the ICER for an additional voluntary screening as $16,000 per case averted. The underlying prevalence was estimated at 1.5%.

2 Methods

2.1 Introduction

The evaluation of the cost-effectiveness of expanded antenatal, HIV screening, described in Chapter 1, requires an economic modelling approach. This model requires the prediction of outcomes that will occur in the future, together with the evaluation of the costs that are associated with repeat universal screening. Modelling facilitates the combination of data on costs and benefits from different sources and allows these to be extrapolated into the future. In this approach, the short term nature of some costs is offset against the long term nature of the benefits.

A budget impact analysis (BIA) is a further valuable piece of information for a healthcare decision maker, as it provides a means of predicting the potential financial impact of introducing a new technology into the healthcare system. Budget impact analysis provides a means of assessing the 'affordability' of a technology (the net annual financial costs of adopting the technology for a finite number of years).[5]

2.2 Multidisciplinary advisory process

At the outset of this project, the Authority set up a multidisciplinary advisory process, which consisted of a number of identified individual experts, to advise it on aspects of the project. These aspects included the provision of advice in respect of the economic modelling approach, the provision of appropriate data in the model and the review of drafts of the report as they were being generated. Individuals in this process included the expert clinicians developing the national guidelines referred to in the introduction, a representative of the HSE clinical care programmes, a representative of the National Virus Reference Laboratory, a Clinical Nurse Specialist with expertise in HIV and an international reviewer. A full listing of these expert advisors is included in the Acknowledgements section.

2.3 Framework for economic evaluation undertaken

The Authority has published guidelines on best practice in performing cost-effectiveness and budget impact analysis in HTA studies that are produced for the Irish healthcare system.[4;5] These guidelines have been followed in this evaluation. Table 2.1 on the next page provides details on the framework used for the cost-effectiveness and budget impact analysis.

Table 2.1 Framework for the economic evaluation

Study question	"What is the impact on costs and outcomes of repeat universal antenatal screening for HIV in the third trimester, compared to the current policy of universal screening at antenatal booking combined with opportunistic screening in the third trimester for those identified to have an ongoing risk of HIV-infection?"
Type of economic evaluation	A cost-effectiveness analysis was chosen in this study. A lack of available quality of life data for infants who are born HIV-positive precludes a cost-utility analysis.
Study perspective	Only direct medical costs associated with antenatal screening for HIV in the third trimester are included in the evaluation, that is, fixed and variable medical costs associated with the provision of a technology. Indirect costs, such as decreased productivity due to disease or death are excluded.
Technology and study comparator	The technology being assessed in this study is defined as universal screening for HIV at antenatal booking combined with repeat universal antenatal screening for HIV in the third trimester (weeks 30-36). The comparator is defined as universal screening for HIV at antenatal booking combined with opportunistic screening in the third trimester for those identified to have an ongoing risk of HIV infection.
Target Population	Pregnant women attending antenatal services during their third trimester in Ireland.
Outcomes	Outcomes are defined as the difference in the number of HIV-infected infants born as a result of introducing the technology, and the number of life years gained arising from cases of HIV being averted. All health benefits accruing to infants are included in the assessment of outcomes. Benefits to the mother from earlier diagnosis were not included.
Timeframe of the economic evaluation	A timeframe of 1 year was used for the proposed antenatal screening programme. Health benefits were measured to the point of full life expectancy for exposed infants with life years gained measured to the point of natural life expectancy. Lifetime costs of treatment of HIV infected infants were included in the analysis.
Discount rate	A discount rate of 4% was adopted for costs and outcomes in the cost-effectiveness analysis. Consistent with recommendations from the Department of Finance, the discount rate was not varied in the probabilistic sensitivity analysis.[4]

2.4 Description of the cost-effectiveness model

The cost-effectiveness analysis was conducted using a model developed by the Authority.

The cost-effectiveness model is composed of two distinct components: the effectiveness model and the cost model.

2.4.1 The effectiveness model

The effectiveness model estimates the number of exposed of infants acquiring HIV from their infected mother, and the likely impact of third trimester screening in reducing that infection risk. This component of the model is constructed to mimic the real-life process of screening, testing and effective management during pregnancy and following childbirth to reduce the mother-to-child-transmission (MTCT) rate.

Parameters that the model takes into account include the:

- prevalence of known HIV in the pregnant population
- estimated prevalence of undiagnosed HIV in the third trimester
- probability that HIV will be transmitted to the infant (i.e., in women undergoing Highly Active Anti-Retroviral Therapy (HAART) and in those not treated)
- increase in average life expectancy of infants who do not acquire HIV due to the implementation of risk reduction measures.

The effectiveness model aims to measure the number of life years gained (LYG) at a population level due to a reduction in the vertical transmission following the introduction of repeat universal antenatal screening for HIV in the third trimester (between 30 and 36 weeks gestation). The benefits to the mother or infant from earlier diagnosis are not included in the model.

The model is a probabilistic model which allows the inherent uncertainty around parameter estimates to be incorporated. A range of data parameters (inputs) were required in order to develop this approach and provide an estimate of the likely outcomes and costs in Ireland. The model uses simulation to allow the main parameters to vary within defined ranges thereby allowing uncertainty to be encompassed in the model. Thus, outputs can include both a point estimate and confidence bounds for the estimated number of future cases avoided and life years gained. This is important as there is substantial uncertainty regarding a number of the model parameters.

A range of input parameters were required for the effectiveness model. For each parameter, the most likely value and a range of uncertainty around this value were determined from empirical data and from the literature. All values and ranges for the key model parameters were endorsed through a multidisciplinary expert advisory process.

Table 2.2 outlines the distributions, point estimates and the associated confidence bounds used for the key parameters. Note that both the average life expectancy at birth for HIV-positive infants and the discount rate were not varied in the main model, but were varied in the univariate sensitivity analysis. The point estimates presented are median values and are accompanied by the 2.5th and 97.5th percentiles (as confidence bounds). The model was developed and executed in the open source statistics package R.[17]

Table 2.2 Point estimate, range and distribution of parameter estimates*

Parameter	Distribution	Median (95% range)
Prevalence of known HIV in pregnant population (%)	Beta	0.2 (0.15 – 0.25)
Number of pregnancies per year (000's)	Normal	75 (60 – 90)
Screening uptake rate (%)	Beta	99 (98 – 99.9)
Estimated prevalence of undiagnosed HIV at delivery (per 100,000)	Beta	7 (5 – 9)
MTCT rate without intervention (%)	Beta	27.5 (25 – 30)
MTCT rate with HAART treatment beginning after 28 weeks (%)	Beta	2.6 (0.7 – 4.1)
Life expectancy of HIV-positive infant (yrs)	-	19
Discount rate (%)	-	4

HAART – highly active anti-retroviral therapy; HIV – human immunodeficiency virus; MTCT – mother-to-child-transmission
**The data sources, methods and assumptions used to derive the parameter estimates are described in detail in Appendix 3*

2.4.2 Costs

The cost model estimates the cost of introducing antenatal screening for HIV in the third trimester as a function of the number of women screened, taking into account the cost of the HIV test and its processing, phlebotomy staff time, pregnancy and delivery costs for those women diagnosed HIV-positive to reduce transmission of HIV and prophylactic treatment of exposed infants. Cost data are used in the cost component of the cost-effectiveness model and as the basis for the budget impact analysis (BIA). Only direct costs relevant to the publicly-funded health and social care system are included in the evaluation.

The costs used in the cost-effectiveness model relate to the incremental cost of repeat screening, that is, added costs over and above the current screening costs. Costs included in this study are the cost of additional blood draws, initial HIV test, any subsequent HIV confirmatory tests, treatment of the mother during pregnancy and delivery, prophylactic treatment of infants and testing of infants born to HIV-positive mothers. Costs savings were limited to the avoidance of lifetime treatment costs for infants that would otherwise have been born HIV-positive. Benefits to the mother from earlier diagnosis or additional costs of treating the mother arising from earlier diagnosis were not included. Transfer payments (VAT) are excluded. Costs

were provided by the National Virus Reference Laboratory (NVRL), St James's Hospital, and the Coombe Women & Infants University Hospital. No set-up costs and no additional capital investments related to the introduction of antenatal screening for HIV in the third trimester were identified.

As the model does not include benefits to the mother from earlier diagnosis, it also for consistency only includes direct costs associated with infants born to HIV-positive women and costs which occur due to a diagnosis being made during pregnancy. Thus, it does not include the routine initial tests that would be carried out as part of a new HIV diagnosis, for example, initial bloods and baseline viral load, as these women would receive this care regardless of when they were diagnosed.

The data sources, methods and assumptions to derive the costs are described in detail in Appendix 4. A summary of the costs associated with the implementation of antenatal screening for HIV in the third trimester is outlined in Table 2.3.

Table 2.3 Estimated costs (exclusive of VAT) for repeat universal antenatal screening for HIV in the third trimester

Item	Antenatal Screening in the third trimester	Source
Unit cost of HIV test(s)		
Standard HIV test	€10.91	NVRL
Additional testing*	€57.21	NVRL
Additional consumables for screening per woman		
Blood draw resources**	€0.98	Coombe
Annual staffing costs		
Phlebotomist	€55,181	HSE
Average treatment costs for newly diagnosed HIV women in pregnancy		
Weekly HAART	€263.62	SJH
Intrapartum cost	€34.75	SJH
Incremental delivery costs	€2,720.96	Casemix
Average treatment costs for infants born to HIV-positive women		
HAART per infant	€323.20	SJH
HIV testing per infant***	€924.65	NVRL

Coombe – Coombe Women & Infants University Hospital; HAART – highly active anti-retroviral therapy; HIV – human immunodeficiency virus; NVRL –National Virus Reference Laboratory; SJH – St James's Hospital
**Additional testing includes the additional HIV tests required for both HIV-positive and problematic samples*
***Includes gloves, cotton wool, swabs, needles, blood bottles and tape*
**** Includes all testing within the first two years*

2.4.3 Sensitivity analysis of the cost-effectiveness model

In a cost-effectiveness analysis, the use of a probabilistic sensitivity analysis is recommended to determine the impact of varying the values of key parameters within plausible ranges.[4] A probabilistic sensitivity analysis was therefore performed thus allowing uncertainty to be encompassed in the model.

A univariate sensitivity analysis was carried out in addition to the probabilistic analysis referred to above. This shows how influential each parameter is and how sensitive the results are to fluctuations in them. Given the uncertainty around the parameters themselves, it is important to understand how this translates into uncertainty about the results. Each parameter in turn is fixed at its upper and lower bounds while all the other parameters are varied as per the fully probabilistic model. The variance in results due to each parameter can be displayed as a tornado plot that makes the results of the univariate analysis easy to interpret.

There is no uncertainty about the discount rate in the fully probabilistic model, but uncertainty is incorporated as part of a univariate sensitivity analysis. The discount rate may vary between 0 and 6%. In line with the other parameters, the 95% confidence bounds are used for the upper and lower parameter values in the univariate sensitivity analysis. A beta distribution is used for discounting that results in lower and upper bounds of 1.7% and 5.7%, respectively.

2.5 Budget impact analysis

The BIA is conducted from the perspective of the publicly-funded health and social care system and reports the costs for each year in which they occur, in this case for a timeframe of five years. The data for the BIA are the same as those used in the cost-effectiveness analysis with the difference being that prices are inclusive of VAT, and no discounting is applied.

The cost of the disposable items when taking a blood sample, and non oral drugs are subject to VAT at 21%. The HIV tests and oral drugs are classified as VAT-exempt. The results are reported as the annual cost of repeat universal antenatal screening for HIV in the third trimester.

3 Results

Results are presented for a one-year timeframe for the potential number of infected infants in the absence of repeat screening and the number of infections prevented and the number of life years gained if repeat universal antenatal screening for HIV in the third trimester were adopted. The discounted cost and the incremental cost-effectiveness ratio (ICER) of adopting repeat universal antenatal screening for HIV in the third trimester are reported. Finally, the results of the budget impact analysis (BIA) over five years are presented.

