Cost-effectiveness of vaccination against cervical cancer: A multi-regional analysis assessing the impact of vaccine characteristics and alternative vaccination scenarios

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SUMMARY

Mathematical models provide valuable insights into the public health and economic impact of cervical cancer vaccination programmes. An in-depth economic analysis should explore the effects of different vaccine-related factors and vaccination scenarios (independent of screening practices) on health benefits and costs. In this analysis, a Markov cohort model was used to explore the impact of vaccine characteristics (e.g. cross-type protection and waning of immunity) and different vaccination scenarios (e.g. age at vaccination and multiple cohort strategies) on the cost-effectiveness results of cervical cancer vaccination programmes. The analysis was applied across different regions in the world (Chile, Finland, Ireland, Poland and Taiwan) to describe the influence of location-specific conditions. The results indicate that in all the different settings cervical cancer vaccination becomes more cost-effective with broader and sustained vaccine protection, with vaccination at younger ages, and with the inclusion of several cohorts. When other factors were varied, the cost-effectiveness of vaccination was most negatively impacted by increasing the discount rate applied to costs and health effects.

Introduction

The previous two articles in this supplement reported that many models are already published for the economic evaluation of cervical cancer vaccination, with and without organised or opportunistic cervical screening programmes. The first overview article highlighted the differences between Markov process cohort models and population dynamic models [1]. Cohort models have a high level of transparency and understanding but also difficulties to account for the indirect (or herd) effect of vaccination that generates benefit beyond the vaccinated cohort by reducing the overall infectivity in the population. Cohort models may therefore underestimate the true economic value of the vaccines. Population dynamic models, currently relying on many uncertainties in their evaluation process, may not be the best starting point particularly in circumstances of sparse data inputs. Meanwhile they may offer the possibility of better answering economic questions such as evaluating the indirect effect of vaccination and the effect of vaccinating boys.

The second article revealed that within Markov process cohort models a distinction could be made between models requiring very detailed data inputs and a more succinct model that required fewer inputs [2]. We demonstrated that, if the basic structure of the models remained the same, the outcomes were consistent. However a detailed model is better able to address complicated questions such as those related to screening procedures.

This third article is intended to assist decision-makers to analyse different vaccination programmes independent of screening (changes to screening programmes is the topic of the next article [3]). The analysis includes factors about vaccine characteristics and vaccination strategies that impact economic results. The article applies the evaluation across different regions, in order to demonstrate the influence of location-specific conditions such as screening practices and epidemiology.

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Besides vaccine price, five key features of cervical cancer vaccines and vaccination programmes were investigated for this more in-depth economic analysis. Two features were vaccine-specific, namely cross-type protection and waning of immunity. The remaining three features were vaccination strategy dependent, namely age at vaccination, the number of cohorts at first implementation of vaccination and the target population.

Vaccine characteristics and their economic impact

Cross-protection

Two vaccines are available on the market and their efficacy against HPV-16&18 induced pre-cancer lesions has been reported in the range of 90–100% for 4–6.4 years [4–10]. However the vaccines may also provide broader or "cross" protection against infection by non-vaccine oncogenic HPV-types that are responsible for a remaining 20–30% of invasive cervical cancer cases (ICC). The impact of cross-protection should therefore be investigated by assessing the effect of varying vaccine efficacy against non-vaccine oncogenic types (such as HPV-31, 45, 52, 58, 33).

Waning

The decline in vaccine protection over time is another relevant factor evaluated. This feature is currently difficult to assess due to the lack of long-term data on vaccination, however waning may exist as could be expected from immune responses observed [5,11]. Therefore it is important to include an analysis of different waning scenarios with the effects of differing compliance rates to a booster shot [12–14].

Vaccination strategy decisions and their economic impact

Age of vaccination

Phase II data and subpopulation analysis of phase III trials have shown that vaccination is very effective in preventing HPV infection in individuals aged 15–25 years who were not previously exposed to the HPV-types of the vaccine [4,9]. Economic studies have demonstrated that the impact of vaccination programmes varies dependent on the target age, with diminishing cost-effectiveness results at older ages of vaccination [12,15–17]. The starting age of vaccination and the age cut-off were therefore considered from an economic perspective.

Multiple vaccination cohorts

Intuitively, the more 'catch-up' cohorts vaccinated at the start of a programme, the more pre-cancer and cancer lesions are avoided in the long-term and the faster the vaccination steady-state level will be reached [18]. Whether one or more cohorts should be vaccinated will have economic consequences therefore this formed part of this economic assessment.

Target groups

Cohort models cannot be used to evaluate whether specific target groups should be vaccinated as opposed to generalised vaccination because they lack the ability to analyse the transmission dynamics of the infection. Meanwhile this topic should form part of a complete economic assessment and will therefore be briefly considered in Section 4. The mechanism to answer the question related to whether boys should be vaccinated together with girls will be reviewed as an example, along with the results already published in the literature [17,19,20].

Methods

General model structure

A Markov cohort model was developed in Excel software (Microsoft®) to assess the impact of the cervical cancer vaccine on HPV infections and related cervical cancer cases [2]. The model incorporates a lifetime process simulating the natural history of cervical disease, from infection to cancer, for a single age cohort, from vaccination to death. A simple algorithm to represent cytological screening for cervical precancerous lesions forms part of the model. Screening has been subdivided into organised, opportunistic and no screening at all. Organised screening occurs at regular intervals between pre-specified ages, while opportunistic screening has irregular time intervals. At each screening event, lesions are detected based on the sensitivity of the screening test. Follow-up and/or treatment will occur depending of the type of lesion detected with a certain probability of success. A specific cost to each screening event and subsequent treatment is assigned. The values used for each region are reported in Table 1.

Model inputs

The model transition probabilities between the defined health states were derived from published literature and expert opinion (Table 1). They were held constant across the regions studied unless advised otherwise by local experts. Age-specific HPV incidence and screening parameters (i.e. age, interval, and coverage rates) were obtained for each region. In the model calibration process, the age-specific probability of progression from CIN2/3 to cervical cancer and the screening coverage rates, were varied within valid ranges derived from literature and location-specific guidelines, to fit the model-predicted cervical cancer incidence rates with data taken from local cancer registries.

Data on costs of screening and treatment for CIN and cancer were based on location-specific literature, expert opinion and official tariff lists. All costs were expressed in 2006 local currencies. Due to the paucity of utility estimates, available values were taken from the literature and assumed to be equivalent across all the regions studied. In each location an independent expert panel including clinicians and health economists, was asked to review all data inputs and update them if necessary to ensure they were appropriate for their local environment.

The vaccine effect was modelled by reducing the probability of acquiring persistent HPV infection, taking into account the reduction of cancer cases, the ultimate vaccine target. This reduction was calculated using clinical trial efficacy results and the proportion of cervical cancer cases attributed to each HPV-type, as determined by the HPV-DNA positive status of women in each specific region of the world. The proportion was assumed to be constant across all ages and was included in the calculation of vaccine efficacy. To avoid over-estimation of the vaccine benefit in early infections, the numbers of CIN1 and CIN2/3 cases prevented were reduced by a correction factor corresponding to the difference between vaccine effectiveness against cervical cancer and CIN-lesions. Each effectiveness value corresponded to the proportion of HPV types in each lesion, multiplied by the specific vaccine efficacy against these HPV types (Table 1) [21–23]. The vaccine coverage rate was 100% in the base-case situation, i.e. all women received the required 3 doses within 1 year. Furthermore, in the base-case setting, the vaccine was assumed to provide lifetime protection against acquisition of new infections by HPV-16&18. However the vaccine was assumed to have no impact on HPV infections that had not been cleared pre-vaccination [24].

