



**Health
Information
and Quality
Authority**

An tÚdarás Um Fhaisnéis
agus Cáilíocht Sláinte

The Role of Human Papillomavirus Vaccines in Reducing the Risk of Cervical Cancer in Ireland

A Health Technology Assessment

25th February 2008

Foreword

Cervical cancer is the 8th most frequently diagnosed cancer in women in Ireland. In 2004, 200 women were diagnosed with cervical cancer in Ireland, with more than 90 women dying from the disease. On average, these women were 56 years old at the time of death, and 44 years at the time of diagnosis. Infection with the human papillomavirus (HPV) is the main cause of cervical cancer, without which cervical cancer does not arise. Vaccination against HPV therefore represents a new opportunity to reduce the incidence of, and mortality associated with, cervical cancer.

In July 2007, the Health Information and Quality Authority agreed to undertake a health technology assessment on the role of vaccination against HPV in reducing the risk of cervical cancer in Ireland in response to a request by the National Cancer Screening Service Board.

The purpose of this assessment was to establish the cost-effectiveness of a combined national HPV vaccination and cervical cancer screening programme compared to a cervical cancer screening programme alone in the prevention of cervical dysplasia (the condition that can lead to cervical cancer) and cervical cancer due to HPV types 16 and 18 in Ireland.

The Authority commissioned the National Centre for Pharmacoeconomics (NCPE) to conduct the health technology assessment on its behalf. To lead and oversee the process and advise the Authority, a multidisciplinary Expert Advisory Group was convened. The draft technical assessment was submitted by the NCPE to the Expert Advisory Group for consideration. The Expert Advisory Group has approved the findings of the technical report. The Board of the Authority has subsequently authorised the report and recommended it to be submitted to the Minister for Health and Children, the National Cancer Screening Service Board and the National Immunisation Advisory Committee. A decision on the adoption and implementation of a HPV vaccine as part of the national immunisation schedule will be taken by the Minister for Health and Children, following due consideration of all available evidence.

The following report contains an outline of the health technology assessment as well as the technical report prepared by the NCPE.

The Authority would like to thank the National Centre for Pharmacoeconomics, the members of the Expert Advisory Group and all who contributed to the production of this report.

Dr Tracey Cooper

*Chief Executive Officer
Health Information and Quality Authority*

25 February 2008

Health Technology Assessment Process

In August 2007, the Authority commissioned the National Centre for Pharmacoeconomics (NCPE) to conduct the health technology assessment on its behalf. To lead and oversee the process and advise the Authority, a multidisciplinary Expert Advisory Group was convened, the inaugural meeting of which was held in September 2007. The terms of reference for this group were to:

- *Provide advice on refining the scope of the evaluation including, but not limited to, factors such as the patient groups to be considered (for example, gender, age), the appropriate comparison as standard of care, and the type of modelling approach to be used.*
- *Review the project plan outline and advise on priorities as required.*
- *Review the draft report prepared by the Evaluation Team at the National Centre for Pharmacoeconomics and recommend amendments as appropriate.*
- *Contribute to the development of the Authority's approach to health technology assessment by participating in an evaluation of the process on its conclusion.*

The membership of the group was as follows:

Chairperson: Jon Billings, Director of Healthcare Quality, Health Information and Quality Authority

Dr. Patricia Harrington, HTA Project Manager, Health Information and Quality Authority

Hilary Coffey Farrell, Patient representative, Irish Cancer Society

Joan Kelly, Public representative, Irish Cancer Society

Professor Brian Keogh, National Immunisation Advisory Committee

Dr. Gráinne Flannelly, Institute of Obstetricians and Gynaecologists

Dr. Alan Smith, National Cancer Screening Service

Dr. Darina O'Flanagan, Health Protection Surveillance Centre

Dr. Jack Lambert, Consultant in Infectious Disease, Mater Hospital

Dr. Kevin Kelleher, Health Service Executive

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Dr. Dearbhaile O'Donnell, Irish Society of Medical Oncologists

Dr. Rod Taylor, Peninsula Technology Assessment Group (PenTAG), Peninsula Medical School, Universities of Exeter and Plymouth, UK

Diana Reerman, Danish Centre for Health Technology Assessment, National Board of Health, Denmark

In attendance: Debra Scott, PA to Director of Health Technology Assessment

Conflict of Interest: No conflicts declared

This HTA will be considered for review in February 2011.

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Outline

The Role of Human Papillomavirus Vaccines in
Reducing the Risk of Cervical Cancer in Ireland –
A Health Technology Assessment

25 February 2008

1 Introduction

In July 2007, the Health Information and Quality Authority agreed to carry out a health technology assessment (HTA) on the role of vaccination against human papillomavirus (HPV) in reducing the risk of cervical cancer in Ireland in response to a request by the National Cancer Screening Service Board.

The purpose of this assessment was to establish the cost-effectiveness of a combined national HPV vaccination and cervical cancer screening programme compared to a cervical cancer screening programme alone in the prevention of cervical dysplasia (the condition that can lead to cervical cancer) and cervical cancer due to HPV types 16 and 18 in Ireland.

Cervical cancer is the 8th most frequently diagnosed cancer in women in Ireland. In 2004, 200 women were diagnosed with cervical cancer in Ireland, with more than 90 women dying from the disease. On average, these women were 56 years old at the time of death, and 44 years at the time of diagnosis. Infection with HPV is the main cause of cervical cancer.

The following explains what HTA is and describes the findings of this HTA. A more detailed description of the HTA and its findings can be read in the Technical Report. A glossary of technical terms used in the report can be found at the end of the Technical Report.

2 Background

What is the role of the Health Information and Quality Authority in HTA?

The Health Information and Quality Authority is an independent Authority reporting to the Minister for Health and Children established on May 15, 2007. The Authority is the statutory organisation in Ireland with a remit to carry out national Health Technology Assessments (HTAs) and to develop standards for the preparation of these HTAs across our health system.

What is Health Technology Assessment (HTA)?

Health technology assessment is a form of health research that generates information about the clinical and cost-effectiveness of health technologies as well as information on their wider impact. The term 'technology' includes drugs, medical equipment, diagnostic techniques, surgical procedures and public health programmes for example, cancer screening programmes. This information is for use by the public, service providers and the Department of Health and Children. The main issues investigated as part of any HTA are:

- *Does the technology work?*
- *For whom does it work?*
- *What is the benefit to the patient?*
- *At what cost?*
- *How does it compare to the alternatives?*

How is a HTA carried out?

A health technology assessment usually consists of two interlinked parts: a systematic review of the available published and unpublished literature and an economic evaluation.

The literature review is used to collect important information on the disease process that the technology is targeting and on the efficacy (how well it works) and safety of the technology in comparison to the other alternatives. In this case, it included information on the efficacy, safety and duration of action of the HPV vaccine, the relationship between HPV and cervical cancer and the occurrence of cervical dysplasia and cancer in Ireland.

The economic evaluation includes a cost-effectiveness analysis, in which alternative courses of action are compared (in this case, vaccination of all 12 year old girls against HPV combined with a cervical screening programme versus a cervical screening programme alone). The health benefit of the technology is measured in natural units (for example, life years gained) and the costs are measured in euro.

What measurements are used?

The cost per life year gained (LYG) measures the impact of a technology on patient survival, and is frequently used in published economic evaluations of vaccine programmes. If the effect of a technology on the quality of life as well as on survival is to be considered, both are combined into a single common unit of measure called the Quality Adjusted Life Year (QALY), and the cost per QALY is calculated. Both LYG and QALYs are widely used in HTAs in other countries.

In this HTA, LYG was used to allow comparisons to be made with two recent economic evaluations of vaccines in the Irish setting. Using LYG to measure the impact of the vaccine makes the estimate of the cost-effectiveness more conservative as it only takes into account the effect on the duration of life (mortality) rather than the effect on both illness (morbidity) and mortality.

The question is then, how much more benefit is achieved from a technology for the additional cost. To answer this question, the “incremental cost-effectiveness” of one technology over the other is calculated, with the results presented as an incremental cost-effectiveness ratio (ICER). The ICER, therefore, describes how much additional benefit is achieved for the additional cost incurred.

One of the implications of making comparisons of the cost-effectiveness of different technologies is that there is a threshold ratio above which a programme would not be considered to be cost-effective. In practice, there is no fixed threshold above which an ICER would not be considered cost-effective, or below which it would. However, if a technology has an ICER that is significantly higher than other healthcare technologies that are already reimbursed, other factors such as the innovative nature of the technology, or the wider costs and benefits to society would need to be taken into consideration.

The ICER is a measurement that allows the cost-effectiveness of different technologies to be compared and should not be considered as putting a value on a year of life.

3 Human Papillomavirus (HPV) and Cervical Cancer

Human papillomavirus describes a family of viruses, of which over 100 types have been identified. The virus is transmitted mainly through sexual contact. HPV types vary in their ability to cause cancer and other conditions and are classified as “low-risk” or “high-risk” in terms of their ability to cause cancer.

In Europe, the most common “high-risk” HPV types are types 16, 18, 45, 31, 52, 58 and 35. Of these, types 16 and 18 cause about seven out of ten cases of cervical cancer. While HPV types 6 and 11 are classified as being “low-risk” in terms of their ability to cause cancer, they cause nine out of ten cases of anogenital warts.

Infection with the human papillomavirus (HPV) infection is the main cause of cervical cancer. Important points in relation to this are as follows:

- *Typically, there may be 10 to 20 years between infection with HPV and the development of cervical cancer. During this time, changes in the cells of the cervix occur (cervical dysplasia), which gradually progress in severity from mild (CIN 1) to moderate (CIN 2) to severe dysplasia and cancer (CIN 3), before ultimately developing into invasive cancer of the cervix. (CIN stands for cervical intraepithelial neoplasia).*
- *While up to eight out of ten women become infected with HPV during their lifetime, most do not experience any symptoms from the virus and clear the infection within two years.*
- *Even if the infection persists and changes in the cells of the cervix occur, such changes can return to normal without treatment.*
- *Because cervical cancer usually develops slowly, changes in the cells can be detected and treated at an early stage when women participate in cervical cancer screening programmes.*
- *Vaccination against HPV infection does not get rid of the need for routine cervical cancer screening, as the vaccines only target the two HPV types that cause seven out of ten cases of cervical cancer. Also, the vaccines may not be 100% effective, their long-term efficacy has not yet been established in clinical trials longer than five years, and the vaccines are not effective in women already infected with those specific types of HPV.*

A national cervical cancer screening programme is due to be rolled out in Ireland in 2008. It is anticipated that women in the programme will be screened every three years between the ages of 25 and 44 years, and then every five years up to sixty years of age. Similar organised national screening programmes in other countries, such as the United Kingdom and Scandinavia, have resulted in a substantial reduction in the number of new cases and in the death rate due to cervical cancer.

4 Vaccines Against Human Papillomavirus

Two vaccines are licensed in Ireland to prevent HPV infections: Gardasil™ (Sanofi Pasteur MSD) which was licensed in September 2006, and Cervarix™ (GlaxoSmithKline Biologicals) which was licensed in September 2007. Both vaccines target HPV types 16 and 18. Gardasil™ also targets HPV types 6 and 11, which cause anogenital lesions (warts). The vaccines are given as a course of three injections over a six-month period.

The efficacy of these vaccines

These vaccines have been shown to be effective in preventing cervical dysplasia, the condition that can lead to cervical cancer, in follow-up studies over a five-year period of women that did not have HPV at the time of vaccination.

The FUTURE II study published in 2007, examined the efficacy of Gardasil™ against moderate to severe cervical dysplasia (CIN 2+) related to HPV types 16 and 18 in 12,167 women aged between 16 and 26 years. Half of the study group received the Gardasil™ vaccine while the other half received a placebo (dummy) vaccine. Both groups of women were followed at regular intervals over the following three years. Among women who received at least one dose of the vaccine and who were not infected with HPV types 16 and 18 at the time of first vaccination, the vaccine was 95% effective in preventing cervical dysplasia.

Interim results from the PATRICIA trial published in 2007, reported the efficacy of Cervarix™ in preventing moderate to severe cervical dysplasia (CIN 2+) related to HPV types 16 and 18 in 18,644 women aged between 15 and 25 years of age. The interim results at 14.8 months follow-up indicated a vaccine efficacy of 90.4% for women who received at least one dose of the vaccine and were not infected with HPV types 16 and 18 at the time of first vaccination.

The safety of both vaccines has been shown in clinical trials. Both vaccines have been well tolerated without serious vaccine-related side effects. The vaccine is not currently recommended in pregnant women. For both vaccines, up to nine out of ten women (90%) have reported mild-to-moderate reactions at the injection site.

Studies of vaccine safety and efficacy are ongoing, as current studies are not longer than five years in duration. Future research will look at the question of whether or not a booster dose of the vaccine will be needed to keep them immune from HPV, or if the vaccine will protect against HPV infection indefinitely. The current vaccines protect against two types of HPV that cause cervical cancer. Future research may develop other vaccines that cover against a broader range of HPV types.

5 Health Technology Assessment on the Role of HPV Vaccination in Reducing the Risk of Cervical Cancer

The availability of vaccines targeted against HPV provides a new opportunity to reduce the risk of cervical cancer. In response to a request by the National Cancer Screening Service Board, the Health Information and Quality Authority agreed to carry out a HTA to look at the role of these vaccines in reducing the risk of cervical cancer in Ireland.

The purpose of this assessment was to estimate the cost-effectiveness of a combined national HPV vaccination and cervical cancer screening programme compared to a cervical cancer screening programme alone in the prevention of cervical dysplasia and cervical cancer related to HPV types 16 and 18 in Ireland.

The Health Information and Quality Authority commissioned the National Centre for Pharmacoeconomics (NCPE) to conduct the health technology assessment on its behalf. NCPE has extensive experience in HTA of pharmaceuticals and vaccines and has recently completed HTAs on universal infant hepatitis B vaccination and universal infant pneumococcal vaccination. To lead and oversee the process and advise the Authority, a multidisciplinary Expert Advisory Group was convened. This group included both public and patient representatives.

To complete the assessment, the NCPE used established economic modelling techniques, which included adapting an independent economic model to the Irish setting. Much of the published literature relates to economic models funded by the two vaccine manufacturers. The NCPE analysis incorporated an independent model funded by the Danish National HTA Agency, DACEHTA, for use in its assessment of the HPV vaccines.

Estimates and data on the efficacy of the vaccines and on Irish costs for vaccination and treatment of cervical cancer, resource use, as well as data on the frequency and treatment of HPV-related cervical cancer were incorporated into the model. These data were taken from published randomised controlled clinical trials, from Irish databases and from consultation with members of the HPV Vaccine HTA Expert Advisory Group.

The HPV Vaccine HTA Expert Advisory Group agreed that vaccination against HPV should be completed at a younger age to reduce the chance of being exposed to HPV prior to vaccination. It was agreed that the main focus would be on a school-based vaccination programme for all girls in the first year of secondary school, that is, 12 year olds. A school-based programme was recommended to try and maximize the number of children that would be vaccinated. A programme that looked at the first year of secondary school rather than the last year of primary school was preferred in consideration of potential parental concerns and for logistical reasons, for example, there are far fewer secondary schools than primary schools.

Assumptions:

The Expert Advisory Group agreed on a number of assumptions to be included into the economic model, such as:

- *Eight out of ten girls eligible to receive the vaccine through school-based immunisation programmes would complete the course of three doses based on observed uptake in other school-based immunisation programmes*
- *Eight out of ten women would attend a national cervical cancer screening programme*
- *The vaccine would:*
 - *Prevent 95% of cases of cervical cancer related to HPV types 16 and 18 in individuals that did not have HPV at the time of vaccination*
 - *Provide lifelong protection*
 - *Cost €100 per dose*
 - *Cost €30 per dose to administer, if given as part of a school-based programme*

6 Findings

Vaccination of 12 year old girls only against HPV types 16 and 18, assuming eight out of ten girls receive the vaccine, results in an incremental cost-effectiveness ratio (ICER) of approximately €17,383/life year gained (LYG). This compares favourably with the recent economic evaluations of universal infant pneumococcal conjugate vaccination (€5,997/LYG) and universal infant hepatitis B vaccination (€37,018/LYG) in the Irish setting.

The cost-effectiveness of implementing a catch-up programme for the following age groups in the first year of vaccination only was investigated: 13 to 15 years, 13 to 17 years, 13 to 19 years and 13 to 26 year olds. Although, the most cost-effective strategy is vaccination of 12 year old females only, vaccination of 13 to 15 year old females in the first year of the programme is likely to be the most cost-effective catch-up scenario. The catch-up scenario for 13 to 15 year olds is associated with a relatively large increase in health benefits compared to the other catch-up scenarios.

Setting up of a catch-up programme for 13 to 15 year olds would incur an extra one off cost of €29.2 million in the first year of the vaccination programme. Following that, the cost of HPV vaccination of all 12 year old girls is estimated at €9.7 million per annum.

The results suggest that the additional benefit of vaccinating 15 to 26 year olds may be very small compared to the associated increase in vaccine costs. At older ages, the vaccine becomes less effective due to an increased likelihood of being exposed to HPV before vaccination, thereby reducing its cost-effectiveness.

As noted, the economic model is based on a number of key assumptions. These assumptions were varied in order to estimate the level of uncertainty around the results. The results of the economic model varied with changes in a number of key assumptions, including the duration of protection from vaccination, the proportion of cases of CIN and cervical cancer caused by HPV types 16 and 18, as well as the rate of vaccine coverage. However, the vaccination of 12 year old girls remained cost-effective when these assumptions were varied.

In the main analysis, lifelong protection from vaccination was assumed. If a booster dose is required after ten years, the vaccination programme would be less cost effective, increasing the ICER from €17,383 to €24,320/LYG.

The results of this evaluation are considered conservative as the benefits of including improvements in quality of life, potential cross-protection of the vaccine against other HPV types, as well as the efficacy of the vaccine against HPV types 6 and 11 which cause anogenital warts were not included. On the other hand, the additional resources required to introduce a HPV vaccination programme, such as implementing surveillance systems and running educational campaigns, have not been included in the analysis.

Vaccination against HPV types 16 and 18 is a long-term investment, as the initial costs of vaccination will only be offset by improved health outcomes and treatment savings 15 to 30 years in the future.

7 Conclusions

The results of the cost-effectiveness analysis of the introduction of HPV vaccination for the prevention of cervical cancer in Ireland show that universal HPV vaccination of 12 year old females would be a cost-effective technology in the Irish healthcare setting. In relation to a catch-up programme, vaccination of 13 to 15 year old females in the first year of the programme would be the most cost-effective catch-up strategy.

HPV vaccines do not eliminate the need for a cervical cancer screening programme, as currently available HPV vaccines do not offer protection against all types of HPV that can cause cervical cancer. Screening is also essential to protect adult women who have not been vaccinated. Therefore, it is important that women are informed and motivated to attend for screening when invited to do so, even if they have received a HPV vaccine.

Vaccination (primary prevention) and screening (secondary prevention) are complementary approaches to controlling cervical cancer in Ireland. In due course, the impact of HPV vaccination on a population-based cervical screening programme, together with new technologies such as HPV DNA testing will need to be monitored.