3.1 Predicted health benefits

The model predicted that, in the absence of repeat universal antenatal screening for HIV in the third trimester, there will be 5 (range: 4-7) women undiagnosed with HIV. This would lead to 1 (range: 1-2) infant being infected with HIV. There was at least one transmitted infection in 97% of simulations.

As a result of introducing a policy of further universal screening in the third trimester, it is estimated that one HIV-infection in an infant will be avoided, with 14.4 LYG. This is based on 12 months of screening (see Table 3.1). The model predicts that risk reduction management implemented subsequent to a HIV-positive screening in the third trimester prevents 90% of potential cases of HIV in exposed infants.

3.2 Predicted costs

If a policy of repeat universal screening in the third trimester was introduced, there would be an additional 74,141 women screened at a cost of €955,234 in a 12-month timeframe. This includes the discounted life-time cost savings due to a reduction in the number of HIV-positive births. An overall summary of the numbers screened, treated, benefits and costs of repeat universal screening is shown in table 3.1

Table 3.1 Predicted numbers screened, treated, benefits and costs of repeat universal antenatal screening for HIV in the third trimester

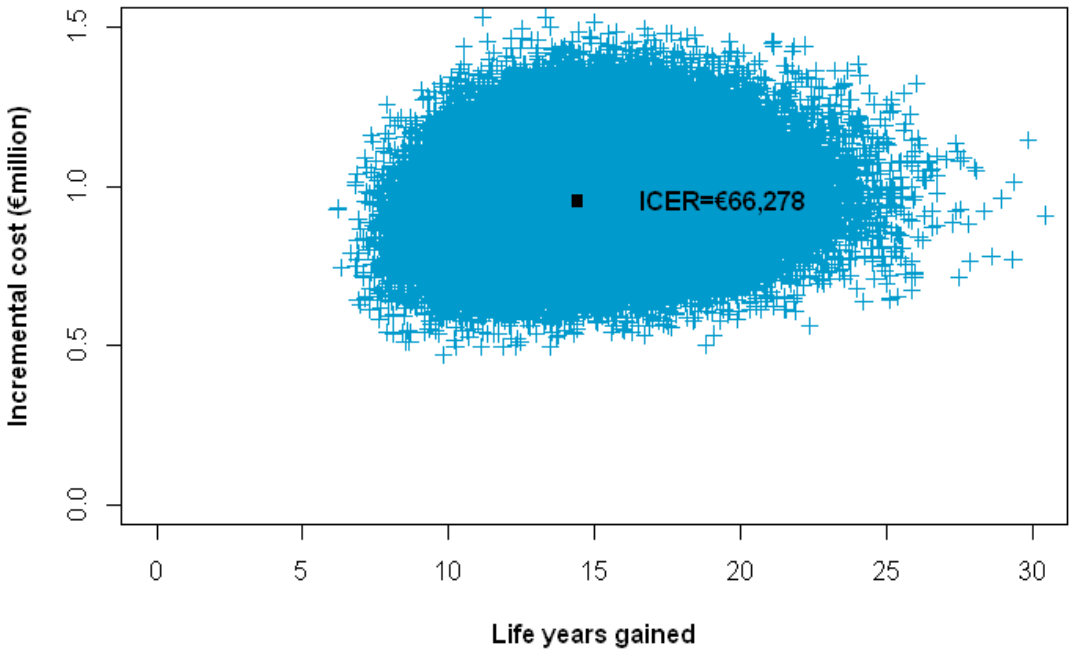
Outcome	Median	(95% CI)
Additional women screened	74,141	(59,214 – 88,990)
Women & infants treated	5.1	(3.5 – 7.2)
HIV-infections prevented	1.3	(0.87 –1.84)
Life years gained (discounted)	14.4	(9.8 –20.1)
Cost (€000's) (discounted and exclusive of VAT)	955	(706 –1,240)

3.3 Incremental cost-effectiveness ratio

An incremental cost-effectiveness ratio (ICER) can be calculated and used as an indicator of the additional cost of a life year gained by the introduction of repeat universal antenatal screening for HIV in the third trimester.

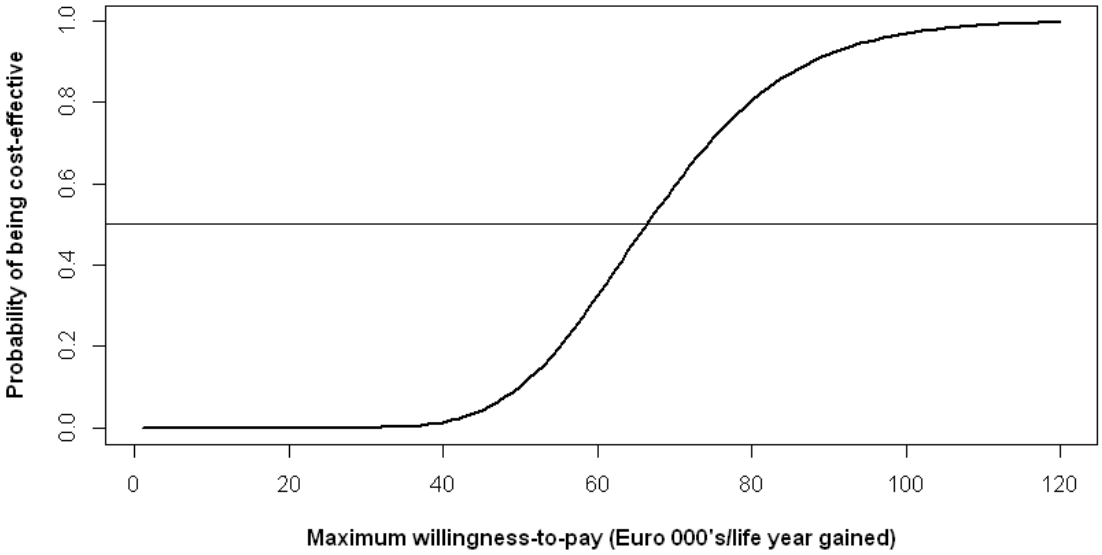
The ICER associated with repeat universal antenatal screening for HIV in the third trimester was estimated at €66,278 per life year gained (LYG) (95% CI: €42,369-€101,089). The variation in the ICER value associated with the plausible range of values for each of the input parameters can be seen visually in Figure 3.1.

Figure 3.1 Cost-effectiveness of repeat universal antenatal screening for HIV in the third trimester



The cost-effectiveness acceptability curve (CEAC) for repeat universal antenatal screening for HIV in the third trimester is provided in Figure 3.2. The CEAC shows the probability that repeat universal antenatal screening for HIV in the third trimester could be considered cost-effective over a range of willingness-to-pay thresholds. The probability of repeat universal antenatal screening for HIV in the third trimester being cost-effective at the €20,000/LYG threshold is 0%, and at €45,000/LYG it is 4.4%.

Figure 3.2 Cost-effectiveness acceptability curve for repeat universal antenatal screening for HIV in the third trimester



3.4 Budget impact analysis

The results of the budget impact analysis are shown in Table 3.2.

Table 3.2 Annual cost of repeat universal antenatal screening for HIV in the third trimester

Year	Cost(€000's)	
	Median	(95% CI)
1	1,255	(973–1,566)
2	1,232	(955–1,540)
3	1,210	(936–1,514)
4	1,187	(917–1,488)
5	1,165	(898–1,463)
Total	6,049	(4,679–7,572)

The year-on-year decrease in cost reflects the increased cost savings due to the cumulatively larger number of infants not being treated for HIV year-on-year.

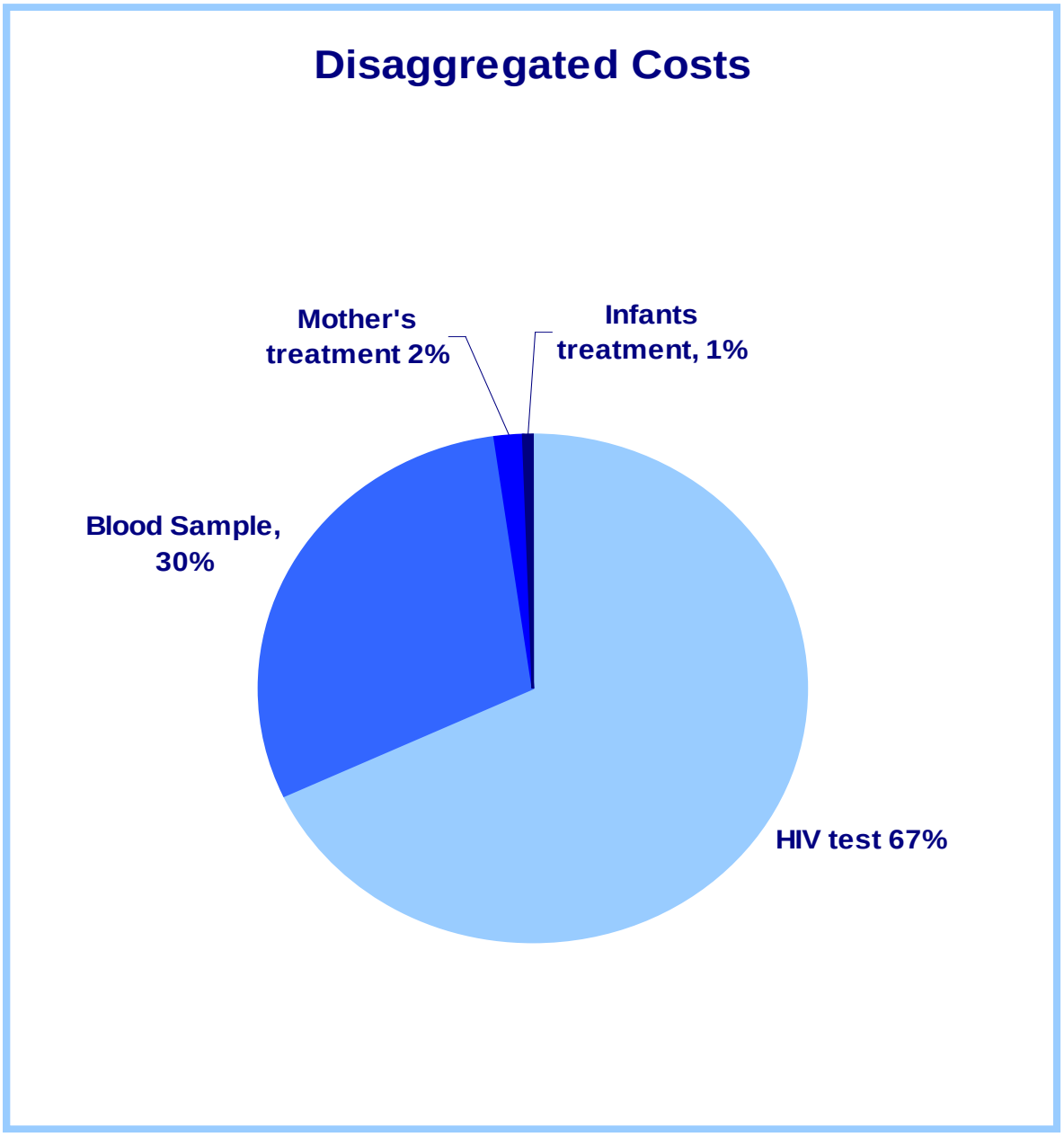
The disaggregated costs for the implementation of repeat antenatal screening for HIV in the third trimester are presented in Table 3.3 with a breakdown of costs by category in Figure 3.3

Table 3.3 Annual disaggregated direct costs associated with repeat antenatal screening for HIV in the third trimester

Disaggregated direct costs* associated with repeat universal antenatal screening for HIV in the third trimester (€000's)					
Year	**1**	**2**	**3**	**4**	**5**
HIV testing					
Initial test	801	801	801	801	801
Additional/Confirmatory Test	56	56	56	56	56
Blood Sample					
Staffing	286	286	286	286	286
Consumables	87	87	87	87	87
Treatment for the mother					
Antepartum	7	7	7	7	7
Intrapartum**	13	13	13	13	13
Treatment for the infant					
HIV testing	4	4	4	4	4
HAART	1	1	1	1	1
Cost savings	-	-23	-45	-68	-91
Total	1,255	1,232	1,210	1,187	1,164

**All costs inclusive of VAT, where relevant.*
***Includes the increase in delivery costs compared to the national average*

Figure 3.3 Five-year costs of repeat universal antenatal screening for HIV in the third trimester.



