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Would the effect of HPV vaccination on non-cervical HPV-positive cancers make the difference for its cost-effectiveness?

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ABSTRACT

Besides cervical cancer, the human papillomavirus (HPV) is found in other cancers and may be preventable with HPV vaccination. However, these other cancers are often not accounted for in cost-effectiveness analyses of HPV vaccination. This study estimates the potential maximum effect on the cost-effectiveness ratio (CER) of HPV vaccination in preventing non-cervical HPV-positive cancers.

For the Dutch situation, a mathematical equation was used to estimate the maximum impact if all cancer cases of the penis, vulva/vagina, anus, oral cavity and oro-pharynx with HPV16/18 are prevented, in terms of number of life years gained, savings and improvement in the CER of the vaccination. For other countries and for future developments, we show how the impact on the CER varies depending on the incidence of cervical/non-cervical HPV 16/18-positive cancers, vaccine costs and clinical costs.

If in the Netherlands all HPV 16/18-positive cancers are prevented by vaccination in women only, compared to if only HPV 16/18-positive cervical cancer is prevented, the life years gained increase with 14%, the savings increase with 18%, and the CER decreases with 13%. If vaccination prevents HPV-positive cancers in both men and women, these figures increase to 25%, 26% and 21%, respectively. In conclusion, if HPV vaccination fully prevents all non-cervical HPV-positive cancers, this would substantially increase its cost-effectiveness. The impact of the vaccination varies depending on the incidence of cervical/non-cervical HPV16/18-positive cancers, the vaccine costs and clinical costs. Observed combinations of these parameters in different countries show a decrease in the CER between 10% and 31%.

1. Introduction

Cervical cancer is the most important human papillomavirus (HPV) – related cancer worldwide. In the Netherlands, the incidence and mortality trends of cervical cancer have been steadily declining with rates of 6.3 and 1.4 per 100,000 woman years (age-adjusted rates, standardised to the world population), respectively, in 2007.[1] However, HPV infections are also found in other cancer types, notably cancer of the penis, vulva/vagina, anus, oral cavity and oro-pharynx.[2] Since we are able to vaccinate against HPV types 16 and 18, a part of these cancers is potentially preventable. The possible effect of vaccination on non-cervical HPV-positive cancers has generally not been accounted for in cost-effectiveness analyses of

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HPV vaccination.[3–7] This is valid, since estimates of the effect of vaccination on the incidence of non-cervical HPV-positive cancers, except for vulval and vaginal lesions,[8] are not yet evidence based. On the other hand, Chesson and colleagues[9] and Kim and colleagues[10] estimated that including the effect of vaccinating 12-year-old girls on non-cervical HPV-positive cancers will decrease the cost-effectiveness ratio (CER) by 25% or 18–30%, respectively; thus, the effect of HPV vaccination on these cancers might be substantial.

To estimate the costs and effects of HPV vaccination microsimulation models are generally used, which simulate individual event histories for an idealised population of interest.[11] Microsimulation is flexible but complex and not always necessary. Compared to the simulation of screening, the simulation of HPV vaccination is sometimes much simpler, depending on the assumptions made. For analyses that evaluate the effect of waning or combining vaccination with a variety of screening strategies, a (micro-) simulation approach is indicated. For herd immunity, a dynamic model is required. However, when the assumed effect of vaccination is a certain percentage reduction in incidence and mortality a more direct epidemiological approach, using a mathematical equation, is sufficient.

We used such a direct approach to estimate the potential maximum effect on the CER of HPV vaccination in preventing non-cervical HPV-positive cancers. Since we wanted to estimate the maximum effect of preventing these cancers, the analyses were performed under the favourable assumption that 100% of the female population is vaccinated against HPV types 16 and 18. We assumed that men are not vaccinated. So, in case the vaccine prevents cancers in women only we assumed 0% herd immunity, in case it also prevents cancers in men we assumed 100% herd immunity. The effects concern the number of life years gained (LYsG) and savings due to preventing treatment costs. Subsequently, in the Dutch situation we calculated the decrease of the CER of HPV vaccination as a result of these effects. The characteristics that influence the relative effect of preventing also non-cervical cancers with HPV differ between countries. For example, cervical cancer burden differs between countries, amongst others due to variation in cervical cancer screening.[12,13] Therefore, we show for other countries and for future developments how the impact on the CER varies depending on the incidence of cervical and non-cervical HPV16/18-positive cancers, the vaccine costs and the costs of clinical healthcare.

