

Cost-Effectiveness Analysis of Human Papillomavirus Vaccination in the Netherlands

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- Background** In the Netherlands, low cervical cancer incidence and mortality rates might limit the cost-effectiveness of vaccination against the human papillomavirus (HPV). We examined the effect on cervical cancer incidence and mortality of adding HPV vaccination to the current Dutch cervical cancer screening situation and calculated the cost-effectiveness.
- Methods** Costs and effects were estimated under favorable assumptions (ie, that HPV vaccination provides lifelong protection against 70% of all cervical cancers, has no side effects, and is administered to all women regardless of their risk of cervical cancer) by using the microsimulation screening analysis (MISCAN) model. The impact of changes in the price of vaccination, number of booster vaccinations, vaccination attendance rate, vaccination efficacy, cervical cancer incidence level, and quality-of-life assumptions was investigated in sensitivity analyses.
- Results** Using the current price of €118 per vaccine dose and with discounting of costs and effects at an annual rate of 3%, adding HPV vaccination to the current Dutch screening situation had a cost-effectiveness ratio of €53 500 per quality-adjusted life-year (QALY) gained. The threshold price per vaccine dose at which the cost-effectiveness of vaccination would correspond to an acceptability threshold of €20 000 per QALY gained was €40. With the addition of one or more (up to four) booster vaccinations during a lifetime, this threshold price decreased to €33 for one booster (to €16 for four boosters). With a doubling of the cervical cancer incidence level, the cost-effectiveness ratio was €24 400 per QALY gained and the maximum price per dose at threshold of €20 000 was €97. All threshold prices were lower under less favorable effectiveness assumptions.
- Conclusions** In the Netherlands, HPV vaccination is not cost-effective even under favorable assumptions. To become cost-effective, the vaccine price would have to be decreased considerably, depending on the effectiveness of the vaccine.

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Multiple analyses of the cost-effectiveness of vaccination against the human papillomavirus (HPV) have concluded that vaccination should be cost-effective (1–6). However, this conclusion mainly depends on the incidence and mortality rates of cervical cancer. Low incidence and mortality rates imply a limited maximum effect of HPV vaccination.

The low cervical cancer incidence and mortality rates in the Netherlands are associated with an efficient national screening program, in which women are invited to have a free Pap smear every 5 years from age 30 to 60 years (7). Cervical cancer mortality in the Netherlands has steadily declined over the last five decades, and in 2005, it was 1.6 per 100 000 woman-years [World Standardized Rate (WSR) (8)]. This rate is lower than the WSR of 2.5 per 100 000 woman-years in the United States for the period 2001–2005 and 1.9 per 100 000 woman-years in the United Kingdom in 2005 (9,10).

This study explores the cost-effectiveness of adding HPV vaccination to the current screening situation in the Netherlands. Earlier decisions by the Dutch government on the cervical cancer screening program were based on cost-effectiveness analyses

that used a cost-effectiveness acceptability threshold of €20 000 per quality-adjusted life-year (QALY) gained (11), that is, an intervention with a cost-effectiveness ratio of more than €20 000 per QALY gained was not considered acceptable. We used this threshold in this analysis; in addition, we explored a threshold of €50 000 per QALY gained. For comparison with other cost-effectiveness analyses, the main analyses were performed under the favorable assumptions for vaccination, that is, that vaccination provides lifelong protection against 70% of all cervical cancers, has no side effects, and is administered to all women regardless of their risk of cervical cancer. Given that the price

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CONTEXT AND CAVEATS

Prior knowledge

Cervical cancer incidence and mortality rates in the Netherlands are low, which could limit the cost-effectiveness of human papillomavirus (HPV) vaccination.

Study design

A simulation model was used to estimate costs and effects of adding HPV vaccination to the current screening situation in the Netherlands and to examine the impact of changes in the price of vaccination, number of booster vaccinations, vaccination attendance rate, vaccination efficacy, cervical cancer incidence level, and quality-of-life assumptions on the cost-effectiveness of HPV vaccination.

Contribution

HPV vaccination is not cost-effective, even under favorable assumptions, in the Netherlands.

Implications

To become cost-effective, the vaccine price would have to be decreased considerably, depending on the long-term effectiveness of the vaccine.

Limitations

The impact of herd (or community) immunity was underestimated because viral transmission was not included in the model. The impact of vaccination on other HPV-related diseases was not taken into account.

From the Editors

per vaccine dose for a vaccination program is negotiable, we performed a threshold analysis to determine the unit price per vaccine dose that would result in an acceptable cost-effectiveness ratio under these assumptions. Because uncertainty exists about the duration and strength of protection afforded by HPV vaccination, we performed a sensitivity analysis in which we varied the lifetime number of vaccinations as well as the vaccine's efficacy rate. Finally, for maximum generalizability of the results, we examined the cost-effectiveness of HPV vaccination in situations in which the cervical cancer incidence differs from that in the Netherlands.

Model and Methods

Costs and effects were estimated using the microsimulation screening analysis (MISCAN) model (12). The MISCAN model generates a large study population with fictitious individual life histories, in which women will, at a certain rate, acquire an HPV infection and develop a preinvasive cervical lesion and/or cervical cancer, and some will die from the disease. This simulation results in an age-specific and time-specific output of disease incidence and mortality. This fictitious population then undergoes simulated screening and/or vaccination; these interventions will change some of the life histories. These changes constitute the effects of the intervention and are represented by the numbers of events and stages induced or prevented by the intervention that are linked with its costs and quality-of-life outcomes.

