

A cost–utility analysis of adding a bivalent or quadrivalent HPV vaccine to the Irish cervical screening programme

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Background: Cervical cancer is a leading cause of death worldwide, and in Ireland it is the ninth most commonly diagnosed cancer in women. Almost 100% of these cancers are caused by human papillomavirus (HPV) infection. Two newly developed vaccines against HPV infection have become available. This study is a cost–utility analysis of the HPV vaccine in Ireland, and it compares the cost–effectiveness profiles of the two vaccines. **Methods:** A cost–utility analysis of the HPV vaccine in Ireland was performed using a Markov model. A cohort of screened and vaccinated women was compared with an unvaccinated screened cohort, and both cohorts were followed over their lifetimes. The model looked at uptake of services related to HPV disease in both cohorts. Outcomes were measured in quality adjusted life years (QALYs). Extensive sensitivity analysis was done. **Results:** For the base case analysis, the model showed that the incremental cost–effectiveness ratio (ICER) for quadrivalent HPV vaccination would be €25 349/QALY and €30 460/QALY for the bivalent vaccine. The ICER for the quadrivalent vaccine ranged from €2877 to €36 548, and for the bivalent from €3399 to €45 237. At current prices, the bivalent vaccine would need to be 22% cheaper than the quadrivalent vaccine in order to have equivalent cost effectiveness. **Conclusion:** HPV vaccination has the potential to be very cost effective in Ireland. The quadrivalent vaccine is more cost effective than the bivalent vaccine.

Keywords: cervical cancer, cost–utility analysis, genital warts, human papillomavirus vaccine, Markov model.

Introduction

Cervical cancer is an international problem,¹ and in Ireland it is the ninth commonest cancer in females, averaging 191 cases and 75 deaths annually.² A pilot screening programme serving 10% of the population was introduced in 2000, the Irish Cervical Screening Programme (ICSP),^{3,4} and since 2008 this has been extended nationally and has been renamed CervicalCheck.

Human papillomavirus (HPV) exists in over 100 different types, causing cutaneous, plantar and genital warts, respiratory papillomata and other lesions. There are low- and high-risk HPV types. Low-risk types include types 6 and 11, which cause up to 100% of genital warts.⁵ High-risk types, including types 16 and 18, are a necessary, but not sufficient, causal factor for cervical cancer. Types 16 and 18 are found in 73% of cervical cancers in Europe.⁶ Only limited data on HPV type prevalence are available for Ireland.^{7–11}

Two vaccines against HPV are available. The quadrivalent vaccine (Gardasil[®], Merck Laboratories) targets HPV types 6, 11, 16 and 18. The bivalent vaccine (Cervarix[®], GlaxoSmithKline Laboratories) targets HPV types 16 and 18 only. Clinical trials^{12–18} show evidence of vaccine efficacy of almost 100% for preventing genital warts,¹³ and between 90 and 100% efficacy for preventing high-grade cervical dysplasia caused by the HPV types targeted by the vaccine, when given to women who are naïve to the

types targeted by the vaccine.^{12,14,15,17,18} The duration of efficacy is unknown.

Both vaccines are shown to be cost effective using modelling methods which followed the natural history of HPV disease.^{19–27} The model in this study uses a different approach, modelling the effects that the vaccine will have on the uptake of services being provided for those with genital warts, abnormal smear tests and cervical cancer.

In Ireland, a Health Technology Assessment on the cost effectiveness of the bivalent vaccine was positive,²⁷ however, a decision on a commencement date and the vaccine to be used in a national programme has been delayed.

As no studies looked at the cost effectiveness of the quadrivalent vaccine in Ireland or compared the cost effectiveness of the two vaccines in any European setting, this study was performed. It is a cost–utility analysis of HPV vaccine in Ireland using a Markov model and examines the potential cost effectiveness of both vaccines, using Irish data wherever possible.