3.5 Univariate sensitivity analysis

Univariate sensitivity analyses were carried out separately for effectiveness, the incremental cost-effectiveness ratio and the budget impact analysis.

3.5.1 Effectiveness

Five parameters were identified that might have a significant impact on the number of the number of life years gained (Figure 3.4)

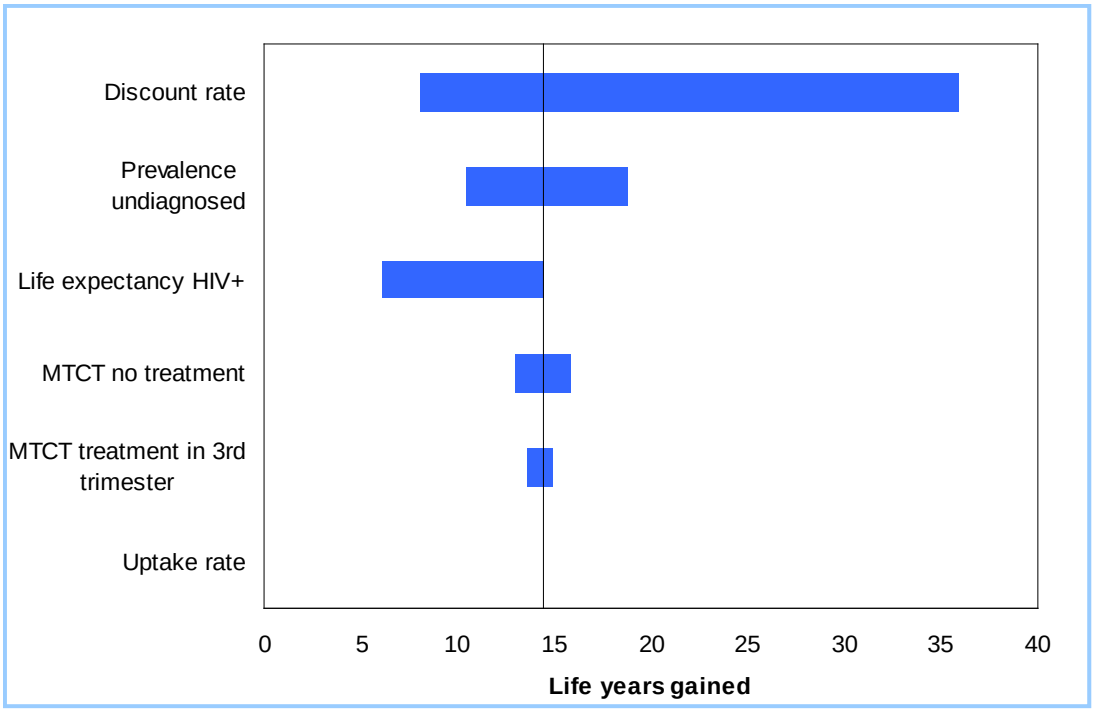
The most influential parameter is the prevalence of undiagnosed HIV-infected women in the third trimester. This was expected as this parameter directly dictates the potential number of infected infants. As treatment to prevent MTCT is estimated to be efficacious and prevent most potential infections, a higher number of infected mothers would translate directly into a higher number of life years saved. In the base case, the prevalence is five cases nationally resulting in 14 life years gained. If the prevalence is only three infected mothers nationally, then there will be 10 life years gained. If, however, there are six infected mothers nationally, the point estimate is that 19 life years will be saved.

The next most influential parameter is the estimate of the average life expectancy for infants born HIV-positive. In the base case, the estimated average life expectancy for infants born HIV-positive was 19 years. In the sensitivity analysis, an increase in average life expectancy to a maximum of 38 years was considered. The closer the average life expectancy of children born HIV-positive is to the normal life expectancy the fewer potential life years there are to be gained. Thus, this doubling of life expectancy greatly reduces the effectiveness of the proposed screening programme to just 6 discounted LYG.

Varying the discount rate causes the health benefits to fluctuate between 8 and 36 life years gained.

All of the remaining parameters have a relatively small impact on the estimated life years gained.

Figure 3.4 Univariate sensitivity analysis of the number of life years gained



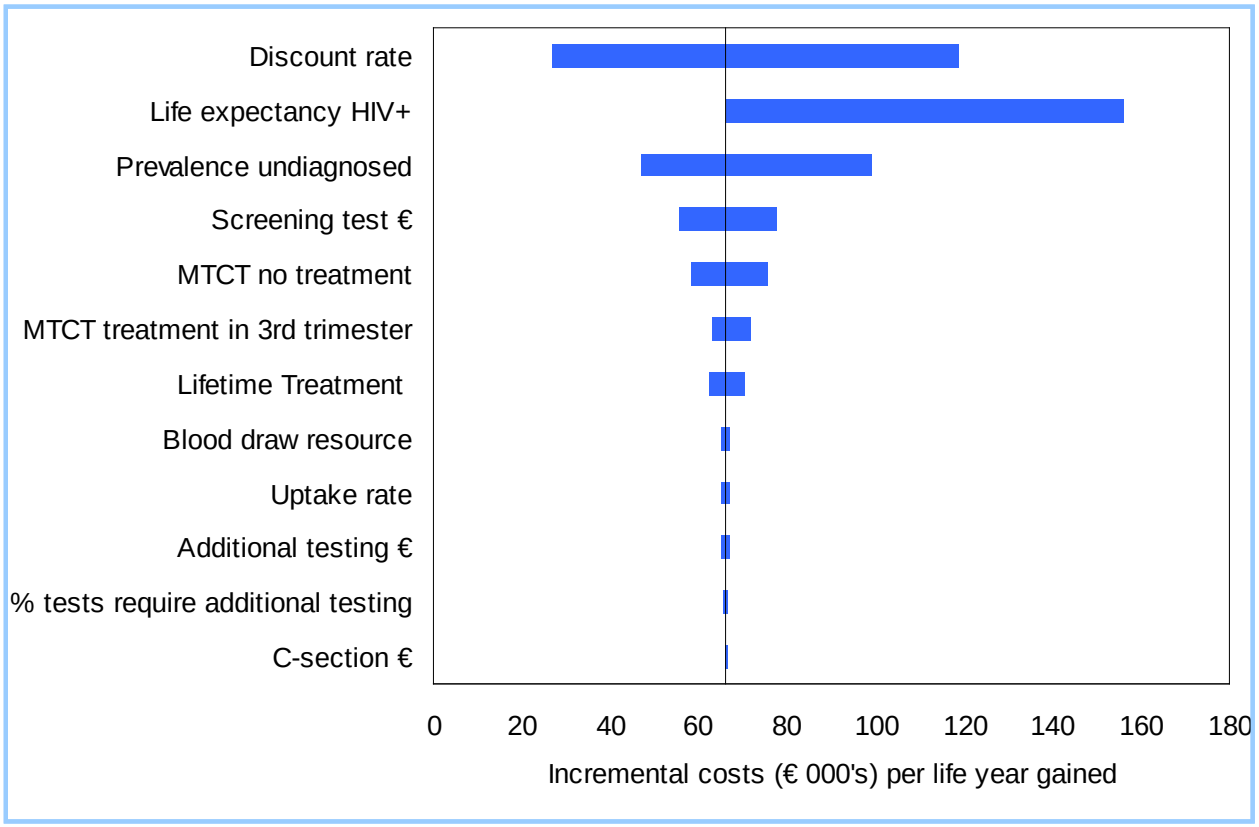
3.5.2 Incremental cost-effectiveness ratio

A univariate sensitivity analysis was carried out to assess the influence of different parameters on cost-effectiveness, that is, on the ICER (Figure 3.5).

Average life expectancy for infants born HIV-positive is the single most influential parameter that impacts on the ICER. A doubling of the base case from 19 to 38 years more than doubles the ICER to €156,000 per LYG.

The prevalence of undiagnosed HIV in the third trimester is the next most influential parameter. In the base case, the prevalence is seven cases nationally resulting in an ICER of €66,278 per LYG. If the prevalence of undiagnosed HIV in the third trimester nationally is 9 per 100,000, then the ICER will be close to €47,109 per LYG. If, on the other hand, the prevalence is 5 per 100,000 nationally, then the ICER will be €98,856 per LYG.

Figure 3.5 Univariate sensitivity analysis of the ICER



In this analysis, the discount rate was set at 4% and was not varied in the probabilistic sensitivity analysis. The impact of adopting differential discount rates was tested by running the model with discounts rates of 6% and 0% for costs and benefits, respectively. Varying the discount rate gave an ICER ranging from €26,632 per LYG to €118,910 per LYG.

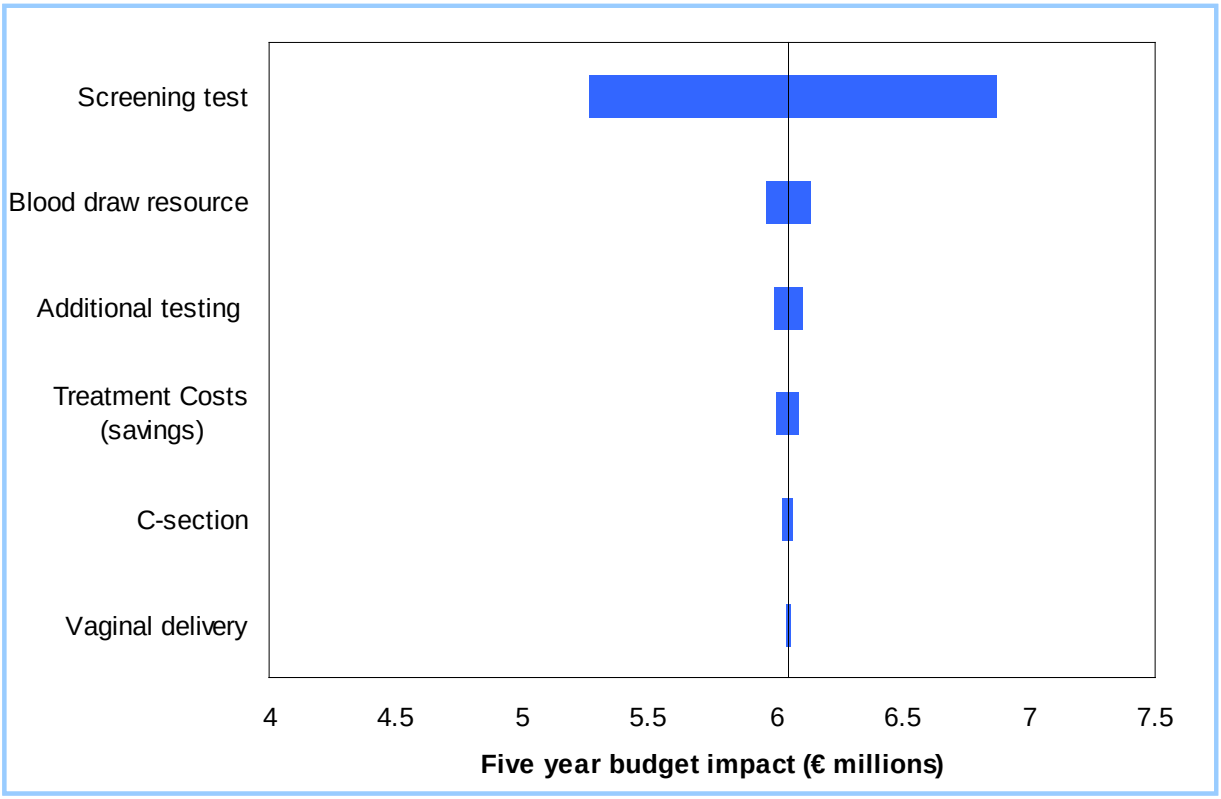
3.5.3 Budget Impact Analysis

A univariate sensitivity analysis was carried out to assess the influence of different parameters on the results of the BIA.