Model Specifications and Assumptions

Demography, Epidemiology, and Natural History. We simulated a Dutch population at risk for cervical cancer based on demographic (13) and hysterectomy (14) data. The age distribution of the incidence of preinvasive neoplasia that will eventually become cancer was calibrated to the age distribution of the prescreening mortality; the latter distribution was corrected for cohort effects based on an age-period-cohort analysis (15). The age distribution of the incidence of preinvasive lesions that will regress before they become cancer was calibrated to the observed cervical intraepithelial neoplasia (CIN) detection rates in the Netherlands (derived from the Dutch Network and National Database for Pathology [PALGA]) for the period 1997–2001. The age distribution of the incidence of HPV infections that will clear before progressing to CIN was calibrated to the observed HPV prevalence (16).

Disease was subdivided into seven sequential stages: HPV infection, three preinvasive stages (CIN grades 1, 2, and 3 [CIN 1, CIN 2, and CIN 3, respectively]), and three invasive stages [International Federation of Gynecology and Obstetrics (FIGO) stages IA, IB, and II+ (17)]. The first disease stage—HPV infection (without neoplasia)—cannot be diagnosed because screening is performed with cytology and not with an HPV test; preinvasive stages and FIGO IA cases can only be diagnosed by screening and not clinically because stage IA is asymptomatic, whereas stages IB and II+ cases can be diagnosed by screening as well as clinically. A Weibull distribution was used to assume variation among women in the duration of the different stages. The stage-specific survival used in the model for clinical cases (ie, cases diagnosed based on symptoms as opposed to screen detection) was age specific and based on observed survival and on Dutch mortality to incidence ratios from the prescreening period in the Netherlands (15).

Assumptions Regarding Screening, Vaccination, and Treatment.

We assumed that women were screened as currently occurs in the Dutch program, that is, every 5 years from age 30 to 60 years. The screening attendance rate was based on the observed rates from PALGA for women who had at least one Pap smear in the previous 5 years (18). We assumed that 10% of the population would never attend screening and would have a threefold higher background risk for cervical cancer than the 90% of the population comprising the potential attenders (19). The sensitivity of the smear for different disease stages was estimated at 50% for CIN 1, 65% for CIN 2, 80% for CIN 3, 85% for preclinical invasive stages IA and IB, and 90% for preclinical invasive stage II+ (20). Specificity of the test was assumed to be 98.5% based on the false-positive rate of Pap smears in the Dutch screening program. We assumed that women with a borderline test result (atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion) had a repeat smear and those with a positive test result (high-grade squamous intraepithelial lesion) were referred for colposcopy and biopsy. Detection (and the associated management of preinvasive lesions) was assumed to lead to a 100% cure rate. For screen-detected invasive cancers, survival was modeled as a reduction in the risk of dying from cervical cancer compared with that of dying from clinically diagnosed cancer.

We assumed that the first HPV vaccination (comprising three doses) was at age 12 years. The vaccination participation rate was

assumed to be 85%, with no selection with regard to the risk of cervical cancer. For additional vaccinations (comprising one dose each) during a lifetime, we assumed that only women who received the first vaccinations were invited and that the participation rate was 100%. We assumed that the first round of three vaccinations conferred lifelong immunity. Vaccine efficacy was estimated to be 70% against cancer, 35% against preinvasive lesions, and 1.5% against HPV infections; these estimates were based on the prevalence of HPV types 16 and 18 in cancers; the weighted mean of the prevalence of HPV types 16 and 18 in CIN 1, CIN 2, and CIN 3 lesions worldwide; and the prevalence of HPV types 16 and 18 in women with normal cytology (16,21,22).

Costs and Utilities. Table 1 presents the estimated costs and utilities associated with vaccination, screening, and treatment. Screening costs include costs of the invitational system, time and travel costs for women attending screening, costs of smear taking, costs of cytological evaluation, and costs of registration in PALGA. Vaccination costs include costs of the invitational system; time, travel, and administrative costs for women attending vaccination; and the cost of the vaccine dose itself (23). The costs of screening, diagnosis, and treatment procedures for detected preinvasive lesions, of primary treatment of invasive cervical cancer, and of treatment and palliative care for advanced cervical cancer were derived from a cost

study conducted in the Netherlands (18). Utilities were based on Dutch data and data from other countries (2,15,24).

Model. The model we present is a cohort model. For this cohort analysis, we used the cervical cancer risk level for Dutch women born after 1940 (15). On the basis of Dutch mortality data, we assumed that women born after 1940 have a lower risk of cervical cancer than women born before 1940 (8). The incidence rate of invasive cervical cancer simulated without the current screening program was 12.3 per 100 000 life-years (lifetime risk = 1.0%), and the mortality rate was 4.9 per 100 000 life-years (lifetime risk = 0.4%). The incidence rate of invasive cervical cancer simulated under the current screening program was 6.1 per 100 000 life-years (lifetime risk = 0.5%), and the mortality rate was 2.1 per 100 000 life-years (lifetime risk = 0.2%).

