Vaccine 27 (2009) 4776–4783

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of prophylactic vaccination against human papillomavirus 16/18 for the prevention of cervical cancer: Adaptation of an existing cohort model to the situation in the Netherlands

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ARTICLE INFO

Article history:
Received 27 February 2009
Received in revised form 29 May 2009
Accepted 31 May 2009
Available online 17 June 2009

Keywords:
HPV
Cost-effectiveness
Cervical cancer
The Netherlands

ABSTRACT

Cervical cancer is one of the most prevalent cancers among women worldwide. Implementation of an HPV-vaccination strategy targeting the major oncogenic types 16 and 18 that cause cervical cancer is generally expected to significantly reduce the burden of cervical cancer disease. Here we estimate the costs, savings and health gains with the addition of HPV-16/18 vaccination to the already existing Dutch screening programme. In the base-case analysis, it was estimated that implementation of an HPV-16/18 vaccine would result in an incremental cost-effectiveness ratio (ICER) of €22,700 per life-year gained (LYG). In sensitivity analysis, the robustness of our finding of favourable cost-effectiveness was established. The ICER appeared sensitive to the vaccine price, discount rate and duration of vaccine-induced protection. From our results, it validly follows that immunization of 12-year-old Dutch girls against HPV-16/18 infection is a cost-effective strategy for protecting against cervical cancer.

1. Introduction

Cervical cancer is the second most common cancer among women worldwide, with approximately 500,000 new cases and 250,000 deaths annually [1]. Over three quarters of new cases occur in developing countries [2]. In most developed countries the incidence of cervical cancer has been significantly reduced due to effective cervical cancer screening programmes. However despite screening, the incidence of cervical cancer is still at levels that warrant implementation of further measures to reduce it in most countries. For example, in the Netherlands approximately 600–700 women annually are diagnosed with cervical cancer in a population of 8.3 million women [3,4]. The causal relationship between cervical cancer and infection with human papillomavirus (HPV) is generally accepted [5]. Studies in the last decades have shown that HPV infection is a prerequisite for cervical cancer, and that persistency of the infection is especially important [6]. In particular, infection with one of the oncogenic types of HPV may develop into cervical intraepithelial neoplasia (CIN) of grades 1–3 and ultimately into invasive cancer. Major oncogenic serotypes are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 [7,8], although additional oncogenic types such as 73 and 82 have also been implicated [9–11]. Additional HPV types, other than those subtypes explicitly labelled as oncogenic, may be considered low-risk HPV serotypes regarding their progression to cancer. Of the oncogenic types, HPV-16 and -18 have shown to be responsible for approximately 70% of cervical cancer worldwide [12,13].

Recently two types of prophylactic HPV vaccines, *Cervarix*™ (GlaxoSmithKline) and *Gardasil*™ (Merck & Co., Inc.), have been developed and registered [11–16]. Clinical studies have considered vaccine outcomes relating to CIN stages 2 and 3 (CIN2+ and cancer in situ), in addition to HPV infections. These studies have shown that the HPV vaccines have good safety profiles and are effective in preventing (persistent) infection with HPV types 16 and 18, in preventing CIN2+ related to types 16 and 18 and partially effective in preventing CIN2+ related to other oncogenic HPV types. Vaccine efficacies for up to 6.4 years of protection ranged

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doi:10.1016/j.vaccine.2009.05.085

from 94 to 100 for (persistent) infection with HPV types 16 and 18 [14–20], 90–99% for CIN2+ with HPV types 16 and 18 [18,21] and 46–68% for CIN2+ of all HPV types [22,23]. Additionally, evidence on cross-protection regarding infections with other non-vaccine types have been reported [17,18,24,25]. Finally, efficacy against persistent infection with all non-vaccine oncogenic types was found at 27% over a time period of 12 months [18].

For reimbursement decisions on prophylactic HPV vaccination in the Netherlands, health-economic assessments are essential in the present situation; i.e. a favourable cost-effectiveness ratio currently has to be provided before a positive recommendation for any drug or vaccine is given [26,27]. For example, health-economic studies were crucial in deciding whether or not to implement meningococcal C and 7-valent pneumococcal infant vaccinations in the Dutch National Immunization Programme (NIP) [27–29]. Also, one of both HPV vaccines was initially rejected for reimbursement in the Dutch Drug Reimbursement System (DRS), on grounds of insufficient evidence of a favourable health-economic profile [26]. For HPV vaccines both the DRS and the NIP present potential routes for reimbursement in the Netherlands, with health economics as one predominant criterion [30].