The influence of parameters on the cost of antenatal screening in the third trimester is shown in Figure 3.6 below.

The most influential parameter affecting the budget impact of antenatal screening for HIV is the cost of the HIV test(s). Varying the cost of the HIV test(s) by ±20% causes a ±13% fluctuation in the total cost. Of the remaining parameters, only the cost of the disposables used when taking a blood sample and the cost of additional testing for HIV-positive and problematic samples have any substantial impact on the overall cost of repeat universal antenatal screening for HIV in the third trimester.

Figure 3.6 Univariate sensitivity analysis of five year budget impact



3.6 Summary

Based on the model assumptions and input parameters, it is likely that

- over a one-year period in the absence of repeat universal antenatal screening for HIV in the third trimester in Ireland, five infants will be exposed to HIV
- one of these infants will become HIV-positive
- introduction of repeat universal antenatal screening for HIV in the third trimester is likely to prevent this infection with the estimated discounted life years gained being 14.4 years
- the median incremental cost-effectiveness ratio is €66,278 (95% CI: €42,369–€101,089) per life year gained.

The five-year budget impact is estimated at €6 million with an average annual budget impact of €1.2 million, ranging from €1.25 million in the first year to €1.16 million by the fifth year.

The estimated number of life years gained is influenced by the prevalence of undiagnosed HIV during the third trimester and the average life expectancy of infants born HIV-positive. The total costs are most influenced by the cost of the HIV test(s).

The cost-effectiveness model is subject to a number of limitations that may impact on the results or their interpretation. These limitations are discussed in the following sections.

4 Discussion

4.1 Introduction

The cost-effectiveness of antenatal screening for HIV has been evaluated in a number of published international studies. Repeat antenatal screening for HIV has been found to be cost-effective only in settings with HIV prevalence rates in pregnancy much higher than in Ireland. As economic evaluations are not readily transferable between countries due to differing cost bases and healthcare systems, it was deemed appropriate that an economic evaluation should be undertaken to consider the cost-effectiveness in the Irish setting.

A cost-effectiveness model was developed to predict the impact on HIV-infections in infants and the costs of introducing repeat universal antenatal screening for HIV in the third trimester.
The cost-effectiveness model is subject to a number of limitations that may impact on the results or their interpretation. These limitations are discussed in the following sections.

4.2 Availability, robustness and quality of data to populate the model

The accuracy of the cost-effectiveness results depends on both the accuracy of the input parameters and the manner in which the model combines those parameters.

There is uncertainty around both the suitable point estimates and the associated ranges of probable values for many of the key model parameters. Parameter estimates were based on empirical data and the literature where available. However, for a number of parameters estimates were not available from these sources (for example, life-time cost of treating vertically acquired HIV) and the choice of point estimates was in these cases pragmatic and guided by expert opinion.

The estimated number of life years gained is influenced primarily by the prevalence parameter. There are no data available on the prevalence of undiagnosed HIV in women during the third trimester. The estimate used in the model is based on the number of HIV-positive infants born to women with undiagnosed HIV between 2007 and 2009.[7] These women had consented to HIV screening and had documented negative tests at the time of antenatal booking, but did not receive further testing during pregnancy. It is not known if women who decline antenatal testing have a different prevalence of HIV to those who accept routine screening.

The uncertainty is captured in the wide ranges of probable values that parameters can take and is reflected in the wide confidence bounds of the results. When assessing the outcomes, it is important to look not only at the point estimates, but also at the ranges of probable values each outcome can take.

4.3 Limitations of the cost-effectiveness model

The cost-effectiveness model was developed to mimic the process of screening, detection and effective antenatal management and following childbirth for HIV positive women. The model combines the input parameters to estimate outcomes such as life years gained and costs. The model is stochastic in nature to reflect the randomness associated with factors that impact on the true process. Models of real-life processes are simplifications and generally make a number of assumptions. Greater model complexity does not ensure greater accuracy and generally model transparency is preferred. We have endeavoured to include the factors that were felt to be most likely to have a large impact on the findings.

The quality of the model is difficult to assess. One way to evaluate the plausibility of the results is by comparison to observed outcomes. In the absence of repeat universal antenatal screening for HIV in the third trimester in Ireland, the model predicts approximately one infected infant annually. This is similar to the number of observed cases with three instances of MTCT seen during the three years 2007-2009.[7]

Another way to assess the quality of the model is to compare the findings with those from similar models. The systematic review of economic studies identified four studies where repeat screening in late pregnancy was modelled using a similar approach to the one used in this study.[13-16] One reason for our differing conclusions is that the estimated prevalence of HIV in pregnancy in each of the four studies was considerably higher (range 0.3%-29.5%) than that estimated in Ireland (0.2%).[6] The results of the univariate sensitivity analysis indicate that if the prevalence of undiagnosed HIV in the third trimester increased, which we would expect if the overall prevalence was higher, this would lead to a significant decrease in the ICER and subsequent increase in the cost-effectiveness.

The known prevalence of HIV-infection among pregnant women in Ireland has decreased from 3.2 and 3.3 per 1,000 in 2002 and 2003, respectively to 2.0 per 1,000 women tested in 2007 and 2008.[6] During this time period there has also been a reduction in the number of cases identified as a result of screening, with a 70% decrease in the number of women diagnosed as HIV positive due to antenatal screening.[6] If prevalence continues to decrease, this is likely to lead to fewer women identified in a third trimester screening, thus lowering the effectiveness and therefore the cost-effectiveness of the proposed screening programme.

The lifetime treatment costs will undoubtedly change over time as new agents become available. Whether total treatment costs will increase or decrease is however not clear. Thus, the impact of these future changes on the cost-effectiveness of the proposed screening programme is unknown.

The average life expectancy of infants born HIV-positive is expected to increase due to improving management and treatment. The base case value of 19 years used in the model is considered at the low end of plausible values. Any large increases in

average life expectancy would have a major effect on the number of potential life years gained leading to increased treatment costs and therefore a higher ICER, that is, repeat screening would become less cost-effective.

There are benefits to the mother of earlier diagnosis due to the proposed screening programme where a diagnosis might otherwise not occur until the presentation of clinical symptoms.[18] For the infant, even if vertical transmission is not averted, that infant will benefit from initiation of antiretroviral therapy from birth. Including these benefits in the model, would likely lead to a lowering of the ICER.

4.4 Costs and cost perspective

Consistent with national HTA guidelines, this economic evaluation was conducted from the perspective of the publicly-funded health and social care system. The costs considered were limited to the direct costs to the HSE. Costs to the individual (for example, out-of-pocket expenditure related to treatment or transport to appointments) or to society (for example, lost productivity in those women or their infants diagnosed with HIV) were not considered. As the model does not include benefits to the mother from earlier diagnosis, it also for consistency only includes direct costs associated with infants born to HIV-positive women and costs which occur due to a diagnosis being made during pregnancy. Thus, it does not include the routine initial tests that would be carried out as part of a new HIV diagnosis in the mother e.g., initial bloods, baseline viral load etc. as these women would receive this care regardless of when they were diagnosed.

The effect of discounting is not inconsiderable in this cost-effectiveness analysis. Repeat universal antenatal screening for HIV in the third trimester is predicted to result in 14.4 (95% CI: 9.8 to 20.1) life years gained with discounting compared to 78.6 (95% CI: 53.3 to 112.3) life years gained without discounting. Use of a higher discount rate would translate into a lower number of estimated life years gained.

The application of the same discount rate to both costs and outcomes is not without controversy, particularly when potential benefits do not accrue for a long time, such as in vaccination programmes and other preventative public health strategies.

5 Conclusion

This economic evaluation examined the additional costs and health benefits associated with the introduction of repeat universal antenatal screening for HIV in the third trimester together with the budget impact of such a policy.

Based on the model assumptions and input parameters, it is estimated that repeat universal antenatal screening in the third trimester would cost on average €1.2 million per annum. When followed by appropriate management, this would prevent one infant from being infected with HIV a year resulting in 14.4. discounted life years gained. The estimated incremental cost-effectiveness ratio (ICER) of repeat universal antenatal screening is €66,278 per life year gained. This would be considered not cost-effective by traditional standards of cost-effectiveness. Although there is no fixed threshold below which an intervention is automatically reimbursed in Ireland, most interventions with an ICER less than €20,000/QALY have been recommended for reimbursement. These include national vaccination programmes for 12-year-old girls against human papillomavirus to reduce the risk of cervical cancer and a programme of universal infant pneumococcal conjugate vaccination which had ICERs of €17,383/LYG and €5,997/LYG, respectively.[9,12]

The known prevalence of HIV in pregnancy is comparatively low in Ireland and has declined in recent years.[6] If prevalence continues to decrease, fewer women would be expected to be diagnosed in a repeat third trimester screening programme, lowering the effectiveness and therefore the cost-effectiveness of such a programme.

The cost of repeat universal screening is not insubstantial. In the context of a finite healthcare budget, consideration must be given to the existing services that may need to be displaced should a decision be made to introduce repeat testing at a cost of to €1.25 million per annum.

This study had a secondary purpose of examining the utility of a mini-HTA pro forma as a decision support tool. It demonstrates how the economic impact of guidelines under development can be carried out in a relatively short period of time. It provides an example of how a mini-HTA can be prepared in a short period of time, but still provide an appropriate evidence base to inform decision making.

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Appendix 1: Mini-HTA Pro forma

All mini-HTA questions should be answered in clear and comprehensible language: **a simple yes or no is not sufficient**

Questions 1 - 3: Introduction

1: **Who is the proposer** (hospital, department, person)?
Please state which hospital(s), department(s) and/or person(s) make the proposal(s).

Dr Fiona Lyons (Consultant in HIV and Genitourinary Medicine, St James's Hospital, Dublin)
Professor Karina Butler (Consultant in Paediatrics & Paediatric Infectious Diseases, Our Lady's Children's Hospital, Crumlin, Dublin)
This mini-HTA is being carried out to support the updating of the national guidelines for the management of HIV in pregnancy.[1]

2: What is the name/designation of the health technology?
Please state the specific subject of the application - for instance new drug for a specific patient group.

In Ireland, the antenatal HIV screening programme, first introduced in April 1999, recommends that all women booking for antenatal care are offered a HIV test. This programme covers almost all women attending for antenatal care with the latest available data reporting uptake rates of greater than 99% during 2007 and 2008.[2] For the minority of women who decline screening, the reasons for same are explored as part of a consultant-led discussion. If the reasons for not screening are firmly held, then rescreening is not offered; if not, the subject is broached again at later in the pregnancy. The current national guidelines recommend that in addition to the universal screening test for HIV at the time of antenatal booking that 'Women with ongoing risk factors for acquisition of HIV (active injecting drug use, known HIV-infected partner, partner from high prevalence country or partner with identified risks for HIV-infection and unknown HIV status) and an initial negative test should be offered repeat testing throughout pregnancy'.[1]

As not all women at ongoing risk will be identified, there will be a small number of individuals who will initially test negative, but go on to seroconvert during pregnancy and miss out on treatment. Between 2007 and 2009, there were three HIV-positive births to women with documented negative HIV- tests results from their antenatal screening.[3] One option being considered to reduce the risk of this occurring is the introduction of a repeat universal antenatal HIV screening programme during the third trimester (between 30-36 weeks gestation).