Cost-Effectiveness and Sensitivity Analyses

The results account for the simulated effects and costs until all simulated women have died. The effects are presented as numbers of clinical cases, screen-detected cancers, disease-specific deaths, life-years lost, and QALYs lost to cervical cancer. Costs were calculated by multiplying the unit costs linked to specific events (ie, invitations, tests, vaccinations, detection of preinvasive lesions, cancer diagnosis, and deaths) by the numbers of those events. The

Table 1. Assumptions about the costs and the amount and duration of the utilities of different events and health states*

Effect	Costs per effect, €	Utilities	
		Amount	Duration
Vaccination			
Initial vaccination (three doses)		0.995	3 wk
Vaccine material†	354.00		
Time and travel costs	9.42		
Administration	18.00		
Organization‡	22.50		
Booster vaccination (one dose)		0.995	1 wk
Vaccine material†	118.00		
Time and travel costs	5.60		
Administration	6.00		
Organization‡	7.50		
Screening			
Primary test§	53.64	0.994	2 wk
Costs of surveillance test	51.00	0.994	1 y
Treatment			
Diagnoses and treatment of preinvasive stages			
False positive	265.00	0.995	0.5 y
CIN 1	825.00	0.970	0.5 y
CIN 2	1221.00	0.930	0.5 y
CIN 3	1430.00	0.930	0.5 y
Diagnoses and treatment of invasive cancer			
FIGO IA	4683.00	0.940	5.5 y
FIGO IB	11 105.00	0.940	5.5 y
FIGO II+	10 223.00	0.823	5.5 y
Terminal care	24 870.00	0.288	1 mo

* CIN 1 = cervical intraepithelial neoplasia grade 1; CIN 2 = CIN grade 2; CIN 3 = CIN grade 3; FIGO = International Federation of Gynecology and Obstetrics.

† Includes injection fluid and needle.

‡ Includes invitation and database registration.

§ Includes invitation, time and travel, smear taking, cytological evaluation, and database registration.

same methodology was applied to calculate utilities. The cost-effectiveness calculations were conducted from a societal perspective. The costs and effects calculations were made for screening plus vaccination vs screening alone. Costs and effects were discounted at an annual rate of 3% to convert future costs and health effects to their value at the point in time when all women were 12 years old.

In sensitivity analyses, we examined the impact on cost-effectiveness of varying the unit price of vaccination, the need for booster vaccinations to keep up lifelong vaccine protection, the attendance rate to vaccination, the efficacy of vaccination, and the utilities. We varied the background cervical cancer risk level (in other words, the incidence level of cervical cancer in situations in which no screening exists) to allow our results to be compared with those of other cost-effectiveness analyses for situations with different cervical cancer incidence and mortality levels. For example, when we doubled the background risk, the incidence in the situation with screening (which we did not change and continued to use as the comparator situation) also doubled. For each sensitivity analysis, we calculated the cost-effectiveness ratio with the assumed vaccination costs and the threshold price per dose for vaccination to be cost-effective with an acceptability threshold of €20 000 per QALY gained. As an alternative, we also used an acceptability threshold of €50 000 per QALY gained, in keeping with cost-effectiveness policies in other countries (25). To evaluate the impact of quality-of-life estimates on the cost-effectiveness ratio and threshold price, we calculated the cost-effectiveness ratio and threshold prices under unfavorable quality-of-life assumptions for vaccination (ie, disutilities of vaccination doubled and disutilities of the other health states halved) and under favorable quality-of-life assumptions for vaccination (ie, disutilities of vaccination halved and disutilities of the other health states doubled).

Finally, we specifically adjusted our assumptions regarding the cervical cancer risk level and costs of vaccination to match those in cost-effectiveness analyses for other countries.

Results

Analysis Under Favorable Assumptions

We first determined the undiscounted effects and costs per 100 000 simulated women (Table 2). Adding one vaccination (of three doses) with lifelong effectiveness to the current screening program in the Netherlands prevented 36% of the CIN 2 and CIN 3 lesions detected by screening alone (850 lesions), 60% of the cervical cancers diagnosed (240 cancers), and 61% of the deaths from cervical cancer (100 deaths). There were 60% fewer life-years lost (2470 life-years) and 61% fewer QALYs lost (2680 QALYs). Based on the over-the-counter price per vaccine dose, the total costs increased by 64%, from €42.4 million per 100 000 women to €69.5 million per 100 000 women, which is an increase of €272 per woman during her lifetime.

We then examined the total costs and effects before and after discounting (Table 3). The cost-effectiveness ratios with discounting at 0% were €11 000 per life-year gained and €10 100 per QALY gained and with discounting at 3%, €59 700 per life-year gained and €53 500 per QALY gained.

Threshold Vaccine Price and Sensitivity Analysis

The threshold price per vaccine dose at which the cost-effectiveness of HPV vaccination would be €20 000 per QALY gained was €40 under favorable assumptions. Adding one or more booster vaccinations during a lifetime decreased the threshold price per vaccine dose to €33 for one booster and to €16 for four boosters (Figure 1, Table 4). At a cost-effectiveness threshold of €50 000 per QALY gained, the threshold price per vaccine dose was €110 and

Table 2. Estimated costs and effects of adding human papillomavirus 16/18 vaccination to the current screening program in the Netherlands (under favorable assumptions) compared with the costs and effects of the current screening program*