Methods

Cost–utility analysis

This study compared cervical screening alone with screening and vaccination of a cohort of 12-year-old girls over their lifetime. The perspective was that of the Health Service Executive (HSE). Direct medical costs were measured. Outcomes were measured in quality adjusted life years (QALYs). Costs and outcomes were discounted at 4%, as recommended by the Irish government. The threshold value was €45 000/QALY. The threshold value is the value set by a country below which it is prepared to consider a technology or drug to be cost effective. In Ireland, the Health Information and Quality Authority (HIQA) is the organization with responsibility for health technology assessment, and they have recommended this value in their first Health Technology Assessment.²⁸

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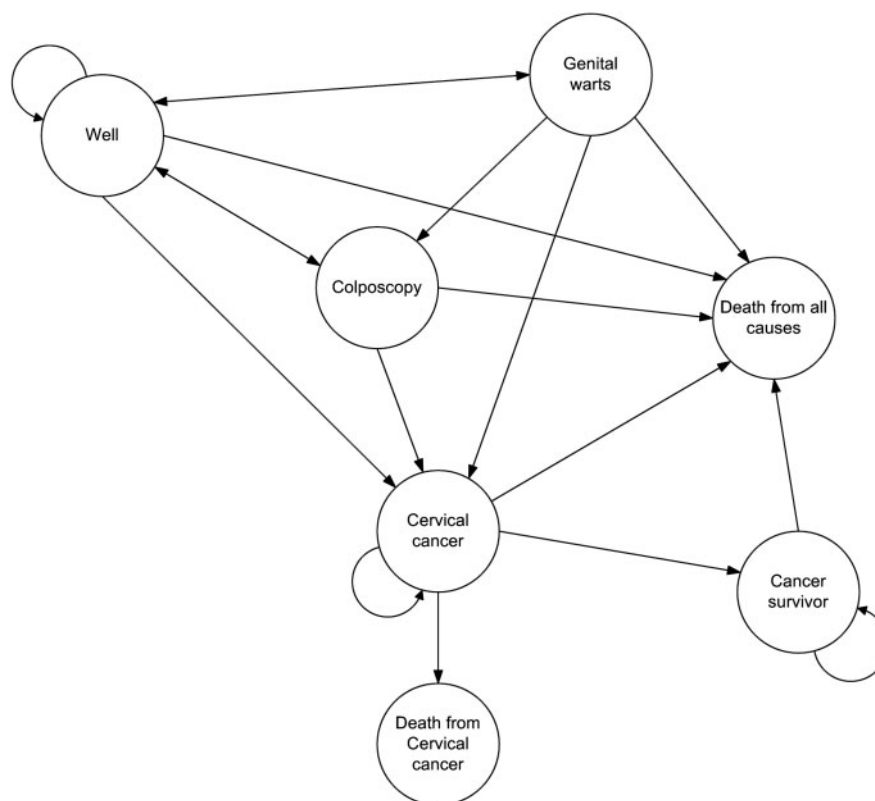


Figure 1 Possible transitions within the model

Model used

The model was designed using TreeAge Pro 2008® (TreeAge, Williamstown, MA, USA). It is a cohort model examining the effect on service provision over time of vaccinating a cohort of 12-year-old girls. The comparator is a cohort of unvaccinated girls. Both cohorts are screened for cervical cancer. It is a seven-state model running for 88 years and the cycle length is 1 year. The model was run separately for each vaccine and follows the uptake of services related to HPV disease over the lifetime of the women. Each cohort has 26 000 women, reflecting the size of the cohort of 12-year-old girls in Ireland, based on the 2006 census.²⁹ The health states within the model and the possible transitions between states are shown diagrammatically in figure 1.

In Ireland screening is through Pap smear, and in practice, all abnormalities apart from borderline changes are referred for colposcopy. The numbers of colposcopies performed in the pilot screening programme includes women with abnormal smear results of CIN 1–3. No data are yet available from the CervicalCheck programme, and so all the data came from the pilot programme. By using the ICSP data on numbers of colposcopies performed, and extrapolating to the general population, the provision of services related to all grades of CIN has been estimated. Colposcopy outcomes are modelled according to ICSP findings as reported in 2006.³ The pilot screening programme offered screening to women aged 25–60 years at 3 yearly intervals.

The probability of developing cancer in unscreened women is modelled according to cervical cancer incidence rates from the National Cancer Registry of Ireland (NCRI).³⁰ The probability of developing genital warts is based on incidence data in Northern Ireland.³¹ These rates are given in the supplemental data as is the list of the transition probabilities derived from them.