3: Which parties have been involved in the development of the proposal?
Often it is beneficial to be able to discuss a proposal with a local drug committee, a device committee, other affected departments or any other relevant cooperation forum. Please state with whom the proposal has been discussed, if any, and the conclusion.

A multidisciplinary expert advisory process was used to evaluate this particular technology and included individuals with relevant expertise within the Irish healthcare system (SJH, Crumlin, Coombe and the NVRL) and the Health Information and Quality Authority.

Questions 4 -12: Technology

4: For which indication will the proposed technology be used?

Please state the indication for which the proposed technology should be applied (for instance diagnosis or procedure).

The technology being assessed is repeat universal antenatal screening for HIV during the third trimester (weeks 30-36) using the Architect HIV Ag/Ab test, for those whose initial HIV test was negative or who declined screening at their first antenatal booking and who later consent to screen.

5: How is the proposed use of the technology new compared to usual practice?

A proposed technology often replaces another technology. Thus, please state in which way use of the proposed technology is new compared to usual practice in the department or service(s). Apart from the fact that a proposed use of a technology often replaces other existing technology there also may be other alternatives to the new proposal. Consequently the mini-HTA should comprise an assessment of benefits and drawbacks compared to current practice and any other alternatives.

The current national guidelines recommend that in addition to the universal screening for HIV at antenatal booking that "Women with ongoing risk factors for acquisition of HIV (active injecting drug use, known HIV-infected partner, partner from high prevalence country or partner with identified risks for HIV-infection and unknown HIV status) and an initial negative test should be offered repeat testing throughout pregnancy".[(1)] The proposed technology is to expand the current screening programme to offer repeat universal screening for HIV during the third trimester, between weeks 30 to 36.

6: Has an assessment of literature been carried out (by the department/service(s) or by others)?

A health technology assessment should primarily be based on documented knowledge. An assessment of the present evidence can benefit from the principles of high quality literature review (see Appendix 2)

Yes, to support the development of an economic model a systematic review was undertaken to identify existing literature on the economic evaluation of antenatal screening for HIV to reduce the risk of mother-to-child-transmission (MTCT) of HIV. This search was performed in June 2011.
Eighteen economic evaluations of antenatal screening for HIV were identified during the literature search.

These included four studies which looked at repeat screening in late pregnancy.[(4-7)] The studies have found rescreening to be cost-effective or even cost saving, however, the estimated known prevalence of HIV in pregnancy in all four studies was considerably higher (range 0.3%-29.5%) than that estimated in Ireland (0.2%).[(2)]

Postma et al. (UK) [(4)] concluded that if test costs were between £4 and £40 then an expanded antenatal screening would be cost-effective in London, which has a high prevalence of known HIV in pregnancy (0.3%) relative to the rest of the UK. The additional benefits to both the mother and partner of earlier diagnosis of HIV were also included by Postma et al..[(4)] Sansom et al. (US) [(5)] found that a repeat universal screening test was cost-effective only when the known prevalence was greater than 1.2 per 1,000. Soorapanth et al. (South Africa) [(6)] found rescreening to be cost saving if there was at least 3 to 18 weeks

between tests, however known prevalence of HIV in pregnancy was estimated at 29.5% with the incidence during pregnancy estimated at 2.3% . Teerawattananon et al. (Thailand) [7] estimated the ICER for an additional voluntary screening as $16,000 per case averted; the underlying prevalence of diagnosed HIV was estimated at 1.5%.

7: State the most important references and assess the strength of the evidence.
The documentation of the evidence of the effect of the proposed use of the technology should be stated giving the most important references at the highest possible level. For the benefit of the reader the evidence level should be stated for each reference.

Effective interventions (including the identification of women who are HIV positive in pregnancy, administration of antenatal and neonatal antiretroviral therapy, selective use of elective caesarean section for delivery and exclusive formula feeding) exist to substantially reduce the risk of transmitting HIV from mother to child. The earlier in pregnancy antiretroviral therapy begins, the greater the reduction in the MTCT rate; however, the risk of transmission can still be significantly reduced even after a late diagnosis of HIV during the third trimester of pregnancy if effective interventions are introduced at that time. Additionally, even if a diagnosis of HIV late in pregnancy does not avert vertical transmission, that infant has the benefit of early initiation of antiretroviral therapy.

A reduction in MTCT to 2.6% can be achieved when HAART is initiated after 28 weeks gestation. This effectiveness of treatment beginning in the third trimester is based on the conference abstract by Tubiana et al. [8] which followed a cohort of 684 women in France between 2000 and 2008.

8: What is the effect of use of the proposed technology for patients in terms of diagnosis, treatment, care, rehabilitation and prevention?
Please provide a short summary of the most important conclusions of above references (for instance the effect of the proposed technology on the mortality, morbidity, functional capacity, quality of life etc. of patients).

Reducing the MTCT rate would lead to a reduction in the number of infants born HIV-positive.
Along with reducing the MTCT rate, there would also be benefits to the mother from earlier diagnosis. For those infants where HIV transmission still occurred, the earlier diagnosis would also be beneficial to their health.

9: Does use of the proposed technology imply any risks, adverse effects or other adverse events?
The risks, adverse effects and other adverse events should be assessed in relation to the benefit. These drawbacks should be compared to the drawbacks of current practice and any alternatives.

For the majority of pregnant women, there is currently no routine blood draw during the third trimester, thus women may experience discomfort due to the additional blood test.

The use of potent antiretroviral agents in pregnancy may incur risks due to the potential for toxicity to the mother and the developing foetus. However, these risks would be outweighed by the benefits in reducing the MTCT rate. The use of antiretroviral therapy in pregnancy to reduce MTCT is international best practice.

10: Are there any known ongoing studies in other hospitals/services in Ireland or abroad of the effect of the proposed technology?
Please state any ongoing studies of the effect of the proposed technology.

There are no other known ongoing studies in Ireland or abroad examining the effects of the proposed technology.

11: Has the proposed technology been recommended by any department within the HSE, any national health committee, medical associations etc.? If YES, please state institution.
Please state any recommendations.

The multidisciplinary expert advisory process drew on relevant clinical expertise within the Irish healthcare system (SJH, Crumlin, Coombe and NVRL) and from the HTA Directorate within HIQA. The purpose of the mini-HTA is to support the updating of the national guidelines for the management of HIV in pregnancy, in assessing the cost-effectiveness of implementing a universal antenatal screening programme for HIV in the third trimester.

12: Has this department previously or on any other occasions, applied for introduction of the proposed technology?
Please state if introduction of the proposed technology has previously been applied for (to whom, when) and any reason for the rejection.

No

Questions 13 -14: Patient

13: Does the proposed use of the technology entail any special ethical or psychological considerations?
Please state ethical and psychological aspects of the proposed use of the technology. It should be stated if the proposal could affect the patient's experience of insecurity, discomfort or anxiety. The considerations should be related to current practice and any alternatives.

Ethical Issues There are implications for partners and children and disclosure to, and testing of those at risk must be considered. Where a HIV positive women decides not to inform her sexual partner of her status, ethical issues may arise on the disclosure of this information. Psychological considerations Women may experience anxiety due to the screening test, particularly in the case of false positives where repeat sampling may be required. A diagnosis of HIV in pregnancy can be traumatic and extremely difficult.

14: Is the proposed use of the technology expected to influence the patients' quality of life, social or employment situation?
Please state if – and if so how – the patient's quality of life, social or employment situation is expected to be affected by the proposed use of the technology. The considerations should be related to current practice and any alternatives.

Quality of Life
Antiretroviral therapy initiated during pregnancy can greatly reduce the risk of MTCT and thus significantly improve the quality of life for those infants who may otherwise develop HIV without intervention.

Earlier detection can improve quality of life for both infants born HIV positive and those asymptomatic women identified through screening.

Social Situation and Employment Situation
A diagnosis of HIV may negatively impact on a woman's social situation. A diagnosis of HIV, with certain exceptions, should not impact on a woman's employment situation.

Questions 15 -20: Organisation

15: What are the effects of the proposed use of the technology on the staff in terms of information, training or working environment?
Please state the effects of the proposed use of the technology on the staff, including which staff groups will be affected. Possible consequences should be stated in relation to need for information and training and effect on the working environment.

Universal antenatal screening for HIV is currently undertaken at the first booking appointment during early pregnancy at 10 – 14 weeks gestation. (range10 - 20 weeks gestation). The introduction of a repeat test should therefore not require any additional staff training on test administration. However, information and training may be required on the reasons why repeat testing is necessary, and on how to explain the necessity of repeat testing to women so that informed consent will be provided.

16: Can the proposed use of the technology be accommodated within the current infrastructure?
For the purpose of planning please state if the proposed use of the technology can be accommodated within the current infrastructure. If not, please state how this could be addressed.

Currently there are no routine blood tests carried out universally for women during the third trimester, thus the introduction of the proposed screening test would require an additional blood draw, as well as the additional laboratory testing. Few institutions currently have spare capacity, thus, it may not be possible to implement the proposed screening programme without additional staffing resources.

17: Will the proposed use of the technology affect other departments or service functions in the hospital?
Often a proposed use of a technology will entail changes in the working relationship between the department proposing the technology and other departments. If this is the case, please state in which way the use proposed technology might be expected to affect other departments. It may be a question of changed collaboration pattern, work load etc.

Screening will lead to an increase in the number of women detected with HIV. This will lead to increased workloads for those managing these women and their infants.
Given the short time frame in which to initiate antiretroviral therapy for women diagnosed during the third trimester, good links need to exist between the routine obstetric services and those responsible for the management of HIV in pregnancy, to ensure timely referral.

18: How does the proposed use of the technology affect the working relationship with other hospitals, other pillars of the HSE, primary care providers etc. (e.g. the impact on usual care pathways)?
A proposed use of a technology can often change the working relationship with other sectors - e.g. the referral criteria may be changed. If this or something else is the case please state changes to the care pathway, including the location of the preliminary examination, treatment and post treatment course and also which budgets will likely be affected.

Rapid access to a HIV specialist team is critical for women diagnosed during the third trimester due to the short time frame in which to initiate antiretroviral therapy. Referral pathways and governance structures have been in place for several years since the introduction of universal antenatal screening.

19: When can the proposed use of the technology be implemented?
For the purpose of planning please state when the proposed use of the technology can be implemented.

Universal antenatal HIV is already part of routine care in Ireland. If repeat screening were approved as part of a national guideline, time to implementation would be based on capacity issues at an institutional level.

20: Has the proposed use of the technology been implemented in other hospitals/services in Ireland or internationally?
Please state if the proposed use of the technology has been implemented – or is approved for implementation elsewhere. Please state if any countries are known to have recommended that the technology not be approved.

The current practice is for universal screening for HIV at the time of antenatal booking and additional opportunistic screening for those considered at risk.
The UK has opted not to approve a second universal screening in the third trimester for the following reasons: the prevalence of undiagnosed HIV at delivery although unknown is considered to be very low; the interval between the first and second screening test for HIV would be short thus the number of seroconversions in the timeframe is likely to be extremely low; and although children have been born to mothers who were not diagnosed at the time of delivery, the proportion of those mothers who seroconverted after delivery while breastfeeding, as opposed to before delivery, is unknown. [(9)]

Questions 21 -26: Cost-effectiveness, Finance and Resources

21: Are there any start-up costs of equipment, building, training etc.?
Please state the expected start-up costs. The costs may cover building, new equipment, training, preparation of guidelines or patient information etc.

There are no anticipated start-up costs.

22: What are the consequences in terms of activities for the next couple of years?
Please state the consequences in terms of activities per year, for instance how many patients the proposal is expected to involve within the next couple of years. (The number of patients is often lower the first year due to a start-up phase). Depending on circumstances,

consequences in terms of activity may be assessed based on number of patients, number of discharges, number of outpatient clinic visits, number of bed days, casemix etc.

The introduction of the proposed screening programme would involve an additional 74,141 blood draws to be taken and tested for HIV annually with an additional five women and their infants requiring antiretroviral therapy for HIV during pregnancy.