The draft technical assessment was submitted by the NCPE to the Expert Advisory Group for consideration. The Expert Advisory Group has approved the findings of the technical report. The Board of the Authority has subsequently authorised the report and recommended it to be submitted to the Minister for Health and Children, the National Cancer Screening Service Board and the National Immunisation Advisory Committee. A decision on the adoption and implementation of a HPV vaccine as part of the national immunisation schedule will be taken by the Minister for Health and Children, following due consideration of all available evidence.

Note: No recommendation was made as part of this HTA as to which of the two licensed HPV vaccines should be offered.

Advice to the Minister for Health and Children

The Health Act 2007 states that one of the functions of the Health Information and Quality Authority is “to evaluate the clinical and cost effectiveness of health technologies including drugs and provide advice arising out of the evaluation to the Minister and the Executive.”

The advice to the Minister for Health and Children on the role of human papillomavirus vaccines in reducing the risk of cervical cancer in Ireland is as follows:

The results of this HTA suggest that vaccination against HPV types 16 and 18 would be cost-effective from the perspective of the Irish healthcare payer. However, it is clear that any economic evaluation is only as accurate as the data inputs included in the model. As economic models incorporate a number of assumptions, the results are subject to a degree of uncertainty. Bearing in mind the estimates and assumptions that were used in this analysis, the following conclusions can be drawn:

- *If annual vaccination against HPV types 16 and 18 is introduced for 12 year old girls only, with a vaccination coverage rate of 80%, an ICER of approximately €17,383/LYG is estimated. This result compares favourably with the findings of the economic evaluations of universal infant pneumococcal conjugate vaccination (€5,997/LYG) and universal infant hepatitis B vaccination (€37,018/LYG) in the Irish setting^{32, 33}. Had the model incorporated impact on quality of life in addition to impact on mortality, it is likely that the cost/QALY would be lower than the cost/LYG, yielding an ICER well below the guideline threshold of €45,000/QALY routinely used for economic evaluation of drugs in Ireland (Section 1.3.2).*
- *A catch-up programme for 13 to 15 year olds in the first year of vaccination results in a relatively high increase in health benefits compared to the other catch-up scenarios. In contrast, the results suggest that the marginal benefit of vaccinating 15 to 26 year olds may be negligible compared to the associated vaccine expenditure. At older ages, the vaccine becomes less effective due to an increased likelihood of pre-vaccination HPV exposure reducing cost-effectiveness.*
- *The ICER for annual vaccination of 12 year old girls plus catch-up for 13 to 15 year olds in the first year of vaccination was estimated to be €52,968/LYG. While acknowledging the implicit uncertainty in the model, had the impact on quality of life in addition to impact on mortality been incorporated, it is likely that the cost/QALY would be lower than the cost/LYG, yielding an ICER close to the guideline threshold of €45,000/QALY; therefore, this scenario is likely to be cost-effective.*

- *The ICER for extending the catch-up programme to 17 year olds compared to a catch-up to 15 year olds is €1,071,532/LYG and would clearly not represent a cost-effective use of resources. Cost-effectiveness of extending catch-up beyond 17 years is not considered, as the appropriate comparison is for each scenario to be compared to the one before, but only if the preceding one is cost-effective.*
- *It must be appreciated that implementation of the catch-up programme for 13 to 15 year olds would incur a one off additional cost of €29.2 million in the first year of the vaccination programme. Thereafter, the annual cost of HPV vaccination of all 12 year old girls is estimated at €9.7 million.*
- *The results of the economic model were sensitive to a number of key parameters, including the duration of protection from vaccination, the discount rate, the proportion of cases of CIN and cervical cancer caused by HPV types 16 and 18, as well as vaccine coverage. However, annual vaccination for 12 year olds remained cost-effective in all sensitivity analyses examined.*
- *In the base case analysis, lifelong protection from vaccination was assumed. If a booster dose was required after ten years, annual vaccination for 12 year olds remains cost-effective, although the ICER increases from €17,383 to €24,320/LYG.*
- *The longest duration of follow-up in relation to vaccine efficacy is currently five years and thus the protective effect against invasive cervical cancer has not yet been demonstrated. Although lifelong protection was assumed in the base case analysis future evidence is required to establish long-term safety and efficacy of HPV vaccination.*
- *The results of this evaluation are considered conservative as the benefits of including improvements in quality of life, potential cross-protection of the vaccine against other HPV types, as well as, vaccine efficacy against HPV types 6 and 11 were not included. For example, it is acknowledged that there are significant detriments in quality of life in many long term survivors of cervical cancer. On the other hand, the additional resources required to introduce a HPV vaccination programme, such as implementing surveillance systems and running educational campaigns, have not been included in the analysis.*

- *HPV vaccines do not eliminate the need for a cervical cancer screening programme as currently available HPV vaccines do not offer protection against all types of HPV that cause cervical cancer. Screening is also essential to protect adult women who have not been vaccinated. Therefore, it is important that women be informed and motivated to attend for screening when invited to do so even if they have received a HPV vaccine. Vaccination (primary prevention) and screening (secondary prevention) are complementary approaches to controlling cervical cancer in Ireland. In due course the impact of HPV vaccination on the operational structure of a population-based cervical screening programme, together with new technologies such as HPV DNA testing will need to be monitored.*
- *Vaccination against HPV types 16 and 18 is a long-term investment, as the initial costs of vaccination will only be offset by improved health outcomes and treatment savings 15 to 30 years in the future.*
- *Universal HPV vaccination of 12 year old females can be recommended as a cost-effective intervention in the Irish healthcare setting. In relation to a catch-up programme, vaccination of 13 to 15 year old females in the first year of the programme would be the most cost-effective catch-up strategy.*

Technical Report

The Role of Human Papillomavirus Vaccines in
Reducing the Risk of Cervical Cancer in Ireland –
A Health Technology Assessment



Report Prepared by

**The National Centre for Pharmacoeconomics
for the Health Information and Quality
Authority**

21 February 2008

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Summary

In Ireland, 200 women were diagnosed with cervical cancer and more than 90 women died from the disease in 2004. Cervical cancer is the 8th most frequently diagnosed cancer in women in Ireland. On average, these women are 56 years old at the time of death, and 44 years at the time of diagnosis. It is well established that human papillomavirus (HPV) infection is the primary cause of virtually all cervical cancers and deemed a necessary cause for the disease, without which, cervical cancer does not arise.

Two vaccines have been developed to prevent HPV infections, Cervarix™ and Gardasil™. Both vaccines target HPV types 16 and 18. Gardasil™ is also directed against HPV types 6 and 11, which are related to anogenital lesions. These vaccines have been shown to be effective in preventing cervical dysplasia (the condition that can lead to cervical cancer) in follow-up studies over a five-year period of women that did not have HPV at the time of vaccination.

The Health Information and Quality Authority agreed to undertake a health technology assessment on the role of vaccination against HPV in reducing the risk of cervical cancer in Ireland in a response to a request by the National Cancer Screening Service Board. The Authority commissioned the National Centre for Pharmacoeconomics (NCPE) to conduct the health technology assessment on its behalf. To lead and oversee the process and advise the Authority, a multidisciplinary Expert Advisory Group was convened.

The purpose of this assessment was to establish the cost-effectiveness of combining a cervical cancer screening programme with a national HPV vaccination programme compared to a screening programme alone to prevent cervical dysplasia and cervical cancer related to HPV types 16 and 18 in Ireland.

An independent dynamic model incorporating Irish costs, resource utilisation and epidemiological data was adapted to the Irish setting. Outcome data were obtained from published randomised controlled clinical trials. The parameters incorporated in the economic model were agreed with the HPV Vaccine HTA Expert Advisory Group, and included:

- *Vaccine efficacy: 95%*
- *Lifelong protection from vaccination*
- *Vaccine coverage: 80% (for school-based programme)*
- *Vaccine cost (per dose): €100*
- *Vaccine administration cost (per dose) for a school-based programme: €30*
- *Population cervical screening coverage: 80%*

Vaccination of 12 year old girls only, against HPV types 16 and 18, with vaccination coverage of 80%, results in an incremental cost-effectiveness ratio (ICER) of approximately €17,383/life year gained (LYG). This compares favourably with the recent economic evaluations of universal infant pneumococcal conjugate vaccination (€5,997/LYG) and universal infant hepatitis B vaccination (€37,018/LYG) in the Irish setting. Had the model incorporated impact on quality of life in addition to impact on mortality, it is likely that the cost/QALY would be lower than the cost/LYG, yielding an ICER well below the guideline threshold of €45,000/QALY routinely used for economic evaluation of drugs in Ireland.

The cost-effectiveness of implementing a catch-up programme for the following age bands in the first year of vaccination only was investigated: 13 to 15 years, 13 to 17 years, 13 to 19 years and 13 to 26 year olds. Although, the most cost-effective strategy is vaccination of 12 year old females only, vaccination of 13 to 15 year old females in the first year of the programme would be the most cost-effective catch-up scenario. The catch-up scenario for 13 to 15 year olds is associated with a relatively high increase in health benefits compared to the other catch-up scenarios.

The ICER for annual vaccination of 12 year old girls plus catch-up for 13 to 15 year olds in the first year of vaccination was estimated to be €52,968/LYG. While acknowledging the implicit uncertainty in the model, had the impact on quality of life in addition to impact on mortality been incorporated, it is likely that the cost/QALY would be lower than the cost/LYG, yielding an ICER close to the guideline threshold of €45,000/QALY; therefore, this scenario is likely to be cost-effective.

It must be appreciated that implementation of the catch-up programme for 13 to 15 year olds would incur a one off additional cost of €29.2 million in the first year of the vaccination programme. Thereafter, the annual cost of HPV vaccination of all 12 year old girls is estimated at €9.7 million.

The results suggest that the marginal benefit of vaccinating 15 to 26 year olds may be negligible compared to the associated vaccine expenditure. At older ages, the vaccine becomes less effective due to an increased likelihood of pre-vaccination HPV exposure reducing cost-effectiveness.

The ICER for extending the catch-up programme to 17 year olds compared to a catch-up to 15 year olds is €1,071,532/LYG and would clearly not represent a cost-effective use of resources. Cost-effectiveness of extending catch-up beyond 17 years is not considered, as the appropriate comparison is for each scenario to be compared to the one before, but only if the preceding one is cost-effective.

As economic models incorporate a number of assumptions, thereby resulting in some degree of uncertainty in ICER calculations, a sensitivity analysis was conducted. The results were sensitive to a number of key parameters, including the duration of protection from vaccination, the discount rate, the proportion of cases of CIN and cervical cancer caused by HPV types 16 and 18, as well as vaccine coverage.

The longest duration of follow-up in relation to vaccine efficacy is currently five years, thus the protective effect against invasive cervical cancer has not yet been demonstrated. Although lifelong protection was assumed in the base case analysis, future evidence is required to establish long-term safety and efficacy of HPV vaccination.

The results of this economic evaluation are considered conservative as the benefits associated with improvements in quality of life, potential cross-protection of the vaccine against other HPV types as well as vaccine efficacy against HPV types 6 and 11 were not included. On the other hand, the additional resources required to introduce a HPV vaccination programme, such as implementing surveillance systems and running educational campaigns, have not been included in the analysis.

Universal HPV vaccination of 12 year old females can be recommended as a cost-effective intervention in the Irish healthcare setting. In relation to a catch-up programme, vaccination of 13 to 15 year old females in the first year of the programme would be the most cost-effective catch-up strategy.

HPV vaccines do not eliminate the need for a cervical cancer screening programme as currently available HPV vaccines do not offer protection against all types of HPV that cause cervical cancer. Screening is also essential to protect adult women who have not been vaccinated. Therefore, it is important that women be informed and motivated to attend for screening when invited to do so even if they have received a HPV vaccine. Vaccination (primary prevention) and screening (secondary prevention) are complementary approaches to controlling cervical cancer in Ireland. In due course, the impact of HPV vaccination on the operational structure of a population-based cervical screening programme, together with new technologies such as HPV DNA testing will need to be monitored.

The draft technical assessment was submitted by the NCPE to the Expert Advisory Group for consideration. The Expert Advisory Group has approved the findings of the technical report. The Board of the Authority has subsequently authorised the report and recommended it to be submitted to the Minister for Health and Children, the National Cancer Screening Service Board and the National Immunisation Advisory Committee. A decision on the adoption and implementation of a HPV vaccine as part of the national immunisation schedule will be taken by the Minister for Health and Children, following due consideration of all available evidence.

Abbreviations

ACIP	Advisory Committee on Immunisation Practices
AIS	Adenocarcinoma in situ
AR-DRG	Australian Refined Diagnosis Related Groups
ARTISTIC	A Randomised Trial in Screening to Improve Cytology
ASCUS	Atypical Squamous Cells of Undetermined Significance
ASC-H	Atypical Squamous Cells: cannot exclude a high-grade squamous epithelial lesion
CAST	Centre for Applied Health Service Research and Technology Assessment
CDC	Centre for Disease Control and Prevention
CERVIVA	Cervical Screening Research Consortium
CI	Confidence Interval
CIN	Cervical Intraepithelial Neoplasia
CIN 1	CIN: Mild cell changes
CIN 2	CIN: Moderate cell changes
CIN2+	CIN: Histological lesions CIN 2 and above (CIN 2, CIN 3, SCC)
CIN 2/3	CIN: Cell changes that may be moderate (CIN 2) or severe (CIN 3)
CIN 3	CIN: Most severe cell changes
CLAN	College Lifestyle and Attitudinal National Surveys
CSO	Central Statistics Office
CT	Computed Tomography
DNA	Deoxyribonucleic acid
DTP	Diphtheria Tetanus and Pertussis
EMEA	European Medicines Agency
ESRI	Economic and Social Research Institute
EU	European Union
FDA	Food and Drug Administration
GMS	General Medical Services
GMT	Geometric mean titre
GP	General Practitioner
GSK	GlaxoSmithKline
GUM	Genitourinary Medicine
HSE	Health Service Executive
HPSC	Health Protection Surveillance Centre
HPV	Human Papillomavirus

HSIL	High-grade Squamous Intraepithelial lesion
HTA	Health Technology Assessment
IARC	International Agency for Research on Cancer
ICER	Incremental Cost-Effectiveness Ratio
ICSP	Irish Cervical Screening Programme
ISSHR	Irish Study of Sexual Health and Relationships
ITT	Intention to treat
LEEP	Loop Electrosurgical Excisional Procedure
LLETZ	Large Loop Excision of the Transformation Zone
LSIL	Low-grade Squamous Intraepithelial Lesion
LYG	Life Year Gained
MITT	Modified intention to treat (RCT population)
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp and Dohme
NCPE	National Centre for Pharmacoeconomics
NICE	National Institute for Health and Clinical Excellence
PCR	Polymerase Chain Reaction
PET	Positron Emission Tomography
PP	Per-Protocol (population)
QALY	Quality Adjusted Life Year
RCT	Randomised Control Trial
RNG	Random Number Generator
SLAN	Survey of Lifestyle, Attitudes and Nutrition
SPMSD	Sanofi Pasteur Merck Sharp and Dohme
STI	Sexually Transmitted Infection
TVC-E	Total Vaccinated Cohort for Efficacy
TOMBOLA	Trial of Management of Borderline and Other Low-grade Abnormal smears
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VLP	Virus-Like-Particle
WHO	World Health Organisation
YLS	Year of Life Saved

1 Background

In Ireland, 200 women were diagnosed with cervical cancer in 2004 and more than 90 women died from the disease. Cervical cancer is the 8th most frequently diagnosed cancer in women in Ireland and the 12th most common cause of cancer-related death. On average, these women were 56 years old at the time of death and 44 years at the time of diagnosis (National Cancer Registry Ireland). It is well established that human papillomavirus (HPV) infection is the primary cause of virtually all cervical cancers and deemed a necessary cause for the disease, without which, cervical cancer does not arise^{1,2}.

1.1 Natural history of human papillomavirus infection

HPV infection is the most common sexually transmitted infection (STI) worldwide, with the highest rates of HPV infection occurring in women aged between 18 and 28 years^{1,3}. The estimated lifetime risk of HPV infection for women is between 50 and 80%⁴. Only a very small proportion of infected women, however, will develop cervical cancer or its precursors. This is due to the fact that in the majority of individuals, HPV infections are transient and asymptomatic with most new infections resolving within two years¹. Overall, HPV infection is estimated to be responsible for 5.2% of all cancers¹.

HPV types can be classed as “low-risk” or “high-risk” in terms of their potential to cause cancer. The eight most common high-risk HPV types in Europe are 16, 18, 45, 31, 33, 52, 58, 35⁵. HPV types 16 and 18 can be detected in approximately 70% of women with cervical cancer³. Of the low-risk types, HPV types 6 and 11 cause 90% of all cases of anogenital warts⁶. HPV has also been causally related to some other cancers in the anogenital region and in the oropharynx in men and women. However, cervical cancer represents the main burden of HPV-related cancers.

Persistent infection with a high-risk HPV type is associated with an increased risk of cervical dysplasia (changes in the cells of the cervix) and cervical cancer⁷. There are many systems in use for classifying pre-malignant conditions of the cervix, based on cytology and histology (Table 1). In this health technology assessment (HTA), we use the classification system of cervical intraepithelial neoplasia (CIN). It is used for histological reports, whereas the Bethesda system is used for cytological reports. In the Bethesda system, CIN 2 and CIN 3 are combined into one group, termed high-grade squamous intraepithelial lesions (HSIL), as cytologically it is difficult to distinguish CIN 2 and 3. Atypical cells are divided into ASC-US (atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells: cannot exclude a high-grade squamous epithelial lesion).

Table 1. Classifications of pre-malignant conditions of the cervix.

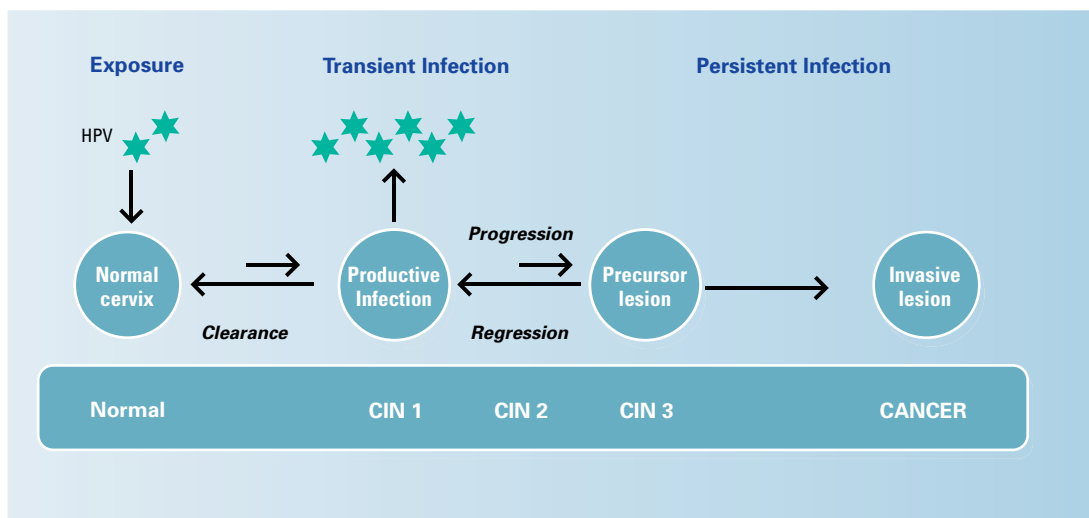
Cytological classification (used for screening)	Histological classification (used for diagnosis)	
Bethesda system	CIN	WHO descriptive classifications
Normal	Normal	Normal
ASC-US ASC-H	Atypia	Atypia
LSIL	CIN 1	Koilocytosis
HSIL	CIN 2	Moderate dysplasia
HSIL	CIN 3	Severe dysplasia
HSIL	CIN 3	Carcinoma in situ
Invasive carcinoma	Invasive carcinoma	Invasive carcinoma

CIN: cervical intraepithelial neoplasia; LSIL low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; ASC-US: atypical squamous cells of undetermined significance; ASC-H atypical squamous cells: cannot exclude a high-grade squamous epithelial lesion.