Assumptions

The main assumptions are

- Women only develop genital warts from the 'Well' state. One remains in that state for a year and then reverts back to 'Well' or goes to another state. Genital warts can recur within the model. The majority of cases of genital warts (63%) occur before the age of 25 years,³¹ and in any case, most women remain for their lifetime in the 'Well' state due to the relatively low probability of ever being referred for colposcopy or developing cervical cancer, and therefore most cases of genital warts are adequately captured.
- Referral for colposcopy is modelled for a population with a screening uptake rate of 61%.³ It is assumed that 39% of the population does not seek cervical screening, while the remaining 61% perfectly adhere to the guidelines.
- All women offered colposcopy undergo the procedure.
- All cases of CIN 1–3 are offered colposcopy.
- All women requiring colposcopy return to the 'Well' state after one year, unless they have invasive cancer, based on data calculated by Insigna *et al.*,³² estimating time from abnormal smear to negative cervical smear of 12.3 months.
- Cervical screening outcomes for low-grade abnormalities do not vary significantly between cohorts. (Borderline abnormality on cervical smear testing requires a repeat smear, occurs in 3.5% of all screened women.³ Based on estimates by Clifford *et al.*,⁶ vaccination would reduce this by 17%, i.e. 0.6% of screened women.)
- On developing cervical cancer a woman has an increased mortality from cervical cancer for 10 years, and then reverts to the population mortality rate from all causes.
- Women are only offered colposcopy within the screening programme.
- Vaccination is at age of 12 years.
- Vaccine uptake is 90% and varied in the scenario analysis.

- Vaccine efficacy of 90% against cervical cancer,¹⁵ and 95% against genital warts was assumed.¹⁸ HPV 16/18 is assumed to cause 73% of cervical cancer, 57% of CIN 2 and 3, 24% of CIN 1 and 19% of borderline changes.⁶
- HPV 6/11 causes 100% of genital warts.^{5,24}
- Lifelong immunity after vaccination is assumed.

The effects of vaccination on incidence of genital warts, the probability of referral for colposcopy and the probability of developing cervical cancer were calculated using equations which are provided in the supplemental data.

Cost data

Vaccination

Vaccination costs include the cost of the vaccine, delivery, storage and wastage. Both vaccines cost the same in Ireland at €97 per dose. A national vaccination programme would expect to procure it at a lower price and €90 per dose was used for this model.

A recent report estimated the potential costs of a national vaccination programme using a schools-based vaccination programme (SBVP) and a general practitioner (GP) programme.³³ The cost of administering each dose for an SBVP was calculated as €25 and for a GP programme it was €44. Based on three doses and adding 10% to cover storage and wastage, the cost of vaccinating a girl through an SBVP would be €380, increasing to €442 if given by GPs. For the base case, the model uses €400 and this was varied in the sensitivity analysis.

Vaccine uptake was varied in the scenario analysis.

Colposcopy and cervical cancer

Costs of colposcopy and cervical cancer were calculated using data provided by the Casemix Unit (CU) of the HSE.

The average cost of colposcopy was €704 based on 2006 data (Casemix Unit, HSE, 2007, personal communication). A figure of €700 was used in the model.

Going from the 'Colposcopy' state back to the 'Well' state is assumed to incur a cost. This cost is calculated by assuming that only those who have CIN 2 or 3 require a repeat colposcopy before returning to the 'Well' state. As 55% of colposcopies are performed for CIN 2 and 3, this cost is calculated as €700 × 0.55.

The cost of hysterectomy for cervical cancer in 2006 was €6759, the cost of chemotherapy was €3289 and of radiotherapy was €1020 per case (Casemix Unit, HSE, 2007, personal communication). Data from a private insurer indicated that the cost of treatment for cervical cancer was ~€10 000 (Voluntary Health Insurance, 2007, personal communication). As the HSE data were less certain, a cost per case of €10 000 was used and varied widely in the sensitivity analysis. It represents a once-off cost of cervical cancer. Thereafter, while cancer sufferers remain in the 'Cervical cancer' state, they incur a cost associated with living with cervical cancer. This is estimated conservatively as the cost of two out-patient visits (€172/visit) and one magnetic resonance imaging (MRI) scan (€350/scan) annually, based on cost information from a university teaching hospital providing cancer services for approximately one-eighth of the country. Assuming that 10 days are spent in hospital prior to death at a cost of €800 per day, the cost of death from cervical cancer was calculated at €8000 [Cork University Hospital (CUH), 2007, personal communication]. If a cervical cancer patient survives beyond 10 years, they become cancer survivors and incur no additional costs.

Genital warts

On the basis of a contact time survey carried out to facilitate this study, the annual cost of treatment of a female case of genital warts used in the model was €360.³⁴

Utility data

Genital warts

The utility value of 0.96 for genital warts was taken from a UK study.³⁵ The QALY decrement for genital warts in this study of 0.04 was small compared with that used in previous studies,^{23,32} but was varied in the sensitivity analysis to include these other values.