23: What is the increased or decreased cost per patient for the hospital / service?
Please state the increased or decreased expenditure per patient per year for the hospital/service if the proposed use of the technology is implemented.

The increased cost of HIV testing (including taking the blood sample) per woman is estimated at €16.76.
The increased cost of treatment per woman detected during pregnancy is estimated at €4,144.
The increased cost of prophylactic treatment and testing of infants born to women diagnosed as a result of screening per infant is estimated at €1,248.
Cost savings due to a reduction in the transmission of HIV from mother to child is estimated at €218,412 (discounted at 4%) per HIV infection avoided.

24: What is the total increased or decreased cost for the hospital/service in the next couple of years?
Please multiply the number of patients by the increased or decreased expenditure per patient, resulting in the total increased or decreased expenditure.

The five-year budget impact is estimated at €6 million with an average annual budget impact of €1.2 million ranging from €1.25 million in the first year to €1.16 million by the fifth year.

25: Will proposed used of the technology result in increased or decreased costs to other hospitals, services, HSE pillars etc.?
Please state if the proposed use of the technology results in increased or decreased expenditure for other hospitals, PCCC.

There are no anticipated changes in costs to other hospitals or services.

26: Which uncertainties apply to these calculations?
Please state the assumptions underlying the above calculations and indicate any uncertainties in the assumptions.

The key assumptions underlying the above calculation are listed below:

The current MTCT without intervention is assumed to be 25-30%. For an Irish or European population, the MTCT is anticipated to be between 15 - 20%.[10] However, typically over 80% of the cohort of HIV-positive women giving birth in Ireland are of African origin[11] for whom a higher MTCT of 25 - 40%[10] in the absence of interventions could be expected. Some of the differences between these rates is due to a higher prevalence of breastfeeding among the African population,[10] thus, 25-30% was chosen as a conservative estimate for the total cohort of HIV-positive women in Ireland.

The current prevalence of undiagnosed HIV in women at delivery in Ireland is assumed to be in the range of 5-9 per 100,000. The estimated prevalence was based on a total of three

observed cases born to women with undiagnosed HIV at delivery between 2007 and 2009.[3] The total number of births during that period was 221,182.[12] Assuming a MTCT rate of 25%-30%, then there were approximately 10-12 women with unknown HIV at delivery between 2007 and 2009. This gives us a prevalence of approximately 5 per 100,000. This is, however, a minimum estimate as they may be children who have not yet been diagnosed. To estimate how many infants may yet be undiagnosed data from the National Study of HIV in Pregnancy and Childhood (NSHPC) for the UK and Ireland was used. This suggests for those born in the UK and Ireland, 48% are diagnosed by 1 year and 28% by age 4.[13] Thus, we can assume that there is approximately between 25%-50% yet to be diagnosed equating to an additional 1-2 cases. Using the maximum to give an upper value of a total of five cases, this gives of an estimated maximum prevalence of 9 per 100,000. The midpoint of this range 7 per 100,000 was used as the base case value in the model.

The number of additional HIV-positive births avoided was based on a MTCT rate of 2.6% (95% CI 1.7%, 4.1%) for HAART beginning after 28 weeks.[14] Although the proposed screening programme would result in antiretroviral therapy beginning between 30-36 weeks, we assume that the MTCT of 2.6% is not reduced by this slightly later starting time.

The number of life years gained was based on the difference between the current life expectancy at birth and the estimated average life expectancy of 19 years for those born HIV-positive, with a maximum life expectancy estimated as twice this at 38 years.[15]

Only the costs to the publicly-funded health and social care system in Ireland have been included.

Benefits to the mother of earlier diagnosis have not been included, and for consistency only direct costs associated with infants born to HIV positive women and costs which occur due to a diagnosis being made during pregnancy were included. Thus any initial tests that would routinely be carried out as part of a new HIV diagnosis e.g. initial bloods, baseline viral load etc. were not included as these women would receive this care regardless of when they were diagnosed.

27. Has a cost-effectiveness analysis been undertaken in Ireland or in another country on the proposed use of the technology?

Please summarise the methodology, underlying assumptions and the results of any cost-effectiveness analysis undertaken on the proposed use of the technology and any limitations in applying the results to the Irish setting.

In this mini-HTA, the additional costs and health benefits associated with the introduction of repeat universal antenatal screening for HIV in the third trimester are compared with the usual standard of care (i.e., universal screening at antenatal booking and opportunistic screening in third trimester for those identified to have ongoing risk of HIV-infection).

A HIV-infected mother can transmit the virus to her child during pregnancy, delivery or breastfeeding. The MTCT can be dramatically reduced by treatment of the mother and child, management of the delivery and avoidance of breastfeeding.[1] Antenatal screening can identify HIV-positive women and their exposed infants, thus, providing the opportunity to intervene and reduce the number of infants who become HIV-infected.

Economic analyses carried out in a HTA typically use models to project the future health benefits and costs of an intervention. The economic analysis in this mini-HTA was conducted using a model developed by the HTA Directorate of the Health Information and Quality

Authority. National guidelines for the economic evaluation of health technologies in Ireland as published by the Authority were applied. In summary:

- a cost-effectiveness analysis was used
- the perspective of the evaluation was the publicly-funded healthcare system
- the study comparator was routine practice, that is, universal screening at antenatal booking followed by opportunistic screening for those at risk in the third trimester
- a life time for costs of treatment for infected infants with health outcomes modelled to full life expectancy for infected infants
- a standard discount rate of 4% was applied to both costs and benefits
- a range of data parameters (inputs) required to populate the model were agreed through the multidisciplinary expert advisory process.

A probabilistic sensitivity analysis was performed to allow the main parameters to vary within defined ranges, thereby allowing uncertainty to be encompassed in the model.

The costs used in the cost-effectiveness model related to the incremental cost of repeat universal screening in the third trimester, that is, added costs over and above the current operational costs. Cost savings related to the reduced consumption of existing resources due to a reduction in the number of infants infected with HIV at birth. When estimating the marginal unit cost for the intervention, the costs of blood draws, HIV tests and treatment costs were included as appropriate. Cost data were provided by the National Virus Reference Laboratory (NVRL), Health Service Executive, St James's Hospital and the Coombe Women & Infants University Hospital.

In the absence of repeat universal antenatal screening in the third trimester in Ireland, it was estimated that annually there will be:

5 (range: 4-7) undetected HIV-infected women giving birth
1 (range: 1-2) HIV-positive births to those undiagnosed.

The incremental cost-effectiveness ratio (ICER) associated with a repeat universal antenatal screening for HIV in the third trimester was estimated at €66,278 per life year gained. A repeat universal antenatal screening for HIV is therefore not cost-effective by traditional standards for cost-effectiveness.

The cost-effectiveness model is subject to a number of limitations that may impact on the results or their interpretation. There is substantial uncertainty around both the suitable point estimates and the associated ranges of probable values for many of the key model parameters. Universal antenatal screening in the third trimester could therefore have a true ICER that is far higher than €66,278 per life year gained. The costs considered were limited to the direct costs to the HSE. Costs to the individual (for example, out-of-pocket expenditure related to exclusive formula feeding or transport to appointments) or to society (for example, lost productivity in those women diagnosed with HIV) were not considered.

Over a five-year timeframe, the budget impact of implementing a repeat antenatal screening for HIV was estimated at €6 million.

Questions 27-30: Conclusions and Recommendations

27. What conclusions have been drawn from the deliberations of the Mini HTA group on this subject.

Please state conclusions drawn in terms of i) benefits and drawbacks of the use of the proposed technology, ii) uncertainties related to the level of evidence available, iii) impact on patient, resources, and services etc.

The introduction of a second universal HIV test in pregnancy is currently not cost-effective and the recommendations surrounding the offer of a second test should remain, that is, "Women with ongoing risk factors for acquisition of HIV (active injecting drug use, known HIV-infected partner, partner from high prevalence country or partner with identified risks for HIV-infection and unknown HIV status) and an initial negative test should be offered repeat testing throughout pregnancy".[(1)] There is an ongoing need to monitor the number of HIV-infected children born to women not known to be HIV positive and to monitor the prevalence of HIV in pregnant women.

28. Please state recommendations to Decision Making Group(s)

Please give recommendations to decision making group e.g.

Sufficient evidence to support funding		
Insufficient evidence to support funding		
Product is clinically effective, but not cost-effective		X
Conduct a full HTA on this technology		

If funding recommended please specify group/situations for which technology should apply

Comments or caveats on recommendations

29. Membership of mini-HTA group

Please list members of the decision making group

30. References

List references to documents, research, information used to complete the form.

Reference List

(1) Society for the Study of Sexually Transmitted Diseases in Ireland. Irish Guidelines for the management of HIV-1 in pregnancy. 2011.

(2) Health Protection Surveillance Centre. Report on Voluntary Antenatal HIV Screening: 2002 to 2008. 2010 March.

(3) Dr Fiona Lyons. 17-5-2011.
Ref Type: Personal Communication

(4) Postma MJ, Beck EJ, Hankins CA, Mandalia S, Jager JC, de Jong-van den Berg LT, et al. Cost effectiveness of expanded antenatal HIV testing in London. AIDS 2000 Oct 20;14(15):2383-9.

(5) Sansom SL, Jamieson DJ, Farnham PG, Bulterys M, Fowler MG. Human immunodeficiency virus retesting during pregnancy: costs and effectiveness in preventing perinatal transmission. Obstet Gynecol 2003 Oct;102(4):782-90.

(6) Soorapanth S, Sansom S, Bulterys M, Besser M, Theron G, Fowler MG. Cost-effectiveness of HIV rescreening during late pregnancy to prevent mother-to-child HIV transmission in South Africa and other resource-limited settings. Journal of Acquired Immune Deficiency Syndromes 42 (2) (pp 213-221), 2006;Jun.

(7) Teerawattananon Y, Vos T, Tangcharoensathien V, Mugford M. Cost-effectiveness of models for prevention of vertical HIV transmission - Voluntary counseling and testing and choices of drug regimen. Cost Effectiveness and Resource Allocation 2005;7.

(8) Roland Tubiana, S Matheron, Le Chenadec, C Dollfus, A Faye, S Blanche, et al. Extremely Low Risk of MTCT of HIV in Women Starting HAART before Pregnancy: French Perinatal Cohort, ANRS EPF CO1/11. 18th Conference on Retroviruses and Opportunistic Infections 2011 Mar.

(9) UK National Screening Committee. Infectious Diseases in Pregnancy Screening Programme 2008 - 2009 Annual Report . 2010 Nov.

(10) Thorne C, Newell ML. Mother-to-child transmission of HIV infection and its prevention. Curr HIV Res 2003 Oct;1(4):447-62.

(11) Dr Karina Butler. 28-6-2011.
Ref Type: Personal Communication

(12) Central Statistics Office Ireland. Number of Births, Deaths and Marriages. http://www cso ie/statistics/bthsdthsmarriages htm 2011

(13) Haile-Selassie H, Masters J, Tookey PA. HIV-infected children diagnosed in the UK and Ireland, 2000-2009: country of birth, timing and reason for testing. 2010.

(14) R Tubiana, S Matheron, Le Chenadec, C Dollfus, A Faye, S Blanche, et al. Extremely Low Risk of MTCT of HIV in Women Starting HAART before Pregnancy: French Perinatal Cohort, ANRS EPF CO1/11. 18th Conference on Retroviruses and Opportunistic Infections 2011 Mar.

(15) Rozenbaum MH, Verweel G, Folkerts DK, Dronkers F, van den Hoek JA, Hartwig NG, et al. Cost-effectiveness estimates for antenatal HIV testing in the Netherlands. Int J STD AIDS 2008 Oct;19(10):668-75.

Appendix 2: Literature search strategy and summary of economic studies

A list of the search terms associated with the chosen concepts is given in Table App2.1, along with the initial search results from PubMed and Embase. No restrictions by date, study design or document type were applied. A flowchart illustrating how the studies were located is included in Figure App2.1.