Source: Adapted from WHO, *Comprehensive Cervical Cancer Control*⁶.

The majority of CIN regresses, but they have the potential to develop into invasive cervical cancer (Figure 1). Pre-malignant changes in the cervix represent a spectrum of histological abnormalities ranging from CIN 1 (mild dysplasia) to CIN 2 (moderate dysplasia) to CIN 3 (severe dysplasia and carcinoma in-situ). The preliminary stages of cervical cancer represent a significant disease burden. From the time of infection with a high-risk HPV, invasive cancer may develop 10 to 20 years later, in a minority of women⁷.

Figure 1. The natural history of cervical cancer.



Secondary prevention strategies include cervical cytology screening (i.e., smear test) for early stage detection, HPV screening, and removal of HPV-infected precancerous lesions by laser, cryotherapy, LEEP excision and cervical conisation. Organised, cytology-based cervical cancer screening programmes are effective in reducing incidence and mortality from cervical cancer in a population⁹. Compared to opportunistic screening, organised screening programmes have a greater potential to reduce cancer incidence and mortality due to higher achievable levels of population coverage, follow-up and quality¹⁰.

Primary prevention strategies include reduced exposure by changes in sexual practices (for example, lifelong monogamy). Recently, two vaccines have been developed to prevent HPV infections, Cervarix™ and Gardasil™. Both vaccines target HPV types 16 and 18. Gardasil™ is also directed against HPV types 6 and 11, which are related to anogenital lesions.

1.2 HPV vaccines

The two virus-like-particle (VLP) vaccines are based on the self-assembly of recombinant L1 protein into non-infectious capsids devoid of genetic material¹¹. Intramuscular injection of the vaccines induces high titres of neutralising antibody, more than 50 times the titres induced by natural infection¹². The longest duration of follow-up in relation to vaccine efficacy, reported in published clinical trials, is approximately five years. Consequently, the protective effect of the vaccine against invasive cervical cancer has not yet been demonstrated. Data from randomised controlled trials (RCTs), however, have demonstrated vaccine efficacy against CIN 2/3 (CIN 2 or CIN 3). These cell changes have been acknowledged by the World Health Organisation (WHO) and the US Food and Drug Administration (FDA) as a valid indicator for the protection against cervical cancer. Both vaccines are administered in three doses within 6 to 12 months. There are some important differences between the vaccines:

Gardasil™

Gardasil™, a quadrivalent vaccine, produced by Merck and Co., Inc is marketed in Europe by Sanofi Pasteur MSD (SPMSD). The vaccine offers protection against HPV types 6 and 11, which are responsible for 90% of genital warts, and HPV types 16 and 18, which are associated with 70% of cervical cancers. This vaccine is formulated with a classic alum adjuvant. Data on this vaccine's safety, immunogenicity, efficacy and effectiveness are available from Phase 2 (five-year duration) and Phase 3 (three-year duration) trials that included approximately 20,000 participants (Section 3.4)¹³⁻¹⁹.

Cervarix™

Cervarix™, a bivalent vaccine, is produced by GlaxoSmithKline (GSK) Biologicals. The vaccine protects against HPV types 16 and 18. The vaccine is formulated with a new ASO₄ adjuvant that contains monophosphoryl lipid A, a derivative of bacterial cell walls. ASO₄ is also incorporated into Infanrix Hexa. Data are available from Phase 2 (five-year duration) and Phase 3 (15-month duration) trials that included in excess of 18,000 participants (Section 3.4)²⁰⁻²².

A comparison of the characteristics of Gardasil™ and Cervarix™ is provided in Table 2.

Table 2. Characteristics of the HPV vaccines Gardasil™ and Cervarix™

Characteristic	Gardasil™	Cervarix™
Manufacturer	SPMSD	GSK
Type	Prophylactic vaccine consisting of VLPs containing L1 capsid proteins.	Prophylactic vaccine consisting of VLPs containing L1 capsid proteins.
Antigens	Quadrivalent vaccine	Bivalent vaccine
	HPV types 6 (20 µg/dose), 11 (40 µg/dose), 16 (40 µg dose), 18 (20µg/dose).	HPV types 16 (20 µg/dose), 18 (20µg/dose).
Antigen expression system	Yeast	Baculovirus
Adjuvant	Alum	ASO ₄
	(225µg aluminium hydroxyphosphate sulphate).	(500 µg aluminium hydroxide and 50 µg 3-deacylated monophosphoryl lipid A).
Dose and schedule	0.5 ml intramuscular injection at 0, 2 and 6 months.	0.5 ml intramuscular injection at 0, 1 and 6 months.

Source: Summary of Product Characteristics for Gardasil™ and Cervarix™^{23, 24}.

1.3 Pharmacoeconomic evaluation

Pharmacoeconomic evaluation is the comparative analysis of alternative courses of action (in this case, universal HPV vaccination together with a cervical screening programme versus the screening programme alone) in terms of both their costs and health outcomes. The health benefit is measured in natural units (for example, life years gained) and the costs are measured in monetary terms. If there are two interventions A and B, the important question for resource allocation is how much additional

benefit is achieved with one intervention for the additional cost incurred. It is therefore essential to calculate the “incremental cost-effectiveness” of one therapy over the other. The results of a cost-effectiveness analysis are presented as an incremental cost-effectiveness ratio (ICER) and this describes how much additional benefit is achieved for the additional cost incurred²⁵.

1.3.1 Incremental cost-effectiveness ratio (ICER)

The ICER for two healthcare interventions A and B can be calculated as follows:

$$\text{ICER} = (\text{Cost A} - \text{Cost B}) / (\text{Effect A} - \text{Effect B})$$

The cost per life year gained (LYG) is an outcome measure which is frequently used in published economic evaluations of many vaccination programmes²⁶⁻³⁰. When quality of life is included, the outcome measure converts to the cost per Quality Adjusted Life Year (QALY). The National Institute for Health and Clinical Excellence (NICE) in the UK recommend measuring health effects in terms of QALYs³¹. This enables the effect of treatment on quality of life as well as survival to be considered together by converting both into a single common unit of measure – the QALY. Quality of life is measured as a utility value on a scale of 0 to 1 (0 equating to death).

In this economic evaluation of the HPV vaccination programme, health outcomes are measured in terms of survival (LYG), rather than QALYs. A more conservative estimate is obtained by limiting the evaluation of consequences to mortality (LYGs), rather than morbidity and mortality combined (QALYs). Measurement of health outcomes in terms of LYG in this evaluation facilitates comparison with two recent economic evaluations in the Irish healthcare setting, i.e., universal infant pneumococcal conjugate vaccination and universal infant hepatitis B vaccination, where health outcomes were also measured in terms of LYG^{32, 33}.

1.3.2 Cost-effectiveness thresholds

One of the implications of making comparisons of the cost-effectiveness of different interventions is that there is some threshold ratio above which a programme would be deemed 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 the UK, for example, most of the interventions with an ICER below £30,000/QALY (€40,430/QALY) are recommended routinely or for certain groups of patients. The NICE Guide to the Methods of Technology Appraisal states that³¹:

“The NICE Appraisal Committee does not use a fixed ICER threshold above which a technology would automatically be defined as not cost effective or below which it would. The Appraisal Committee has been given discretion when determining cost effectiveness to take into account those factors it considers most appropriate to each appraisal which include:

- *The broad clinical priorities of the Secretary of State for Health and the Welsh Assembly government*
- *The degree of clinical need of the patients*
- *The broad balance of costs and benefits*
- *Any guidance from the Secretary of State for Health and the Welsh Assembly government on the resources likely to be available*
- *The effective use of available resources.*

Below an ICER of £20,000/QALY (€26,953/QALY), judgements about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost effectiveness estimate. Above a most plausible ICER of £20,000/QALY (€26,953/QALY), judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including:

- *The degree of uncertainty surrounding the calculation of ICERs*
- *The innovative nature of the technology*
- *The particular features of the condition and population receiving the technology*
- *Where appropriate, the wider societal costs and benefits.*

Above an ICER of £30,000/QALY (€40,430/QALY), the case for supporting the technology on these factors has to be increasingly strong.”

In some circumstances, interventions that exceed a threshold of £30,000/QALY (€40,430/QALY) have been accepted by NICE, for example, the highest cost per QALY that NICE has accepted is an estimated £39,000 (€52,559) (range €45,820 - €58,623) for riluzole to treat motor neurone disease³⁴.

In Ireland, most drug interventions with an ICER less than €45,000/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.

There are three recent examples of the use of economic evaluation in the Irish healthcare system where the outcome measure was LYG:

1. An evaluation of the statins for primary prevention of coronary heart disease, demonstrated that statin therapy was cost-effective, with ICERs ranging from €17,900- €33,800/LYG under the General Medical Services (GMS) scheme³⁵.
2. The National Centre for Pharmacoeconomics (NCPE) recently conducted an economic evaluation of a universal infant hepatitis B vaccination programme in Ireland, using a six-component vaccine, compared with the current selective strategy of vaccinating high-risk infants with a monovalent hepatitis B vaccine. Assuming an incidence of acute Hepatitis B infection in Ireland of 8.4 per 100,000 population, the ICER for the universal vaccination programme compared with the selective vaccination programme was estimated to be €37,018/LYG. The study concluded that universal infant Hepatitis B immunisation would be a cost-effective intervention in Ireland³².
3. In 2007, the cost-effectiveness of implementing a universal infant pneumococcal conjugate vaccine as compared to no 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 highly cost-effective in the Irish Healthcare setting³³.

1.4 Review of the literature on the cost-effectiveness of HPV vaccination.

A literature review of published economic evaluations of the HPV vaccine was performed (Appendix 1). Scientific literature published in the English language since 1990 was searched using Medline (PubMed), Embase, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database and TRIP Database. Additional references were identified from the reference lists of published articles. Combinations of the following search terms were used: human papillomavirus, HPV, vaccine, cervix, cervical, economic, cost-effectiveness and screening. The search was concluded at the end of January 2008.

The first full economic evaluation of HPV vaccination was published in 2003. Therefore, the economic impact of HPV vaccination is a recent topic with all the early economic evaluations being conducted in the US³⁶⁻⁴⁰.

Dasbach et al. and Newall et al. critically reviewed the strengths and limitations of the models used in these studies^{41, 42}. Vaccine effectiveness, cervical screening and model design were identified as the most influential parameters in the studies conducted in the US. Although the studies suggested that vaccinating females can be cost-effective, the authors highlighted that there was substantial uncertainty around some of the key parameters included in the models.

More recently, economic evaluations of HPV vaccination in Canada, Australia, The Netherlands, Mexico, Brazil, Israel and France have been published^{30, 43-48}. Furthermore, independent reports from the Belgian, Danish and Norwegian HTA agencies are publicly available⁴⁹⁻⁵¹.

The results from these studies varied considerably. This may in part be explained by differences in methodologies and assumptions, including variations in key parameters such as: the discount rate, potential vaccine coverage, vaccine efficacy, duration of protection of the vaccine, estimated cost of administration of the vaccine, as well as direct medical costs. The Danish HTA, for example, assumed lifelong protection from vaccination in the base case analysis⁵⁰. In contrast, the Belgian and Norwegian HTAs assumed a booster dose would be required after ten years^{49, 51}. There were also differences in terms of the type of economic model used, the cervical cancer screening programmes and the clinical management of pre-malignant and invasive cervical cancer between countries. Some studies evaluated the cost-effectiveness of the vaccine against HPV types 16 and 18 only, whereas other studies also included the benefits of protection from HPV types 6 and 11.

Three types of HPV economic models have been reported in the literature: (1) cohort, (2) dynamic and (3) hybrid models⁴¹. Cohort models are static models and are typically based on Markov models. Hybrid models are a combination of cohort and dynamic models. Hybrid and dynamic models are the only models which take into account the transmission of infection in the population, i.e., susceptible persons have a lower risk of infection over time, even if they have not been vaccinated themselves. This is called the herd immunity effect. However, dynamic models require more information on sexual activity patterns within a population, as well as the natural history of HPV infection. Therefore, dynamic models require more assumptions and are associated with a greater level of uncertainty compared with cohort models.

A dynamic model populated with Irish epidemiological, resource utilisation and cost data as available was used to evaluate the cost-effectiveness of HPV vaccination programmes in Ireland.

2 Epidemiology

2.1 Sexual behaviour patterns in Ireland

The disease transmission component of the economic model uses Irish data on sexual behaviour patterns that influence the spread of HPV infection, including age of onset of sexual activity, number of partners, duration of relationships and number of concurrent partners (Section 4.2.2). A number of studies on sexual behaviour in Ireland have been undertaken in recent years and are described in detail in the Health Protection Surveillance Centre (HPSC) report on "Human Papillomavirus in Ireland."⁵²

Data from the Irish Study of Sexual Health and Relationships 2006 (ISSHR) were used to populate the transmission dynamic model. The results suggested that the median age at which women became sexually active was between 17 and 23 years⁵³. Of those between 18 and 24 years at the time of the survey, 31% of men and 22% of women reported sexual activity before the age of 17 years. Data on the number of sexual partners and the number of concurrent partners were obtained from this report. Additional data on the distribution of number of heterosexual partners by age group and sex, as well as, sexual frequency by age and relationship type were obtained from the authors.

The findings of the ISSHR report were consistent with those reported in the SLAN (Survey of Lifestyle, Attitudes and Nutrition) and CLAN (College Lifestyle and Attitudinal National Surveys) surveys. The SLAN surveys from 1998 and 2002 showed that a high proportion of those under age 20 years of age are sexually active⁵⁴. The CLAN survey (2003) reported that as many as 25% of college students are sexually active by the age of 16⁵⁵.

2.2 HPV type distribution in pre-malignant and invasive cervical cancer

Data on prevalence of HPV types in women with invasive cervical cancer and its precursor lesions are essential to predict the potential impact of the HPV 16/18 vaccines (i.e., vaccines targeted against HPV types 16 and 18) on cervical cancer. Variability between HPV prevalence in different populations has been highlighted in numerous studies although comparison of the results is complicated by study design, sample collection and methods used for HPV detection and typing^{5, 56-59}.

Epidemiological studies employing a variety of HPV typing protocols have been collated in meta-analyses and highly standardised multicentre studies⁵⁷⁻⁶². HPV types 16 and 18 are estimated to account for 70% of all cervical cancers worldwide, although the estimated HPV 16/18 fraction is slightly higher in more developed (74-77%) than in less developed (65-70%) countries^{5, 60}. About 50% (31-58%) of CIN 2/3 and approximately 35% (21-44%) of CIN 1 are also estimated to be HPV 16/18 positive^{59, 60}. After

HPV types 16 and 18, the six most common HPV types in invasive cervical cancer are HPV types 31, 33, 35, 45, 52 and 58 and this appears to be similar in all continents^{56, 60}.

HPV types 16, 18 and 45 are significantly more common in invasive cervical cancer than in CIN 2/3 and CIN 1, whereas the reverse is true for other HPV types⁶⁰⁻⁶². The difference in HPV type distribution across cervical lesions of increasing severity highlights the importance of HPV type in the risk of progression to cancer, even from CIN 2/3.

Regional variations in the distribution of certain HPV types have also been highlighted and this should be considered when evaluating the relevance of a HPV 16/18 vaccine to the local cervical cancer burden^{56, 60}. For example, a recent study in Iceland estimated that vaccination against HPV types 16 and 18 would achieve a minimum 40% reduced rate of CIN 2/3 and a minimum 60% reduced cancer rate⁶³.

In summary, vaccination against HPV 16/18 has the potential to prevent over two-thirds of all cases of invasive cervical cancer, half of all cases of CIN 2/3 and one-third of all cases of CIN 1 (Table 3). These proportions may even be higher if cross-protection against other high-risk HPV type infections also proves to be relevant for preventing cancer and pre-cancerous lesions.

No country-specific data on distribution of HPV types 16 and 18 were available for Ireland. For the base case scenario in our economic model, we assumed the proportions of CIN 1, CIN 2/3 and cancer caused by HPV types 16 and 18 were 35%, 50% and 74%, respectively, based on estimates from developed countries (Table 3). In a sensitivity analysis, more conservative values based on the results from the study conducted in Iceland were included⁶³.

Table 3. HPV 16/18 type distribution in invasive cervical cancer and its precursor lesions included in the economic model

	CIN 1	CIN 2/3	Cervical cancer	Reference
Base case	35%	50%	74%	Smith J et al., 2007 ⁶⁰ , Clifford G et al., 2005 ⁵⁹
Sensitivity Analysis	21%	40%	60%	Sigurdsson K et al., 2007, Clifford G et al., 2005 ^{59, 63}

2.3 Prevalence of HPV infection

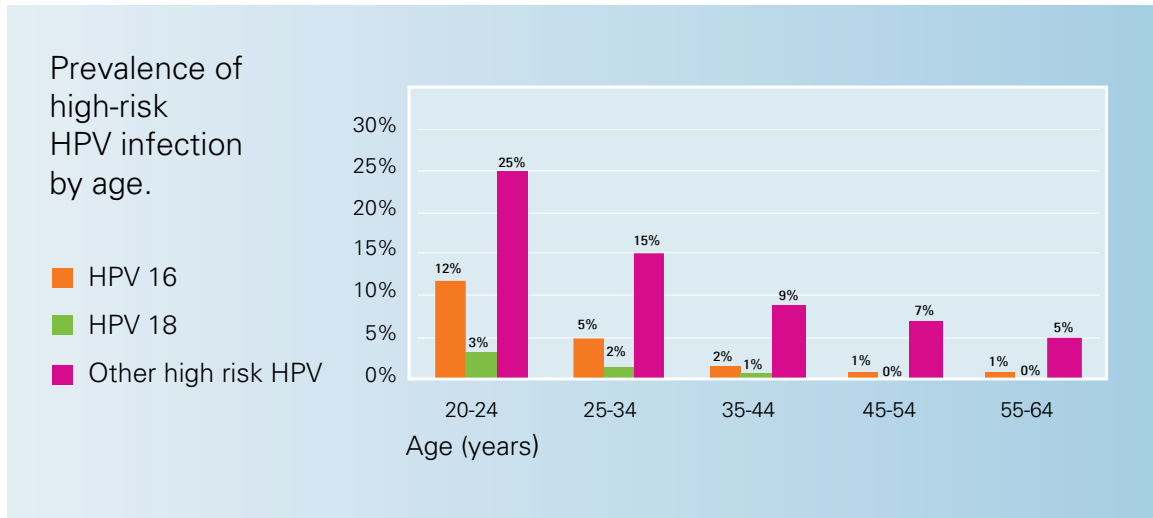
Data on Irish type-specific HPV prevalence by age and grade of cytology are required for this HTA. The burden of disease related to HPV in Ireland was clearly documented in the HPSCs report "Human Papillomavirus in Ireland."⁶⁴ The authors highlighted that studies undertaken in Irish women consistently identified a high prevalence of HPV types 16 and 18⁶⁵⁻⁶⁸. It should be noted however, that the sample sizes in these studies were small (n=20-38).