As mentioned, in the Netherlands 600–700 cases of cervical cancer occur every year, despite the existence of an effective screening programme [3]. The National Cervical Cancer Screening Program (NCCSP) in the Netherlands includes approximately 68–81% of women between the ages of 30 and 60 years in their invitational screening where women get screened every 5 years [3,31,32]. Within this programme approximately 490,000 cytology tests are analyzed annually, preventing an estimated number of 1500 cervical cancer cases per year [33].

This paper aims to estimate the costs and effects of introducing HPV vaccination for girls to be covered by the Dutch NIP. Life-years gained (LYG) are considered as the primary effect measure of interest, and quality-adjusted life-years (QALYs) gained are additionally provided. Costs and health outcomes are compared within the formal incremental cost-effectiveness ratio (ICER) by comparing vaccination on top of the NCCSP with the NCCSP alone. Ballpark figures on acceptable ICERs for vaccines included in the Dutch NIP are available: low-risk elderly influenza and elderly pneumococcal vaccination both at approximately €10,000 per LYG and infant pneumococcal vaccination at €16,200 per LYG or €14,600 per QALY gained (all updated to 2007) [28,29,34]. It has been suggested that ICERs below €20,000 per QALY might be considered as acceptable cost-effectiveness for vaccination programmes in the Netherlands [35]. Finally, a further alternative threshold for the ICER may be derived from a country's Gross National Product (GNP) per capita, which is just over €30,000 for the Netherlands [36], implying favourable cost-effectiveness if the ICER is below €30,000 (once the GNP/capita) or €60,000 (twice) per DALY [37].

A number of differences between both vaccines now registered should be noted. In particular, both include protection against HPV serotypes 16 and 18, yet one of them is bivalent (*Cervarix*™), and the other is quadrivalent (*Gardasil*™, also including serotypes 6 and 11). The differences between the branded vaccines were not elaborated in this paper, since we chose to focus on cancer outcomes.

2. Methods

2.1. General model design

Cost-effectiveness modelling of cervical cancer screening and HPV vaccination has previously been reviewed [38–40] and both static [41–44] and dynamic [45,46] models have been developed. Dynamic models explicitly model the transmission of HPV in the population with the force of infection being dependent on the number of infected individuals at any moment in time. In a static model the force of infection remains constant over time. It has been noted that for the initial questions relating to policy decisions about HPV vaccination – in particular, whether teenage girls should be vaccinated – static and dynamic models provide similar results when vaccine coverage is assumed to be high. When coverage is high, model choice should be driven by preferring the least complex model that still provides valid results [47–49]; i.e. a static model would suffice. When vaccine coverage is low, dynamic models could be used because in dynamic models benefits in unvaccinated individuals, due to a reduced transmission, are taken into account. For our analysis on vaccinating teenage Dutch girls, we selected a previously published static model and adapted it to the Dutch situation [40,50]. Given the similarity of the static models developed so far, we would not expect major differences if another model were selected for adaptation.

The model was designed as a generic model to be applied in various country-specific settings. The Markov model simulates the progression from HPV infection through CIN stages 1–3 to cervical cancer (Fig. 1). Notably, women progress through the model according to transition probabilities that were estimated from the literature [40,50]. The model version we applied distinguishes seven categories of HPV types: 16, 18, 31, 45, 52, other oncogenic subtypes and low-risk HPV [50]. In the model it was assumed that concomitant infections with different HPV types were not possible. Further, a subdivision into histology-identifiable health states was made: normal histology, CIN1, CIN2, CIN3, and four sub-stages for cervical cancer as defined by the Federation of Gynaecology and Obstetrics (FIGO), stages 1–4. The model was calibrated by varying parameter estimates over the ranges specified in a literature review, taking the NCCSP explicitly into account (see below). For calibration, age and type specific HPV prevalence, HPV-type distribution in normal and disease states, CIN stage-specific prevalence, cervical cancer incidence and cervical cancer mortality were used to parameterize the model [51–54].