Colposcopy

The utility value for colposcopy of 0.89 was taken as the total QALY loss per episode of care for all three grades of CIN, as per Insigna *et al.* in 2007.³² An episode of care in this instance was taken as lasting 1 year.

Cervical cancer

In this model the term cervical cancer covers all stages. To ensure that the loss of quality of life associated with cervical cancer is not overestimated, the QALY rating used for cervical cancer in this model is that which is commonly used for localized disease. In addition, for the state of 'Cancer survivor' no further QALY decrement is applied. The value of 0.76 used was taken from a recent UK study.²²

A list of the main input parameters within the model and their sources is given in table 1.

Sensitivity and scenario analysis

The model was run separately for both vaccines. All costs and utilities were varied in a series of one-way sensitivity analyses and the discount rate was varied in one-way and two-way sensitivity analyses incorporating costs and outcomes. The discount rate was also varied to include the differential discount rate used in some European countries.^{19,20} Those costs for which accurate data were available were varied by 25% (cost of vaccine, genital warts and colposcopy), and where the cost information was less certain, the costs were varied by 50% (cost of cervical cancer, cost of living with cervical cancer and cost of death from cervical cancer). The cost of the vaccine was also varied to show the difference between a SBVP and a GP programme. The utility values were varied to include a range of values that have been used in previous analyses.

In the scenario analysis vaccine uptake was varied from 60 to 100% (equations included in the supplemental data). This was done by fixing the administration costs and reducing the cost of the vaccine in line with reduced amount used if uptake was 60 or 70%, etc. The consequent reduced effects on genital warts, colposcopy and cervical cancer were all adjusted in the model tables (outlined in the supplementary data).

The model also examined at what cost differential the two vaccines would have equivalent cost effectiveness.

Results

Model validation

The incidence rate for genital warts in the model was 92.2/100 000. The average incidence according to Health

Table 1 Main input parameters for the model

Description	Frequency of costs incurred	Value ^(source)
Cost of vaccine (both vaccines)	€90	
Vaccination average cost/girl: Uptake = 60%	Once/lifetime	€260 ³¹
Vaccination average cost/girl: Uptake = 70%	Once/lifetime	€290 ³¹
Vaccination average cost/girl: Uptake = 80%	Once/lifetime	€320 ³¹
Vaccination average cost/girl: Uptake = 90%	Once/lifetime	€350 ³¹
Vaccination average cost/girl: Uptake = 100%	Once/lifetime	€400 ³¹
Cost of colposcopy	Annual cost incurred for colposcopy	€700 ^a
Cost of cervical cancer	Incurred once upon diagnosis (dx)	€10 000 ^a
Cost of living with cervical cancer	Annual cost for ten years after dx	€700 ^b
Cost of death from cervical cancer	Cost incurred upon dying of cervical cancer	€8 000 ^b
Cost of a female case of genital warts	Annual cost of a female case of genital warts	€360 ³²
Cost of becoming well post colposcopy	Cost incurred upon returning to the well state	€385 ^a
Utility Values for Genital warts		0.96 ³³
Utility Values for Colposcopy		0.89 ³⁰
Utility Values for Cervical cancer		0.76 ²⁰
The probability of cancer at colposcopy		0.004 ²⁸
Probability of dying from cervical cancer		0.0035 ^c
Discount rate for costs		4% ^d
Discount rate for outcomes		4% ^d

a: Health Service Executive, Casemix Unit

b: Cork University Hospital

c: National Cancer Registry of Ireland

d: Department of Finance

Protection Surveillance Centre (HPSC) data were 99/100 000³⁶ (which includes males and females).

The model gives an incidence rate for cervical cancer of 8.5/100 000, slightly lower than the average crude incidence rate given by the NCRI of 10.0/100 000 for the years 1994–2005, but the model assumes a nationwide cervical screening programme.

The mortality rate from cervical cancer is 3.1/100 000. The overall crude mortality rate given by the NCRI is 3.9/100 000.

Results from model

Vaccination with either HPV vaccine causes a reduction of 32% in the number of colposcopies performed, 51% in cervical cancer and 60% in the number of cervical cancer deaths (table 2). In addition, vaccination with the quadrivalent vaccine caused an 85% reduction in genital warts. Table 2 also outlines the cumulative QALYs gained and costs accrued as a result of vaccination with both vaccines.

The incremental cost–effectiveness ratio (ICER) for adding the quadrivalent vaccine to a national screening programme was €25 349/QALY and for the bivalent vaccine it was €30 460/QALY.