More recently, Keegan et al. evaluated the prevalence of HPV in an opportunistically screened female Irish urban population (n=996)⁶⁹. Overall HPV prevalence was 19.8%, similar to data from a Scottish cohort (n=3,444), which reported an overall HPV prevalence of 20%⁷⁰. Keegan et al. found that HPV prevalence decreased with age; from 31% in women less than 25 years, to 23% in women in the 25 to 35 age group and to 11% in women over 35. The prevalence of HPV increased with grade of cytology, from 11.4% of samples with normal cytology, to 85.4% of borderline samples, 84% of mild samples and 100% of samples with moderate and severe dyskaryosis. The prevalence of HPV reported for borderline and mild grades of cytology were high compared to findings of other studies and this could be explained by the small sample size of the Irish study^{70, 71}. HPV type 16 (20%) and HPV type 18 (12%) were the most common high-risk types detected in the study, followed by HPV types 66, 33 and 53, respectively.

In addition to this, the Cervical Screening Research Consortium (CERVIVA <http://www.cerviva.ie/>) is currently conducting a study on HPV prevalence with the aim of recruiting between 2,500-3,000 women who attend for screening. The sample represents an east-coast, urban population. Preliminary data (n=730) highlighted that the most prevalent type was HPV type 16, followed by HPV types 59 and 66, respectively. The preliminary data indicated a high-risk HPV prevalence of 20%. Although, the dataset was not as large as those from the UK, some differences in terms of prevalence of the different HPV types have been observed (personal communication: CERVIVA project). A recent study, conducted by Hibbitts et al. in South Wales, also highlighted some differences in prevalence of HPV types⁷¹. HPV types 16, 35, 66 and 59, respectively, were the most prevalent high-risk HPV types reported in the Welsh study.

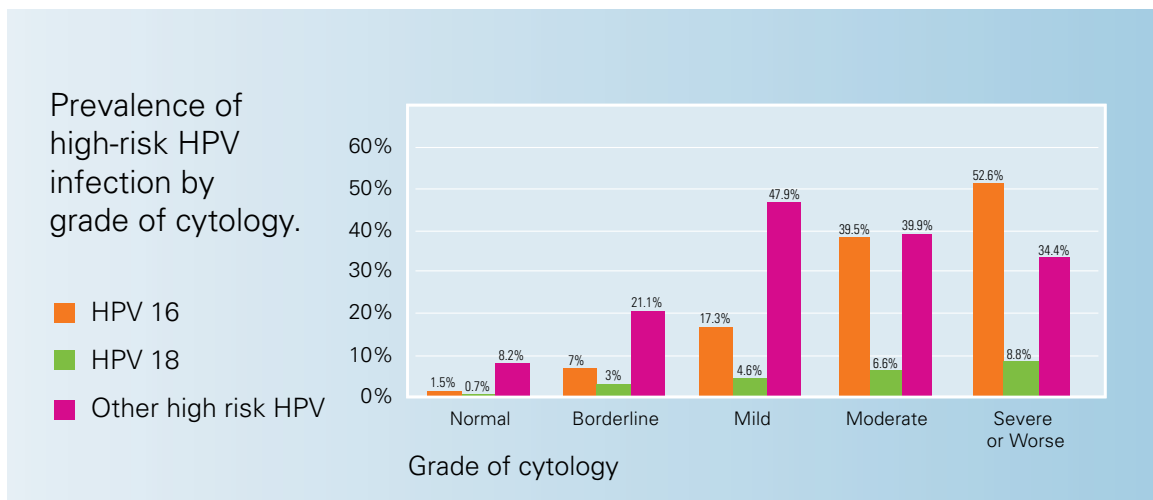
The largest study on HPV prevalence in the UK was conducted by Kitchener et al. in 2006 in the Greater Manchester area (n=24,510)⁷². Type-specific HPV prevalence rates by age as well as cytological and histological findings at study entry were reported (Figures 2 and 3). A high-risk HPV prevalence of 15.6% was found, with HPV types 16 and 18 noted to be the most prevalent high-risk types. Data from the ARTISTIC trial cohort in Manchester were included in the Irish economic model as it represented the largest population of women studied (in a population similar to Ireland) and was the only study to provide a detailed report of HPV type-specific prevalence by age and cytological grade (Figures 2 and 3). The data from the study by Keegan et al. were not included as the sample size was considered too small.

Figure 2. Prevalence of high-risk HPV infection by age.



Source: ARTISTIC Study. Kitchener et al. 2006⁷².

Figure 3. Prevalence of high-risk HPV infection by grade of cytology.



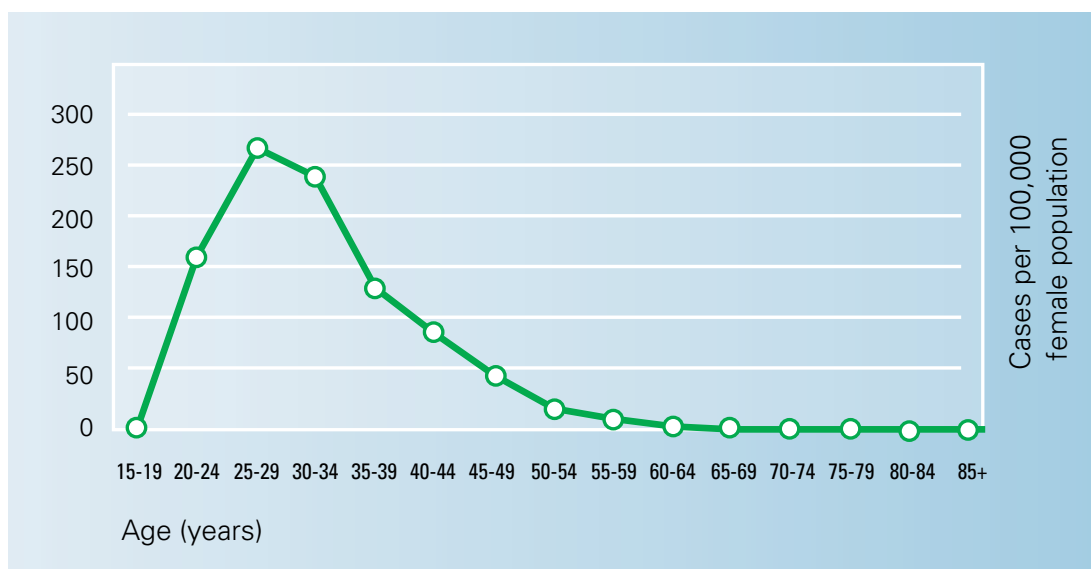
Source: ARTISTIC Study. Kitchener et al. 2006⁷².

To gain a better understanding of the relationship between HPV type, dyskaryosis and carcinoma and the impact of vaccination, further studies are required including assessment of specific HPV types found in invasive cervical cancer in Ireland.

2.4 Incidence of pre-malignant and invasive cervical cancer

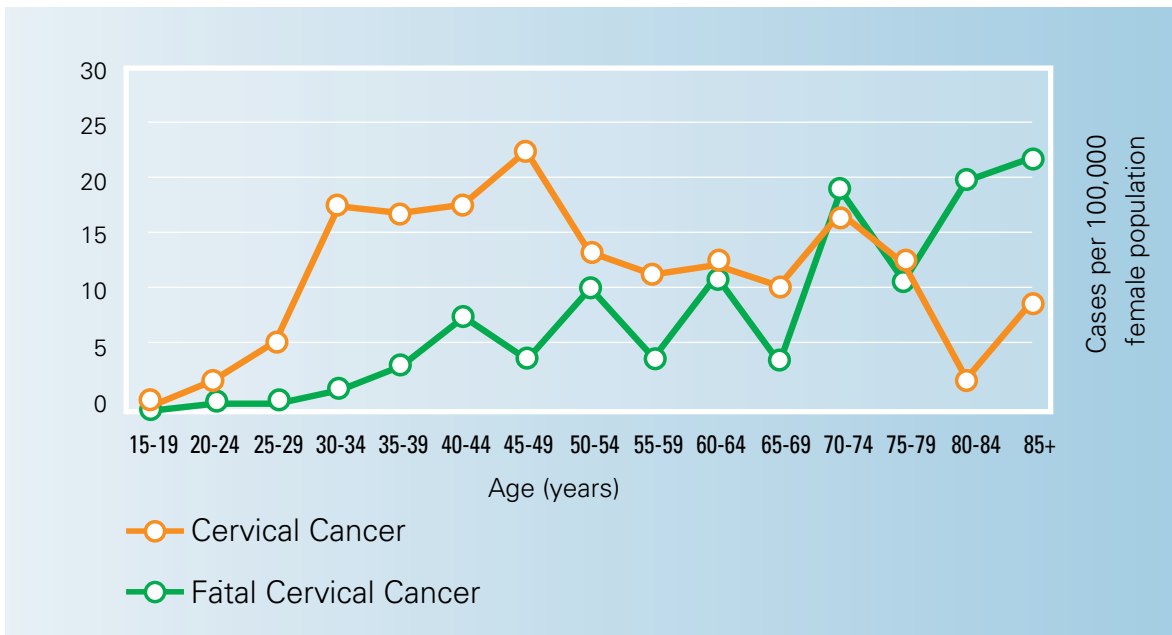
There were 1,528 cases of CIN 3 (94.2 cases per 100,000 female population) and 200 cases of invasive cervical cancer (12.3 cases per 100,000 female population) reported in Ireland in 2004. The incidence of CIN 3 peaked at 25-29 years of age (Figure 4). The incidence of cervical cancer peaked at 45-49 years and a second peak was observed in women aged 70-74 years (Figure 5). This may be attributed to a second peak in HPV incidence in older women as has been observed in other countries, although there are no Irish data to confirm this. There were 93 deaths from cervical cancer (5.7 cases per 100,000 female population) in 2004. The peak in cervical cancer mortality occurred in the 70+ age group, 20-25 years after the peak in cancer incidence (Figure 5).

Figure 4. Incidence of CIN 3 in Ireland, 2004.



Source: National Cancer Registry.

Figure 5. Incidence of cervical cancer and fatal cervical cancer in Ireland, 2004



Source: National Cancer Registry.

Incidence data for CIN 1 and 2 in Ireland were also required to calibrate the economic model. National cytology statistics for 2005 (Performance Monitoring Unit, HSE) were used to estimate the incidence of CIN 1 and 2 in Ireland. The total annual number of cytology samples (i.e., smear tests) from general practitioner (GP) and public health clinics, STI/genitourinary medicine (GUM) clinics, colposcopy and other hospital clinics were included in this data set. The data were based on the number of cytology samples taken, and not on the number of women screened. The screening programmes in the UK also produce cytology-based results. As part of the Trial Of Management of Borderline and Other Low-grade Abnormal smears (TOMBOLA) in the UK, estimates of numbers of women from numbers of cytology samples taken were produced⁷³. The authors suggested that the overall number of women having low-grade cytology samples was smaller than anticipated because many of the women were having repeat cytology samples. The number of repeat samples was higher for the more severe lesions (personal communication TOMBOLA trial, November 2007). Using this data, we estimated the number of women from the number of cytology samples taken by grade of dysplasia in Ireland, i.e., the ratio of women with CIN 1: 2: 3 (4.75: 1.3: 1) was estimated by applying the data from the TOMBOLA trial to the Irish cytology-based results. Estimates of the incidence of CIN 1 and 2 were then estimated from the CIN 3 incidence data from the National Cancer Registry. Therefore, we included national cytology-based data rather than biopsy confirmed CIN 1/2.

Other data sources were considered, but not used due to limitations and included:

- *Data on the results of all cytology results from the Irish Cervical Screening Programme (ICSP) MidWest Region pilot study. However, there are a number of important issues when considering using this data:*
 1. ICSP data are limited to that from women who have given explicit signed consent for the sharing of their data and therefore, underestimate activity in the MidWest.
 2. The data only reflect the characteristics of women participating in the MidWest programme and may differ significantly from the wider population.
 3. The results are recorded using the Bethesda classification (ASCUS, LSIL, HSIL). While these are somewhat comparable to the CIN classification, they are not the same. Therefore, there are difficulties in estimating the likely frequencies of underlying CIN 1, 2 and 3 in women with each grade of cytology.
 4. The screening data are based on the number of cytology samples taken, and not on the number of women screened. This presents difficulties when estimating the incidence of CIN 1 and 2 as we do not know what proportion of women have repeat cytology samples each year.
 5. Women-based data are available for histologically confirmed CIN or invasive cancer by age group. However, this may be an underestimate of the true incidence of CIN (i.e., it would assume that women who do not have a colposcopy, do not have CIN). The data are based on those women attending colposcopy, which is a highly selected group.

- *The results for all cytology samples from 2002 to 2006 were provided from the Well Woman Clinics in Dublin. The results for 8,341 cytology samples in 2005 were available. The results were recorded using the CIN classification. However, the two main limitations were that these are cytology-based (as opposed to woman-based) data and the data may not be nationally representative.*

3 Vaccine Efficacy and Safety

The longest duration of follow-up in relation to vaccine efficacy is currently five years and thus, the protective effect against invasive cervical cancer has not yet been demonstrated. Therefore, it is necessary to use a surrogate endpoint, and not invasive cervical cancer, to define efficacy of HPV vaccines.

A literature review of published RCTs of the HPV vaccine was performed. Scientific literature published in the English language since 1980 was searched using Medline (PubMed), Embase, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effects and TRIP Database. Additional references were identified from the reference lists of published articles. Combinations of the following search terms were used: human papillomavirus, HPV, vaccine, cervical intraepithelial neoplasia, cervix, cervical, cancer, efficacy and safety. The search was concluded at the end of January 2008.

While the efficacy data in this economic model were limited to published data, consideration was given to unpublished data that provided some added value or when it was the only possible reference source for important data. The NCPE invited the two vaccine manufacturers, GSK (Cervarix™) and Sanofi Pasteur MSD (Gardasil™) to present their clinical data, in order to clarify issues regarding vaccine efficacy and safety. To assist with this process, the HPV HTA Advisory Group members compiled a series of questions for consideration at these meetings. Responses to these questions were provided by the manufacturers to the NCPE.

3.1 Endpoints for vaccine efficacy

The WHO advocates assessment of vaccine efficacy against CIN grade 2 or 3, adenocarcinoma in situ (AIS) and cervical cancer, collectively referred to as CIN 2+⁷⁴. Furthermore, the FDA accepted CIN 2+ as the preferred primary endpoint for clinical trials assessing the efficacy of HPV vaccines against cervical cancer⁷⁵.

Since persistent infection with high-risk HPV types is considered a predictor for moderate or high-grade cervical dysplasias and cancer, this may also represent a useful endpoint for vaccine efficacy. Persistent infection is defined in RCTs as two positive HPV-DNA polymerase-chain-reaction (PCR) assays for the same viral genotype separated by a given time period, often six or twelve months.

In this evaluation, we focused on the histological endpoint CIN 2+ because of its clinical significance, as well as the fact that this endpoints has been identified by the WHO and FDA as the preferred endpoint for the evaluation of the efficacy of HPV vaccines. This outcome measure is also the standard against which the planned cervical cancer screening programme will be measured.

3.2 Description of populations included in randomised controlled trials

In the HPV vaccine trials the “**per-protocol population**” (**PP population**) was defined as women who received all three doses of vaccine and had no significant protocol violations. The subjects were naïve to the HPV types included in the vaccine through six months after study entry.

In addition to the PP population analyses, the Phase II studies on Cervarix™ included results based on an **Intention-To-Treat (ITT)** population, while the studies on Gardasil™ included results based on a **modified Intention-To-Treat (MITT)** population. These two populations (ITT and MITT) included participants who received at least one dose of the vaccine and had negative results on PCR and serologic assays to the relevant type of HPV at enrolment (subjects may have become infected during the course of vaccination).

The studies on Gardasil™ also analysed another Intention-To-Treat (ITT) population that included all women regardless of HPV DNA findings, serostatus, or presence of CIN at the time of vaccination. This ITT population received at least one dose of the vaccine.

Interim results of the Phase III study of Cervarix™ only included results for the Total Vaccinated Cohort for Efficacy (TVC-E)²². The TVC-E included all participants who received at least one dose of vaccine, had normal or low-grade cytology at month zero and had negative results on PCR and serologic assays to the relevant type of HPV at enrolment.

The current published data with regard to the vaccine efficacy in the MITT (Gardasil™) /ITT (Cervarix™) population against CIN 2+ related to HPV 16 and/or 18 infection were considered the most appropriate measure of vaccine efficacy for this HTA, i.e., women were HPV-naïve (to the specific HPV vaccine types) at enrolment and received at least one dose of the vaccine. This was considered a more conservative estimate than the vaccine efficacy in the PP population, where all girls received all three doses of the vaccine. Efficacy in HPV-naïve participants is assumed to approximate more closely the efficacy obtained when vaccinating sexually-naïve girls.

3.3 Vaccine HPV type-specific efficacy

In the clinical trials, vaccine efficacy is expressed against endpoints associated with vaccine type-specific HPV infection, i.e., endpoints associated with HPV 16 and/or 18. Efficacy is also expressed against endpoints regardless of HPV type, i.e., the proportion of all clinical events prevented by the vaccine regardless of HPV type. The economic model exclusively simulates HPV types 16 and 18, and as such does not consider the remaining potentially high-risk HPV types. Thus, vaccine efficacy against vaccine type-specific HPV infection is included in this evaluation.

3.4 Summary of data from randomised controlled trials

Quadrivalent vaccine - Gardasil™ (HPV types 6, 11, 16 and 18)

The effect of the quadrivalent vaccine was investigated in four placebo-controlled randomised phase II and III trials (protocols 005, 007, 013 and 015) (Table 4). The vaccine was administered to women between 15 and 26 years of age.

Table 4. Description of the Gardasil™ randomised controlled trials

	Type of study	Sample size	Follow-up (post 1 st dose)	Primary endpoint
Protocol 005 (Mao C et al. 2006) ⁷⁶	Phase II	2,391	48 months	Persistent HPV type 16 infection and HPV type 16- related CIN 2/3
Protocol 007 (Villa et al. 2005/06) ^{13, 15}	Phase II	551 (extension post 3 years 241)	5 years	Infection with HPV types 6, 11, 16, 18*
Protocol 013 (FUTURE I) ¹⁶	Phase III	5,455	3 years	Infection with HPV types 6, 11, 16, 18*
Protocol 015 (FUTURE II) ¹⁷	Phase III	12,167	3 years	CIN2+ related to HPV types 16, 18

*Persistent HPV infection, CIN, cervical cancer or external genital lesions caused by HPV types 6, 11, 16 or 18.