Table 1
Model input data [with references]

	Chile	Finland	Ireland	Poland	Taiwan	References
Screening						
Proportion CIN1 detected	58% [52]	65% [53]	58% [52]	58% [52]	58% [52]	
Proportion CIN1 treated	100%	0%	50%	100%	0%	(expert opinion)
Proportion CIN2/3 detected	61% [52]	81% [53]	61% [52]	61% [52]	61% [52]	
Proportion CIN2/3 treated	100%	100%	100%	100%	100%	(expert opinion)
Organised screening						
Start (age)	25 [54,55]	30 (extended to 25)[a] [56]	25 [57]	25 (expert opinion)	30 [58]	
Stop (age)	65 [54,55]	60 (extended to 70)[a] [56]	65 [57]	59 (expert opinion)	70 [58]	
Interval (years)	3 [54,55]	5 (shortened to 2)[a] [56]	3 [57]	3 (expert opinion)	1 [58]	
Coverage	64% [54,55]	70%[a] [56]	40% [57]	15% (expert opinion)	30% [58,59]	
Opportunistic screening						
Ages	35, 42 [54,55] (expert opinion)	38, 41, 44, 47, 50, 53, 56, 59, 62 (expert opinion)	20, 25, 30, 35 [57]	30, 60 (expert opinion)	NA	
Coverage	20% [54,55]	14% (expert opinion)	20% [57]	55% (expert opinion)	NA	
Costs						
Vaccine cost per dose	$ 70.00	€ 150.00	€ 115.00 [60]	zł 373.00	NT$ 4 000.00	
Cancer treatment	$ 3 966.82	€ 7 388.60 [61,62]	€ 10 449.00 [60]	zł 2 547.77 [63] (expert opinion)	NT$ 70 020.69 [64]	
Screening & CIN treatment newly detected (year 1)						
Regular screening negative Pap	$ 12.98 [65] (expert opinion)	€ 29.00 (expert opinion)	€ 116.00 [60]	zł 40.00 [63] (expert opinion)	NT$ 530.00 [64]	
Regular screening positive Pap	$ 13.08 [65] (expert opinion)	€ 33.90 (expert opinion)	€ 119.72 [60]	zł 49.13 [63] (expert opinion)	NT$ 580.43 [64]	
CIN1 detected	$ 575.98 [65] (expert opinion)	€ 279.00 [61,66] (expert opinion)	€ 483.50 [60]	zł 814.50 [63] (expert opinion)	NT$ 2 713.00 [64]	
CIN2/3 detected	$ 575.98 [65] (expert opinion)	€ 529.00 [61,66] (expert opinion)	€ 661.00 [60]	zł 1 409.50 [63] (expert opinion)	NT$ 10 785.00 [64]	
CIN treatment year following detection (year 2)						
CIN1, year 2	$ 287.27 [65] (expert opinion)	€ 265.05 [61,66] (expert opinion)	€ 116.00 [60]	zł 32.00 [63] (expert opinion)	NT$ 530.00 [64]	
CIN2/3, year 2	$ 287.27 [65] (expert opinion)	€ 327.20 [61,66] (expert opinion)	€ 232.00 [60]	zł 80.00 [63] (expert opinion)	NT$ 1 060.00 [64]	
Utilities (QALY)						
No HPV, HPV infection, CIN1/2/3	1	1	1	1	1	[67–69]
CIN1 detected	0.987	0.987	0.987	0.987	0.987	[67–69]
CIN2/3 detected	0.991	0.991	0.991	0.991	0.991	[67–69]
Cancer treated	0.727	0.727	0.727	0.727	0.727	[67–69]
Cancer cured	0.938	0.938	0.938	0.938	0.938	[67–69]
Death	0	0	0	0	0	[67–69]
Discounting						
Cost, outcomes	3%, 3%	3%, 1.5%	3.5%, 3.5%	3.5%, 3.5%	3%, 1.5%	[29] (expert opinion)

Table 1 (*Continued*)

	Chile	Finland	Ireland	Poland	Taiwan	References
Transition probabilities						
Normal to HPV	0–0.09 [70]	0–0.12 [71–75]	0–0.18 [76]	0–0.09 [77–79]	0–0.17 [80]	
HPV to CIN1	0.049	0.049	0.049	0.049	0.049	[81]
CIN1 to CIN2/3	0.12 [82]	0.091 [82–84]	0.091 [82–84]	0.091 [82–84]	0.091 [82–84]	
CIN2/3 to persistent CIN2/3	0.125 [82]	0.114 [82,83]	0.114 [82,83]	0.114 [82,83]	0.114 [82,83]	
HPV clearance to normal	0.5 (expert opinion)	0.449 [85–89]	0.516 [85–89]	0.449 [85–89]	0.516 [85–89]	
CIN1 clearance	0.50 [82,88]	0.236 [82–84]	0.449 [82–84]	0.24 [82,88]	0.449 [82–84]	
CIN2/3 clearance	0.275 [82]	0.227 [82–84]	0.227 [82–84]	0.227 [82–84]	0.227 [82–84]	
Persistent CIN2/3 to cancer	0–0.10	0–0.10	0–0.10	0–0.07	0–0.10	Assumption
Vaccine efficacy						*Explanation:*
Cervical cancer	=0.62 × 0.95 + 0.38 × 0.27 = 0.69 [4,8,22,23,90]	=0.74 × 0.95 + 0.26 × 0.27 = 0.77 [4,8,22,23,90]	=0.74 × 0.95 + 0.26 × 0.27 = 0.77 [4,8,22,23,90]	=0.7 × 0.95 + 0.3 × 0.27 = 0.75 [4,8,22,23,90]	=0.71 × 0.95 + 0.29 × 0.27 = 0.752 [4,8,91–93]	Proportion of HPV-16&18 in CC × vaccine efficacy against HPV-16&18 + Proportion other oncogenic HPV in CC × efficacy against other oncogenic HPV
CIN1	=0.37 × 0.95 + 0.63 × 0.27 = 0.52 [4,8,22,23,90]	=0.37 × 0.95 + 0.63 × 0.27 = 0.52 [4,8,22,23,90]	=0.37 × 0.95 + 0.63 × 0.27 = 0.52 [4,8,22,23,90]	=0.37 × 0.95 + 0.63 × 0.27 = 0.52 [4,8,22,23,90]	=0.37 × 0.95 + 0.63 × 0.27 = 0.52 [4,8,22,23,90]	Proportion of HPV-16&18 in CIN1 × vaccine efficacy against HPV-16&18 + Proportion other oncogenic HPV in CIN1 × efficacy against other oncogenic HPV
CIN2/3	=0.52 × 0.95 + 0.48 × 0.27 = 0.65 [4,8,22,23,90]	=0.52 × 0.95 + 0.48 × 0.27 = 0.65 [4,8,22,23,90]	=0.52 × 0.95 + 0.48 × 0.27 = 0.65 [4,8,22,23,90]	=0.52 × 0.95 + 0.48 × 0.27 = 0.65 [4,8,22,23,90]	=0.52 × 0.95 + 0.48 × 0.27 = 0.65 [4,8,22,23,90]	Proportion of HPV-16&18 in CIN2/3 × vaccine efficacy against HPV-16&18 + Proportion other oncogenic HPV in CIN2/3 × efficacy against other oncogenic HPV

NA: Not applicable.

[a] Current screening is every 5 years from 30 to 60 years; however this scheme does not match the current number of Pap smears observed in Finland [56], the screening frequency has therefore been increased to match the observed number of Pap smears taken.

Outcome measures

The outcome measures included the number of cervical cancer cases prevented and deaths avoided, plus the life-years and quality-adjusted life-years (QALY) gained for one age cohort studied over lifetime in each location. The accumulated total cost difference (in local currency) and the QALY gained per woman, expressed as the incremental cost-effectiveness ratio (ICER), was also calculated. Future costs and outcomes were discounted at location-specific rates. A discount factor converts values (e.g. costs or health effects) that will occur in the future, to their present value. The general belief is that society prefers to get the benefits sooner and likes to pay the costs later [25]. The cost perspective considered in the analysis was that of the local healthcare payer.

Vaccine characteristics and their economic impact

Cross-protection

The impact of varying the efficacy of the vaccine against non-vaccine oncogenic HPV-types was assessed for each location. The cross-protection was increased on a continuous scale ranging from 0% (no cross-protection) to 50% corresponding to vaccine efficacy of 50% against non-vaccine oncogenic HPV-types. The upper limit was selected based upon the best estimate of vaccine efficacy by HPV-type reported in the literature related to its prevalence in cervical cancer [8].

Waning

The impact of waning on the ICER was calculated after varying both the decline in vaccine protection over time and the compliance level to a booster. This allowed for a large range of possible scenarios. Waning was assumed to apply to HPV-18 and to other cross-protected HPV-types, beginning 10–25 years post-vaccination [26]. The waning effect on vaccine efficacy was assumed to increase linearly over a 5-year period until no vaccine efficacy remained for the targeted HPV-types. A vaccine booster was given the year after the waning process started and this was assumed to give lifelong protection. Compliance to the booster might be different in different populations. It is expected that women undergoing organised screening are better followed and therefore are more likely to receive a booster shot than women undergoing opportunistic screening. The booster coverage was therefore varied from 25% to 70% to encompass a large range of scenarios.

Vaccination strategies and their economic impact

Age of vaccination

The impact of starting vaccination from 11 to 35 years on the ICER estimates was determined for each location with and without discounting. The wide age range allowed for the identification of the age after which starting vaccination was no longer cost-effective. It should be noted that the model assumed no lifelong immunity due to natural infection, rather that re-infection could be avoided by vaccination (the susceptible-infected-susceptible (SIS) modelling approach) [20,27]. This SIS type of model defines at each time point whether a person is *S*usceptible (=without infection, being able to contract an infection) or *I*nfected and therefore infectious (=can contaminate someone else). If the infection does not confer lifelong immunity, the person will become *S*usceptible again which means that they can contract an infection again, but later in time. This is the scenario considered in this model for HPV infection.