The model evaluated a lifetime cohort of uninfected 12-year-old girls once in the absence of vaccination (screening only) and once in the presence of vaccination at the age of 12 being added to screening (vaccination added), with respect to epidemiological and screening outcomes, such as HPV infections, screening tests, cases of various CIN stages, cases of cervical cancer, cancer deaths and life-years lost to cervical cancer. The cohort size was set at

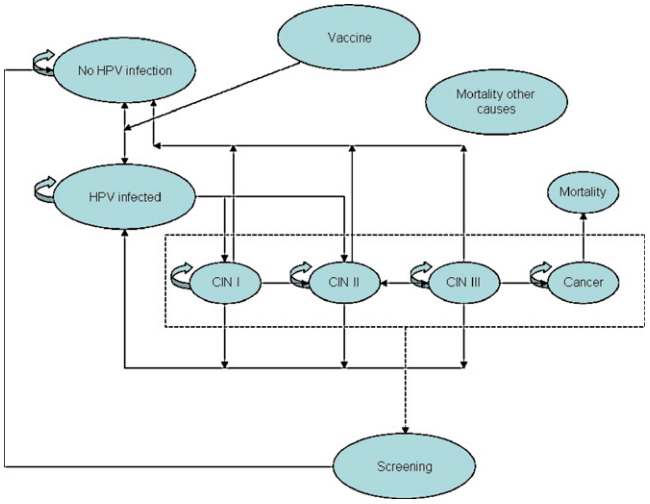

Fig. 1. Schematic representation of the model. The model specifies between seven types of HPV infections: serotypes 16, 18, 31, 45, 52, other oncogenic serotypes and non-oncogenic serotypes.

100,000, reflecting the approximate number of 12-year-old girls in the Netherlands today [4] and was simulated in the Markov model during the entire lifetime of the cohort members. In addition to cervical cancer death, overall mortality was included in the model [55]. In the next stage, epidemiological outcomes were linked to economic costing parameters, regarding cytology tests, colposcopies, biopsies, treatment of CIN stages and treatment of cervical cancer. Quality of life parameters were also assessed. Differences between the "screening only", and "vaccination added" cohort evaluations, regarding outcomes and costs, provided the basis for estimating the ICERs in terms of net costs per life-year and quality-adjusted life-year (QALY) gained. Below we provide more details on several model aspects.

2.2. Inclusion of the screening programme

Transitions within the progression-of-disease component of the model are impacted by the probability of being screened and treated. Asymptomatic cancer and pre-cancerous CIN lesions can be detected through screening. Cytology-based screening has been present in the Netherlands for a number of decades now, and the programme has been optimized based on various evaluations, inclusive of cost-effectiveness analyses, with an estimated cost per LYG at €15,500 for screening versus no screening [31,56–58]. Since 1996, all Dutch women between the age of 30 and 60 are invited through the organized screening programme to visit their General Practitioner to have a cytology test every 5 years.

The cytological outcome determines the follow-up, which can be (i) referral to a specialist for treatment of lesions, (ii) repeat cytology in the short term (6 months) for CIN abnormalities or (iii) repeat cytology in 5 years if no abnormalities are detected. In addition, the specification of cytology tests to be further followed up has been narrowed further since 1996 to enhance the efficiency of the programme [59]. Modelled screening parameters were based on literature values indicating that the compliance to the programme is up to about 80% during a 5-year period [32] and approximately 10% of women do not attend screening at all [60]. Furthermore, opportunistic screening occurs, with preventive cytology tests being taken on the initiative of the woman or her physician. However, as these tests are not reimbursed if performed without clear medical need, these opportunistic cytology tests are limited in number and have recently further decreased [61]. Therefore, the small number of opportunistic cytology tests were not explicitly captured in our model. All relevant assumptions made in the model regarding the Dutch NCCSP were previously reported, including performance characteristics of cytology, biopsy and colposcopy [40].

2.3. Assumptions on costing and quality of life

Due to vaccination, the number of CIN and cervical cancer cases in the Dutch population are projected to decrease. Estimated direct medical costs for the management of cervical disease used in the model are listed in Table 1, in addition to the estimated quality-of-life impacts [33,57,61–64]. In line with the Dutch guidelines for pharmacoeconomic research, both direct and indirect non-medical costs were included in the costing, for example travel costs and production losses, respectively [65]. Also in line with the Dutch guidelines, we used QALY as an additional outcome measure. For the vaccine €100 per single dose was analyzed in the base-case (in sensitivity analysis a range of €80–120 was investigated). Additionally, an administration cost of €5 per dose was included in each of the model simulations [28].

The total annual cost of the Dutch NCCSP amounted to €26 million in 2001, comprising €16 million for cytology-related costs, €9 million for regional organization and €1 million for a variety of other aspects [32]. The majority of these costs will remain unaltered with adding vaccination to the screening programme if the screening intensity and other programme characteristics remain unchanged (as is currently assumed). However, as the number of positive cytology tests will decrease due to vaccination, the number of referrals and repeat cytologies will also decrease. These changes were explicitly taken into account in our analysis [50].

As implementation of HPV vaccination in the Dutch NIP was envisaged for 2008/2009, all costs were assumed to reflect 2008 price levels [64].