A combined analysis of the four trials included 20,583 women in the age-group 16 to 26 years¹⁹. The primary composite endpoint in this study and in the Future II study (Protocol 015) was a reduction in the combined incidence of HPV 16/18 related CIN 2+. However, the results of the FUTURE II (Protocol 015) study were used in the economic model as it represented the largest single trial of the four Gardasil™ trials¹⁷. In addition, the results of MITT analysis of the FUTURE II study (95% vaccine efficacy) were considered more conservative than the combined results (98% vaccine efficacy) (Table 5).

Table 5. Summary of results from the FUTURE II study and the combined analysis of the four studies (Ault et al.).

HPV16/18 related CIN2+		Vaccine		Control		Efficacy (95%CI)
		n	Cases	n	Cases	
PP	FUTURE II ¹⁷	5,305	1	5,260	42	98% (86-100)
	Combined analysis (Ault et al.) ¹⁹	8,579	1	8,550	85	99% (93-100)
MITT	FUTURE II	5,865	3	5,863	62	95% (85-99)
	Combined analysis (Ault et al.)	9,729	3	9,737	121	98% (93-100)
ITT	FUTURE II	6,087	83	6,080	148	44% (26-58)
	Combined analysis (Ault et al.)		142	10,292	255	44% (31-55)

No evidence of vaccine efficacy was observed in women with existing HPV infection or HPV-related disease caused by vaccine-specific types⁷⁷. Therefore, our economic model assumes no vaccine efficacy for those who have already been exposed to HPV 16/18 infection.

In the FUTURE II study of women who had negative results on PCR and serologic assays to HPV 16/18 at enrolment (MITT population), GardasilTM reduced the rate of HPV 16/18 related CIN 2+ by 95% (95%CI 85-99). In the ITT population, that included all subjects regardless of baseline HPV status, efficacy against HPV16/18 related CIN2+ was 44% (95%CI 26-58). Finally, in the same ITT population, efficacy against lesions associated with any HPV type was 17% (95%CI 1-31).

Bivalent vaccine - CervarixTM (HPV types 16 and 18)

The effect of the bivalent vaccine was investigated in phase II studies and an ongoing phase III study²⁰⁻²². The vaccine was administered to women between 15 and 25 years of age. The interim findings from the phase III study (PATRICIA study) have been published and include results for the TVC-E population²². This was similar to the ITT population in the phase II studies, i.e., all women were negative for HPV (by DNA) and seronegative at enrolment and all women received at least one dose of the vaccine. Results from the PP population will be published in the final analysis of

the PATRICIA study, which is expected in 2009. In contrast to the phase II studies, presence of HPV infection was not an exclusion criterion for women in the PATRICIA trial. Therefore, the PP sample represents a population that may include those with current or prior HPV infection.

Data from an abstract of the phase II trial, including 5.5 year follow-up data are expected to be published in early 2008⁷⁸. Women in the Phase II trial will be followed for a further four years (9.5 years in total) (Table 6).

Published efficacy data on CIN 2+ lesions related to vaccine types were similar to GardasilTM. However, the primary endpoint for the phase II studies was HPV infection^{20, 21}. Although data were provided on CIN 2+ endpoints, the authors acknowledged that the phase II study was not powered to show efficacy for histological endpoints (Table 7). Publication of the interim results of the PATRICIA study was triggered when at least 23 cases of CIN 2+ associated with HPV 16/18 DNA were detected. Therefore, this analysis only provided short-term efficacy data. The primary endpoint of the interim analysis of the PATRICIA study was in the population who were HPV16/18 negative at enrolment.

Table 6. Summary of CervarixTM randomised controlled trials.

	Type of study	Sample size	Follow-up (post 1 st dose)	Primary endpoint
HPV001 (Harper et al. 2004) ²⁰	Phase IIB	1,113	27 months	HPV 16/18 infection
HPV007 (Harper et al. 2006) ²¹	Phase II (follow-up of HPV001)	776	Combined follow-up 4.5 years	HPV 16/18 infection
Gall et al. Abstract 2007 ^{78*}	Phase II (follow-up of HPV007)	776	Combined follow-up 5.5 years	HPV 16/18 infection
HPV008 (PATRICIA; Paavonen et al. 2007) ²²	Phase III – Interim results**	18,644	14.8 months (pre-specified, event defined)	CIN 2+ related to HPV 16/18

*Full manuscript due for publication in 2008. Follow-up of women in the HPV007 trial is expected to last for 9.5 years. ** Final analysis expected 2009.

Table 7. Cervarix™ efficacy against CIN 2+ in participants that were HPV 16/18-naïve at baseline

	Vaccine		Control		Efficacy (95%CI)
	n	Cases	n	Cases	
Phase II data for ITT population (naïve for 14 high-risk HPV types at baseline, received at least one dose of vaccine, cases counted from month 1).					
4.5 years follow-up: Harper et al. 2006					
HPV 16/18 related CIN 2+	481	0	470	5	100% (-7.7 to 100)
All CIN 2+ (regardless of HPV type)	505	3	497	11	73.3% (-1 to 95.2)
5.5 years follow-up: Gall et al. 2007 (abstract)					
HPV 16/18 related CIN 2+	NA	0	NA	7	100% (33-100)
All CIN 2+ (regardless of HPV type)	NA	5	NA	15	68.0% (7 to 91)
Phase III data (PATRICIA study Paavonen et al. 2007). Population HPV 16/18 negative at enrolment, received at least one dose of vaccine, cases counted from month 1.					
CIN 2+ HPV 16/18 in lesion (pre-specified analysis)	7,788	2	7,838	21	90.4% (53.4-99.3)
CIN 2+ HPV 16/18 in lesion and in a previous cytology sample (additional analysis)	7,788	0	7,838	20	100% (74.2-100)

In the ITT analysis of the phase II study (Harper 2006), no cases of CIN 2/3 were found in the vaccine group compared to five in the control group. It is not possible to calculate any meaningful estimates for this endpoint and it is acknowledged that the study was not powered to show efficacy for CIN 2+ endpoints.

Paavonen presented interim phase III data from the PATRICIA study, which demonstrated efficacy against CIN 2+ associated HPV 16/18 of 90.4%. Additional analysis was also presented for cases with multiple infections found in the biopsy, where preceding cytological samples were examined for persistent infection. Three cases were excluded from the analysis, where the vaccine type (HPV 16/18) was only found in the biopsy, but not in any of the preceding cervical cytological samples. The manufacturers highlighted that this is relevant because only persistent HPV infection can cause development of lesions. From this analysis, the vaccine efficacy was 100% against HPV 16/18 related CIN 2+.

Efficacy data used in the economic analysis

In this economic evaluation, published vaccine efficacy data against CIN 2+ related to HPV 16/18 infection, in an unrestricted susceptible HPV-naïve population were included, i.e., vaccine efficacy of 95.2% (95% CI: 85-99)¹⁷. The population received at least one dose of the vaccine and had negative results on PCR and serologic assays to the relevant type of HPV at enrolment. This was considered a more conservative estimate than the per-protocol vaccine efficacy of 98%, where all girls received all three doses of the vaccine.

3.5 Cross-protection against non-vaccine HPV types

Administration of the HPV vaccines has been shown to reduce the incidence of persistent infection caused by non-vaccine specific high-risk HPV types. Data from the interim analysis of the phase III trial of Cervarix™ showed cross-protection against six-month persistent infection (at 14.8 month follow-up) with HPV types 45, 31, 33, 52 and 5822. Preliminary evidence on the use of Gardasil™ has also demonstrated cross-protection against HPV types 31 and 45, however this cross-protective effect was against CIN 2+ and the effect was evident up to four years post-vaccination⁷⁹. Further evidence is required however, before definitive answers can be given on the cross-protective effects of the vaccines against other high-risk types.

3.6 Duration of protection of vaccines

Clinical trials of both vaccines have evaluated long-term efficacy against HPV infection to a maximum of five years^{13, 16, 17, 19, 21}.

Evidence from clinical trials on Gardasil™, where women aged 15 to 26 years were followed for up to three years, indicated that the vaccine had the potential to substantially reduce the incidence of HPV type 16- and 18-related cervical pre-cancers and cancers^{16, 17, 19}. After three years there was a significant reduction in the incidence of high-grade CIN related to either HPV types 16 or 18. A long-term, placebo-controlled phase III trial evaluating efficacy in 16 to 17 year old women (22,412 invited participants) and 18 year old unvaccinated controls (30,947 invited participants) is currently ongoing in Finland⁸⁰.

Evidence from the phase II trials on Cervarix™ indicated sustained efficacy for up to 4.5 years²¹. Cervarix™ is also currently being evaluated with the goal of providing long-term efficacy data against cervical carcinoma in situ by the year 2020⁸⁰. A total of 24,046 women aged 16 to 17 years were invited to participate in the vaccination arm and 58,996 women aged 18 to 19 years were invited to participate as unvaccinated controls. Similar to the population-based trials on Gardasil™, these women will be passively followed for the cumulative incidence of cervical carcinoma in situ using a population-based cancer registry.

Clinical trial data is currently limited to five-year follow-up. Long-term immunity beyond this is unknown and therefore, it is not yet clear whether booster doses of the vaccine will be required. Analysis of the long term benefits and costs are, therefore, complicated by this uncertainty. Currently, there are two ongoing double-blind, population-based phase III-IV Nordic trials which aim to determine the long-term protection of HPV vaccination against cervical cancer and CIN 3 using cancer registry follow-up. These trials will have the power to detect the impact of HPV vaccination on HSIL lesions by the years 2015 to 2020⁸¹.

In this economic evaluation, lifelong protection from the three-dose course of the HPV vaccine is assumed in the base case analysis. However, in a sensitivity analysis the inclusion of a booster dose (i.e., one injection) after ten years is investigated.

Immune response in women aged 16 to 26 years

Both Gardasil™ and Cervarix™ are highly immunogenic, with vaccine-induced antibody titres that are many times higher than those induced by natural HPV infections. Gardasil™-induced antibody titres peak seven months following initiation of the vaccine series. The titres then decline, reaching a plateau 18 to 24 months later. The plateau is maintained for at least five years, with five-year levels that are similar to the titres naturally induced by HPV types 6 and 18 and that are higher than the titres naturally induced by HPV types 11 and 16¹³. At 24 months follow-up, over 96% of participants in the Gardasil™ trial were seropositive for HPV types 6, 11 and 16. However, only 68% were seropositive for HPV type 18¹⁷. The significance of this reduction remains unclear, given that immune memory is induced by the vaccine⁸².

Cervarix™-induced antibody titres follow the same profile as Gardasil™, except for two differences: the 18-month plateau is several fold higher than the levels induced by natural infection, and after 51 to 53 months, 100% of the women were seropositive for both HPV types 16 and 18²¹.

Immune response in adolescent females aged 9 to 15 years.

Recent data demonstrating immunogenicity with Gardasil™ in preadolescents come from Reisinger et al., (2007), who compared the immunogenicity (albeit as a secondary objective in the study) of the quadrivalent vaccine in young male versus female adolescents for 12 months following completion of the vaccination regime⁸³. The study population included sexually-naïve boys and girls aged 9 to 15 years, and results showed that one year post completion of the vaccine programme (i.e., month 18) more than 91.5% of all vaccine recipients in the PP population remained seropositive (regardless of gender). Geometric Mean Titres (GMTs) at month 18 were approximately four- to seven-fold lower than GMTs observed at month seven. This is similar to the response shown in women aged 16 to 23 years, where vaccine-induced anti-HPV responses decline post vaccination, plateau between months 18 to 24 and remain stable then for five years¹⁴. Additional data are needed however, to determine if the anti-HPV response in 9 to 15 year olds plateau in a similar manner.

With regard to Cervarix™, Pedersen et al., (2007) evaluated the immunogenicity and safety of the vaccine in females aged 10 to 14 years (mean age 12.4 years), compared to those aged 15 to 25 years (a secondary objective of the study)⁸⁴. Serologic evaluation was performed at the initial visit and at month seven. Although the sample size was small in the 10 to 14 year old group (n=158), immunogenicity analyses (per protocol) demonstrated non-inferiority between groups.

3.7 Significance of the adjuvant

The immunogenicity of the vaccines may also be determined by the type of adjuvant used. An adjuvant is an excipient that is included in a vaccine to enhance the immunogenicity of the vaccine antigen. In recent years, researchers have been very interested in the development of new adjuvants to enhance the immunogenicity of vaccination antigens.

Aluminium salts are the most frequently used adjuvants, and collectively these salts are referred to as "alum." These adjuvants are thoroughly tested and widely used. Gardasil™ is formulated with an amorphous aluminium hydroxyphosphate sulphate adjuvant. This "alum" adjuvant has been shown in a mouse model to be more immunogenic in the context of HPV L1 VLP vaccines than aluminium hydroxide or aluminium phosphate, and most likely enhances memory immune responses to L1 peptides⁸⁵.

Cervarix™, on the other hand, is formulated with the ASO₄ adjuvant system, which produces an enhanced immune response that persists for more than 3.5 years after vaccination. The ASO₄ adjuvant is also reported to induce a higher frequency of HPV L1 VLP-specific memory B cells and a higher antibody response compared with aluminium hydroxide⁸⁶. The clinical relevance of increased immunogenicity associated with ASO₄ as compared with HPV vaccines manufactured with a conventional alum adjuvant is unclear. A randomised double-blind Phase IIIb study of Cervarix™ versus Gardasil™ is ongoing. The study is designed to compare the immunogenicity of Cervarix™ to Gardasil™ in healthy women 18 to 45 years of age. Interim results are expected in 2008.

3.8 Vaccine safety

Mild-to-moderate local reactions in up to 90% of recipients have been reported for both vaccines^{16, 17, 20-22, 82, 87}. Systemic adverse events such as headache, fatigue, gastrointestinal upset and rash occurred in 69% to 86% of recipients and were only partially causally related. Since Gardasil™ was licensed in the US, the most common reports to the Vaccine Adverse Event Reporting System (VAERS) were local injection site reactions, as was seen in clinical trials⁸⁸. There were some cases of fainting after vaccination. This has also been reported with other vaccines administered to adolescents. A possible association between Gardasil™ and Guillian-Barre Syndrome is being investigated by the US VAERS⁸⁹. With its US approval in June 2006, Merck committed to a safety surveillance study that is due to report in 2009, as well as monthly and quarterly adverse event reporting for the first three years post-licensing⁹⁰.

In the US, three deaths were closely related in time to immunisation with Gardasil™. No causal relationship was established between the deaths of the young women and the administration of Gardasil™⁹¹. On the 24th January, 2008, the European Medicines Agency (EMA) issued a statement relating to the safety of Gardasil™ following reports of sudden, unexpected deaths in two women who had previously received Gardasil™⁹². The cases in question occurred in Austria and Germany. In both cases, the cause of death could not be identified. No causal relationship was or has been established between the deaths of the young women and the administration of Gardasil™. It is estimated that about 1.5 million patients have been vaccinated with Gardasil™ in Europe. On the basis of the evidence currently available, the EMA was satisfied that the benefits of Gardasil™ continued to outweigh its risks and that no changes to its product information were necessary.

4 Economic Evaluation of Vaccination against HPV Types 16 and 18 in Ireland

4.1 Objective

To evaluate the cost-effectiveness of a combined primary (vaccination against HPV types 16 and 18) and secondary (population-based cervical cancer screening) approach to managing CIN 1-3 and cervical cancer compared to a population-based cervical cancer screening programme alone in Ireland using an independent economic model.

4.2 Methods

4.2.1 Study comparator

The study comparator is a population-based cervical cancer screening programme. A coverage rate of 80% was included as the base case for the comparator in the model. It is important to note the current status of cervical cancer screening in Ireland.

A national population-based cervical screening programme does not currently exist in Ireland. However, a pilot programme was established in 2000 in the HSE Mid-West region whereby women aged 25 to 60 years are offered a screening test every three to five years. A national expansion of this pilot programme is anticipated in 2008. Women in the national programme will be screened every three years between the ages of 25 and 44 and then every five years up to the age of 60. Based on experience from other countries it may take upwards of five years or more to achieve a coverage rate of 80%, internationally accepted as the target that all national programmes should aim for. It was agreed that for the purpose of this economic evaluation that 62% be used as the lower limit for the screening programme in the sensitivity analysis based on the 2006 coverage data obtained from the Mid-West regional cervical cancer screening programme.

4.2.2 Description of the economic model

Model Structure

The economic analysis was conducted using an independently developed dynamic model, which takes account of the herd immunity effect of the vaccine. The model was developed in Denmark and was used in the Danish HTA of the HPV vaccine

(http://www.sst.dk/publ/Publ2007/MTV/HPV/HPV_vaccination_en.pdf).

Essentially, there are two components to the model. In the first phase, infection by HPV types 16 and 18 is modelled under different assumptions. Based on the results, the frequency of occurrence of CIN 1-3 is estimated in different vaccination scenarios. The resultant data are then entered into an economic analysis to assess the cost-effectiveness of the vaccination scenarios. The two parts of the model are described in more detail below:

- 1. Transmission dynamic model:** The model is an individual-based simulation model and is programmed in Netlogo. The model includes individuals from age 10 to 79 years of age. All individuals in the model die at age 79. A detailed description of this component of the model is described in a separate technical appendix, available on request.

The model simulates different sexual behaviour patterns, i.e., aspects of sexual behaviour in Ireland including number of partners, age of onset of sexual activity, etc. Irish-specific data from the Irish Study of Sexual Health and Relationships (October 2006) are used to populate this component of the model⁵³. The parameters used in the model are provided in the text, table and figures of a technical appendix, available on request.

The model simulates infection caused by HPV types 16 and 18. Other potentially oncogenic HPV types are not considered. Data on age and type-specific HPV prevalence from the ARTISTIC trial (Kitchener et al.) are incorporated in the model (Section 2.3)⁷².

In the model, only individuals infected with HPV types 16 or 18 are at risk of developing CIN. The model uses a range of transition probabilities to progress and regress from one CIN stage to another and onto cervical cancer (Technical Appendix, available on request). The transition probabilities were derived by calibrating the model with the estimates of CIN 1-3 and cervical cancer incidences in Ireland (Section 2.4).

The model also includes simulation of the screening programme for cervical cancer, whereby 80% of women between the ages of 25 and 44 will be screened every three years, while 45 to 60 year old individuals are screened every five years.

The model is calibrated to match the estimated HPV prevalence in Ireland, using the individual preference for number of concurrent partners and the length of relationships as adjustable. Once the calibration is carried out, the base case and the catch-up scenarios (Section 4.2.3) are simulated and the results fed into the economic component of the model to assess the effect and economics of these strategies.

- 2. Cost-effectiveness model:** This component of the model was developed in Microsoft Excel. The outputs from the transmission dynamic model are combined with Irish resource use and cost data. Vaccination costs as well as direct medical costs are described in more detail in section 4.2.3.

The transmission model estimates annual incidence of HPV types 16 and 18 and CIN 1 for the population of 12 year old Irish girls and then estimates the annual incidence of CIN 2/3 and cervical cancer for the various vaccination scenarios in Microsoft Excel*.