Multiple age cohorts

An incremental approach was adopted such that the vaccination of an 11-year-old cohort was compared with the addition of a supplementary annual vaccinated cohort in a stepwise manner until the final added cohort was aged 29 years at vaccination. The vaccine compliance rate for each supplementary cohort was fixed at 70%.

Additional sensitivity analyses

In addition to the two vaccine characteristics (cross-protection and waning) and vaccination strategies (age at vaccination and multiple 'catch-up' cohorts), the impact of additional variables on the number of cervical cancer cases averted and the ICER estimates were explored in one-way sensitivity analyses. These included vaccine cost, vaccine efficacy against HPV-16&18 infections, HPV incidence rates, the proportion of invasive cervical cancer cases caused by HPV-16&18 infections, and the utility estimates. Each parameter was varied from minus 20% to plus 20% of the base-case value in univariate sensitivity analysis. Also in probabilistic sensitivity analysis all variables were tested within a range of 20% (Table 2). In addition, the discount rate was varied from 0% to 5% for both costs and health effects corresponding to the range observed across the regions. Given that vaccine coverage rate does not affect the ICER (for any coverage change, the changes in costs and effects are proportional such that the ratio remains the same) the impact of this variable on the ICER was not explored.[1]

The combined effect of variations in model inputs was explored via multivariate probabilistic sensitivity analysis using @Risk® software (Palisade Corporation) in the Excel model. In this analysis, distributional functions were assigned to each variable. When a mean and standard deviation were available these were directly used. When only a range of values was available, a normal distribution function was selected with the average value taken as the mean and 25% of the difference between the maximum and the minimum values taken as the standard deviation. When no range was available a uniform distribution from −20% to +20% of the value was applied (Table 2). Thereafter 10,000 replicates were calculated after sampling each variable, with replacement, from the specified distributions. This approach was arbitrarily limited to Ireland, the location having the most readily available distribution of data needed for this analysis. With this large number of replicates it is possible to construct an acceptability curve to explore the probability of the ICER being at or below a certain threshold. In addition a multivariate stepwise linear regression analysis was performed to investigate which variable of the probabilistic analysis had the largest impact on the ICER result. The regression coefficients measured were normalised by which a value of 0 corresponds to no significant relationship between the input variable and the output result. A value of 1 or −1 indicates that a +1 to −1 standard deviation change in the output result will be obtained with an equivalent change in standard deviation of the input variable [28].

Results

Overall cost-effectiveness results

Tables 3a and 3b show the base-case results of the incremental cost-effectiveness ratios (ICERs) for each location in the study, reporting the number of cervical cancer cases and specific deaths avoided per 100,000 women, the life-years and QALYs gained per

[1] If an unvaccinated person accrues costs of 850€ for 72.00 QALYs, whilst a vaccinated person accrues 1090€ for 72.05 QALYs, than the ICER is 4800€/QALY. Comparing 5 unvaccinated girls (4250€, 360 QALY) with a group of 2 unvaccinated (1700€ and 144 QALY) plus 3 vaccinated girls (3270€ and 216.2 QALY), the ICER is still 4800€/QALY.

Table 2
Distributions for probabilistic analysis for Ireland (base-case values in Table 1)

Parameter	Distribution used	Distribution parameters
Transition probabilities		
Age-dependent mortality data	Multiplied at each age by a uniform distribution from 0.8 to 1.2	0.000031–0.3993; 0.000047–0.5990 [94]
Age-dependent HPV incidence		0–0.1470; 0–0.2205 [76]
HPV Onc regression	Normal distribution between 0 and 1 using as mean the observed mean and as standard deviation 25% of the difference between the minimum and maximum value reported in the literature	0.516 (S.D. 0.14) [87–89]
HPV Onc to CIN1 progression		0.049 (S.D. 0.009) [81]
CIN1 Onc regression		0.449 (S.D. 0.1415) [82–84]
CIN1 Onc to CIN2/3 progression		0.0908 (S.D. 0.142) [82–84]
CIN2/3 regression to no HPV		0.227 (S.D. 0.02275) [82,83]
CIN2/3 progression to persistent CIN2/3		0.114 (S.D. 0.01175) [82,83]
Proportion CIN1 Onc detected and treated	Multiplied by a uniform distribution from 0.8 to 1.2 (with a maximum of 100%)	0.40–0.60 (expert opinion)
CIN1 treatment success		0.76–1.0 (expert opinion)
Proportion CIN2/3 detected and treated		0.80–1.0 (expert opinion)
CIN2/3 treatment success		0.76–1.0 (expert opinion)
Cervical cancer to death		0.0683–0.1025 [95]
Cervical cancer to cured		0.1478–0.2218 [95]
Utility data		
No HPV	Fixed (1)	1 [67–69]
HPV		1 [67–69]
CIN1		1 [67–69]
CIN2/3		1 [67–69]
Death	Fixed (0)	0
CIN1 detected	Disutility multiplied by a uniform distribution from 0.8 to 1.2	0.01024–0.01536 [67–69]
CIN2/3 detected		0.007504–0.11256 [67–69]
Cancer		0.2184–0.3276 [67–69]
Cancer cured		0.0496–0.0744 [67–69]
Screening sensitivity		
CIN1 detected	Normal distribution between 0 and 1 using as mean the observed mean and as standard deviation 25% of the difference confidence interval.	0.58 (S.D. 0.045) [52]
CIN2/3 detected		0.61 (S.D. 0.045) [52]
Percentage estimated positive pap smear	Multiplied by a uniform distribution from 0.8 to 1.2	0.0496–0.0744 [96,97]
Vaccine effectiveness		
Vaccine effectiveness against HPV-16 & 18	Normal distribution with a mean of 95% and a standard deviation of 0.09	0.95 (S.D. 0.0895) [4]
Vaccine effectiveness against HPV-16 & 18 in CIN1		0.95 (S.D. 0.0895) [4]
Vaccine effectiveness against HPV-16 & 18 in CIN2/3		0.95 (S.D. 0.0895) [4]
Vaccine effectiveness other HPV-types	Normal distribution with a mean of 27% and a standard deviation of 0.12	0.27 (S.D. 0.11575) [8]
Vaccine effectiveness other HPV-types in CIN1		0.27 (S.D. 0.11575) [8]
Vaccine effectiveness other HPV-types in CIN2/3		0.27 (S.D. 0.11575) [8]
HPV Onc incidence	Normal distribution with a mean of 74% and a standard deviation of 0.17	0.74 (S.D. 0.17) [22]
HPV-16 & 18 in CIN1	Multiplied by a uniform distribution from 0.8 to 1.2	0.200–0.300 [22]
HPV-16 & 18 in CIN2/3		0.426–0.624 [22]
% HPV waning	Proportion of HPV impacted by the waning (all HPV Onc except 16) multiplied by a uniform distribution from 0.8 to 1.2	0.2304–0.3457 (assumption)
Waning delay	Uniform distribution from 10 to 70 years	10–70 (assumption)
Miscellaneous		
Cost data	Multiplied by a uniform distribution from 0.8 to 1.2	92.8; 8 359.2–139.2; 12 538.8 [60]
Screening coverage		0.32–0.48 (organised) [57] 0.16–0.24 (opportunistic) [57]

woman, and the total cost per woman for an 11-year-old cohort over lifetime, vaccinated and unvaccinated. The ICER results indicate that vaccination of girls aged 11 years with screening, is cost-effective compared with screening alone when the WHO threshold of 3 times the gross domestic product (GDP) per capita per region is considered as being cost-effective and below 1 times the GDP per capita considered as being very cost-effective [29].

Vaccine characteristics and their economic impact

Cross-protection

Fig. 1 shows for each location studied the ICER results as a function of the level of cross-protection of the vaccine against non-vaccine oncogenic HPV-types. In each region, the ICER improves at higher cross-protection levels for both discounted and undiscounted scenarios. A higher rate of improvement is seen with discounted results.