Table 1
Assumptions on costing applied in the model in € (2008 price level) and quality of life impacts in QALY-losses per stage and per 6-month model cycle (if different during 1st half year post-diagnosis, values provided between parentheses).

	Mean costs (€)	Distribution costs[a]	QALY-losses
HPV vaccine per dose	100	NA[b]	NA
Administration costs per dose	5	NA	NA
Cytology	50	NA	NA
Colposcopy	143	NA	NA
Biopsy	49	NA	NA
Treatments			
CIN stage			
1	1,483	Gamma(100,14.8)	0.026
2	1,718	Gamma(100,17.2)	0.010
3	1,868	Gamma(100,18.7)	0.080
Cervical cancer FIGO stage			
1	19,114	Gamma(100,191.1)	0.03 (0.273)
2	20,762	Gamma(100,207.6)	0.10 (0.273)
3	20,762	Gamma(100,207.6)	0.10 (0.273)
4	26,528	Gamma(100,265.3)	0.38 (0.273)

QALY: quality-adjusted life-year.
[a] Distribution applied to unit costs in probabilistic sensitivity analysis.
[b] Not applicable.

2.4. Vaccine characteristics

The vaccine effect is modelled by reducing the risk of acquiring HPV infection, i.e. the transition probability from normal to HPV infection is reduced according to the vaccine efficacy. This implementation was chosen in the absence of evidence for the HPV-16/18 vaccine on actually lowering cervical cancer incidence. Obviously, studies have not yet had a long enough follow-up to establish efficacy of the vaccination on cervical cancer directly. Vaccine efficacy was set at 95% against HPV-16/18 infection [16,17] in the base-case (90–100% in sensitivity analysis). Additionally, cross-protection was assumed to be 50% against serotype 31 and 90% against serotype 45 [17]. Vaccine efficacies were assumed to apply after the full scheme of three vaccinations.

Duration of protection of the vaccine is now evidenced for approximately 6.4 years [19,66]. Based on the extended phases of clinical trials, lifelong persistence of antibodies or lifelong protection may not be unrealistic [22,67]. Obviously, if less favourable protection scenarios become a reality, booster vaccinations would become an option for achievement of maximal vaccine benefits. For the base-case analysis, we assumed lifelong protection after the initial set of vaccinations. In an alternative scenario, we assumed that lifelong protection would potentially be achieved with the inclusion of a booster after 20 years (approximately coinciding with the first visit within the context of the NCSSP) [30]. Full coverage for the initial set of vaccinations was assumed for both scenarios. In the sensitivity analysis we analyzed different coverage rates for the booster assuming no protection of the vaccine beyond 20 years after the initial vaccinations.

2.5. Cost-effectiveness calculations

From the cohort of 12-year-old girls going through the Markov model, various items were tracked. Outcomes for which we provide results included HPV infections (both overall and serotype specific), CIN2+ cases, cervical cancer cases, cytologies, health-care resource use and life-years lived by the cohort. Next, these items were adequately costed. Numerical results on items and costs were compared for model simulations once including and once excluding vaccination. The ICER was defined as the net costs divided by the life-years gained. Net costs resulted from total investment costs in the vaccination minus savings on CIN2+ and cervical cancer treatments, cytology tests, biopsies and colposcopies. Life-years gained resulted from the difference between total life-years lived with vaccination minus those in the absence of vaccination. QALYs were also calculated in the model, and are included in the reported ratios of costs per QALY gained.

Finally, specific further features of our model include the following. First, calculations were performed for the cohort of 12-year-old girls that was assumed to receive the full scheme of three doses. Second, coverage of vaccination was assumed to be 100% for reporting of our results (given the structure of our model, ICERs will not change with varying the vaccine coverage, with lower coverage providing similar relative reductions in both net costs and life-years gained). Third, if the vaccine is effective in preventing transitions to one type of HPV infection, it was assumed that competing risks of acquiring another oncogenic HPV-type would apply [50].

Discounting costs and life years was done according to the Dutch guidelines for pharmacoeconomic analyses at 4% and 1.5%, respectively [68,69]. Discounting was implemented in the model per half year. Differential discounting is strongly underpinned in the literature [70]. We do note that internationally differential discounting is still controversial [70] and therefore sensitivity analysis was extensively directed at the discount rate – to enhance the applicability of our findings to other countries – besides the aspects mentioned above (duration of protection and vaccine price). Scenario analysis was directed at the potential future inclusion of a booster in the vaccination strategy and at possible price reductions.