The difference between the number of fatal cervical cancer cases between the “no vaccination” scenario and a variety of “vaccination” scenarios (Section 4.2.3) is calculated to give the number of LYG from vaccination. Therefore, the number of LYG from the vaccination programme was the primary outcome of the analysis, and this was compared to the net cost, i.e., the additional cost of universal HPV vaccination minus the expected savings from reduced use of healthcare resources due to a reduction in the burden of disease caused by HPV infection. The reduction in events (CIN and cervical cancer) that would be associated with HPV vaccination and the mortality and cost resulting from these events were analysed.

The “no vaccination” arm portrays the current situation of cervical screening only. Under the “vaccination” arm, the probability of each outcome at each age was reduced in proportion to the expected population effectiveness of the HPV vaccination programme.

In the base case analysis, it is presumed that 74% of cervical cancer, 50% of CIN 2/3 and 35% of CIN 1 cases are caused by HPV types 16 and 18. In a sensitivity analysis, it is presumed that only 60% of cervical cancer, 40% of CIN 2/3 and 21% CIN 1 are caused by HPV types 16 and 18. Furthermore, vaccine efficacy of 95% and coverage of 80% is assumed in the base case analysis.

The analysis also presumes that the screening programme will continue unchanged. This is because HPV types 16 and 18 cause approximately 70% of cervical cancers, so screening for cell changes and cervical cancers caused by other potentially high-risk HPV types will be necessary.

Time horizon

In the base case analysis the model runs over a period of 70 years. The model excludes individuals between the ages of zero and nine years. All individuals in the model die at 79 years of age, in line with the Danish model⁵⁰.

Perspective

The analysis was conducted from the perspective of the healthcare payer, i.e., the Health Service Executive (HSE). Therefore, only direct medical costs were included in the evaluation. Costs associated with productivity changes due to patient time off work were not included.

* Based on Central Statistics Office (CSO) population data 2006 – estimated from published age band data.

Outcome measure

The outcome measure considered in this model was the life year gained (LYG). The numbers of cases of CIN 1, CIN 2/3, cervical cancer and cervical cancer fatalities averted were also calculated.

4.2.3 Data inputs

Vaccination scenarios

The optimal age for HPV vaccination is dependent on numerous factors, including age of sexual debut, ease of administration, and incidence of infection. Data from Ireland indicate that around 22% of young women are sexually active before the age of 17 years⁵³. It was recommended that the universal vaccination programme be school-based in order to maximize vaccine uptake. In consideration of potential parental concerns and logistical issues regarding a school-based programme, it was recommended that first-year students in second-level education would represent the optimal target group for a universal vaccination programme. This would primarily involve children aged 12 to 13 years.

In order to observe the impact of the vaccination programme at an earlier point in time, the cost-effectiveness of a range of catch-up vaccination scenarios were also investigated (Table 8). The catch-up programme involves introducing the vaccination into a cohort that would include a proportion of sexually-active females and this raises an issue in terms of vaccine efficacy. Our economic model assumes no vaccine efficacy for those who have already been exposed to HPV 16/18 infection (Section 3.4). The catch-up programmes were assumed to be temporary, lasting for the first year of vaccination programme only. Routine vaccination of 12 year old girls was assumed to be permanent.

Vaccine coverage

Vaccine coverage of 80% was included in the base case analysis. The selection of this parameter was based on the coverage achieved with the recent Meningitis C catch-up programme (89% in the 5 to 12 year age group; 81% in the 13 to 17 year age group and 30% in the 18 to 22 year age group). However, on the basis that a HPV vaccination programme involves three separate vaccine administrations and that the vaccine uptake may be influenced by potential social and political issues, a lower coverage rate of 60% was included in a sensitivity analysis for the base case scenario. An uptake rate of 30% was used for a catch-up programme for individuals not in school. In all cases it was assumed that the vaccine would be combined with a screening programme, the aim of which is to cover 80% of the population aged 25 to 60 years.

Table 8. *Vaccination scenarios and coverage.*

Scenario	Vaccine coverage - Base case
1. Annual vaccination of 12 year old girls	80%
2. Annual vaccination of 12 year old girls with catch up to 15 years in 1 st vaccination year	80%
3. Annual vaccination of 12 year old girls with catch up to 17 years in 1 st vaccination year	80%
4. Annual vaccination of 12 year old girls with catch up to 19 years in 1 st vaccination year	80%
5. Annual vaccination of 12 year old girls with catch up to 26 years in 1 st vaccination year	80% (school) 30% (GP)

Cost estimates

Cost estimates include the additional costs associated with vaccination, as well as cost savings due to a reduction in the burden of pre-malignant and invasive cervical cancer over time.

a. Vaccination costs

The price of the vaccine excluding VAT is estimated at €100 per dose (Personal communication: National Immunisation Office, HSE). In the event of the introduction of the HPV vaccine as a universal immunisation programme, it can be expected that the price will be the subject of negotiation, which is why sensitivity analysis was performed with varying prices of the vaccine (range €80 to €120).

Based on the meningitis C catch-up programme, an administration fee of €30 (range €15 to €45) per dose was used for a school-based programme. An administration fee of €175 for three doses was included for a GP-based catch-up programme, using a range of €150 to €200 for the sensitivity analysis (Personal communication: National Immunisation Office, HSE) (Tables 9 and 10).

In relation to the cost of a surveillance programme to track patient outcomes, the National Immunisation Office of the HSE have stated that surveillance of vaccine safety and effectiveness will be a long term requirement partly borne by the Irish Medicines Board and also the HPSC. Therefore, this parameter was not included in the cost-effectiveness analysis.

Table 9. Cost estimates for the school-based universal HPV vaccination programme.

Cost of three-dose course	Base case parameter	Sensitivity Analysis
Vaccine	€300	€240 - €360
Administration	€90	€45 - €135
Total	€390	€285 - €495

Table 10. Cost estimates for GP administration of the HPV vaccine (for those who have left school, but are part of the catch-up programme).

Cost of three-dose course	Base case parameter	Sensitivity Analysis
Vaccine	€300	€240 - €360
Administration	€175	€150 - €200
Total	€475	€390 - €560

Booster dose: In the base case of the model, it was assumed that the duration of protection from vaccination was lifelong. However, in sensitivity analysis the impact of the requirement for a booster dose (1 dose of vaccine) at ten years was investigated. The cost of the booster was estimated at €158 (vaccine price of €100 plus GP administration fee of €58).

b. Direct medical costs

At the time of this evaluation, there was a lack of published Irish data for the direct medical costs of the following health states included in the model: Atypia/CIN 1, CIN 2/3, and invasive cervical cancer. Within the timeframe of the analysis it was not possible to conduct specific micro-costing studies.

An assessment of resource use items associated with diagnosis and treatment of pre-malignant and invasive cervical cancer were obtained from the literature and expert opinion from members of the HPV Advisory Group. Data from the National Cancer Registry (2002–2004) were used to determine resource utilisation for the management of invasive cervical cancer. Resource use items were then valued using Irish unit cost data. A detailed description of the resource utilisation and unit cost data is included in a technical appendix, available on request.

Resource use data

□ *Management of atypia/CIN 1*

Resource use data were based on published and unpublished data from the TOMBOLA study in the UK, as well as Irish expert clinical opinion. TOMBOLA is a randomised controlled trial nested within the Cervical Screening Programme in two areas of Scotland (Grampian and Tayside) and one area of England (Nottingham)⁷³. Cytological surveillance, following detection of a low-grade abnormality, involves three repeat cytology samples at six-monthly intervals. If a woman has three consecutive normal cytology samples, she is returned to the routine cervical screening programme. If a woman has a cytology sample that shows moderate dyskaryosis or worse, or three consecutive inadequate cytology samples, referral is made for colposcopy.

The total cost of managing atypia/CIN 1 is estimated to be €617 per patient.

□ *Management of CIN 2/3*

Management of women with CIN 2/3 includes two options:

1. *Colposcopy and biopsy then recall for treatment by large loop excision of the transformation zone (LLETZ) (90%) or conisation (10%), if CIN 2/3 detected.*
2. *Colposcopy and immediate treatment by LLETZ (90%) or conisation (10%).*

Surveillance consists of an outpatient gynaecology visit after six months followed by six cytology samples over five years. Data were obtained from expert clinical opinion and Colposcopy Statistics from the National Maternity Hospital, Holles St. for 2006 (n=1,370).

The total cost of managing CIN 2/3 is estimated to be €1,632 per patient.

□ *Invasive cervical cancer*

Diagnosis includes colposcopy, cervical biopsy, CT (computed tomography) scan, ultrasound, MRI (magnetic resonance imaging) pelvis, PET (positron emission tomography) scan, staging (includes day case general anaesthetic). First line treatment consists of either:

1. *Surgery (62%): hysterectomy (69%), trachelectomy (5%) or conisation (26%);*
2. *Radiotherapy/chemotherapy (30%);*
3. *Systemic chemotherapy (5%);*
4. *Inpatient palliative care (3%).*

Management of patients diagnosed with invasive cervical cancer in Ireland was estimated from National Cancer Registry data related to diagnostic or treatment procedures for 619 women diagnosed with invasive cervical cancer (2002-2004), as well as expert clinical opinion. Follow-up includes four examinations in the first three years, followed by six-monthly screening for two years, and annual screening thereafter⁹³.

The total cost of managing invasive cervical cancer is estimated to be €18,160 per patient.

Unit cost data

Unit cost data for in-patient procedures were obtained from 2005 Australian Refined Diagnosis Related Group (AR-DRG) data provided by the National Casemix Unit of the HSE⁹⁴. Unit costs for cytology tests were obtained from the Irish Cervical Screening Programme (ICSP), and those for cervical biopsy and conisation were obtained from Colposcopy Unit Finance Departments reported in an abstract by Rash et al.⁹⁵. Costs of chemotherapy, which include the ingredient cost as well as the pharmacy compounding and administration costs, were obtained from the Pharmacy Department of St. James's Hospital, Dublin. Every effort was made to incorporate Irish unit cost data. However, where data were not available it was adapted from the UK. UK costs were converted to euro using the exchange rate published by the Central Bank of Ireland and all costs were inflated to 2005 euro, using the consumer price index for health.

It is presumed that the planned cervical screening programme will continue unchanged for both vaccination and current practice, thus no costs were estimated for screening as it is included in both scenarios.

A range of assumptions were used to estimate the overall costs for managing pre-malignant and invasive cervical cancer. Furthermore, there is wide variation in the direct medical costs of CIN 1, 2, 3 and cervical cancer between countries (Table 11). Uncertainty in the estimation of the direct medical costs was investigated in a series of one-way sensitivity analyses to establish their impact on the results of the cost-effectiveness analysis.

Table 11. Comparison of direct medical costs in different countries

Study	CIN1	CIN 2	CIN 3	Cervical cancer
NCPE estimate for this HTA (CIN1/Atypia)	€617	€1,632		€18,160
GSK Irish data ⁹⁵	€552	€673	€689	€10,449
Belgian HTA ⁴⁹		€369		€16,138
Danish HTA ⁵⁰	€33	€3,002		€25,484
Norwegian HTA ⁵¹	€72	€604		€13,533
The Netherlands ³⁰	€1,446		€1,610	€15,000
Australia ⁴⁴	€572	€576		€8,941

4.2.4 Discount rate

Discounting is a technique that allows comparison between costs and benefits that occur at different times. It accounts for the fact that costs incurred and outcomes realised today are not equivalent to costs and outcomes in the future²⁵. This is particularly important in economic evaluations of vaccination strategies where costs of vaccination occur immediately while benefits occur many years in the future. In this cost-effectiveness analysis both costs and consequences were discounted at an annual rate of 3.5%. This is consistent with conventional practice³¹.

The key parameters incorporated into the base case analysis as agreed with the Expert Advisory Group are shown in Table 12.

Table 12. Summary of key parameters included in the base case analysis

Parameter	Model Input
Time horizon	70 years
Vaccine efficacy	95%
Duration of vaccine protection	Lifelong
Vaccine coverage	80% under 19 years 30% over 19 years
Screening	80% screened every 3 yrs, 25-44 yrs 80% screened every 5 yrs, 45-60 yrs
Incidence of HPV	Manchester (ARTISTIC) trial only
Administration costs (per dose)	€30 under 19 years €58 over 19 years
Cost of vaccine (per dose)	€100
Cost of booster	No booster
Cost cytology test	€140
Cost of CIN 1	€617
Cost of CIN 2/3	€1,632
Cost of invasive cervical cancer	€18,160
Discount rate	3.5% on costs and benefits

4.2.5 Sensitivity analysis

The parameters that were varied in one-way sensitivity analysis are shown in Table 13.

Table 13. Range of parameters included in one-way sensitivity analysis

Parameter	Base Case	Sensitivity Analysis
Cost of vaccine (per dose)	€100	€80- €120
Cost of vaccine administration in school programme (per dose)	€30	€15- €45
Vaccine efficacy (HPV-naïve girls in the model)	95.2%	95% CI (85-99%)
Proportion of CIN 1, 2, 3 and cervical cancer caused by HPV 16/18.	74% cervical cancer, 50% CIN 2/3 and 35% CIN 1	60% cervical cancer, 40% CIN 2/3 and 21% CIN 1
Vaccine uptake (school-based programme <19 year olds)	80%	60%
Population-based cervical screening programme: proportion of women screened regularly	80%	62%
Direct medical costs: CIN 1 CIN 2/3 Invasive cervical cancer	€617 €1,632 €18,160	+/- 20%
Discount rate	3.5%	0%, 6%
Duration of protection/booster	Lifelong	10 years / booster (€158)

4.3 Results

4.3.1 Result of simulation model

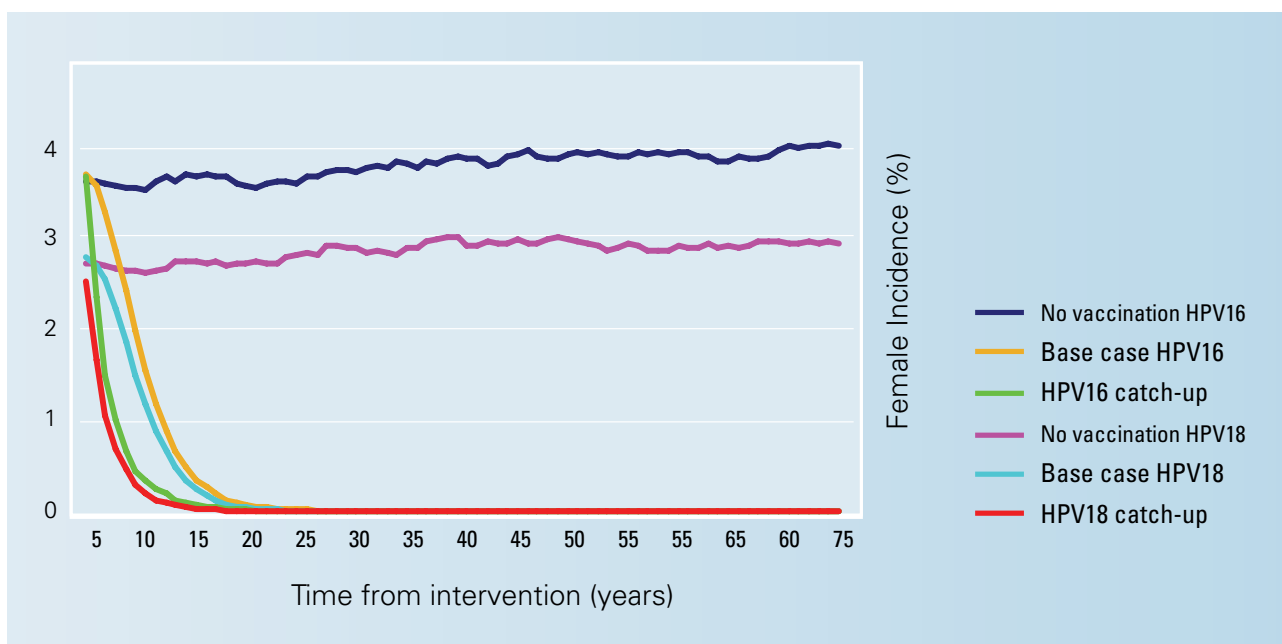
The transmission model estimates the prevalence of HPV types 16 and 18. Initially, the model ran simulations for the “no vaccination” strategy against HPV types 16 and 18, i.e., baseline.

Various vaccination scenarios were subsequently simulated. The simulated change in prevalence of HPV types 16 and 18 after introduction of vaccination is illustrated in Figure 6. The vaccination scenarios are started in the model at a point where the simulation reaches a steady state. A marked decline in HPV incidence in the vaccinated groups is projected.

The data in Figure 6 indicate that introduction of a catch-up programme, from 12 to 19 years of age, would accelerate the decrease in incidence of infection. Complete eradication of HPV types 16 and 18 is predicted, in spite of the assumption of 80% vaccine coverage, as it is assumed that persons susceptible to infection will have a lower risk of infection, even if they themselves have not been vaccinated (i.e., herd immunity).

Figure 6. Simulated incidence of HPV types 16 and 18 with no vaccination, base case (annual vaccination of all 12 year old girls) and a catch-up scenario (annual vaccination of all 12 year old girls and catch-up to 19 years of age in the first year of vaccination).

Figure 6. Simulated incidence of HPV types 16 and 18 with **no vaccination, base case** (annual vaccination of all 12 year old girls) and a **catch-up scenario** (annual vaccination of all 12 year old girls and catch-up to 19 years of age in the first year of vaccination).



4.3.2 Cost-effectiveness of annual vaccination of all 12 year old girls without a catch-up programme

In the base case model, an annual average of 111 cases (56%) of cervical cancer and 52 deaths (56%) related to cervical cancer were averted, as a result of routine HPV vaccination of all 12 year old girls (Table 14). Approximately, 30% of CIN 1 and 40% of CIN 2 cases were prevented. In the model we assumed that 74% of cervical cancer, 50% of CIN 2/3 and 35% of CIN 1 are caused by HPV types 16 and 18. Furthermore, we assumed 95% vaccine efficacy, 80% vaccination coverage and a herd immunity effect.

Table 14. *Estimated number of cases of CIN1, CIN2/3 and cervical cancer averted due to vaccination.*

Health state	Estimated total number of cases in 2004	Average annual number of cases averted due to HPV vaccination
CIN 1	7,259	2,245
CIN2/3	3,515	1,435
Cervical cancer	200	111
Deaths from cervical cancer	93	52

The total average life years gained per vaccinated year group was estimated at 401.8 years (Table 17).

The total cost of the three-dose vaccine schedule (€100 per dose), including an administration fee of €30 per dose, would be approximately €9.73 million per year for a cohort of 12 year old girls with a vaccine coverage of 80% (Table 15). These costs will recur every year. The reduction in new cases of CIN and cervical cancer will occur with some delay after the reduction in prevalence of HPV types 16 and 18. This means that the time aspect factored into the analysis has a certain influence on the results on the cost and effect sides. The treatment costs saved in the first few years after introduction of vaccination against HPV types 16 and 18 will be relatively modest. However, the average savings from cases averted due to vaccination, over the 70 year time horizon, were estimated at €2.74 million per year (present day value)(Table 15). The main savings occur as a result of avoiding management of CIN 2/3 (Table 16).

Table 15. *Estimated incremental cost per year per cohort of 12 year old girls vaccinated.*

Description	Cost per year*
Total cost of vaccination per year	€9,725,820
Savings in treatment costs per year (due to disease avoided)	€2,741,324
Average incremental cost per year	€6,984,496

*Discount rate for costs and outcomes: 3.5%.