Waning

Fig. 2 shows by location, the two-way sensitivity analysis of the ICER as a function of the starting time of waning and the level of compliance to the booster vaccine. In all locations, the ICER decreases the longer the delay in starting the waning process. The improved booster compliance also increases the ICER in all countries except for the 10-year duration of protection. The effect of booster compliance combined with short duration of protection (10 years) differs between locations. For the early waning scenario: Finland, Ireland and Poland show decreased ICERs with increased

Table 3a
Base-case results: Undiscounted lifetime health and cost outcomes

Undiscounted	Cancer cases per 100,000 women	Cancer deaths per 100,000 women	LY per woman	QALY per woman	Total cost per woman
Chile[a]					
Non-vaccinated	576	329	69.333	69.323	$ 226.62
Vaccinated	191	109	69.373	69.370	$ 371.02
Difference	−385	−220	0.040	0.046	$ 144.40
Finland					
Non-vaccinated	668	249	72.017	71.998	€ 850.59
Vaccinated	172	64	72.050	72.045	€ 1 087.50
Difference	−496	−185	0.033	0.047	€ 236.91
Ireland					
Non-vaccinated	849	379	70.096	70.080	€ 1 081.23
Vaccinated	220	97	70.155	70.151	€ 1 188.03
Difference	−629	−282	0.059	0.071	€ 106.80
Poland					
Non-vaccinated	1392	859	69.159	69.137	zł 296.71
Vaccinated	397	245	69.287	69.280	zł 1 333.95
Difference	−995	−614	0.128	0.143	zł 1 037.24
Taiwan					
Non-vaccinated	1237	456	66.523	66.497	NT$ 9 776.33
Vaccinated	352	129	66.593	66.585	NT$ 19 480.22
Difference	−885	−327	0.070	0.089	NT$ 9 703.89

[a] US$ are expressed in 2006 values based on exchange rate of 523 Chilean peso to 1US Dollar.

booster compliance whilst Chile and Taiwan show increased ICERs with increased booster compliance. It is likely that Finland, Ireland and Poland have an older population compared with Chile and Taiwan. The former countries therefore have more cancer cases to avoid over a longer period of time and this might affect the ICER results differently, combined with the location-specific discount rates applied to costs and effects.

Vaccination strategies and their economic impact

Age of vaccination

Fig. 3 shows the effect of the starting age for vaccination on the ICER for the five regions. The results indicate that the undiscounted ICER is lowest when vaccination occurs at younger ages. The discounted data however vary from one region to another depending upon the local variation of HPV incidence with age. All discounted data show that the youngest ages of vaccination have a slightly higher incremental cost per QALY because of the increased delay between the intervention and the vaccine effect.

Multiple cohort 'catch-up' scenarios

The inclusion of additional cohorts substantially decreases the number of cervical cancer cases and deaths in all locations (Table 4). Vaccinating additionally from age 12 through 15 could avert fivefold more cancer cases and deaths compared with vaccinating a single age cohort. Catch-up until the age of 29 years further improved the health outcomes, preventing 16 times more cervical cancer

Table 3b
Base-case results: Discounted ICER (cost/QALY)

Discounted	QALY per woman	Cost per woman	ICER	1 × GDP/capita (very cost-effective) [25]	3 × GDP/capita (cost-effective) [25]
Chile[a]					
Non-vaccinated	29.528	$ 83.23			
Vaccinated	29.537	$ 272.24			
Difference	0.010	$ 189.01	$ 19 685	$ 9 033	$ 27 098
Finland					
Non-vaccinated	44.046	€ 307.59			
Vaccinated	44.067	€ 684.70			
Difference	0.021	€ 377.11	€ 18 431	€ 32 013	€ 96 038
Ireland					
Non-vaccinated	26.612	€ 369.43			
Vaccinated	26.623	€ 653.33			
Difference	0.011	€ 283.90	€ 24 799	€ 41 764	€ 125 291
Poland					
Non-vaccinated	26.476	zł 93.49			
Vaccinated	26.497	zł 1 191.20			
Difference	0.022	zł 1 097.71	zł 66 687	zł 27 586	zł 82 757
Taiwan					
Non-vaccinated	41.873	NT$ 3 279.58			
Vaccinated	41.914	NT$ 14 559.78			
Difference	0.040	NT$ 11 280.20	NT$ 278 665	NT$ 503 625	NT$ 1 510 875

[a] $ are expressed in 2006 values based on exchange rate between Chilean peso and US Dollar.

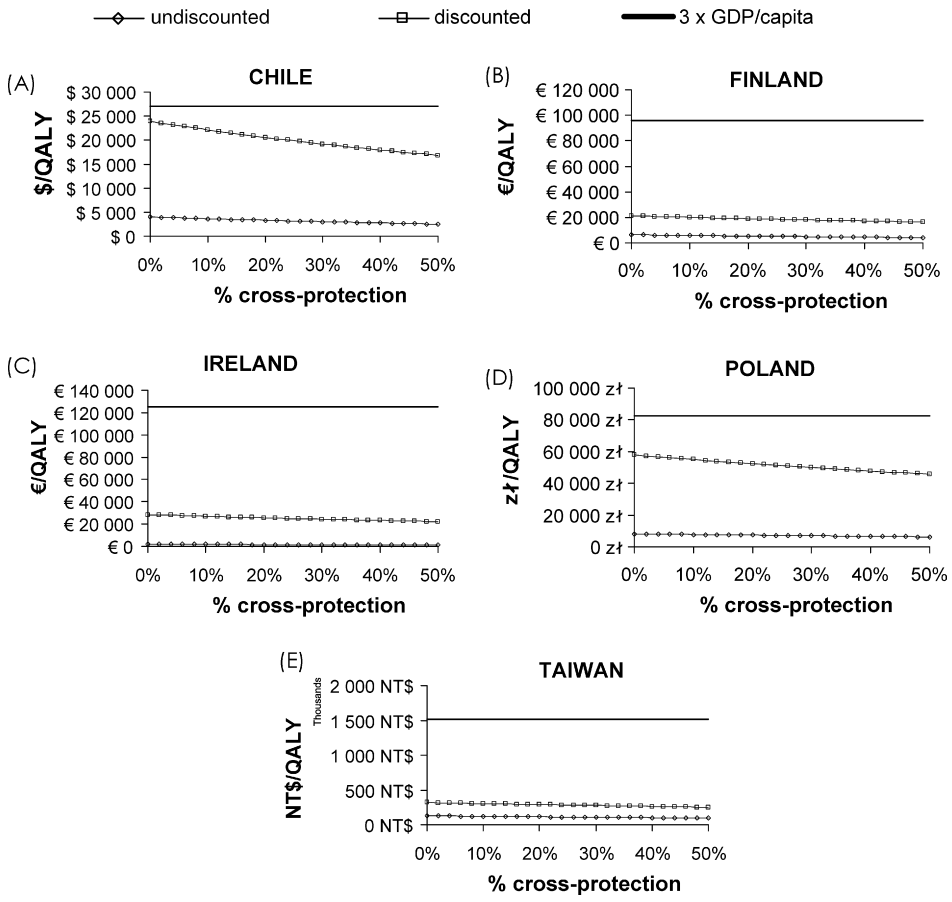


Fig. 1. The relationship between ICER and level of cross-protection.

cases and deaths. Fig. 4 shows the graphical results of the discounted and undiscounted ICER against adding an age cohort year by year up to 29 years of age compared with the preceding scenario. In all locations, the addition of the last catch-up cohort of 29-year-old could still be cost-effective in all countries except Chile where it is borderline cost-effective at the 3 times GDP per capita threshold.

Sensitivity analysis

For all five locations the ICER is most sensitive to varying discount rates. Increasing the discount rate to 5% substantially increases the ICER in Finland, adding about €80,000 per QALY gained to the base-case condition. The same increase in discount rate added around €40,000 per QALY gained in Ireland and about $30,000 in Chile. Sensitivity analyses on other parameters showed modest to negligible impact on the ICER (Fig. 5). Sensitivity analysis on the lifetime number of cervical cancer cases and related deaths prevented per 100,000 women are reported in Tables 5a and 5b. The percentage of cases prevented is similar across all countries. The relative impact of the vaccine cost on the ICER result varies across the regions, but it is interesting to observe that the impact is as large as for the next 2–3 variables on the diagrams by region (Fig. 5).

Multiple probabilistic sensitivity analysis for Ireland

The overall results are expressed as a cost-effectiveness 'acceptability' curve. This represents the cumulative probability (*Y*-axis) in function of ICER value defined (*X*-axis) for different discount rates (Fig. 6). The results are also plotted as a scatter-plot figure in a cost-effectiveness plane presented in Fig. 7. The probability that vaccination with screening is dominant over screening alone (i.e. more QALYs gained and lower costs resulting in a negative ICER) is 22% for undiscounted results, 1% for a 2% and 0.1% for a 3.5% discount rate as shown on the curve. The probability of the ICER being below 3 times the GDP per capita in Ireland is close to 100% for all discount rates (Table 3b). The probability of the ICER being below 1 GDP per capita in Ireland was 100%, 98% and 82%, respectively, at 0%, 2% and 3.5% discount rates (Fig. 6).