Costs and effects	Screening only	Vaccination plus screening	Vaccination plus screening compared with screening only, No. (%)
Effects, No.			
First primary screens	84 810	84 846	36 (0.04)
Follow-up primary screens	380 780	380 752	-28 (-0.01)
Triage screens	19 010	18 140	-870 (-5)
First rounds of three vaccinations	N/A	84 220	84 220 (100)
Screen-detected CIN 2 or CIN 3 lesions	2 370	1 520	-850 (-36)
Screen-detected cases of invasive cancer	86	33	-53 (-61)
Clinically detected cases of invasive cancer	410	170	-240 (-60)
Deaths from cervical cancer	170	70	-100 (-61)
Life-years lost	4 130	1 660	-2 470 (-60)
QALYs lost	4 390	1 710	-2 680 (-61)
Costs, €			
Screening test (including triage test)	28 850 710	28 808 950	-41 760 (-0.14)
Vaccination	N/A	34 018 710	34 018 710 (100)
Treatment of preinvasive lesions	4 308 520	3 039 290	-1 269 230 (-29)
Treatment of (advanced) cancer†	9 192 210	3 659 530	-5 532 680 (-60)
Total	42 351 430	69 526 470	27 175 040 (64)

* Based on 100 000 simulated women followed from birth to death; no discounting. CIN 2 = cervical intraepithelial neoplasia grade 2; CIN 3 = CIN grade 3; QALYs = quality-adjusted life-years; N/A = not applicable.

† Includes costs of terminal care.

Table 3. Cost-effectiveness of adding human papillomavirus 16/18 vaccination to the current screening program in the Netherlands (under favorable assumptions) compared with the current screening program only*

Costs per effect	Vaccination plus screening compared with screening alone	
	0% discounting	3% discounting
Total costs, €	27 175 000	22 153 400
Total LYs gained	2470	370
Total QALYs gained	2680	410
Costs per LY gained, €	11 000	59 700
Costs per QALY gained, €	10 100	53 500

* Based on 100 000 simulated women, followed from birth to death; costs and effects discounted at 0% and 3%. Costs are rounded to the nearest €100. LY = life-year, QALY = quality-adjusted life-year.

decreased to €95 with one booster vaccination and to €59 with four booster vaccinations (Figure 1, Table 4).

The cost-effectiveness ratio of adding HPV vaccination to the current situation varied with the underlying incidence of cervical cancer. For a situation in which the incidence of cervical cancer was 50% of that in the Netherlands, as, for example, is the case in Finland [WSR in 2005 = 3.3 per 100 000 woman-years (9)], the cost-effectiveness ratio of adding HPV vaccination was €105 600 per QALY gained and the maximum price per dose was €14 at a threshold of €20 000 per QALY gained and €50 at a threshold of €50 000 per QALY gained. If, on the other hand, the incidence under the screening program was twice as high as that in the Netherlands, as, for example, is the case in Denmark [WSR in 2003 = 10.8 per 100 000 woman-years (9)], the cost-effectiveness ratio of adding HPV vaccination was €24 400 and the maximum prices per dose at thresholds of €20 000 and

€50 000 per QALY gained were €97 and €241, respectively (Figure 2, Table 4). At a fourfold higher incidence level, as, for example, is the case in Brazil [WSR in 2002 = 23.4 per 100 000 woman-years (26)], the cost-effectiveness ratio was €10 900 per QALY gained. For an eightfold higher incidence level, as, for example, is the case in Zimbabwe [WSR in 2002 = 52.1 per 100 000 woman-years (26)], the cost-effectiveness ratio was €4100 per QALY gained.

Another parameter that had considerable impact on the cost-effectiveness of adding HPV vaccination to the current screening situation was the efficacy of the vaccination for preventing cervical cancer. For example, an absolute increase of 20 percentage points in vaccination efficacy (from 70% to 90%) decreased the cost-effectiveness ratio to €39 600, whereas an absolute decrease of 20 percentage points in efficacy (from 70% to 50%) increased the cost-effectiveness ratio to €76,00. At the €20 000 threshold, the corresponding threshold prices for a 20 percentage point increase and a 20 percentage point decrease in efficacy were €58 and €24, respectively (Table 4). Furthermore, varying the utilities (ie, disutilities of vaccination halved or doubled and disutilities of the other health states halved or doubled) increased the cost-effectiveness ratio to €60 400 under the least favorable quality-of-life assumptions for vaccination and decreased the ratio to €46 000 under the most favorable quality-of-life assumptions for vaccination. At the €20 000 threshold, the corresponding threshold prices for the least and the most favorable assumptions were €34 and €47, respectively (Table 4). The vaccination attendance rate had an impact on the costs and effects of vaccination but only negligible effects on the cost-effectiveness ratio and the threshold price of vaccination (Table 4).

To examine whether HPV vaccination could become cost-effective in the Dutch context, we evaluated HPV vaccination

Figure 1. Sensitivity analysis of the impact of the number of vaccinations during a lifetime and of differences in price per vaccine dose on the cost-effectiveness of adding human papillomavirus 16/18 vaccination to the current screening program in the Netherlands compared with the current screening program only (costs and effects discounted at 3%). The intersections between the **horizontal lines** (ie, the acceptability thresholds) and the **other lines** represent the threshold price per vaccine dose at which the cost-effectiveness of vaccination would correspond to the acceptability threshold. QALY = quality-adjusted life-year.