Probabilistic sensitivity analysis (PSA) was performed on the base-case, assuming beta distributions of efficacies (95% confidence intervals from Harper et al. were used for this purpose [16,17]) and gamma distributions for costs (Table 1; [50]), and beta distribution for disutilities expressed in QALYs. For one probabilistic sensitivity analysis, 1000 model simulations were completed.

3. Results

3.1. Clinical results

To estimate the cost-effectiveness of HPV immunization of 12-year-old Dutch girls, the Markov model was calibrated on data specific for the situation in the Netherlands. Fig. 2 shows the model calibration results for HPV prevalence, cervical cancer incidence and mortality. The figure illustrates a good model fit for the HPV prevalence and cervical cancer mortality. Also the cervical cancer incidence predicted by the model fits the observed incidence quite reasonably. In the base-case, vaccination was estimated to reduce the number of HPV-16 and -18 infections by 95%, those with serotype 31 by 50% and those with 45 by approximately 90%, as was inserted into the model. Corresponding estimated overall reductions in CIN2+ and cervical cancer cases were 57% and 74%, on the baseline numbers of cases in the non-vaccinated arm, which were 1527 and 565, respectively.

3.2. Base-case cost-effectiveness

For the calculation of the ICER, the total cervical cancer-related costs and utilities in the unvaccinated cohort of 100,000 teenagers

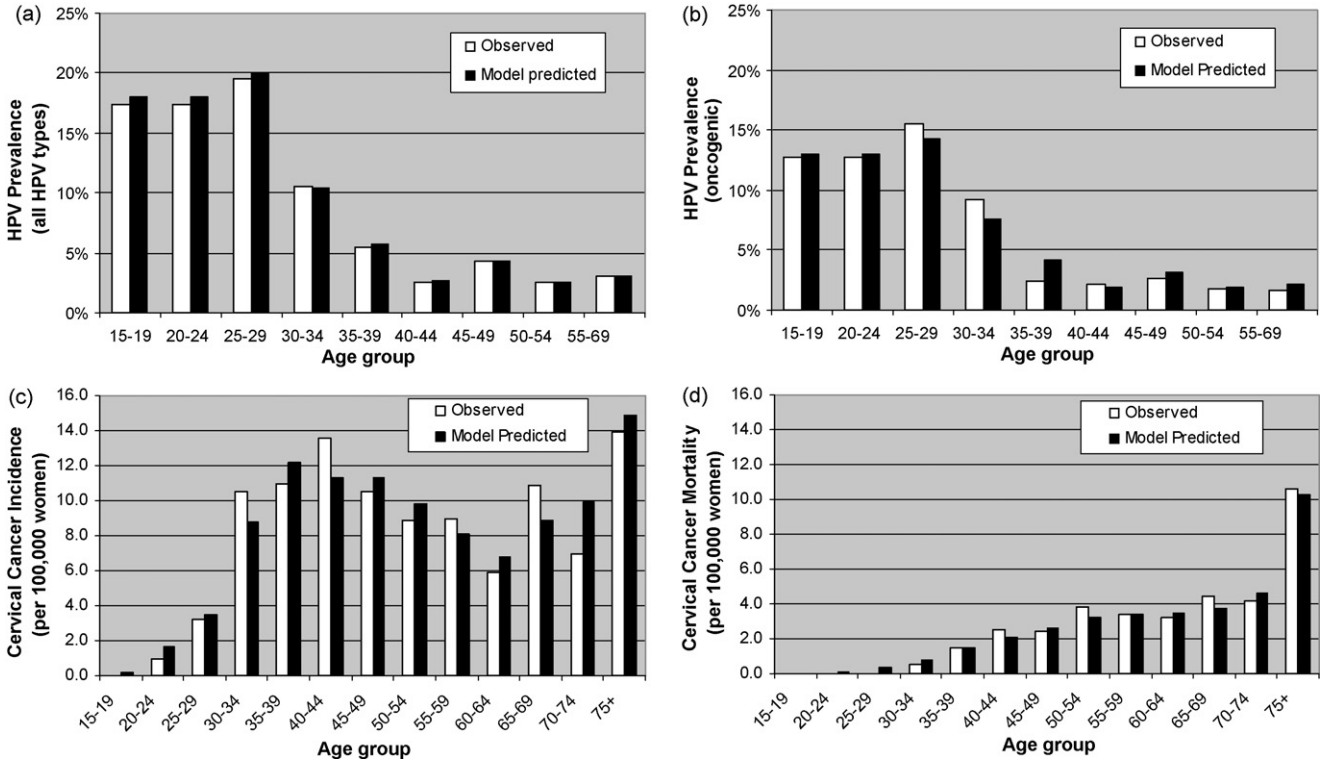

Fig. 2. Model calibration results: all (a) and oncogenic only (b) age-specific HPV prevalence in percentages of population as simulated in the model and as reported by Jacobs et al. [54]. Age-specific cervical cancer incidence (c) and mortality (d) per 100,000 women as simulated by the model compared to observed numbers in the Dutch cancer registry [51] and mortality registry [55].