Finally, Fig. 8 indicates the impact of each variable in a multivariate stepwise linear regression analysis on the ICER by reporting the normalised regression coefficients for each significant result. The parameters related to the natural history of the disease, such as low-grade lesion and HPV regression or progression, the proportion of HPV-16&18 in cervical cancer and HPV incidence, have the greatest impact on the ICER. For vaccine-related parameters, the most important factors are in a decreasing order, the vaccine cost, the vaccine effectiveness against HPV-16&18, the cross-protection level, and the duration in protection (or waning delay). The proportion of waning HPV types and the booster coverage rate, considered separately in the analysis, did not appear to have a substantial impact. All the variables plotted in the analysis explain about 81% of the variation in ICER result as expressed by the R^2-score.

Discussion

The present study assesses the cost-effectiveness of adding HPV vaccination to screening compared with the current management

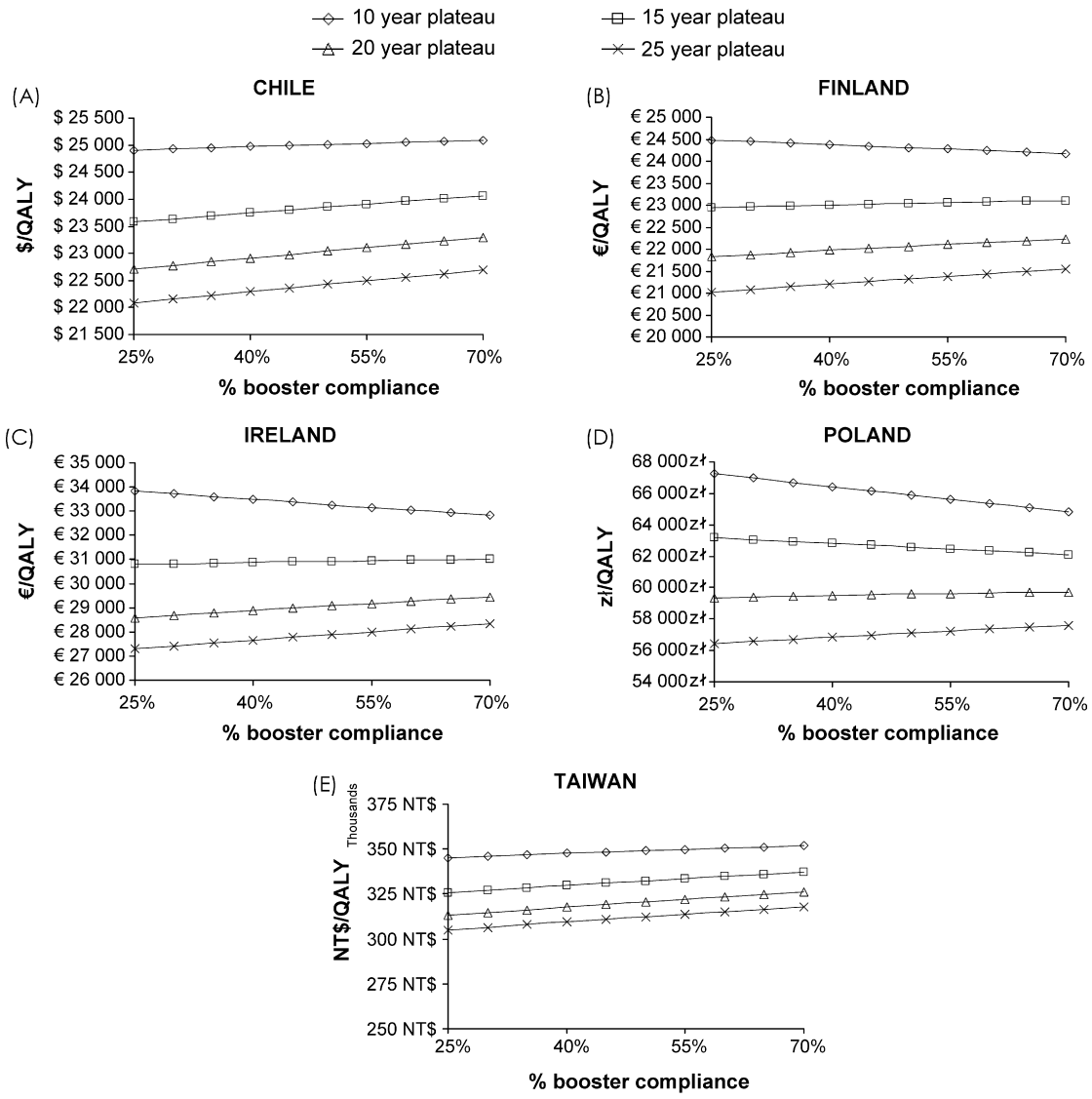


Fig. 2. The impact of waning scenarios on the ICER (discounted incremental costs per QALY gained).

situation of cervical cancer disease in five different regions worldwide (Chile, Finland, Ireland, Poland and Taiwan). The assessment is based on the results of a Markov cohort model adapted to each setting, simulating the lifetime costs and effects of vaccinating 11 year old girls. In all the regions the vaccine produces added benefit expressed in additional QALYs at an incremental cost-effectiveness result that is below 3 times the GDP per capita, a threshold defined by the WHO for being cost-effective. Vaccination against cervical cancer is therefore a cost-effective investment, but vaccine characteristics and vaccination scenarios modify the cost-effectiveness results either by reducing or increasing the costs and/or the QALYs gained.

Vaccine characteristics

Vaccine characteristics

Even though a precise value for cross-protection or duration of protection is not yet known, it is clear from the analysis presented that broader and more sustained protection of the vaccine leads to more favourable economic results. But the total benefit may be masked depending upon the applied discount rates, with higher discount rates worsening the cost-effectiveness results of the vaccine. However, up to 5% discount rates in each region results in ICERs below the approved threshold value proposed by the WHO. A 30% level of cross-protection reduces the ICER by 14% (Finland) to 20% (Chile), whilst waning the efficacy against HPV-18 and cross-protection after 10 years with 50% booster compliance, increases the ICER by 27% (Taiwan) to 37% (Ireland) and after 25 years by less than 13% (Taiwan) to 18% (Finland).

We only focussed on one of the two vaccine HPV-types (HPV-18) in the waning scenarios because there is evidence that HPV-16 has a robust, sustained antibody level maintained over a long period of time as demonstrated by the two vaccine manufacturers [11,26,30].

The differences in outcome between regions are observed because of the location-specific variations in screening and treatment options, costs and HPV epidemiology. The results