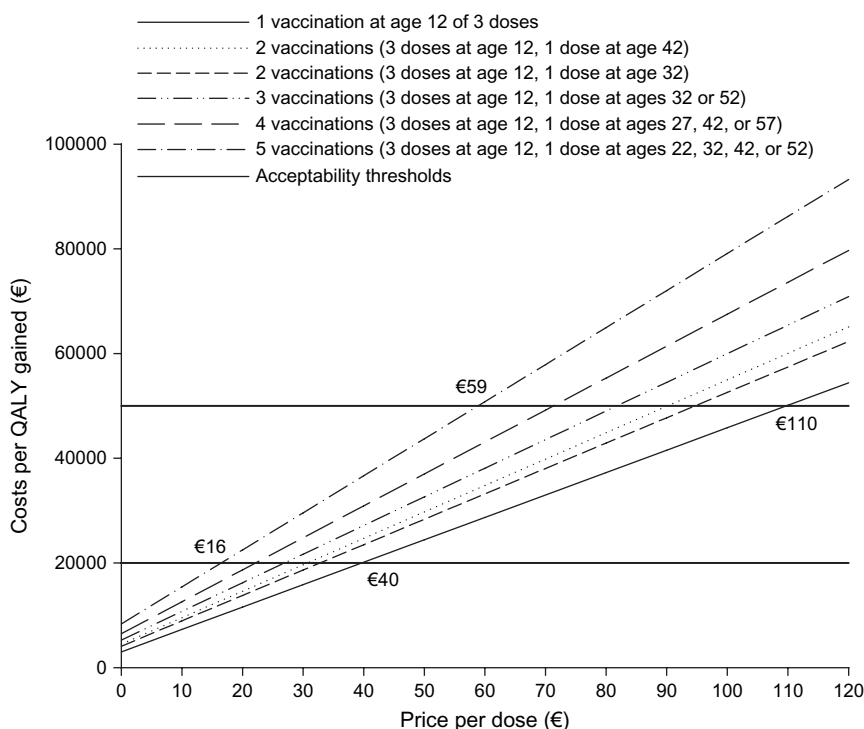


Table 4. Sensitivity analyses of the undiscounted costs and number of quality-adjusted life-years gained per 100 000 simulated women of the cost-effectiveness of adding human papillomavirus 16/18 vaccination (assuming lifelong protection) to the current screening program in the Netherlands compared with the current screening program only and of the threshold price per vaccine dose to be cost-effective considering a cost-effectiveness threshold value of €20 000 or €50 000 per quality-adjusted life-year gained*

Assumption	Undiscounted costs, €1000	Undiscounted No. of QALYs gained	Discounted CER,† €	Price per vaccine dose to be cost-effective, €	
				At €20 000 per QALY gained threshold	At €50 000 per QALY gained threshold
No. of vaccinations during a lifetime					
1 (age 12, three doses)	27 175	2680	53 500	40	110
2 (age 12, three doses; age 42, one dose)	38 722	2680	61 300	33	95
2 (age 12, three doses; age 32, one dose)	38 722	2680	64 100	31	90
3 (age 12, three doses; ages 32 and 52, one dose)	50 269	2680	69 800	27	82
4 (age 12, three doses; ages 27, 42, and 57, one dose)	61 815	2680	78 500	22	71
5 (age 12, three doses; ages 22, 32, 42, and 52, one dose)	73 362	2680	91 800	16	59
Vaccination attendance rate, %					
50	15 994	1580	53 600	40	110
85	27 175	2680	53 500	40	110
100	32 104	3100	54 400	39	108
Vaccination efficacy against cervical cancer, %					
50	29 142	1950	76 000	24	75
70	27 175	2680	53 500	40	110
90	25 197	3520	39 600	58	150
Cervical cancer incidence, fold change relative to the Dutch incidence rate in the model					
0.5	30 053	1450	105 600	14	50
0.75	28 590	2100	70 700	27	81
1‡	27 175	2680	53 500	40	110
1.5	24 291	4020	34 600	67	172
2	21 196	5510	24 400	97	241
4	9 679	10 680	10 900	203	483
6	-1 324	15 580	6 400	304	713
8	-11 785	20 170	4 100	399	931
Assumed amount of utilities lost					
Least favorable assumptions for vaccination	27 175	2540	60 400	34	97
Most favorable assumptions for vaccination	27 175	2920	46 000	47	129

* QALYs = quality-adjusted life-years; CER = cost-effectiveness ratio.

† In costs per QALY gained, with costs and effects discounted at an annual rate of 3%.

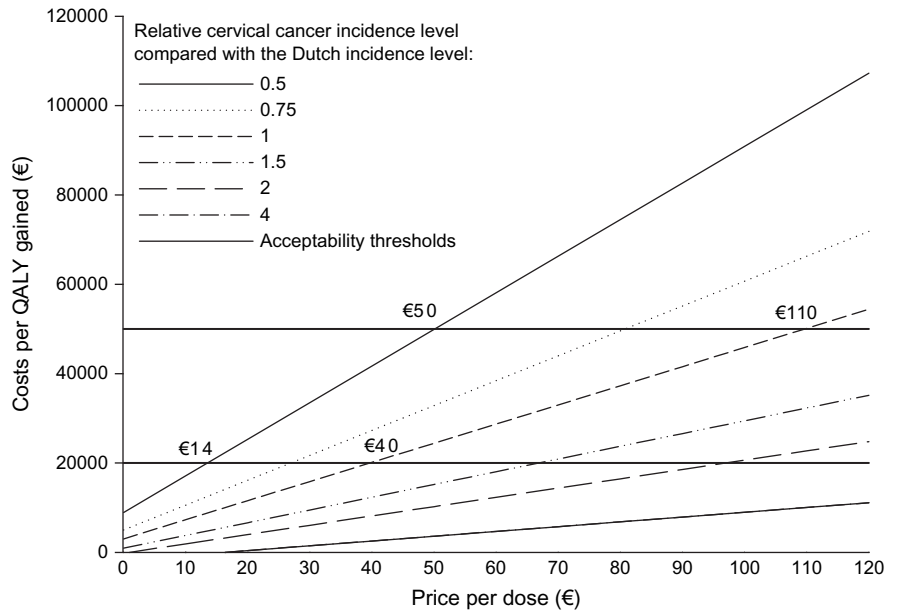
‡ Incidence rate = 6.1 per 100 000 life-years.