Scenario analysis

The model examined at what cost difference the vaccines would have equal cost effectiveness. At a cost reduction of 22% compared with the quadrivalent vaccine, the bivalent vaccine would have an ICER of €25 483, almost equal to the quadrivalent vaccine.

Sensitivity analysis

Sensitivity analysis was performed around all parameters as outlined in table 3.

The model was sensitive to changes in the price of the vaccine and less so to the cost of colposcopy, but is not sensitive to the other costs shown. The ICER for a SCVP is significantly less for both vaccines compared with a GP programme.

Sensitivity analysis was performed around the discount rate for costs and outcomes separately, and then both together and using differential rates for costs and outcomes. The model was

Table 2 Differences between unvaccinated and vaccinated cohorts of 26 000 women for quadrivalent and bivalent vaccines at base case parameters

	Unvaccinated (No. of cases)	Vaccinated (No. of cases)
Health Outcomes		
Genital warts (quadrivalent vaccine)	2 109	321
Colposcopy referrals (both vaccines)	5 135	3 486
Cervical cancer cases (both vaccines)	195	95
Cervical cancer deaths (both vaccines)	70	28
QALY values		
Total QALYs (quadrivalent)	597 412	597 768
Total QALYs (bivalent)	597 412	597 721
QALYs gained (quadrivalent)		355.83
QALYs gained (bivalent)		308.83
Costs		
Total costs for cohort (quadrivalent)	€3 571 469	€12 149 651
Total costs for cohort (bivalent)	€3 571 469	€12 572 622
ICER		
ICER for quadrivalent vaccine		€25 349/QALY
ICER for bivalent vaccine		€30 460/QALY

sensitive to the discount rate for costs, but highly sensitive to the discount rate for outcomes.

The model shows that the ICER was below the threshold level of €45 000 for almost all variations in the discount rate used. Using the differential rates used in France (3.5% costs, 1.5% outcomes) and the Netherlands (4% costs, 1.5% outcomes), the ICER is dramatically reduced.

The ICER was also somewhat sensitive to changes in the utility value for colposcopy, but not for cervical cancer. The quadrivalent vaccine showed some sensitivity to the utility value for genital warts.

Discussion

The cost–utility analysis performed shows that for the base case, vaccination with the HPV vaccine in Ireland would be very cost effective. The quadrivalent vaccine is more cost effective than the bivalent. The result is sensitive to the cost

Table 3 Results of sensitivity and scenario analyses

Costs	Range for sensitivity analysis	ICER range Quadrivalent	ICER range Bivalent
Cost of vaccination	€300–500	€18 931–34 977	€23 087–41 521
Cost of vaccination (SBVP–GP)	€350–€413	€22 942–27 997	€27 695–33 502
Cost of colposcopy	€525–875	€25 865–24 834	€31 053–29 868
Cost of cervical cancer	€5 000–15 000	€25 921–24 778	€31 117–29 804
Cost of Living with cancer	€350–1050	€25 624–25 074	€30 776–30 145
Cost of death from cancer	€4 000–12 000	€25 459–25 239	€30 587–30 334
Cost of genital warts	€270–450	€25 640–25 058	n/a
Discount rate			
Costs	0–5%	€14 910–26 386	€19 387–31 507
Outcomes	0–5%	€4891–35 113	€5 341–43 734
Costs and outcomes	0–3%	€2877–16 728	€3 399–19 650
Both costs and outcomes	3.5%	€20 735	€24 611
Both costs and outcomes	5%	€36 548	€45 237
Costs 4% outcomes 1.5%		€9698	€10 879
Costs 3.5% outcomes 1.5%		€9449	€10 641
Vaccine uptake rates			
Vaccine uptake	60–100%	€29 537–24 108	€35 145–29 146
Utility rate			
QALY value for genital warts	0.91–0.99	€21 820–28 074	€30 466–30 457
QALY value for colposcopy	0.84–0.94	€23 142–28 021	€27 453–34 208
QALY value for cervical cancer	0.71–0.79	€24 392–25 961	€29 146–31 307

n/a: not applicable

of the vaccine and the discount rate used, and to a lesser extent the utility values for colposcopy and genital warts.