Table App2.1 Search terms and initial results for the literature review

Concept	Search Terms	Results	
		Embase	**Pubmed**
HIV	HIV Acquired immunodeficiency syndrome	228829	196738
Antenatal	Pregnancy Antenatal Prenatal	1478535	295714 295714
Screening	Screening Screen* Test	5911108	6254079
Economic	Cost Economic	2087441*	239801

*For Embase the economic search terms were based on the Canadian Agency for Drugs and Technology in Health (CADTH) economic search terms.[19]

Figure App2.1 Flow chart of included studies

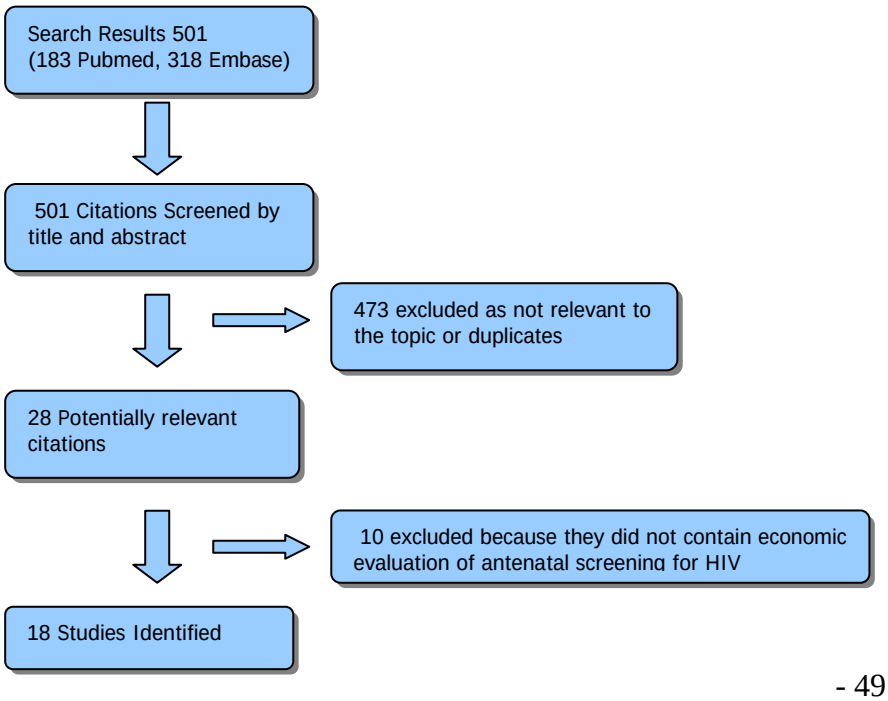

Table App2.2 – Summary of economic evaluations of antenatal screening for HIV to reduce the risk of MTCT

First Author (Year/Setting)	Screening Scenarios Assessed	Prevalence	MTCT Rate	Outcomes considered	Results
Ades[20] (1999/UK)	Universal Selective	0.16% (0.021-0.28)	No intervention: 26.5% With intervention: 7.6%	LYG (infant & mother)	Assuming a WTP of £10,000 per LYG net benefit £49,090
Bramley[21] (2003/New Zealand)	Universal before 28 weeks	0.03% (0.02-0.04)	No intervention: 25% With intervention: 2%	LYG (infant & mother) HIV cases detected HIV cases avoided	ICER per HIV-positive woman identified NZ$115,859
					ICER per HIV case avoided NZ$629,669
	Selective before 28 weeks				ICER per discounted LYG NZ$17,241
Graves[22] (2004/ Australia)	Universal before 28 weeks None	0%-0.02%	No intervention: 28% With intervention: 2%	LYG (infant & mother) HIV cases avoided	Cost-effective if prevalence undiagnosed HIV ≥0.004372%, assuming a LYG gained valued at AU$39,000
Hutton[23] (2003/ Chad)	Voluntary testing	11%	No intervention: 30% With intervention: 15%	HIV cases avoided	US$939 per case avoided
Kumar[24] (2006/ India)	Universal 2nd trimester	0.7% (0.4%-1.0%)	No intervention: 30% With intervention: 17%	HIV cases avoided Reduction in PYLL (infants only)	Rs25,787 per case avoided (high prevalence States only: Rs12,091)
	Universal high prevalence states only 2nd trimester				Rs1,935 per year reduction PYLL, (high prevalence States only: Rs907)
Lee[25] (2007/ Hong Kong)	Universal 25 weeks average	0.02% (0.01-0.05)	No intervention: 25% With intervention: 8.3%	LYG (infant & mother) HIV cases avoided	HKD 2,037,998 per case avoided
					HKD79,099 per discounted LYG
Myers[26] (1998/US)	Mandatory before 34 weeks	0.17% (0.05-1%)	No intervention: 25% With intervention: 12.5% after 34 weeks, 8.5% before	HIV cases avoided	Mandatory screening: US$255,158 average cost per case avoided
	Voluntary before 34 weeks				Voluntary screening: US$367,998 average cost per case avoided
					ICER for mandatory compared to voluntary screening: US$29,478
Patrick[27] (1998/ Canada)	Universal testing	0.037%	No intervention: 25% With intervention: 8%	HIV cases avoided	Can$75,266 net savings per case avoided
Postma[13] (2000/UK)	Universal Repeat universal & partner testing third trimester	0.27%	No intervention: 29% With intervention: 6%	LYG (infant & mother) HIV cases avoided	'Testing costs in the range £4-40 lead to favourable ICERs'
Postma[28] (1999/UK)	Universal before 26 weeks	0.01%-0.15%	No intervention: 29% With intervention: 6%	LYG (infant & mother)	ICER per LYG: £114,000

HIV – Human immunodeficiency virus; ICER – Incremental cost-effectiveness ratio; LYG=Life-years gained; MTCT – Mother-to-child-transmission; PYLL – Potential years of life lost; WTP – Willingness-to-pay; QALY – Quality-adjusted life year

Table App2.2 continued - Summary of economic evaluations of antenatal screening for HIV to reduce the risk of MTCT

First Author (Year/Setting)	Screening Scenarios Assessed	Prevalence	MTCT rate	Outcomes considered	Results
Rely[29] (2003/ Mexico)	Voluntary before end of 2nd trimester	0.09% (0.03-0.15)	No intervention: (15.8%-37.4%), With intervention: (5.2%-28%)	HIV cases avoided (including adult)	Voluntary testing at 85% would lead to $42,517 per case avoided
	Routine postnatal				ICER $7,000 for routine newborn screening
Resch[30] (2005/US)	No screening	5%	No intervention: 25.5% With intervention: 1.6% (11% if treatment for infant only)	HIV cases avoided	ICER $73,603 per case avoided compared with mandatory newborn screening alone.
	Mandatory newborn (MNS)				
	Voluntary at 20 weeks (VS)				
	VS & MNS				
	Routine at 20 weeks (RS)				
	RS & MNS				
Rozenbaum[31] (2008/Netherlands)	None	0.09% (0.05-0.14)	No intervention: (23%-29%) With intervention: 2%	LYG (infant only) HIV cases avoided	ICER is cost saving with a prevalence > 7.5 per 10,000.
	Universal				ICER= €1,979 per LYG with prevalence = 5.0 per 10,000
					ICER= €9,071 per LYG, prevalence = 2.5 per 10,000
Sansom[14] (2003/US)	Universal test early pregnancy	0.62% high risk 0.017% low risk	No intervention: (10%-19%) With intervention: (1%-2%)	LYG (infant only) HIV cases avoided	With incidence > 6.2 per 1,000 a 2nd test would be cost saving.
	2nd universal in third trimester				With incidence= 0.17 per 1,000 ICER $45,708 per LYG
Soorapanth[15] (2006/South Africa)	Early pregnancy	29.5% in pregnancy 2.3% incidence in pregnancy	No intervention: 19% With intervention: (1.9% -15.7%)	QALYs	Cost saving
	Early pregnancy screening plus rescreening in late pregnancy				
Teerawattananon [16] (2005/Thailand)	Early pregnancy	1.5%	OR with <4 weeks compared to>= 4 weeks 1.40,	HIV cases avoided	ICER for adding an additional voluntary screening = $16,000 per case avoided
	Early pregnancy screening plus rescreening in late pregnancy				
Udeh[32](2008/US Virgin Islands)	Screening by 14 weeks	4.9% (3.6%-6.1%) undiagnosed	No intervention: 28% With intervention: 2% < 14weeks, 10% at labour, 13.1% for newborn only	LYG (infant & mother)	All strategies would produce benefits and save costs
	Screening at onset of labour				
	Screening of newborn				
Zaric[33] (2000/US)	Voluntary prenatal screening	0.17% (0.1%-0.5%)	No intervention: (26.6%-44.2%) With intervention: (3%-11.1%)	LYG (infant & mother) HIV cases avoided	ICER of $8,900 per LYG, for improved participation in voluntary testing

HIV – Human immunodeficiency virus; ICER – Incremental cost-effectiveness ratio; LYG=Life-years gained; MTCT – Mother-to-child-transmission; WTP – Willingness-to-pay; QALY – Quality-adjusted life year

Appendix 3: Parameters used in the effectiveness model

This appendix outlines the key parameters used in the effectiveness model and provides details on how the parameter estimates were derived.

App 3.1 Prevalence of current undiagnosed HIV in women during the third trimester

The prevalence of undiagnosed HIV in women in the third trimester is a key parameter as it determines the likely number of exposed infants each year and dictates the probable number of infected infants in the cost-effectiveness model. There are no studies of this prevalence in Ireland. Thus, it was necessary to estimate this.

The estimated prevalence was based on a total of three observed cases born to women with undiagnosed HIV at delivery between 2007 and 2009.[7] The total number of births during that period was 221,182.[34] Assuming a MTCT rate of 25%-30% (see App3.5 for more details), then there were approximately 10-12 women with unknown HIV at delivery between 2007 and 2009. This gives us a prevalence of approximately 5 per 100,000. This is, however, a minimum estimate as there may be children who have not yet been diagnosed. Of note, the three observed cases occurred in women with documented negative screening tests for HIV at antenatal booking and who did not received further testing during their pregnancy. To estimate how many infants may yet be undiagnosed, data from the National Study of HIV in Pregnancy and Childhood (NSHPC) for the UK and Ireland was used. This suggests for those born in the UK and Ireland, 48% are diagnosed by 1 year and a further 28% by age 4.[35] Thus, we can assume that there is approximately between 25%-50% yet to be diagnosed equating to an additional 1-2 cases. Using the maximum to give an upper value of a total of five cases, this gives an estimated maximum prevalence of 9 per 100,000. The midpoint of this range, 7 per 100,000, was used as the base case value in the model.

It should be noted however, that of the three observed cases, two were breastfed and so maternal seroconversion may have occurred during breastfeeding.[7] If this were the case, then the true prevalence of undiagnosed maternal infection at delivery would be lower than we have estimated.

Parameter	Distribution	Median	95% range
Prevalence of undiagnosed HIV at delivery (per 100,000)	Beta	7	(5-9)

App 3.2 MTCT when HAART begins in the third trimester

The ability of HAART to successfully reduce the MTCT is a critical component of the model. The number of additional HIV-positive births avoided was based on a MTCT rate of 2.6% (95% CI 1.7%, 4.1%) for HAART beginning after 28 weeks.[36] Although the proposed screening programme would result in antiretroviral therapy beginning between 30-36 weeks, we assume that the MTCT of 2.6% is not reduced by this slightly later starting time.