under a combination of favorable assumptions regarding the efficacy and effectiveness of the vaccination program. For comparison, we also calculated the cost-effectiveness ratio and threshold price per dose vaccine under much less favorable assumptions, that is, five vaccinations (four boosters after the initial round) during a lifetime to maintain lifelong protection, 50% attendance rate (assuming that the 10% of the persistent nonattenders for screening, who were assumed to have a threefold higher risk of cervical cancer than the attenders, will not attend vaccination), and 50% efficacy of the vaccine on cervical cancer. Under these combined assumptions, we found that adding HPV vaccination to the current screening situa-

tion in the Netherlands had a cost-effectiveness ratio of €362 100 per QALY gained. In this situation, the price per vaccine dose would have to be -€8 to achieve a cost-effectiveness ratio of €20 000 per QALY gained (€3 to achieve a cost-effectiveness ratio of €50 000 per QALY gained). In other words, even if the price per vaccine dose was €0, vaccination would still not be cost-effective.

In the Netherlands, for decisions about whether services are covered by health insurance, costs and effects are discounted at 4% and 1.5%, respectively, per year. Applying these rates in this analysis would reduce the costs for HPV vaccination from €53 500 to €19 700 per QALY gained.

Figure 2. Sensitivity analysis of the impact of variation in the relative incidence of cervical cancer compared with the Dutch incidence level and of differences in price per vaccine dose on the cost-effectiveness of adding human papillomavirus 16/18 vaccination (assuming lifelong protection) to the current screening situation compared with the current screening program only (costs and effects discounted at 3%). The intersections between the **horizontal lines** (ie, the acceptability thresholds) and the **other lines** represent the threshold price per vaccine dose at which the cost-effectiveness of vaccination would correspond to the acceptability threshold. QALY = quality-adjusted life-year.



We then compared our results for HPV vaccination added to screening with published cost-effectiveness ratios from other countries (Table 5). After adjusting for the incidence risk ratio for the specific study compared with that in the Netherlands (in our model) and for the costs of vaccination in the specific study, the cost-effectiveness ratio from this analysis was similar to other cost-effectiveness ratios. For example, Goldie et al. (2) estimated that the cost-effectiveness ratio of HPV-16/18 vaccination that was 90% effective would be US\$24 300 (or €16 300) per QALY gained, assuming vaccination costs of US\$393 (or €264) for the first vaccination round (compared with €404 in this study) and an incidence risk ratio of cervical cancer 1.7 times higher than that in our study (0.86% vs 0.5%). When we adjusted our model for these differences, the cost-effectiveness ratio of HPV vaccination was €18 300 per QALY gained. This analysis suggests that other than differences in vaccination costs, differences in risk level explain to a large extent the differences in cost-effectiveness ratios.

Discussion

In this study, we calculated the cost-effectiveness of adding HPV vaccination to the current screening situation in the Netherlands. Adding vaccination under the favorable assumptions that it would provide lifelong protection against 70% of all cervical cancers, have no side effects, and would be given to all women regardless of their risk of cervical cancer had a cost-effectiveness ratio of €53 500 per QALY gained. This cost-effectiveness ratio is considerably higher than the cost-effectiveness threshold of €20 000 per QALY gained. In this favorable situation (in which only one vaccination round of three doses is required for a 100% lifelong protection against HPV-16/18-related cervical cancer), to achieve a cost-effectiveness ratio of €20 000 per QALY gained, the price per initial vaccination must be approximately €40 per dose. With one additional booster vaccination for lifelong protection, the price per initial vaccination must be €33 per dose and with four booster vaccinations, €16 per dose. All of these threshold prices were lower

Table 5. Published cost-effectiveness ratios of vaccination added to the current situation (costs per quality-adjusted life-year gained) from other countries compared with the cost-effectiveness ratio from this analysis adjusted for the incidence risk ratio of the specific study and the costs of vaccination in the specific study*

Country (reference)	Incidence risk ratio	Costs of vaccination, €		Published CER, €	Adjusted CER,† €
		Costs of vaccine	Program costs		
The Netherlands	1.0	354	50	53 500	53 500
Israel (29)	0.5	242	46	54 700	74 000
United Kingdom (28)	1.4	296	13	26 600	25 200
Canada (26)	1.6	257	Not reported	19 900	19 200
United States (2)	1.7	202	62	16 300	18 300
United States (6)	1.4‡	270	66	29 300	29 100
Mexico (27)	3.8	176	0	2000	3000

* Costs of vaccination and published CERs are converted to Euros, using exchange rates as of August 21, 2008 (€1 = US\$1.4894, £0.7933, CaD\$1.5561, Mex\$15.0302). CER = cost-effectiveness ratio.

† Adjusted for incidence risk ratio (column 2) and costs of vaccine and program costs (columns 3 and 4, respectively).