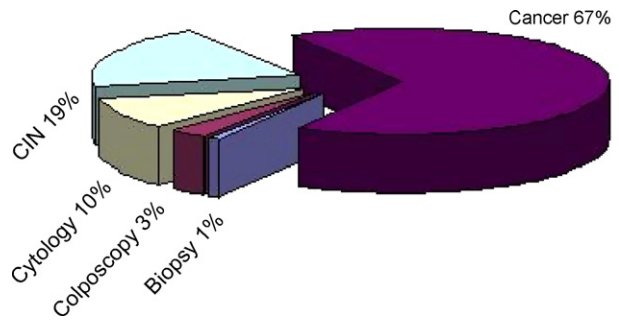

Fig. 3. Distribution of discounted cost offsets due to HPV vaccination (totalling €2,893,000).

were compared to the costs and utilities in the immunized cohort of 100,000 teenagers. After immunization of the full cohort of 12-year-old girls, in the base-case analysis 2907 life years would be saved/gained (1234 if discounted). Discounted cost offsets related to vaccination were estimated at €2,893,000 for the full cohort of 100,000 girls, with two-thirds of the offsets being related to averted cases of cervical cancer (Fig. 3). Discounted vaccination costs minus cost offsets divided by the life-years gained rendered an ICER of €22,700 per LYG (€18,500 per QALY).

3.3. Probabilistic sensitivity analysis

To fully evaluate the level of uncertainty in the outcomes, a probabilistic sensitivity analysis (PSA) was performed. Fig. 4 presents the cost-effectiveness acceptability curve (CEAC) corresponding with the PSA on the base-case, based on 1000 Markov simulations. The CEAC shows the probability of being cost-effective for specific thresholds or ceiling ratios for cost-effectiveness on the *x*-axis, as estimated from the proportion of simulations with an ICER below the specific ceiling chosen. For example, the estimated median ICER from the PSA amounts to approximately €23,000 per LYG. Furthermore, given the model uncertainty, 95% of simulations were found to be below €24,800 per LYG and 100% below €29,000.

3.4. Sensitivity and scenario analysis

The robustness of the estimated base-case ICER was determined in a one-way deterministic sensitivity analysis. In particular, our

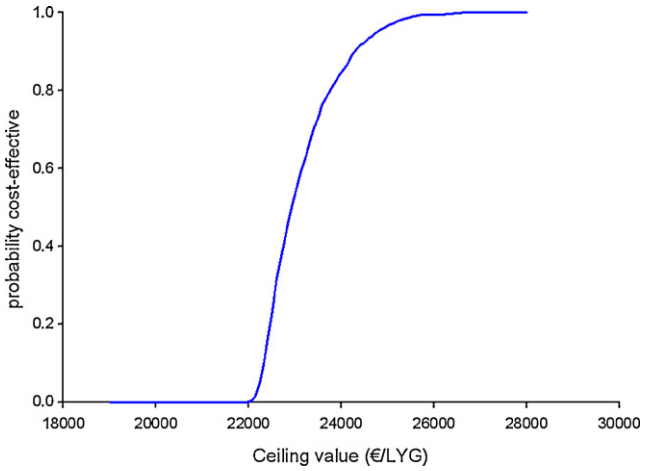

Fig. 4. Cost-effectiveness acceptability curve (CEAC) indicating the proportion of simulations remaining below the threshold or ceiling ratio specified on the *x*-axis (threshold expressed in €s per life-year gained).

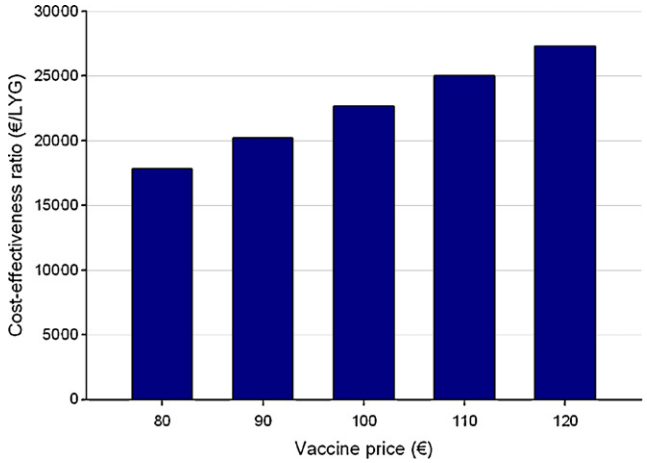

Fig. 5. Sensitivity analysis of the vaccine price (excluding administration) on the incremental cost per life-year gained.

sensitivity analysis was directed to the impact of vaccine price, discount rate, duration of vaccine protection and the potential need for booster immunization.