There are two aspects to the cost of vaccination, the vaccine cost and the cost of administration. An SBVP would have significantly cheaper administration costs than a GP programme.³³

Like many of the published models, the ICER was sensitive to the discount rate used.^{19,20,23,25,26,33,37} If the rate of 3.5% (recommended by NICE³⁸) used in previous Irish studies is used,²⁷ the ICER reduces to €20 735/QALY for the quadrivalent vaccine and €24 611 for the bivalent. When the model was run for the differential rates found in some of the European studies,^{19,20} the ICER in each case was highly cost effective. Discounting has been much debated.^{38–40} Higher discount rates reduce the apparent cost effectiveness of the technology being examined, whereas lower discount rates give more favourable results. Policy makers need to fully understand which rates are used and their implications.

High vaccine uptake rates are necessary to maximize the effectiveness of a vaccination programme. An SBVP would be expected to achieve maximum uptake rates, based on the previous experience of the Meningitis C vaccination programme, which showed high uptake rates were only obtained in the school delivered part of the programme (schools uptake was 85–95% compared with 50–60% uptake from GPs and 25–30% from University programme) (HSE National Immunisation Office, Dublin, personal communication). Scenario analysis of the uptake rate showed that reducing the uptake reduces the cost effectiveness. This was not found to be the case in the study published by Usher *et al.*²⁷ and that could be accounted for if there was a failure on their behalf to recognize the fixed nature of administration costs in such a programme.

This model showed that the bivalent vaccine would need to be 22% cheaper than the quadrivalent vaccine to have equivalent cost effectiveness. Brisson *et al.*²¹ also compared the two vaccines in the Canadian setting and suggested that the bivalent needs to be 26% cheaper than the quadrivalent for equivalent cost effectiveness.

The sensitivity of the model to changes in some of the utility values used highlights that knowledge of the values

used, and the studies used to calculate them, is essential in the appraisal of cost-utility analyses. This is especially important where studies are funded by industry.

The model takes no account of the other HPV-related cancers, e.g. vulval cancer, penile cancer, etc., or of respiratory papillomatosis. Within the model, the effect of vaccination on the numbers of repeat cervical smears performed for borderline abnormality is not modelled for. Genital warts are only allowable from the 'Well' state within the model. In addition, the possible benefits of herd immunity and of disrupted HPV transmission to males have not been modelled. The effect on low-grade abnormalities of vaccination was not accounted for in the model, but was estimated to effect only 0.6% of screened women. While this effect would be small, it would still exist. All these weaknesses mean that the effect of HPV vaccination on service provision has probably been somewhat underestimated.

In using a Markov model, it can be expected that the ICER calculated will be conservative, as they are more likely to underestimate the cost effectiveness of a technology than transmission dynamic models.

The efficacy values for HPV vaccines used in this model were on the lower end of the ranges reported in the literature.^{12–15,17,18}

Choosing more conservative estimates for many of the data used in this model ensured that the result reflected a conservative calculation of cost effectiveness and lends confidence that the cost effectiveness estimated by this model is robust, and from a policy maker's point of view, represents the upper range of likely costs that will be involved in such a programme.

In this model the effects of possible waning immunity were not included. If studies demonstrate that there is a need for booster doses in the future this will increase costs. There is no evidence to suggest this to date,^{12,17} but longer-term follow-up is required.

There were some quality issues in relation to the data used. Much of the cost data was based on information received from one large teaching hospital. Data from the ICSP were of good quality, but only represented 10% of the total population. Extrapolating this was felt to be a better representation of the Irish population than using UK data.

Data from the NCRI was of good quality, but there was no prevalence data for cervical cancer nationally, leading to uncertainties around the calculation of the annual mortality rate from cervical cancer.

The main strength of this model is that it examines the effects of both vaccines. It is now widely accepted that HPV vaccination has the potential to be cost effective, and much of the debate centres on the choice of bivalent or quadrivalent vaccine in national vaccination programmes. The potential cost and quality of life savings from the prevention of genital warts are important considerations.

In conclusion, the model designed for this study shows that HPV vaccination has the potential to be very cost effective in the Ireland. The quadrivalent vaccine is more cost effective than the bivalent vaccine at current prices. Factors influencing the cost effectiveness will be the cost of vaccine and the type of vaccination programme organized.

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Conflicts of interest: None declared.

Key points

- In Ireland, HPV vaccination is likely to be cost effective.
- The quadrivalent vaccine is more cost effective than the bivalent vaccine at current prices.
- A schools vaccination programme is the cheapest way to deliver the vaccine and most likely to achieve highest uptake rates.
- For the base case analysis the ICER for quadrivalent HPV vaccination would be €25 349/QALY and €30 460/QALY for the bivalent vaccine.

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