‡ Because the incidence of cervical cancer in the situation in which vaccination was applied was not published, we used the incidence of cervical cancer in the United States as reported for 2001–2005 (10), which was 8.4 per 100 000 woman-years.

under less favorable effectiveness assumptions and were considerably less than the current over-the-counter per dose price of €118 in the Netherlands. Furthermore, our study revealed that the cervical cancer incidence and mortality level in the context in which the vaccination was applied had a substantial impact on these results.

The long-term efficacy and effectiveness of a national HPV vaccination program are uncertain. To examine whether HPV vaccination could become cost-effective in the Dutch context, we evaluated HPV vaccination under a combination of favorable assumptions. However, almost all cost-effectiveness analyses of HPV vaccination have used these same favorable assumptions, which has resulted in an optimistic bias, to which we are, to some extent, contributing. Thus, for comparison, we also calculated the cost-effectiveness ratio and threshold price per dose vaccine under much less favorable assumptions, that is, five vaccinations (four boosters after the initial round) during a lifetime to maintain lifelong protection, 50% attendance rate (assuming that the 10% of the persistent nonattenders for screening, who were assumed to have a threefold higher risk of cervical cancer than the attenders, will not attend vaccination), and 50% efficacy of the vaccine on cervical cancer incidence. Under these combined assumptions, we found that adding vaccination to the current screening situation in the Netherlands had a cost-effectiveness ratio of €362 100 per QALY gained. In this situation, vaccination would still not be cost-effective even if the price per vaccine dose was €0.

Previous cost-effectiveness analyses of HPV vaccination that compared screening plus vaccination vs screening only (1–6,27–29) produced lower cost-effectiveness ratios than the one produced in this study. We showed that this difference could be explained (to a large extent) by differences in the incidence of cervical cancer in the situation in which vaccination was applied. For example, when the incidence level under the current screening program was doubled or halved in our model, the cost-effectiveness ratio of vaccination plus screening compared with screening only was more than halved and almost doubled, respectively (Table 4). In most of the other cost-effectiveness analyses (except for that conducted in Israel), the incidence of cervical cancer was higher than that in our study for the Dutch situation.

Another explanation for the variation among published cost-effectiveness ratios is differences in the costs of vaccination. The assumed total cost of vaccination in the Netherlands was approximately 1.5 times higher than the assumed cost of vaccination in the studies from other countries. One reason for this difference is that in the Dutch situation, additional costs for the initial vaccination of three doses excluding the price of the vaccine itself (eg, costs of invitations, administration of the vaccine, and time and travel costs for the women) were estimated at €49.92, whereas estimates of these additional costs in other studies ranged from €0 in Mexico (28) to €46 in Israel (30). The studies from the United States assumed higher additional costs (€62 and €66) (2,6). However, the main reason for differences in vaccination costs is that the over-the-counter price of the vaccine itself in the Netherlands was assumed to be €354 (for three doses) compared with the lowest price of €176 (28) and the highest price of €296 (29) in other studies. We accounted for this discrepancy by varying the unit price of vaccination in the sensitivity analysis.

The acceptability of the cost-effectiveness ratio of HPV vaccination also varies depending on the acceptability threshold that is used. The cost-effectiveness acceptability threshold of €20 000 per QALY gained for the Netherlands [which was used for cost-effectiveness analyses of screening in the Netherlands (11)] is relatively low compared with the €50 000 per QALY gained threshold often used for other countries (25). As a result, interventions are often considered not cost-effective (ie, the cost-effectiveness ratio is higher than the threshold). As we have shown, to achieve a cost-effectiveness ratio of €50 000 per QALY gained (under the assumption of lifelong protection), the over-the-counter price per vaccine dose had to decrease only slightly (from €118 to €110) for the Dutch situation (Table 4).

We have also shown that the number of booster vaccinations (which are required to maintain lifelong protection against cervical cancer) has an impact on the cost-effectiveness ratio. However, the efficacy of HPV vaccination is related to other uncertain factors. For example, there is evidence that HPV vaccine can cross-protect against HPV-31 and HPV-45, which are closely related to HPV-16 and HPV-18, respectively (21). In addition, other oncogenic HPV types may fill the biological niche that remains after the elimination of HPV-16/18 infections and as a result cause more cervical cancer than they do in the absence of vaccination. Furthermore, a proportion of 12-year-old girls may have already been exposed to HPV-16/18 at the time of vaccination (31); such exposure is important because the effectiveness of the vaccine is lower if HPV-16/18 is present in the person who is vaccinated (32). As a result of these uncertain factors, the protection offered by vaccination against HPV-16/18 may be larger, but is probably smaller, than initially anticipated. We showed that variation in HPV vaccination efficacy had a considerable impact on the cost-effectiveness ratio of HPV vaccination.

To our knowledge, no data are available on the relationship between participation in vaccination and the risk for cervical cancer. In our base case analysis, we assumed that all simulated women, regardless of their risk of cervical cancer, received HPV vaccination at the initial or the booster vaccination rounds. However, a pilot study in the United Kingdom showed that the uptake of HPV vaccination was lower among girls from less affluent backgrounds and minority groups, who often have a higher cervical cancer risk (33). Because screening is selectively used by women who are at lower risk of cervical cancer (19), it is also plausible that HPV vaccination attendance (especially at the booster rounds, which are given to adults) will also be selective to some extent, which would decrease the cost-effectiveness of vaccination.