Not surprisingly, the cost-effectiveness ratio was sensitive to the vaccine price (Fig. 5). For example, in a scenario where the vaccine price would be reduced to €80, which could be the case within a large-scale NIP vaccination, cost-effectiveness would improve to €17,900 per LYG. If the current pharmacy price of €120 is applied, cost-effectiveness would be around €27,500 per LYG. The corresponding limits for net costs per QALY ranged from €14,600 to €22,400. Given the relative size of the discounted medical cost-offsets compared with the vaccination costs, cost-effectiveness is not sensitive to plausible changes in those savings. For example, a reduction in discounted savings by 10% results in an increase of only 1% in the cost-effectiveness ratio, either per LYG or per QALY (not shown).

Further analysis revealed that the cost-effectiveness ratio is highly sensitive to the discount rate (Table 2). Although not unique, the Netherlands is exceptional in requiring differential discounting of monetary and health units [70]. Applying equal discounting at rates according to international standard (e.g. 3% in UK) easily doubles the net costs per LYG and per QALY gained. However, if the discount rate prescribed for health (1.5%) would be applied equally for costs, then the cost-effectiveness improves to just over €20,000 per LYG (€16,400 per QALY). Table 2 illustrates that results are highly sensitive to the discount rate of life years as these are gained in the relatively distant future (average age mortality 67.3 years), whereas sensitivity to the discount rate for costs is limited as the majority of monetary impact relates to vaccination costs in the short term.

Table 2
Sensitivity analysis of the discount rates for costs and life years, on the incremental cost per life-year gained; between parentheses net costs per QALY gained are shown.

	Costs	Health gains	ICER
Base-case	4%	1.5%	€22,700 (18,500)
No discounting of life years	4%	0%	€9,600 (8,100)
Equal discounting			
i[a]	4%	4%	€84,200 (64,600)
ii	3%	3%	€49,100 (38,700)
iii	5%	5%	€139,100 (103,800)
iv	1.5%	1.5%	€20,100 (16,400)
v	0%	0%	€6,900 (5,800)

ICER: incremental cost-effectiveness ratio.
[a] Reflecting the Dutch guideline up to 2005.

If a single booster vaccination, given 20 years following the original vaccination, was included in the analysis, the ICER was estimated at €26,600 LYG (€21,700 per QALY), assuming full uptake of the booster. If uptake of the booster would be limited to only half of the population that received the initial set of vaccinations, and duration of protection was limited to only 20 years for those who did not receive the booster, the ICER would increase to €29,200 per LYG (€24,000 per QALY). In the absence of a booster for all and duration of protection of 20 years, ICER was €31,700 per LYG (€26,400 per QALY).

4. Discussion

Our analyses illustrate that there is good potential for HPV-16/18 vaccination of 12-year-old girls to be cost-effective in the Netherlands. Generally, cost-effectiveness ratios were found below €30,000 per LYG and QALY both in our base-case and in the sensitivity analyses.

Our analyses are in line with other scientific publications for the Netherlands [3,30,62]. In particular, specifically for the purpose of the reimbursement of the quadrivalent vaccine within the Dutch DRS, one previous analysis focused on the Dutch situation [30]. The base-case estimate from that analysis amounted to net costs of €21,900 per QALY gained for vaccinating Dutch girls aged 13–15 years old. If expressed per life-year gained, these net costs would expectedly be somewhat higher than our base-case estimate at €22,700 per LYG. Yet, the vaccine price applied in the analysis for the quadrivalent vaccine was €118, as opposed to €100 in our analysis. Additionally, we assumed €5 for administration costs of the vaccine within the NIP, whereas in the analysis for the DRS significantly higher costs apply for delivering and administering the vaccine through the network of pharmacists and GPs. For a vaccine price of €100, Boot et al. reported a very similar range as we found for the ICER per LYG at €24,000–28,000 [3]. Here the upper bound was found by assuming a booster at the age of 30 years, and the lower assuming lifelong protection provided with the initial set of vaccination. Finally, the Health Council recently reported a range for the net costs per QALY of €20,000–30,000, based on studies from the Erasmus University in Rotterdam and the Free University in Amsterdam [30].