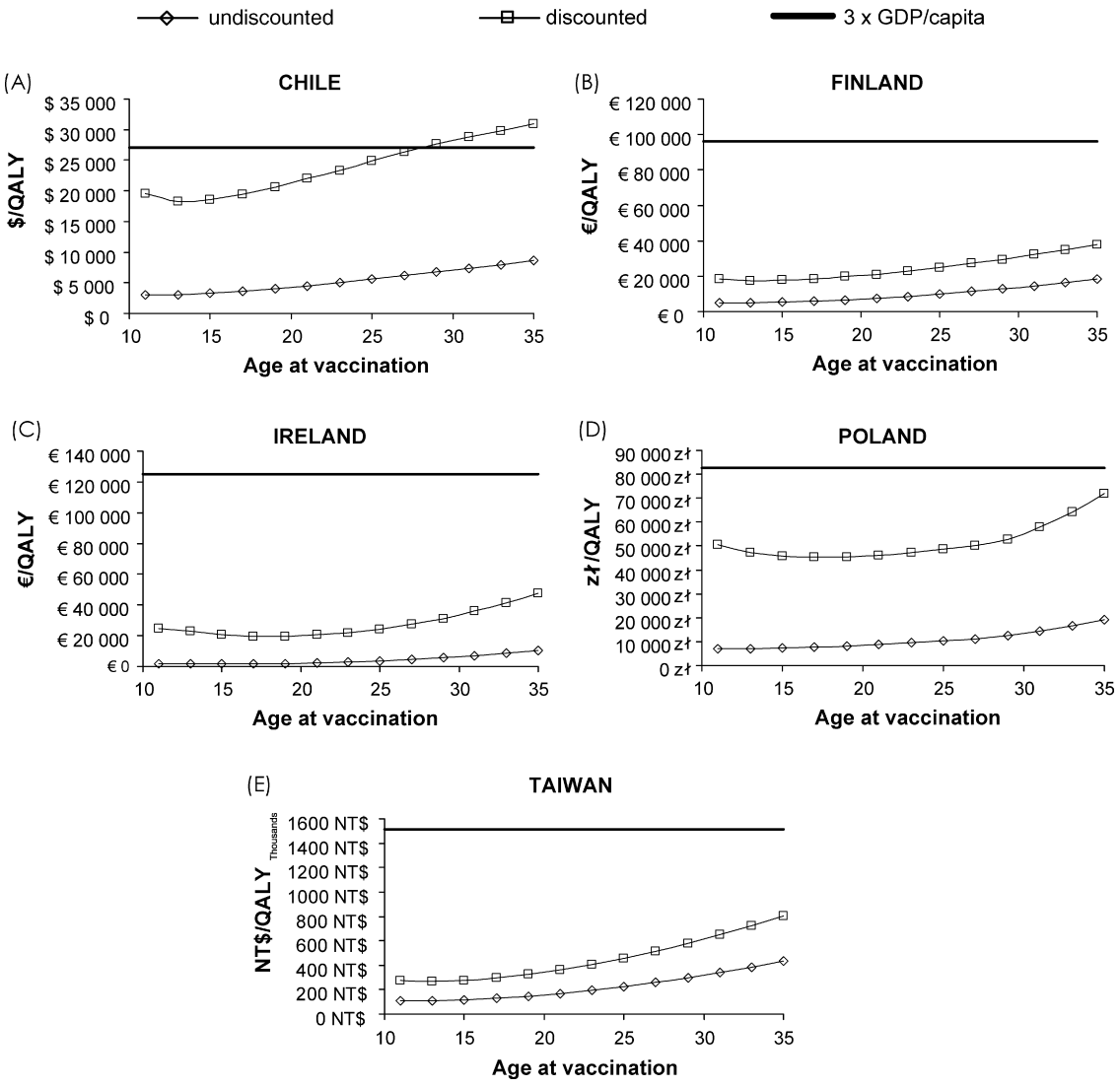


Fig. 3. The relationship between the ICER and starting age of vaccination.

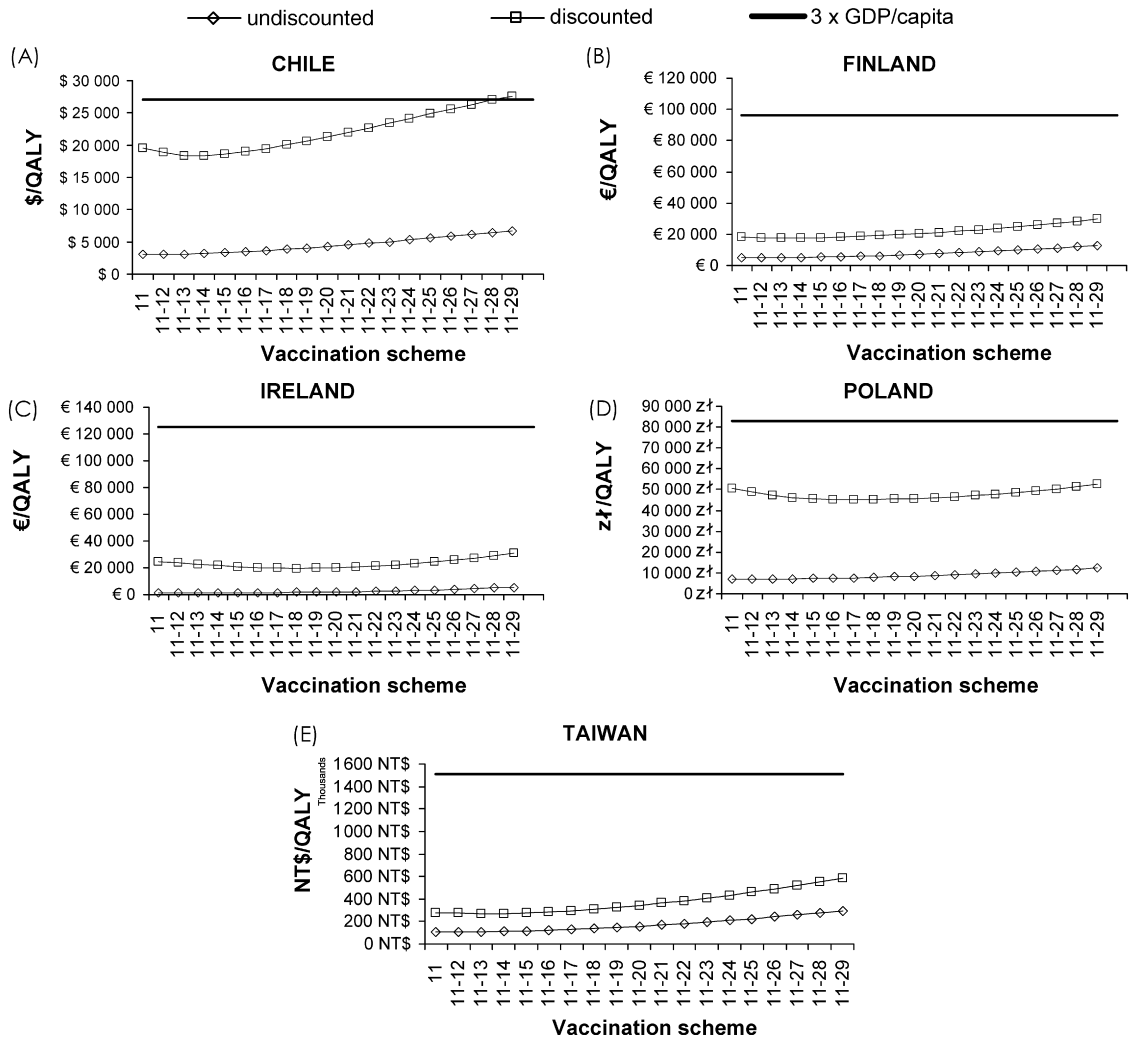
demonstrate that different vaccine characteristics have important health outcome and cost impacts with broader and sustained protection providing the most favourable economic results when proven efficacy is maintained.

Optimal vaccination strategy

For all five locations studied, cost-effectiveness results for cervical cancer vaccination are most favourable at earlier ages of vaccination. The discounted value shows different patterns across regions, driven by location-specific HPV epidemiology. The most favourable cost-effectiveness ratios are found before the age of 15 years except in Poland and Ireland where the most favourable age is 17 and 19 years, respectively, due to a later peak in HPV prevalence in these countries. Other studies have also demonstrated better cost-effectiveness results if vaccination occurs during early adolescence [12,15,16]. These findings are consistent with the natural history of HPV infection since the incidence of HPV infection peaks during the late teens and early twenties [8,28,31,32].

The optimal starting age of vaccination is worth consideration. Previous studies have concluded that vaccinating girls at 12 years of age or younger is more cost-effective than vaccinating at older ages; however, our analysis indicates that shifting the vaccination to a time closer to the moment of infection (i.e. 14 years vs. 11 years) will slightly improve the cost-effectiveness results when discounting is applied. Nonetheless, practical arguments should drive the decision for the optimal starting age of vaccination because the absolute numbers of cancer cases and related deaths averted is unlikely to differ between vaccination at age 11 years vs. 14 years. Additional challenges of vaccinating adolescents might be encountered in practice; experience with hepatitis B vaccination demonstrates that the compliance is lower in adolescents than in young children [33].

Given these challenges, initially vaccinating multiple cohorts could be useful to ensure broader vaccine coverage at the start of a program providing a larger health impact despite a higher initial investment. In all the locations investigated, the superior overall health benefits observed with a catch-up program to age 15 or even 29 years are associated with acceptable cost-effectiveness ratios compared with the vaccination of one age cohort. However, the extent to which additional catch-up cohorts could improve the cost-effectiveness outcome is limited. In practice budget constraints will most likely limit the scenario that will be adopted, although some countries like Australia did not



*Catch-up cohorts: 11 = vaccinate age 11 only and ages 12-29 not vaccinated; 11-12 = vaccinate ages 11-12 and ages 13-29 not vaccinated; 11-13 = vaccinate ages 11-13 and ages 14-29 not vaccinated, etc.

Fig. 4. The impact of catch-up cohorts* on the ICER.

look at budget limitations to recommend and reimburse vaccination up to an age above 25 [34]. An alternative approach has been suggested in Italy where concurrent vaccination of 3 cohorts (ages 11, 18 and 25 years) is a more cost-effective strategy in reducing HPV-related cervical diseases among Italian women [35]. This option has however not been addressed in the current study.

Combined sensitivity analysis

Incremental cost-effectiveness ratios are very sensitive to alternative assumptions on discount rates and starting age of vaccination, among other factors. For instance the cost-effectiveness results for Finland, where base-case discounting of health outcomes is lower than in the other locations, are particularly sensitive to this variation. Increasing the discount rate to 5% adds nearly €80,000 per QALY gained in Finland compared with less than €30,000 in Ireland. Results are less sensitive to alternative assumptions concerning vaccine costs, cross-protection, and HPV epidemiology.