Table 16. Average estimated savings in treatment costs per year caused by reduced incidence of CIN1, 2, 3 and cervical cancer as a result of HPV vaccination.

Health state	Cost savings*
CIN 1	€758,585
CIN2/3	€1,282,887
Cervical cancer	€699,852
Total	€2,741,324

*Discount rate for costs and outcomes: 3.5%

Based on the results derived from Tables 14 and 15 the cost per LYG can be calculated. The baseline ICER is estimated at €17,383 / LYG (Table 17).

Table 17. Baseline incremental cost-effectiveness ratio (ICER) of HPV vaccination plus screening versus screening alone.

Average incremental costs per year (current value)	Total average life years gained per vaccinated year group (current value)	ICER
€6,984,496	401.8 years	€17,383 / LYG

Discount rate for costs and outcomes: 3.5%

4.3.3 Cost-effectiveness of catch-up vaccination programmes

In order to observe the impact of the vaccination programme at an earlier point in time, the cost-effectiveness of a range of catch-up vaccination scenarios are also investigated. All ICERs are calculated by comparing each vaccination scenario to the preceding scenario (i.e. scenario 2 is compared to scenario 1 and scenario 3 is compared to scenario 2). The ICER, for example, for annual vaccination of all 12 year old girls with catch-up to 15 years in the first year of vaccination (i.e., scenario 2) compared to annual vaccination of all 12 year old girls only (i.e., scenario 1) is estimated at €52,968/LYG (Table 18).

If a catch-up programme is introduced, an improved outcome from vaccination is achieved due to a more rapid reduction in the incidence of HPV types 16 and 18, but there is also a noticeable increase in vaccination costs in the first year of the programme (Table 18). A catch-up programme for 13 to 19 year old girls, for example, would increase the potential cost of vaccination (including administration costs) by approximately €68.1 million in the first year of the vaccination programme.

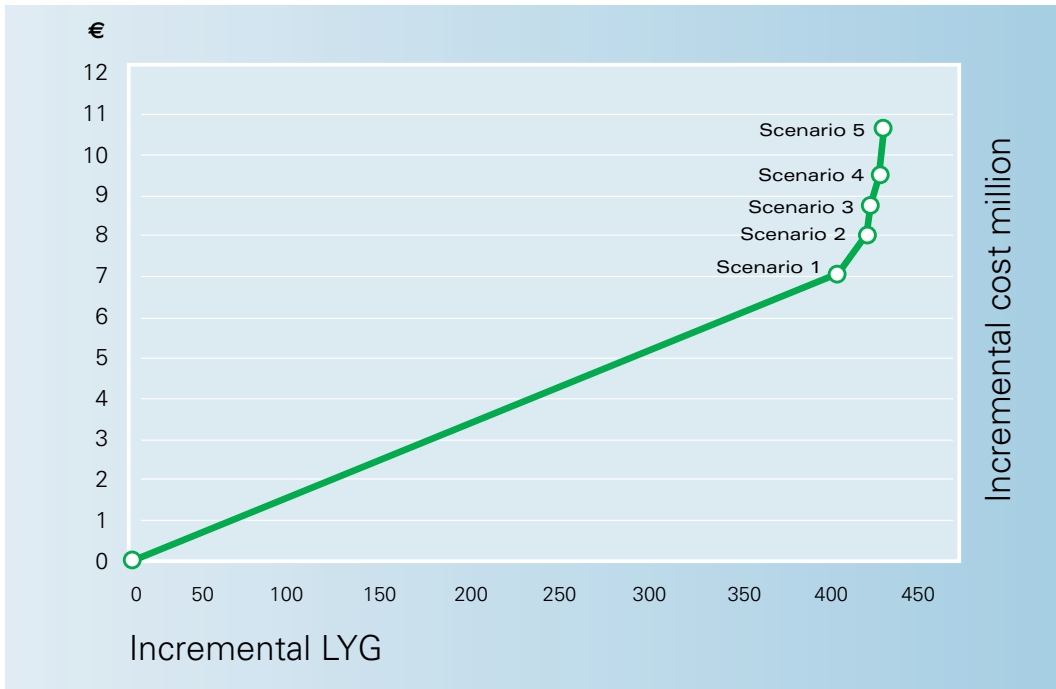
Both scenarios 1 (annual vaccination of all 12 year old girls) and 2 (annual vaccination of 12 year old girls with catch-up to 15 years in the first vaccination year) are considered cost-effective. The graphical representation of the results of the catch-up programmes (scenarios 2 to 5) highlights that implementation of these additional scenarios leads to increases in life years gained, but at an extra cost. At older ages, the vaccine becomes less effective due to pre-vaccination HPV exposure, and this too has an impact on cost-effectiveness. The incremental analysis of catch-up programmes demonstrates that vaccinating girls over 15 years of age in the first year of vaccination would not be cost-effective.

Since the method of simulating the activity of the population was computationally intensive, we were restricted in the number of replicates of each scenario we could generate in the time available. Therefore, in coming up with estimates of LYG for Table 18 and Figure 7 we formally combined the summary statistics using a hierarchical model. Such hierarchical models are coming into common use in the health economics setting⁹⁶. This model uses the fact that the additional interventions tend to increase LYG overall, and borrows strength across scenarios to come up with shrunken estimates of LYG for each scenario. This model was fitted in WinBUGS version 1.4.3.

Table 18. Cost-effectiveness of base case and catch-up vaccination scenarios plus screening versus screening alone. All scenarios are compared to the preceding vaccination scenario

Vaccination scenario	Average incremental costs per year (current value)	Average incremental estimate of LYG per vaccinated year group (current value)	ICER	Total cost of HPV vaccine plus administration costs in 1 st year of vaccination
1. Annual vaccination of 12 year old girls	€6,984,496	401.8 years	€17,383/ LYG	€9.7 million
2. Annual vaccination of 12 year old girls with catch-up to 15 years in 1 st year of vaccination.	€7,927,321	419.6 years	€52,968/ LYG	€38.9 million
3. Annual vaccination of 12 year old girls with catch-up to 17 years in 1 st year of vaccination.	€8,677,394	420.3 years	€1,071,532/ LYG	€58.4 million
4. Annual vaccination of 12 year old girls with catch-up to 19 years in 1 st year of vaccination.	€9,350,890	424.3 years	€168,374/ LYG	€77.8 million
5. Annual vaccination of 12 year old girls with catch-up to 26 years in 1 st year of vaccination.	€10,510,420	428.4 years	€282,812/ LYG	€108.9 million

Figure 7. Incremental costs and effects of base case and catch-up vaccination scenarios plus screening versus screening alone



Scenario 1	Annual vaccination of 12 year old girls
Scenario 2	Annual vaccination of 12 year old girls with catch-up to 15 years in 1 st vaccination year
Scenario 3	Annual vaccination of 12 year old girls with catch-up to 17 years in 1 st vaccination year
Scenario 4	Annual vaccination of 12 year old girls with catch-up to 19 years in 1 st vaccination year
Scenario 5	Annual vaccination of 12 year old girls with catch-up to 26 years in 1 st vaccination year

4.3.4 Sensitivity analysis of the base case model

Key parameters in the base case model (vaccination of 12 year old girls without catch-up) are varied in a series of one-way sensitivity analyses (Table 19). The results are sensitive to the discount rate, requirement for a booster dose, proportion of cases of CIN and cervical cancer caused by HPV types 16 and 18, as well as vaccine coverage. The results are robust to changes in the other parameters which were varied in the sensitivity analysis, including the direct medical costs, vaccine efficacy, population-based cervical screening coverage, cost of the vaccine and cost of vaccine administration, with less than +/- €4,000 change around the base case ICER.

If a 0% discount rate is applied to future costs and benefits, universal HPV vaccination would be highly cost-effective (€3,106/LYG). If the duration of protection from vaccination is only ten years and a booster dose is required, HPV vaccination is less cost-effective and the ICER increases from €17,383/LYG to €24,320/LYG. HPV vaccination is more cost-effective with a lower vaccine coverage rate. A fall in vaccine coverage from 80% to 60% results in a decrease in the ICER from €17,383/LYG to €12,371/LYG.

In the base case analysis, it is presumed that potentially 35% of CIN 1, 50% of CIN 2/3 and 74% of cervical cancers, are caused by HPV types 16 and 18. This is changed in the sensitivity analysis to reflect that 21% of CIN 1, 40% of CIN 2/3 and 60% of cervical cancers are caused by HPV types 16 and 18, as reported by Siggurdson et al.⁶³. Thus the treatment costs saved over time will be reduced, which implies that the average incremental costs will rise and the ICER increases from €17,383 to €23,564/LYG.

Results indicate that vaccination of 12 year old girls remains cost-effective when parameters were varied in all sensitivity analyses considered.

Table 19. One-way sensitivity analysis

Model variable (base case)	Change in parameter	ICER (base case € 17,383/LYG)
Discount rate (3.5% for costs and outcomes)	0%	€3,106/LYG
	6%	€39,546/LYG
Direct medical costs	+20%	€16,018/LYG
	-20%	€18,747/LYG
Cost of vaccine (€100 / dose)	€80 / dose	€13,659/LYG
	€120 / dose	€21,107/LYG
Cost of administration of vaccine (€30 / dose)	€15 / dose	€14,590/LYG
	€45 / dose	€20,176/LYG
Vaccine coverage (80%)	60%	€12,371/LYG
Booster dose at 10 years (€153 for one dose)		€24,320/LYG
Vaccine efficacy (95%)	85%	€17,762/LYG
	99%	€17,120/LYG
74% cervical cancer, 50% CIN 2/3, 35% CIN 1 caused by HPV 16/18	60% cervical cancer, 40% CIN 2/3, 21% CIN 1 caused by HPV 16/18	€23,564/LYG
Population cervical screening coverage (80%)	62%	€17,436/LYG

5 Discussion

The aim of this economic evaluation was to assess the cost-effectiveness of a HPV vaccination programme against cervical cancer together with a cervical cancer screening programme as compared to a population-based cervical cancer screening programme alone, using an independent economic model. As such, infections caused by HPV types 6 and 11, as well as other cancers related to HPV, specifically cancers of the vulva and vagina in women, penile and anal cancers in men and mouth and oropharynx in both genders, were not considered in the present study. While the results of our base case analysis indicate a cost-effective ICER of €17,383/LYG, uncertainties exist in relation to the data inputs used to calculate the cost-effectiveness of the vaccination programme in Ireland at this time, and are addressed below.

Vaccine efficacy

The RCTs of the HPV vaccines have shown over 95% efficacy (ITT analysis) in preventing infections with HPV types 16 and 18 up to five years after vaccination. HPV types 16 and 18 have been found on average in 50% and 20% of cases of cervical cancers, respectively. Therefore, it is assumed that the HPV vaccines could potentially prevent 70% of cervical cancers worldwide. In the future, when more data on cross-protection (against HPV types not included in the vaccine) and possible strain replacement become available, this simple extrapolation may be challenged and vaccine efficacy may increase or decrease from current estimates.

Vaccine efficacy in the long-term in reducing invasive cervical cancer is unknown, as cancer lesions frequently harbour multiple high-risk HPV types (including those other than the vaccine type).

Duration of protection

The duration of protection afforded by the vaccine against CIN 1–3 and cervical cancer is another major determinant of the ICER. In the absence of long-term data, the duration of protection and therefore the need for booster doses remains uncertain. If the base case scenario is examined, where it is assumed that all 12 year old females who receive three doses of the vaccine are conferred with lifelong immunity, the resulting ICER is €17,383/LYG. On the other hand, if it is assumed that immunity provided by the vaccine wanes over time (and that the duration of protection against HPV is ten years) and a booster dose is needed, the ICER increases to €24,320/LYG. Whether more than one booster dose of the vaccine is required is at present unknown and was not examined in the sensitivity analysis in the present study, however results from the Belgian HTA on HPV vaccination found that the number of booster doses did not significantly impact on the cost-effectiveness results⁴⁹.

Absence of Irish-specific data

As stated in section 4.2.3, there is a lack of published Irish data for the direct medical costs of CIN 1-3 and cervical cancer. Within the timeframe of the present study, it was not possible to conduct specific micro-costing studies. To this end, costs of resource use items for CIN 1-3 and cervical cancer were obtained from the literature and expert clinical opinion (from members of the HPV HTA Expert Advisory Group) and were then valued using Irish unit cost data. However, the sensitivity analysis was robust to changes in direct medical costs, with the ICER ranging from €16,018/LYG to €18,747/LYG when the direct medical costs were varied by $\pm 20\%$.

Regarding epidemiological data required to calibrate the model, examination of data sources from Ireland showed that while incidence figures for CIN 3 and invasive cervical cancer were available from the National Cancer Registry, there was no national incidence data for CIN 1 and 2. Various sources were considered in order to estimate the incidence of CIN 1 and 2 (Section 2.4) and it was ultimately decided that data from the National Cytology Statistics 2005 be adapted to the model. While these data are based on the number of cytology samples taken, and not on the number of women, estimates of numbers of women from number of cytology samples were taken from the TOMBOLA trial in the UK (personal communication, TOMBOLA Group). Using the data from the National Cytology Statistics 2005 and the TOMBOLA trial, the ratio of women with CIN 1: 2: 3 was estimated. This ratio was then used to estimate the incidence of CIN 1 and 2 from CIN 3 incidence data provided by the National Cancer Registry. While we feel that using cytology sample-based data is more robust than using histologically confirmed CIN data, it should be noted that the assumption here is that women in Ireland are undergoing a similar management plan with regard to number of cytology samples taken, to their counterparts in the UK (specifically those enrolled in the TOMBOLA trial). In addition, there is some uncertainty about the incidence of cervical dysplasia and cervical cancer in the context of a fully operational population-based cervical screening programme, which was addressed by varying the uptake rate for the screening programme in the sensitivity analysis.

Choice of model

The type of model used in the present study was a transmission dynamic model, and as such displays several advantages over a static cohort model (Section 1.4). For example, it allows us to address population-related issues, such as the catch-up vaccination scenarios, which incorporate a herd immunity effect, but it also requires more detailed information on sexual activity patterns and natural history of infection within a population than the traditional static model. Therefore, dynamic models require more assumptions and are associated with a greater level of uncertainty compared to a static model. This feature alone can explain some of the variation in results reported in the literature and should be borne in mind when considering the cost-effectiveness of HPV vaccination (Appendix 1).

Outcome measure

Since relatively little quality of life data exist with regard to vaccination in the Irish population, coupled with the fact that a more conservative estimate of cost-effectiveness would be obtained by including LYG rather than QALYs, it was agreed that the outcome measure used in the present study would be the LYG. Measuring health outcomes in terms of LYG in this evaluation also facilitates comparison with other economic evaluations of vaccination programmes in the Irish setting^{32, 33}. However, the significant detriment in quality of life in long-term survivors of cervical cancer is acknowledged.

Budget impact

Examination of the ICERs produced in this economic analysis requires a concomitant look at the budget impact of implementing such a vaccination programme. It was estimated that if a universal HPV vaccination strategy of all 12 year old girls was implemented, the gross cost to the healthcare payer, over and above the screening programme, would be in the region of €9.7 million per annum. If a catch-up programme covering 13 to 15 year old females was included, it would incur an additional cost of €29.2 million in the first year only (Table 18).

There are on-going trials examining the safety and efficacy of co-administration of vaccines as part of an adolescent immunisation programme (for example, diphtheria, tetanus and pertussis (DTP) booster at 12 years of age). Results from these studies would inform the healthcare decision maker as to whether there exists a future potential to reduce the number of separate vaccination visits required.

Discounting

Discounting is a technique that allows comparison between costs and benefits that occur at different times. It accounts for the fact that costs incurred and outcomes realised today are not equivalent to costs and outcomes in the future²⁵. This is particularly important in economic evaluations of vaccination strategies where costs of vaccination occur immediately while benefits occur many years in the future (for example, universal infant hepatitis B vaccination strategy). In Ireland it is currently accepted that a rate of 3.5% for both costs and outcomes, as recommended by NICE, is employed³¹. Nevertheless, it is useful to demonstrate how the results vary according to different discount rates, which may be recommended in country-specific settings. The effect of discounting (0% - 6%) made a marked difference to the results of this economic evaluation as the benefits of vaccination are being observed (up to 20 years) in the future.

Other issues

Outside the clinical trial setting, other important questions about the use of HPV vaccines remain:

- *Should boys and young men receive the vaccine? While several countries (for example, Mexico, Australia) have licensed the HPV vaccine for use in both sexes, policy recommendation for dissemination of the vaccine in males awaits HPV vaccine efficacy data from the on-going international trials in males. Several groups have started to evaluate the cost-effectiveness of a HPV vaccination strategy, which includes a male as well as a female population. In the US, Elbasha et al., using a dynamic transmission model, determined that routine administration of the quadrivalent vaccine to 12 year old males and females in addition to a catch-up strategy incorporating 12 to 24 year old males and females was the most cost-effective strategy⁴⁰. However, there are as yet no independent evaluations published and since the vaccine is still unlicensed in the male population, we confined our analysis to the female population.*
- *Cross-protection afforded by the vaccines. Although the vaccines have been developed to protect against the most common high-risk HPV types (i.e., HPV types 16 and 18), infection with other virus types might also lead to cervical neoplasia. Limited data are available from both vaccines with regard to their cross-protective effects against other HPV types. Data from the PATRICIA trial demonstrate some preliminary evidence of cross-protection with HPV types 31 and 45 against persistent HPV infection (up to 6 months post vaccination)²². This cross-protection is attributed to the homology of types 31 and 45 with types 16 and 18, respectively where they share cross-neutralising epitopes. Preliminary evidence on the use of Gardasil™ has also demonstrated cross-protection against CIN2+ due to HPV types 31 and 45, and the effect was evident up to four years post-vaccination⁷⁹. Further evidence is required however, before definitive answers can be given on the cross-protective effects of the vaccines against other high-risk HPV types.*

- *Long-term vaccine safety. Clinical trials have demonstrated the safety of the vaccines in the study populations. Both vaccines have been well tolerated without serious vaccine-related side effects. Studies of vaccine safety (including immunogenicity and efficacy) are ongoing in certain populations, for example, pregnant women, and although the trials so far have reported no increase in spontaneous loss rate or foetal malformations compared to placebo groups, the Advisory Committee on Immunisation Practices (ACIP) in the US does not recommend vaccination in women known to be pregnant.*

Finally, the importance of continued cervical cancer screening in vaccinated women must be emphasised. This is mainly due to the following factors:

- *Approximately 30% of cervical cancers are caused by HPV types not contained in the vaccines.*
- *The vaccines may not be 100% effective.*
- *The vaccines have no reported therapeutic value for those already infected with HPV.*

6 Conclusions

The results of this HTA suggest that vaccination against HPV types 16 and 18 would be cost-effective from the perspective of the Irish healthcare payer. However, it is clear that any economic evaluation is only as accurate as the data inputs included in the model. As economic models incorporate a number of assumptions, the results are subject to a degree of uncertainty. Bearing in mind the estimates and assumptions that were used in this analysis, the following conclusions can be drawn:

- If annual vaccination against HPV types 16 and 18 is introduced for 12 year old girls only, with a vaccination coverage rate of 80%, an ICER of approximately €17,383/LYG is estimated. This result compares favourably with the findings of the economic evaluations of universal infant pneumococcal conjugate vaccination (€5,997/LYG) and universal infant hepatitis B vaccination (€37,018/LYG) in the Irish setting^{32, 33}. Had the model incorporated impact on quality of life in addition to impact on mortality, it is likely that the cost/QALY would be lower than the cost/LYG, yielding an ICER well below the guideline threshold of €45,000/QALY routinely used for economic evaluation of drugs in Ireland (Section 1.3.2).
- A catch-up programme for 13 to 15 year olds in the first year of vaccination results in a relatively high increase in health benefits compared to the other catch-up scenarios. In contrast, the results suggest that the marginal benefit of vaccinating 15 to 26 year olds may be negligible compared to the associated vaccine expenditure. At older ages, the vaccine becomes less effective due to an increased likelihood of pre-vaccination HPV exposure reducing cost-effectiveness.
- The ICER for annual vaccination of 12 year old girls plus catch-up for 13 to 15 year olds in the first year of vaccination was estimated to be €52,968/LYG. While acknowledging the implicit uncertainty in the model, had the impact on quality of life in addition to impact on mortality been incorporated, it is likely that the cost/QALY would be lower than the cost/LYG, yielding an ICER close to the guideline threshold of €45,000/QALY; therefore, this scenario is likely to be cost-effective.