We note that our choice for the model structure was quite conservative. We applied a static model, whereas it might be expected that using a dynamic model would provide even better cost-effectiveness. For example, Chesson et al. showed that by 70% vaccine coverage including herd protection would result in a decrease in ICER from $14,723 per QALY to $10,318 per QALY [71]. Also Regan et al. showed that by using a dynamic model, in the case of 80% vaccine coverage a 7–31% reduction in cervical cancer incidence in unvaccinated women can be achieved [72]. Future work will be directed toward inclusion of herd immunity in our model.

In our analysis we assumed that the current screening programme will stay unaltered. However, as new techniques are coming available (e.g. HPV DNA testing) and the cervical cancer incidence will decrease as a result of the vaccination, changes in the screening programme might be considered. In particular, addition of new screening techniques and changing the setup of the screening programme (e.g. changing the screening interval and age of first visit) might be considered.

Despite relevant differences in the organization of and compliance to the screening, analyses for neighbouring countries indicate similar results for HPV vaccination cost-effectiveness. For the Belgian situation it was calculated that cost-effectiveness of HPV vaccination would be approximately €23,000 per LYG [48]. Inclusion of a booster may be expected to worsen this cost-effectiveness to the same magnitude as indicated in our analysis, i.e. approaching €30,000 per life-year gained. For Germany, Schneider et al. analyzed the public-health impact of HPV vaccination [73]. These authors showed that major potentials for favourable cost-effectiveness exist for a cohort of 400,000 girls with only screening in place. Implementation of HPV vaccination was projected to reduce the number of cervical cancer deaths from 1376 to 250 [73]. Our estimated base-case ICER is also in the same range as reported in a recent review [74].

Our model evaluated the efficacy of the vaccine at reducing infections with HPV types 16, 18, 31 and 45 at stages prior to serious morbidity and mortality. Ultimately, HPV-vaccine clinical trials have been and will be designed to show efficacy/effectiveness on CIN2+ and cervical cancer cases. For validating our model, we compared the model-predicted vaccine effectiveness on CIN2+ cases of all types (not only those related to vaccine types) with findings of vaccine effectiveness on CIN2+ from clinical studies. It is reassuring that the modelled effectiveness of vaccination on CIN2+ in the base-case at 57% in our approach is well in the range found for reductions of CIN2+ cases in the clinical trials with 6-year follow-up (46–68% for CIN2+) [23,75].

As mentioned in Section 1, differences exist between the two available vaccines that may ultimately result in differences in cost-effectiveness for the use of these vaccines, although this has yet to be determined. In particular, the additional inclusion in the quadrivalent vaccine of serotypes 6 and 11 is associated with additional benefits on the incidence of genital warts. As these benefits occur on the short term and are therefore less influenced by discounting, Brisson et al. [41] showed that inclusion of QALY-benefits of genital warts has the potential of improving cost-effectiveness by one-third. Given the higher discount rate of 3% for QALYs used by Brisson et al., we would not expect an impact that high for the Netherlands with a lower guideline-specified discount rate at 1.5% for QALYs in the Netherlands. Obviously, results per LYG would not be influenced by inclusion of genital warts, as genital warts do not cause mortality. Secondly, anti-HPV immunogenicity patterns in time after vaccination differ for both vaccines, in particular regarding serotype 18, where a superior profile is seen for the bivalent over the quadrivalent vaccine [76,77]. The clinical significance of these published differences in immunogenicity have yet to be demonstrated in further studies regarding potential clinically relevant differences in duration of protection [36].

5. Conclusion

Our analyses illustrate that the addition of prophylactic vaccination of 12-year-old girls to prevent cervical cancer to a high-quality screening programme in a setting where the incidence of cervical cancer is low compared with worldwide levels, is likely to be cost-effective compared with screening alone. Generally, cost-effectiveness ratios below €30,000 per life-year gained or QALY were estimated, both in the base-case and sensitivity analyses. Obviously, long-lasting protection by vaccination is crucial for achieving the most favourable cost-effectiveness ratios. Limited duration of protection of the initial vaccination schedule could be supported by boosting, which was also shown to be cost-effective. From a health-economic perspective, introduction of HPV vaccination of young teenage girls seems justified in the Netherlands. Despite this positive outlook, other aspects will need to be considered, including budgetary impact analyses and ethical considerations in relation to vaccination catch-up programmes and the future of cervical screening. Therefore, large follow-up studies have been announced by the Dutch government to estimate the clinical impact of HPV vaccination and to monitor possible changes in screening attendance and sexual behaviour of the vaccinated girls induced by the vaccination.

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