The choice of discount rate can strongly influence the cost-effectiveness result of a cervical cancer vaccination programme. Discount rates are applied in economic analysis because future costs and effects receive less value weight than present or more immediate costs or effects [36]. No consensus exists on the appropriate discount rate to be used. Therefore a large range covering the values reported across country specific guidelines and recommendations has been tested. Meanwhile alternative discounting approaches have been proposed and should be further explored [36–39]. However, discounting health effects in prevention should be reconsidered as it too heavily and negatively affects the estimated cost-effectiveness results of vaccination programmes when outcomes occur much later than the point of intervention [37,40]. Vaccinating at an earlier age involves a longer waiting period before the health effects of the vaccine become apparent compared with vaccinating at an older age. As less weight is given to outcomes that occur later in time, an intervention aimed at younger girls (e.g. aged 11 years) may appear less cost-effective than one aimed at older girls (e.g. aged 14 years in Taiwan, for example), although health outcomes of the two scenarios are comparable. It is debatable whether these adjustments are meaningful

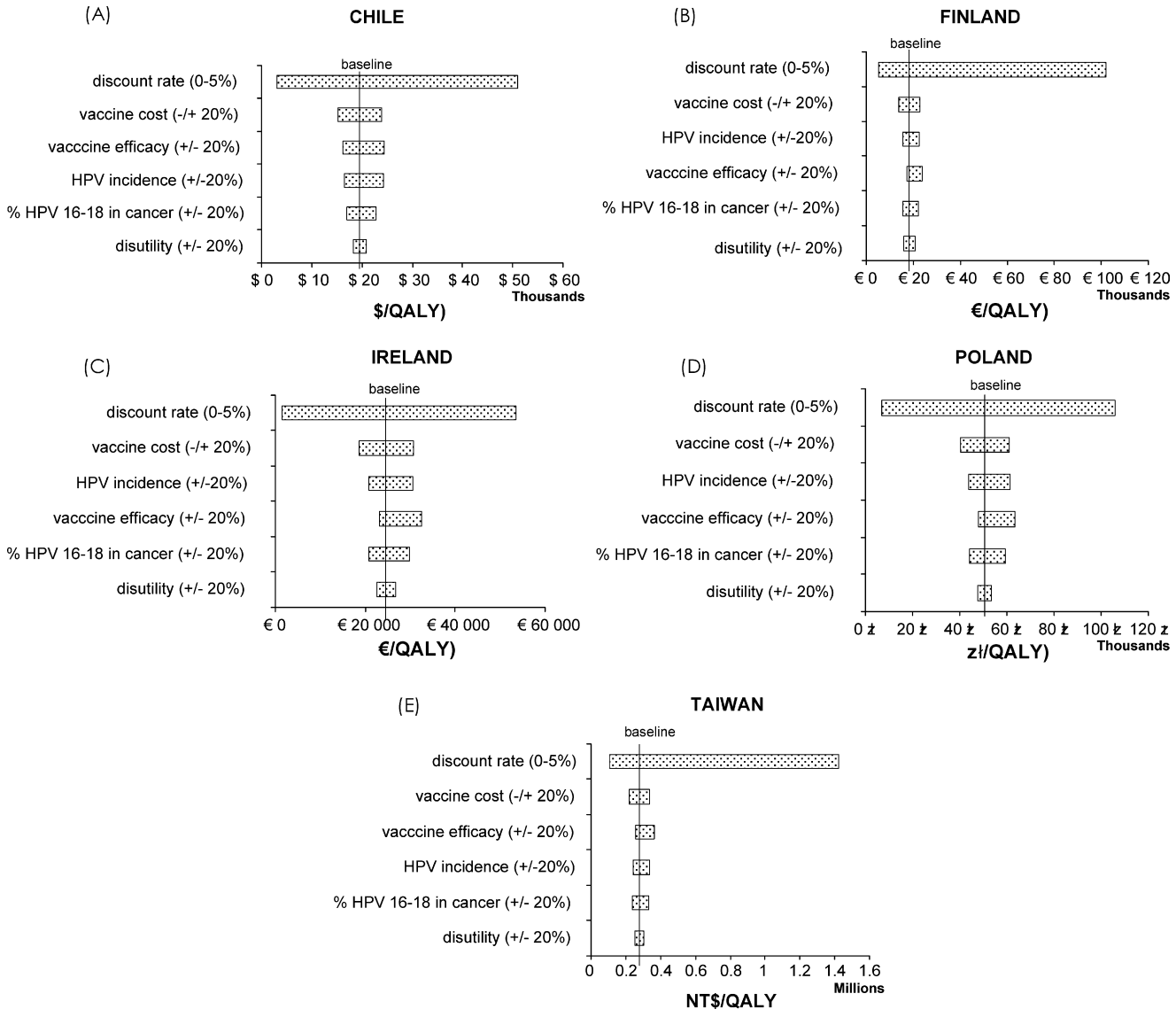


Fig. 5. One-way sensitivity analysis on ICER. Investigation of parameter uncertainty by varying each parameter ±20% and discount rate between 0% and 5%.

to policy decision-makers who must take into account societal, logistical and practical factors when implementing a cervical cancer vaccination programme [41]. Other factors also have an effect on the ICER, however when using a similar ±20% variation for all main parameters in one way sensitivity analysis, the ICER remains below the threshold value of 3 times the GDP per capita in all countries.

Finally, most interestingly in the probabilistic sensitivity analysis is that if equal weight is given to changes in the price of the vaccine as to changes in the values of other variables (+ or −20%), the price of the vaccine appears not to be a first driver of the ICER result as indicated in Fig. 8. The ICER is first driven by all the cancer and pre-cancer lesions to be avoided and to be treated reducing therefore the total disease burden with improvement of the QALY and the cost-offset.

Limitations in using cohort models

As previously discussed, cohort models are useful in assessing the vaccine effect in a single age cohort using information readily available in most countries. However, they do not consider the beneficial effects of herd protection, nor can they be used to clearly evaluate the impact of vaccinating specific groups such as boys in addition to girls with variable vaccine coverage rates [1]. Some analyses have tried to adjust for that lack of information in cohort models by adding correction factors to vaccine efficacy [42]. This hypothetical approach should be studied in-depth before promoting its general application. The method of choice to investigate infection transmission across different age cohorts and genders is through the use of dynamic models which adjust the level of susceptibility in the population with time if a factor other than the virus causes immune protection. These models have indicated that vaccinating males in addition to females may not improve cost-effectiveness results unless the vaccination coverage in females is low [17,43].

Other limitations include the extent of model calibration for a chronic disease that could be influenced by different cohort-related factors such as changes in sexual behaviour, screening programs or population demographics. In addition changes over time are more difficult to simulate in cohort models; these could become

Table 4
Accumulated cervical cancer cases and related deaths (lifetime number and relative change compared with no vaccination) for different catch-up scenarios when evaluating simultaneously 30 age-cohorts (11–29 years)[a]

	Chile		Finland		Ireland		Poland		Taiwan	
	CC cases (% change)	CC death (% change)	CC cases (% change)	CC death (% change)	CC cases (% change)	CC death (% change)	CC cases (% change)	CC death (% change)	CC cases (% change)	CC death (% change)
No vaccine	572	329	664	249	849	380	1391	860	1234	457
11[b]	552 (−4%)	318 (−4%)	638 (−4%)	240 (−4%)	816 (−4%)	365 (−4%)	1339 (−4%)	828 (−4%)	1187 (−4%)	440 (−4%)
11–15	472 (−18%)	272 (−17%)	534 (−19%)	201 (−20%)	683 (−20%)	306 (−20%)	1131 (−19%)	699 (−19%)	1003 (−19%)	371 (−19%)
11–20	380 (−34%)	218 (−34%)	419 (−37%)	155 (−38%)	523 (−38%)	233 (−39%)	888 (−36%)	547 (−36%)	799 (−35%)	295 (−36%)
11–25	298 (−48%)	169 (−49%)	323 (−51%)	113 (−55%)	385 (−55%)	169 (−56%)	672 (−52%)	411 (−52%)	635 (−49%)	230 (−50%)
11–29	239 (−58%)	132 (−60%)	257 (−61%)	82 (−67%)	295 (−65%)	124 (−67%)	522 (−63%)	313 (−64%)	527 (−57%)	187 (−59%)

CC: Cervical cancer.
[a] Expressed per 100,000 women.
[b] Catch-up cohorts: 11 = vaccinate age 11 only and ages 12–29 not vaccinated; 11–15 = vaccinate ages 11–15 and ages 16–29 not vaccinated; 11–20 = vaccinate ages 11–20 and ages 21–29 not vaccinated, etc.