- The ICER for extending the catch-up programme to 17 year olds compared to a catch-up to 15 year olds is €1,071,532/LYG and would clearly not represent a cost-effective use of resources. Cost-effectiveness of extending catch-up beyond 17 years is not considered, as the appropriate comparison is for each scenario to be compared to the one before, but only if the preceding one is cost-effective.
- It must be appreciated that implementation of the catch-up programme for 13 to 15 year olds would incur a one off additional cost of €29.2 million in the first year of the vaccination programme. Thereafter, the annual cost of HPV vaccination of all 12 year old girls is estimated at €9.7 million.
- The results of the economic model were sensitive to a number of key parameters, including the duration of protection from vaccination, the discount rate, the proportion of cases of CIN and cervical cancer caused by HPV types 16 and 18, as well as vaccine coverage. However, annual vaccination for 12 year olds remained cost-effective in all sensitivity analyses examined.
- In the base case analysis, lifelong protection from vaccination was assumed. If a booster dose was required after ten years, annual vaccination for 12 year olds remains cost-effective, although the ICER increases from €17,383 to €24,320/LYG.
- The longest duration of follow-up in relation to vaccine efficacy is currently five years and thus the protective effect against invasive cervical cancer has not yet been demonstrated. Although lifelong protection was assumed in the base case analysis future evidence is required to establish long-term safety and efficacy of HPV vaccination.
- The results of this evaluation are considered conservative as the benefits of including improvements in quality of life, potential cross-protection of the vaccine against other HPV types, as well as, vaccine efficacy against HPV types 6 and 11 were not included. For example, it is acknowledged that there are significant detriments in quality of life in many long term survivors of cervical cancer. On the other hand, the additional resources required to introduce a HPV vaccination programme, such as implementing surveillance systems and running educational campaigns, have not been included in the analysis.

- HPV vaccines do not eliminate the need for a cervical cancer screening programme as currently available HPV vaccines do not offer protection against all types of HPV that cause cervical cancer. Screening is also essential to protect adult women who have not been vaccinated. Therefore, it is important that women be informed and motivated to attend for screening when invited to do so even if they have received a HPV vaccine. Vaccination (primary prevention) and screening (secondary prevention) are complementary approaches to controlling cervical cancer in Ireland. In due course the impact of HPV vaccination on the operational structure of a population-based cervical screening programme, together with new technologies such as HPV DNA testing will need to be monitored.
- Vaccination against HPV types 16 and 18 is a long-term investment, as the initial costs of vaccination will only be offset by improved health outcomes and treatment savings 15 to 30 years in the future.
- Universal HPV vaccination of 12 year old females can be recommended as a cost-effective intervention in the Irish healthcare setting. In relation to a catch-up programme, vaccination of 13 to 15 year old females in the first year of the programme would be the most cost-effective catch-up strategy.

7 References

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8 Appendix 1

Table 1. Summary of peer reviewed published cost-effectiveness evaluations of the HPV vaccine (2003-2008).

Authors (Reference)	Setting	Base case scenarios	Modelling approach	Assumptions	Outcomes assessed	Annual discount rate	Summary Results (base case)	Other scenarios evaluated / not evaluated
Kulasingham and Myers, 2003 ³⁶	US	Vaccination of all 12 year old girls plus screening vs. organised screening alone (every 3 years from 18 years of age)	Cohort, Markov model.	Duration of protection 10 years 100% coverage 90% VE	HPV 16/18 LYG	C: 3% O: 3%	Vaccination plus biennial screening from age 24y \$44,889/LYG	Did not evaluate catch-up or HPV 6/11
Sanders and Taira, 2003 ³⁷	US	Vaccination of all 12 year old girls plus existing cervical screening programme vs. organised screening alone	Cohort, Markov model	Duration of protection 10 years 70% coverage 75% VE	HPV 16/18 LYG and QALYs	C: 3% O: 3%	\$32,066/LYG and \$22,755/QALY	Did not evaluate catch-up or HPV 6/11
Goldie et al., 2004 ³⁸	US	Vaccination of all 12 year old girls plus existing cervical screening programme vs. organised screening alone =	Cohort, Markov model	Lifelong protection 100% coverage 90% VE	HPV 16/18 QALYs	C: 3% O: 3%	\$24,300/ QALY	Did not evaluate catch-up strategies or genital warts
Taira et al., 2004 ³⁹	US	Vaccination of 12 year old girls plus screening vs. organised screening alone	Hybrid, deterministic model	Duration of protection 10 years 70% coverage 90% VE	HPV 16/18 QALYs		\$14,583 / QALY	Vaccination of males and females not cost-effective compared to female only vaccination. Catch-up for women aged 24 and 30 years old. Genital warts not evaluated.

VE: Vaccine efficacy; QALY: Quality-Adjusted Life Year; LYG: Life Year Gained; VLS: Year of Life Saved; C: Costs; O: Outcomes; \$: International Dollar (\$ has the equivalent purchasing power that a US dollar has in the US)

Authors (Reference)	Setting	Base case scenarios	Modelling approach	Assumptions	Outcomes assessed	Annual discount rate	Summary Results (base case)	Other scenarios evaluated / not evaluated
Brisson et al., 2007 ⁴³	Canada	Vaccination of 12 year old girls plus current screening programme vs. screening alone	Cohort model	Lifelong protection 100% coverage 95% VE	HPV 6/11/16/18 QALYs	C: 3% O: 3%	Bivalent \$Can 31,000/QALY Quadrivalent \$Can 21,000/QALY	Did not evaluate catch-up strategies, but investigated different start ages for vaccination and requirement for booster.
Elbasha et al., 2007 ⁴⁰	US	Vaccination of 12 year old girls plus organised screening programme vs. screening alone	Population dynamic model	Lifelong protection 70% coverage 90% VE	HPV 6/11/16/18 QALYs	C: 3% O: 3%	ICER \$4,666/QALY 12 year old girls + catch-up to 24 years.	Vaccination of males, catch-up to 24 years and genital warts also evaluated. Herd immunity included.
Kulasingham et al., 2007 ⁴⁴	Australia	Vaccination of 12 year old girls plus current screening programme vs. screening alone	Cohort, Markov model	Lifelong protection 80% coverage 100% VE	HPV 16/18 LYG and QALYs	C: 5% O: 5%	ICER \$AUS 51,103/LYG, \$AUS 18,735/QALY	Vaccination of males, catch-up to 24 years and herd immunity included. Genital warts not evaluated.
Boot et al., 2007 ³⁰	The Netherlands	Vaccination of pre-adolescent girls plus current screening programme vs. screening alone	Cohort, Markov model	Lifelong protection 80% VE	HPV 16/18 LYG	C: 4% O: 1.5%	€24,000/LYG	Genital warts not evaluated. Requirement for booster considered in sensitivity analysis.

VE: Vaccine efficacy; QALY: Quality-Adjusted Life Year; LYG: Life Year Gained; YLS: Year of Life Saved; C: Costs; O: Outcomes; \$: International Dollar (\$ has the equivalent purchasing power that a US dollar has in the US).

Table 1. Summary of peer reviewed published cost-effectiveness evaluations of the HPV vaccine (2003-2008). continued

Authors (Reference)	Setting	Base case scenarios	Modelling approach	Assumptions	Outcomes assessed	Annual discount rate	Summary Results (base case)	Other scenarios evaluated / not evaluated
Insinga et al., 2007 ⁴⁵	Mexico	Vaccination of 12 year old girls plus screening programme vs. screening alone	Transition dynamic model	Lifelong protection 70% coverage 90% VE	HPV 6/11/16/18 QALYs	C: 3% O: 3%	\$US 2,719/ QALY	Vaccination of males, catch-up to 24 years and herd immunity included.
Goldie et al., 2007 ⁴⁶	Brazil	Vaccination of all 12 year old girls vs. screening alone vs. vaccination plus screening	Transition dynamic model	Lifelong protection 70% coverage	HPV 16/18 YLS	C: 3% O: 3%	IS\$120-820 / YLS (vaccination alone vs screening alone)	Herd immunity included. Genital warts not evaluated.
Ginsberg et al., 2007 ⁴⁷	Israel	Vaccination of 12 year old girls vs. no intervention	Static transition model	Lifelong protection 95% coverage 94.3% VE	HPV 6/11/16/18 QALYs	C: 3% O: 3%	US\$81,404 / QALY	ICERs for adding screening programmes to HPV vaccination also evaluated.
Bergeron et al., 2008 ⁴⁸	France	Vaccination of 14 year old girls plus current screening vs. screening alone	Cohort Markov model	Lifelong protection 80% coverage 100% VE	HPV 6/11/16/18 LYG and QALYs	C: 3.5% O: 1.5%	€20,455/LYG €13,809/QALY	No herd immunity included. No catch-up strategies analysed.

VE: Vaccine efficacy; QALY: Quality-Adjusted Life Year; LYG: Life Year Gained; YLS: Year of Life Saved; C: Costs;

O: Outcomes; IS\$ International Dollar (IS\$ has the equivalent purchasing power that a US dollar has in the US).

Table 2. Summary of publicly available Health Technology Assessments of the HPV vaccine

Setting	Base case scenarios	Modelling approach	Assumptions	Outcomes assessed	Annual discount rate	Summary Results (base case)	Other scenarios evaluated / not evaluated
Belgian Health Care Knowledge Centre, 2007 ⁴⁹	Vaccination of 12 year old girls plus current screening programme vs. screening alone	Static Markov model	Duration of protection 15 years Coverage 84% 46% VE (regardless of HPV type)	HPV 16/18 LYG QALY	C: 3% O: 1.5%	€68,078 / LYG €103,147 / QALY	Booster dose at 10 years. Catch-up programme and herd immunity not evaluated. Genital warts not evaluated.
Danish Centre for Health Technology Assessment, 2007 ⁵⁰	Vaccination of 12 year old girls plus organised screening programme vs. screening alone	Transition dynamic model	Lifelong protection 70% coverage 100% VE	HPV 16/18 LYG	C: 3% O: 3%	€11,441 / LYG	Vaccination of males, and catch-up to 19 years included. Herd immunity included. Genital warts not evaluated.
Norwegian Knowledge Centre, 2007 ⁵¹	Vaccination of 12 year old girls plus current screening programme vs. screening alone	Transition dynamic model	Duration of protection 10 years. 90% coverage 90% VE	HPV 16/18 LYG QALY	C: 4% O: 4%	€60,453 / LYG €50,567 / QALY	Booster dose at 10 years. Catch up programme and herd immunity not evaluated. Genital warts not evaluated.

VE: Vaccine efficacy; QALY: Quality-Adjusted Life Year; LYG: Life Year Gained; C: Costs; O: Outcomes

9 Glossary

Adenocarcinoma

A cancer of glandular tissue. For example, an adenocarcinoma of the lung is a cancer of the mucus-secreting cells that line the airways.

Adjuvant

Excipient that enhances the ability of a vaccine to protect against disease by stimulating the immune response against the antigen.

Anogenital region

Region around the genital organs and anus.

Antibody

Proteins found in the blood, produced by specialised white blood cells called 'B-cells'. B-cells make antibodies when the body recognises that something foreign (unfamiliar) is present, for example infecting bacteria. The antibodies attach themselves to these invaders, which are then destroyed. Scientists can now make synthetic antibodies (sometimes called 'monoclonal antibodies') in the lab, and use them to diagnose and treat disease.

Antigen

Foreign substance that, when introduced into the body causes an immune response. This is indirectly measurable in the form of antibodies or specific cells, for example, T-cells.

Asymptomatic

Having no symptoms of disease.

Atypia

Cells that look different from normal cells. A diagnosis does not mean that cancer is present, but may indicate an increased risk of developing cancer.

B-cell

A type of white blood cell that produces antibodies.

Bivalent

Aimed at two types.

Biopsy

The examination of tissue removed from a patient to discover the presence, extent and cause of disease.

Booster dose

A vaccine injection given to enhance the protection (immunity) obtained from the first vaccination series.

Bridging studies

An informal description of clinical studies that aim at transferring knowledge obtained through studies of a specific group (for example, an age group) to another group.

Cancer registry

Collection of information about the types of cancer that have been diagnosed and treated in a given area or region. Governments and health services run cancer registries so that they can keep a count of cancer rates and monitor how effective their prevention, diagnosis and treatment strategies are.

Carcinoma

A malignant tumour derived from epithelial tissue. Carcinomas are the most common type of cancer.

Carcinoma in situ

An early cancer that has not invaded (grown into) surrounding tissues. Considered as the most severe cell change just prior to invasive cervical cancer.

CIN (Cervical Intraepithelial Neoplasia)

A condition of the cervix, in which abnormal cells are present on the surface of the cervix. Over time, these cells may become cancerous. CIN is classified as 1, 2 or 3, depending on its severity. CIN 1 often clears up without treatment, but a repeat smear test is needed to check.

Cervix

Neck of the womb.

Chemotherapy

The treatment of disease, usually cancer, using chemical substances (drugs).

Co-administration

Administration of two or more drugs at the same time.

Colposcopy

A test performed using a colposcope to examine the surface of the cervix, in order to identify abnormal areas that require treatment. Usually done after an abnormal smear test.

Computed tomography (CT scan)

An image produced by a CT scanner - X-rays are taken from different angles and are put together by a computer to generate a series of cross-sections of the part of the body being scanned. This can build up a very detailed picture of the inside of the body, and provide accurate information on the size and position of a tumour.

Confidence interval

This refers to the range of values within which the true prevalence or percentage lies with a specified degree of assurance. The 95% confidence interval would include 95% of results from studies of the same size and design in the same population.

Cryotherapy

Treatment using a cold probe to remove cells and tissue by freezing. Used to treat abnormal cells found after a cervical smear.

Cytology

The study of cells. Cervical cytology screening is commonly referred to as a smear test.

Dyskaryosis

Abnormal appearance of the nucleus of a cell under the microscope, for example on a cervical smear test. Can be classed as mild, moderate or severe. These are all phases of pre-cancerous cells that could go on to develop into cancer if left untreated.

Dyskaryotic

Means the nucleus of a cell looks abnormal. Mild, moderate and severe dyskaryosis are three levels of abnormality found on cervical smears. None of these are cancer. They are all phases of pre-cancerous cells which could go on to develop into cancer if left untreated.

Dysplasia

Cell changes in an epithelium. The changes often disappear spontaneously, but may also develop into the preliminary stages of cancer.

Herd immunity

A reduction in the probability of infection that is held to apply to susceptible members of a population in which a significant proportion of the individuals have reduced risk of illness because the chance of coming in contact with an infected individual is less.

Histological

Study of a biopsy.

Immune response

The reaction of the immune system.

Immunogenicity

The ability of a vaccine to induce an immune response in the recipient.

Incidence

Number of new cases during a period of time, typically specified in number per year.

Incremental costs

Difference in costs (differential costs) between two comparable interventions.

Incremental effect

Difference in effect (for example, life expectancy) between two comparable interventions.

Intraepithelial

Within the epithelium/cell layer.

Intention to treat

Study results from patients who were randomly assigned to a treatment, regardless of whether or not they completed the study protocol.

Magnetic resonance imaging (MRI)

Method that uses a magnetic field to produce pictures of the structures inside the body. Produces better images of organs and soft tissues than other scanning technologies such as X-rays. Particularly useful for imaging the brain and spine, as well as the soft tissues of joints and the interior structure of bones.

Marker

Measurable parameter that is changed according to the activity of a disease.

Neoplasia

New formation of tissue.

Neoplastic

Result of neoplasia.

Oncologic

Related to cancer (oncology is the study of tumours, their origin, development and treatment).

Papilloma

Benign tumour

PET scan

Short for positron emission tomography scan. A PET scan is a way to find cancer in the body. In a PET scan, the patient is given radioactive glucose (sugar) through a vein. A scanner then tracks the glucose in the body. The scanner's pictures can be used to find cancer, since cancer cells tend to use more sugar than other cells.

Per protocol

Study results from patients who have completed the study protocol (contrary to intention-to-treat).

Persistent

Continuous; used for instance about an infection that remains in the body.

Phase I Trials

Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of efficacy; may include healthy participants and/or patients.

Phase II Trials

Controlled clinical studies conducted to evaluate the efficacy of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

Phase III Trials

Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labelling.

Phase IV Trials

Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

Polymerase chain reaction (PCR) assay

A very sensitive test that measures the presence or amount of RNA or DNA of a specific organism or virus (for example HPV) in the blood or tissue.

Prevalence

The proportion of the population with the disease at a given point in time.

QALY

Quality Adjusted Life Years: an endpoint that incorporates changes in life expectancy (mortality) and quality of life during life expectancy period (morbidity).

Quadrivalent

Aimed at four types.

Radical hysterectomy

Surgery to remove the uterus, cervix and part of the vagina.

Radiotherapy

Cancer treatment that uses high-energy electromagnetic radiation such as x-rays to kill cancer cells. During radiotherapy, a significant amount of healthy normal tissue is sometimes irradiated. To reduce the side effects caused by this, the radiation dose is often split into a number of treatments, enabling the normal healthy tissue to recover before the next treatment is given.

Randomised study

A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilised.

Regress

Relapse of a disease/pathological process.

Seroconvert

Change in the patient's antibodies in the blood against a specific bacterium/virus from negative (no antibodies) to positive (detection of antibodies).

Serologic

Detection in the blood; derived from serology (the study of antigens and antibodies in the blood).

Seropositive

Antibodies in the patient's blood against a bacterium or virus.

Surrogate endpoint

Replacement endpoint.

Trachelectomy

Surgical removal of the cervix, which is carried out in younger women with early cancer of the cervix. The cervix and the upper part of the vagina are removed, but the rest of the uterus is left in place. The lymph nodes in the pelvis are also removed, usually by keyhole laparoscopic surgery, to see if the cancer has spread. After trachelectomy it is sometimes possible for the woman to have children.

Transmission dynamics

The way in which a specific viral or bacterial disease is transmitted from one person to another.