Another factor with an uncertain effect on the cost-effectiveness ratio of HPV vaccination is immigration. Evidence from the Centers for Disease Control and Prevention indicates that the relatively higher incidence and mortality rates of cervical cancer in the United States compared with those in the Netherlands are due to immigration of foreign-born women into the United States, many of whom have not been screened for this disease in their country of origin (34). Given that the application of vaccination is limited to younger ages, which excludes women who immigrate as adults, the effect of vaccination will apply to a low-risk population of women who are raised in the United States. These women may be at even lower risk than women in the Netherlands because of the more intensive screening for cervical cancer that occurs in the United States. As a result, the effectiveness as well as the cost-effectiveness of HPV vaccination

estimated for the US female population will probably be less favorable than that estimated for Dutch women.

This study has two limitations. First, because we did not model viral transmission, the impact of factors such as herd (or community) immunity was underestimated. Herd immunity would have affected, at most, 15% of the simulated women because we assumed that 85% of the women were vaccinated and that vaccination afforded lifelong protection. Second, we did not take into account the impact of vaccination on other HPV-related diseases, such as genital warts and other HPV-related cancer types. To our knowledge, there is no evidence to date from any clinical trials that HPV vaccination has any impact on other HPV-related cancers. One trial (35) showed that among women not infected with HPV-16 or HPV-18, the quadrivalent vaccine against HPV types 16/18/45/11 was 100% effective in preventing vulvar intraepithelial neoplasias (VINs) grades 2 and 3 and vaginal intraepithelial neoplasias (VAINs) grades 2 and 3 that were positive for HPV-16/18. In the total population (ie, including women infected with HPV-16/18), the quadrivalent vaccine was 71% effective in preventing VIN 2–3 and VAIN 2–3 caused by HPV-16/18 and 49% effective in preventing all VIN 2–3 or VAIN 2–3 (35). Chesson et al. (36) and Kim and Goldie (6) estimated that including the effect of the bivalent HPV vaccination against HPV types 16 and 18 on other HPV-related cancers will decrease the cost-effectiveness ratio of vaccination by 25% or 30%, respectively. Another HPV-related disease we did not take into account is genital warts. Results to date show that the quadrivalent vaccine is 51% effective in the prevention of genital warts associated with any type of HPV (37). However, any gain in quality of life due to the prevention of genital warts is expected to be relatively small, given their short duration and nonlethality. Savings due to the prevention of warts will also be limited. For example, in the Netherlands, the estimated annual savings if all genital warts were prevented is €375 000 [assuming 1500 cases (38) and €250 per case (39)], whereas the estimated annual savings due to the prevention of cervical cancers is approximately €3 500 000 [assuming 600 cases (40), €8500 per case (18), and that 70% of the cases are prevented].

Although the HPV vaccine has not been available long enough to evaluate its long-term side effects, it is safe over the short term, with only a small number of adverse events registered in women aged 15–26 years (41). However, most countries intend to vaccinate 12-year-old girls, and vaccine safety and/or efficacy has not yet been tested in this age group. Thereby, depending on the population, cervical cancer is a relatively rare disease (for the Netherlands, one death case will be prevented per 1000 vaccinated girls). As a result, rare adverse events due to vaccination will also influence the risk–benefit ratio of vaccination. Therefore, future studies on the adverse effects among vaccinated 12-year-old girls are important, primarily for safety and also for cost-effectiveness estimates.

Because of the scarcity of resources, trade-offs are often necessary in medical decision making. Gafni and Birch (42) have addressed the value of threshold cost-effectiveness ratios in decision making. They argued that decision makers need information about the opportunity costs of a policy decision (ie, the next best alternative that must be given up as a result of the decision) to improve efficient resource allocation (42). Opportunity costs are the health outcomes that are achievable with other interventions

that were not undertaken because these resources were committed to the intervention under consideration (43). In our analysis, the opportunity costs of HPV vaccination are preventing 100 deaths, or 2500 life-years, for a price tag of €27 million.

The consequences of discounting future costs and effects on the cost-effectiveness ratio can be substantial, especially when the intervention involves current costs and future effects (ie, the time between current costs and future effects is rather long), as it typically is with prevention. In 2006, the Dutch Health Care Insurance Board (College voor Zorgverzekeringen) recommended that costs and effects were to be discounted at 4% and 1.5%, respectively, per year (44). In this analysis, applying these rates would reduce the costs for HPV vaccination from €53 500 to €19 700 per QALY gained. However, in 1996, when policy decisions were being made about cervical cancer screening in the Netherlands, both costs and effects were to be discounted at 4% (45). Because these new cost-effectiveness criteria (ie, 4% for costs and 1.5% for effects) would also favor the cost-effectiveness ratio of cervical cancer screening, we need to reconsider optimal screening (ie, screen ages, interval between screen tests, and frequency) and compare the health effects gained due to allocating more resources to screening with the health effects gained due to adding vaccination to the Dutch screening program. Such an analysis should include the design of an optimal combination of HPV vaccination and screening, including combinations of vaccination with different levels of cytological and HPV screening for the Dutch situation.

In conclusion, many uncertainties still exist about the effects of HPV vaccination on HPV-related diseases. Our cost-effectiveness analysis shows that in the Netherlands, a country with low cervical cancer incidence and mortality, HPV vaccination is not cost-effective (even under as yet unproven favorable assumptions). To become cost-effective, the vaccine price would have to be decreased considerably, depending on the effectiveness of the vaccine.

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