Fig. 6. Acceptability curves for vaccinating 11-year olds compared with screening only in Ireland, with discount rates for both costs and outcomes at 0%, 2% or 3.5%.

important if many individual changes over time occur as seen with individual screening practices. Finally, the modelled effect of vaccine efficacy is based on HPV-type data from women who were HPV-DNA positive. The modelled results assume that the vaccine does not display efficacy against women who are seropositive for HPV, but HPV-DNA negative.

Other HPV types

Our analysis focused on oncogenic HPV-16&18 with the aim of investigating the benefits of vaccination against cervical cancer. The addition of non-oncogenic HPV-types though having no impact on mortality would provide an additional quality of life benefit (genital warts lasting on average 3–6 months in the younger age groups) and a cost offset for the treatment of genital warts [44,45]. A comparison of the two marketed vaccines based on a combination of oncogenic and non-oncogenic HPV-types would be very interesting in order to put into balance the added benefit of genital warts protection and cross- and sustained protection against cervical cancer. However more data about each vaccine, such as the specific vaccine response at equivalent time points for the same population type, would be required than is currently available in the public domain [46–50]. Once the appropriate data are available, future analyses should address these comparisons that have only been explored so far [15,51].

Replicates in the bottom right hand quadrant indicate QALYs gained at a reduced cost; replicates in the top right hand quadrant indicate QALYs gained at an increased cost.

Fig. 7. Incremental cost-effectiveness plane (◊ replicates, ×: mean value) showing percentage of replicates in each plane at 0% and 3.5% discount for vaccinating 11-year olds compared with screening only in Ireland.

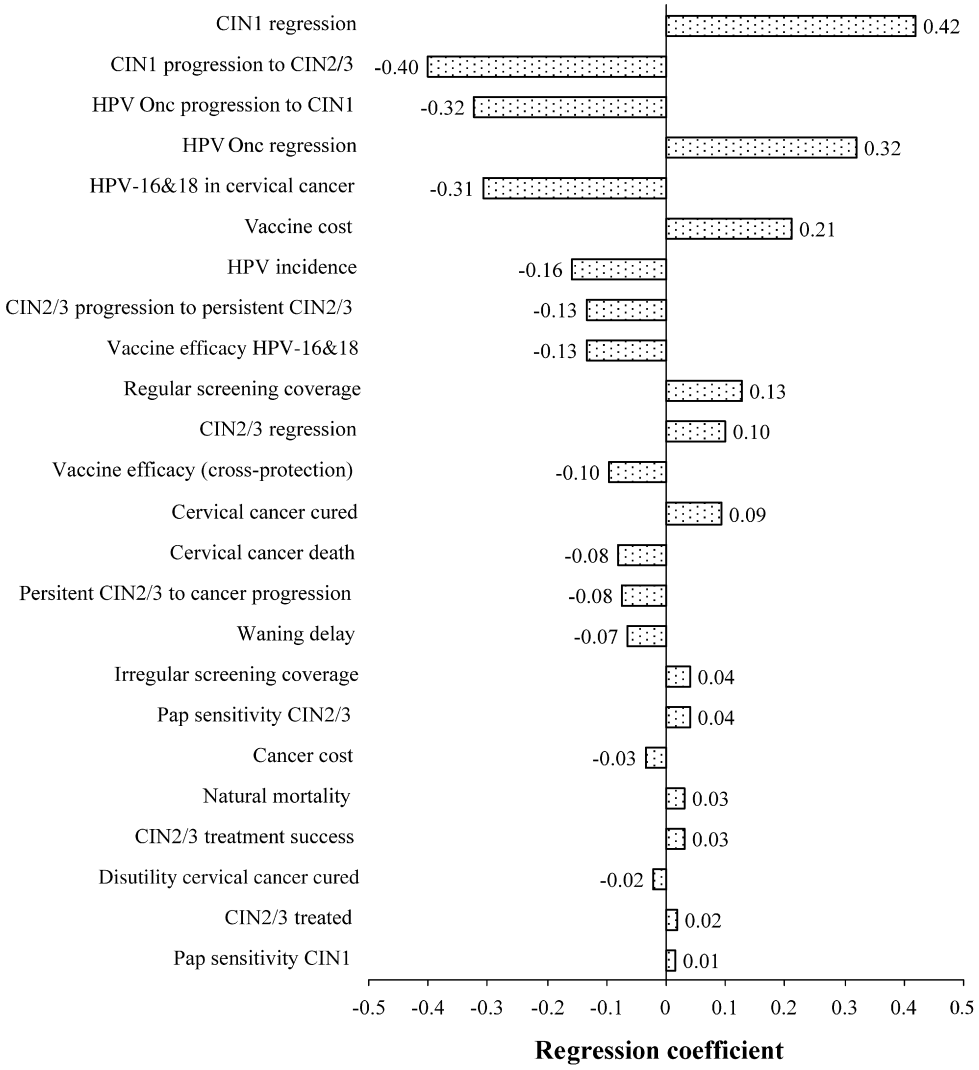


Fig. 8. Normalised regression coefficient obtained from the multivariate stepwise regression analysis against discounted ICER, Ireland (R^2 = 81%).

Table 5a
One-way sensitivity analysis on lifetime number of *cervical cancer cases* avoided for a single age cohort of 100,000 girls vaccinated at 11 years of age

Parameters investigated (minimum; maximum value)	Chile		Finland		Ireland		Poland		Taiwan	
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
Base-case	−385		−496		−629		−995		−885	
Vaccine efficacy (−20%; +20%)	−303	−469	−386	−612	−489	−777	−777	−1224	−687	−954
HPV incidence (−20%; +20%)	−316	−449	−413	−573	−524	−726	−827	−1150	−740	−1015
% HPV-16&18 in cervical cancer (−20%; +20%)	−335	−435	−424	−571	−537	−724	−855	−1140	−756	−1018
Booster coverage, following vaccine protection of 10 years	−288	−353	−367	−447	−460	−573	−702	−889	−703	−823
Booster coverage, following vaccine protection of 25 years	−313	−362	−420	−468	−549	−602	−843	−942	−791	−853
Age at vaccination (35 years old; 11 years old)	−244	−385	−244	−496	−293	−629	−494	−995	−371	−885
Cross-protection (0%; 50%)	−324	−437	−445	−540	−565	−685	−875	−1099	−780	−976
Vaccine coverage (80%; 100%)	−239	−385	−302	−496	−383	−629	−610	−995	−537	−885

Table 5b
One-way sensitivity analysis on lifetime number of *cervical cancer deaths* avoided for a single age cohort of 100,000 girls vaccinated at 11 years of age

Parameters investigated (minimum; maximum value)	Chile		Finland		Ireland		Poland		Taiwan	
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
Base-case	−220		−185		−282		−614		−327	
Vaccine efficacy (−20%; +20%)	−173	−268	−145	−228	−220	−348	−480	−755	−254	−352
HPV incidence (−20%; +20%)	−181	−257	−154	−215	−234	−327	−510	−710	−273	−375
% HPV-16&18 in cervical cancer (−20%; +20%)	−191	−249	−159	−213	−241	−324	−528	−703	−279	−375
Booster coverage, following vaccine protection of 10 years	−162	−202	−133	−167	−204	−257	−429	−554	−256	−303
Booster coverage, following vaccine protection of 25 years	−174	−206	−146	−172	−238	−268	−510	−578	−285	−313
Age at vaccination (35 years old; 11 years old)	−156	−220	−127	−185	−159	−282	−336	−614	−161	−327
Cross-protection (0%; 50%)	−185	−250	−167	−202	−254	−307	−540	−679	−288	−360
Vaccine coverage (80%; 100%)	−137	−220	−114	−185	−173	−282	−377	−614	−198	−327

Conclusion

Mathematical models provide valuable insights into the cost and health impact of a vaccination programme against cervical cancer in different settings. The full benefit of such a prophylactic vaccine will be observed 10–20 years after its introduction, depending upon the age(s) at vaccination and the catch-up scenario selected. Therefore, it is important to consider the impact of cervical cancer vaccination as a long-term investment. The high initial costs would be offset by the morbidity avoided and the lives saved due to the prevention of cervical disease. The economic results presented investigating different vaccine characteristics and vaccination strategies are consistent across five locations with varying cost inputs, HPV infection and disease patterns, and screening practices. The robustness of the findings further validates the use of the model to evaluate the cost-effectiveness of HPV vaccination under a range of circumstances. Economic results are heavily influenced by discounting rates therefore any economic analysis in the area of prevention should also include an assessment with no discounting. In conclusion, cost-effectiveness analyses in this paper demonstrate that vaccination of females is most cost-effective in younger age groups. Cost-effectiveness is also influenced by vaccine characteristics such as the level of cross-protection and the duration of protection, with better economic outcomes observed with broader and more sustained protection. Furthermore, catch-up programmes can greatly decrease the disease burden with acceptable cost-effectiveness compared with single-cohort vaccination programmes.

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