Parameter	Distribution	Median	95% range
MTCT rate with antiretroviral therapy beginning after 28 weeks (%)	Beta	2.6	(0.7, 4.1)

App 3.3 Average life expectancy of infant born HIV-positive

The number of life years gained was based on the difference between the current life expectancy at birth in the general population and the estimated average life expectancy of 19 years for those born HIV-positive, with a maximum life expectancy for this group estimated as twice this at 38 years.[31] The average life expectancy at birth was kept at the base case value in the full model, and only varied in the univariate sensitivity analysis. This was done as it was considered not realistic for the average life expectancy to be less than 19 years. However, as average life expectancy is known to be increasing in those born HIV-positive, the univariate sensitivity analysis allowed the impact on the analysis of a doubling in the current average life expectancy to be investigated.

Parameter	Median	Range
Life expectancy of HIV-positive infant (yrs)	19	(19-38)

App 3.4 Number of pregnancies per year

The number of births per year was used as a proxy for the number of pregnancies. This will lead to an overestimate in the number of pregnancies as it assumes that each birth relates to one pregnancy whereas twin and higher order multiple births mean that the number of pregnancies is lower than the number of births resulting in fewer women in need of repeat screening. In 2009 this would have led to an overestimate of 1.6%.[37] Also as it includes both still and live births the number of exposed infants will be overestimated slightly, by approximately 0.5%.[37] Both these issues would have a negligible effect on the ICER thus the number of births was considered a reasonable proxy for the number of pregnancies. The median value for the base case was set as the number of recorded births in 2008. The range around the annual number of births is based on a lower value seen in 2005 and an upper value that reflects the continued annual increase seen since 2000.[34]

Parameter	Distribution	Median	95% range
Number of pregnancies per year (000's)	Normal	75	(60-90)

App 3.5 MTCT when there is no intervention

For an Irish or European population, the MTCT is anticipated to be between 15 - 20%.[38] However, typically over 80% of the cohort of HIV-positive women giving birth in Ireland are of African origin[39] for whom a higher MTCT of 25 - 40% in the absence of interventions could be expected.[38] Some of the differences between these rates is due to a higher prevalence of breastfeeding among the African population,[38] thus, 25-30% was chosen as a conservative estimate for the total cohort of HIV-positive women in Ireland.

Parameter	Distribution	Median	95% range
MTCT rate without intervention (%)	Beta	27.5	(25-30)

App 3.6 Uptake rate

Published data from the Health Protection Surveillance Centre (HPSC) reports uptakes rates of 99.1% in 2007 and 99.9% in 2008.[6] The HPSC report however, does not include all data from all locations providing antenatal care with approximately 15% of women not included in this data. While testing data is limited to the 85% reported to the HPSC, there is no reason to believe that the screening acceptance rate differs among those in the reported cohort and those in the non-reporting hospitals. Obviously, not all of these women may be currently

offered screening; however, all are eligible and entitled to screening and antenatal screening in early pregnancy for HIV represents best practice. Thus, the conservative approach was to include all women eligible for screening as this would represent the maximal cost to the publicly-funded healthcare system.

Parameter	Distribution	Median	95% range
Screening uptake rate (%)	Beta	99	(98-99.9)

App 3.7 Prevalence of known HIV in pregnant women

The most recent data from the HPSC reports the prevalence of known HIV in pregnant women in Ireland as 2 per 1,000 in 2007 and 2008.[6]

Parameter	Distribution	Median	95% range
Prevalence of known HIV in pregnant population (%)	Beta	0.2	(0.15-0.25)

App 3.8 Discounting

For a cost-effectiveness analysis, it is standard practice to compute the present value of future events using discounting. The further into the future the event occurs, the lower the (discounted) present day value. In this study, standard discounting applies to life years gained and costs at a rate of 4% per annum.[4]

Parameter	Distribution	Median	95% range
Discount rate (%)	Beta	4	(1.7-5.7)

Appendix 4: Cost estimates

App 4.1 Methodology

Recurring costs related to the introduction of antenatal screening for HIV in the third trimester were identified based on discussions with the National Virus Reference Laboratory (NVRL), the Coombe Women & Infants University Hospital and individuals involved in the multidisciplinary advisory process. The costs inputs for the cost-effectiveness model relate to the incremental cost of repeat universal antenatal screening for HIV in the third trimester, that is, added costs over and above the current costs of universal screening at antenatal booking combined with opportunistic screening in the third trimester for those identified to have an ongoing risk of HIV-infection. Cost savings related to the reduced consumption of existing resources were included as appropriate. Costs considered in estimating the marginal unit cost for the intervention included: the cost of the blood draw (including phlebotomy staff time and disposable items); the HIV test; any additional HIV tests for confirmation or clarification; pregnancy-related treatment costs for mothers found to be HIV-positive; treatment of exposed infants to reduce mother-to-child-transmission (MTCT); and testing of exposed infants for HIV. Costs were provided by the NVRL, St James's Hospital and the Coombe Women & Infants University Hospital.

Consistent with national guidelines, VAT was not applied to costs for the cost-effectiveness analysis.[4] VAT at the relevant rate was applied when assessing the budget impact of introducing repeat universal antenatal screening for HIV in the third trimester. In assessing costs, consistent with national guidelines, the perspective adopted was that of the publicly-funded health and social care system. Consistent with this, only direct costs to the HSE were included in the analysis.

App 4.2 Assumptions

All costs were allowed to vary by ±20% from the base case value. The distribution of costs for each item is assumed to centre on the base case value and follow a beta distribution (□□= 2, □= 2).

App 4.3 Recurring costs

When calculating the cost of introducing repeat universal antenatal screening for HIV in the third trimester, it is the additional number of women screened compared to the current practice of opportunistically screening those at high risk that we must consider rather than the total number of women screened.

Those women identified as HIV-positive during screening early in pregnancy were assumed not to be retested. The uptake rate in the third trimester was assumed to be the same as that seen in the current universal screening for HIV carried out at antenatal booking. We assume that screening is offered to all eligible women and that all women will attend an antenatal appointment before 36 weeks gestation. The estimated proportion of women retested opportunistically during pregnancy was based on 2010 data from the Coombe Women & Infants University Hospital which showed that 0.8% of women were retested during their pregnancy.[40]

Thus, the additional number to be screened was calculated by first excluding those known to be HIV-positive, those found to be HIV-positive during the first universal screening and those who would be re-screened because of identified risk factors subsequent to this. The national uptake rate was applied to the remaining cohort to give the number of additional HIV tests.

App 4.4 HIV test costs

Cost of the additional HIV test includes the initial cost of the routine HIV test and the cost of any subsequent HIV confirmatory tests required.

The initial HIV test used is Architect HIV Ag/Ab at €10.91 per test.[41] The additional HIV tests used when confirming a HIV-positive sample or when dealing with problematic samples will vary according to the results of the sample, but will typically consist of some combination of the following tests: Vidas Ultra anti-HIV Ag/Ab €36.55, Innolia HIV confirmation 1+2 €76.19, Biorad Genscreen HIV Ultra Ag/Ab €32.04 and Innotest HIV 1+2 Antigen €90.03. In the model, an average cost for a problematic or HIV-positive sample of €57.21 was used; this was based on the average cost seen by the NVRL in 2010.[42] All costs are based on current list prices, are inclusive of labour and do not attract VAT.

App 4.5 Blood sampling costs

The cost of taking the blood sample includes the phlebotomy staff time and the disposable material costs.

The disposable costs for taking a blood sample are as follows: Nitrile Gloves €33.27 per 100; sterile cotton wool balls €0.12 per pack of five; injection swabs €0.01 each; blood sampling needles (Needle 1373) €0.33 each; blood bottle (Monovette 1167) €0.13 each; tape (Leukopor) €0.92 per roll. All prices include VAT at 21%. The total cost per individual patient is €1.19 per single blood sample.[43]

The additional staff costs arise when taking the blood sample for the initial HIV test. It was assumed that the blood sample would be taken by a phlebotomist and it was estimated that a phlebotomist could take 8-9 samples an hour.[44] Thus it would take the equivalent of 5.2 full time phlebotomists working 7 hours a day for 225 days a year to take the additional 74,141 blood samples. The published Department of Health salary scales were used to calculate pay-related costs for the phlebotomist. The payscale for a phlebotomist is €30,392 to €38,716 and has a total of seven increments.[45] The additional cost of new staff was calculated and adjusted for pay-related costs in accordance with national guidelines, that is, standard PRSI contributions of 10.75%, imputed pension costs at 17% and general overheads at 30% of salary were applied.[5]

App 4.6 Treatment costs for the mother

The average cost of Highly Active Anti-Retroviral Therapy (HAART) from diagnosis to delivery is assumed to be based on the antiretroviral therapy regimen outlined in draft national guidelines for the management of HIV in pregnancy. This regimen is: Combivir® one tablet twice daily (€461.59 per 60)[46] and raltegravir (Isentress®) one 400mg tablet twice daily (€867.74 per 60)[46] from approximately 33 weeks to delivery. Delivery was expected to occur by elective caesarean-section between 38 and 39 weeks. Thus, it was assumed that antiretroviral therapy would last on average 5.5 weeks. As these are hospital-only drugs, a 15% discount was applied to these costs to reflect the average cost to the publicly-funded healthcare system as per guidelines from the National Centre for Pharmacoeconomic (NCPE).[47]

The cost of treatment during delivery includes intravenous zidovudine (Retrovir®) at a dose of 2mg/kg loading over 1 hour then 1mg/kg per hour until cord clamped (€96.31 200mg/20ml per box of five vials). [46] The average weight of women during the 1st trimester is 68kg[48] assuming that the average weight gain during pregnancy falls within the recommended range of 11.5kg-16kg[49] then the average women will weigh approximately

80kg at delivery. For women undergoing an elective caesarean-section, the transfusion would start 4 hours prior to surgery; if we assume up to 1 hour in theatre, an 80kg female would require 160mg/hr for 1 hour then 80mg/hr for 4 hours or 400mg or 2 vials. As these are hospital-only drugs a 15% discount was applied to these costs as per NPCE guidelines.[47]

An estimated 95% of women identified with HIV in the third trimester will deliver via caesarean-section[50] compared with 26.2% in the general population.[37] The average cost per delivery method were calculated using casemix data and estimated as €6,305 for a caesarean-section and €2,448 for a vaginal delivery.[51] The incremental cost of caesarean delivery is calculated based on the additional cost of this delivery method over a vaginal delivery and based on the number of additional caesarean deliveries required in the HIV cohort.

App 4.7 Treatment costs for the infant

All exposed infants born to HIV-positive women receive prophylactic HAART for 4 weeks. This regimen includes zidovudine (Retrovir®) 4mg/kg/dose every 12 hours (€33.47/200ml),[46] lamivudine (Epivir®) 2mg/kg/dose every 12 hours (€55.45/240ml)[46] and nevirapine (Viramune®) 2mg/kg/dose two doses only (€78.42/bottle).[46] We assumed an average infant weight of 3.5kg [37] and again as these are hospital-only drugs, a 15% discount was applied to these costs as per NPCE guidelines.[47]

If the mother is known to be HIV-positive and managed accordingly in pregnancy, infants will have five HIV viral loads during the first 2 years months of life. Viral loads at 3-6 months intervals are required to confirm the infant is HIV-negative, and that HIV was not acquired during delivery. Infants are tested with Architect HIV Combo Ag/Ab €10.91, Innolia Confirmation HIV 1+2 €76.19 and HIV Viral (Abbott M200) €97.83.[52]

App 4.8 Cost Savings

Cost savings in the avoidance of lifetime treatment costs for HIV-positive births are based on costs contained in Rozenbaum et al..[31] These costs were provided at 2003 prices for the Netherlands. To convert these into 2011 Irish costs they were first inflated using the consumer price index (CPI) for health from the Netherlands [53] into 2011 costs. These costs were then transferred into Irish costs using the most recent purchasing power parities.[54] The purchasing power parity index takes account of both the currency exchange rate as well as the different purchasing power of the countries.

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For further information please contact:

Health Information and Quality Authority
George's Court
George's Lane
Dublin 7

Phone: +353 (0)1 814 7400
Email: info@hiqa.ie
URL: www.hiqa.ie