2. Methods

To calculate the number of LYsG due to preventing HPV16/18-positive cancers, the number of life years lost due to these cancers was estimated using data from the Netherlands Cancer Registry (NCR). The NCR contains nationwide data on all cancer types in the Netherlands since 1989 and is more than 95% complete.[14] The present study includes patients with cancer of the cervix, penis, vulva/vagina, anus, oral cavity and oro-pharynx. We used the number of incident cancer cases and the number of deaths by cancer type and gender in the period 1999–2003. Incidence and mortality rates were calculated using the population size, stratified by gender, in the period 1999–2003.[15] Rates are given as the number of cases per 100,000 persons (men or women, followed from birth till death) (Table 1). However, because for this period no data were available on oro-pharynx cancers, but only on total pharynx cancer, the sub-group of oro-pharynx cancer rates were calculated by multiplying pharynx cancer rates by the gender-specific proportions of oro-pharynx cancer (54% in males and 67% in females), based on the NCR data over earlier periods.[16] Per cancer site, the preventable proportion was estimated as the HPV 16/18-positive proportion described in a published review, based on worldwide data (Table 1).[2] The mean number of LYsG per prevented cancer death was calculated as the life expectancy at the mean age at cancer death in 1999–2003, separately for men and women (Table 1).[15]

To calculate the medical savings due to preventing treatment costs of HPV16/18-positive cancers (Table 1), the

Table 1 – Summary data on HPV-positive cancers in the Netherlands (1999-2003) for women (W) and men (M).

		Cervix	Penis	Vulva/vagina	Anus	Oral cavity	Oro-pharynx
Lifetime incidence per 100,000 persons	W	547	–	246	53	274	42
	M	–	75	–	39	362	78
Mortality per 100,000 persons	W	196	–	91	12	80	21
	M	–	16	–	11	104	41
Mean age at diagnosis (years)	W	52	–	71	65	64	60[a]
	M	–	68	–	63	60	60[a]
Mean age at death (years)	W	64	–	77	74	70	66[a]
	M	–	70	–	67	64	63[a]
Mean number of Life Years Gained per prevented case	W	21	–	10	13	16	19
	M	–	12	–	14	17	17
Proportion with HPV16/18		70%	25%	32%	83%	3%	11%
Costs of care per incident case		€8000	€4000	€8000	€5000	€6000	€6000
Costs of care per death case	W	€19,600	–	€16,600	€18,800	€19,500	€19,500
	M	–	€19,500	–	€19,500	€19,600	€19,600

[a] Mean age at diagnosis and mean age at death are for all pharyngeal cancer (data for the sub-site oro-pharyngeal cancer are not available).

healthcare costs for treatment per cancer case were estimated using 'diagnosis treatment combinations' (DBCs).[17,18] The DBC system was introduced in the Netherlands for the registration and reimbursement of hospital and medical specialist care. The fixed prices for reimbursement per DBC were based on information about unit costs of healthcare services and the average number of healthcare services applied per cancer treatment. To calculate the savings due to preventing costs of HPV16/18-positive cancer deaths (Table 1), the costs per cancer death were estimated as the average costs in the last year of life at the mean age at death per cancer site. These costs were based on health insurance, home care, nursing homes and mortality data.[19,20]

The number of LYsG due to preventing HPV16/18-positive cancers (Table 2) were calculated for a cohort of 100,000 persons (men only, women only, or both genders, followed from birth till death) as the number of HPV16/18-positive cancer deaths times the mean number of LYsG per prevented cancer death. The savings due to preventing HPV16/18-positive cancers (Table 2) were calculated for a cohort of 100,000 persons (men only, women only or both genders) as the number of HPV16/18-positive cancers times the costs per cancer case, and the number of HPV16/18-positive cancer deaths times the costs per cancer death (Table 2). The number of LYsG and the cost savings were discounted at a rate of 3% towards 12 years of age (since, in the Netherlands, vaccination is advised at that age).

The proportional decrease in the total costs of vaccination, as a result of increased savings due to preventing the non-cervical HPV-positive cancers, was calculated as (the extra savings per 100,000 persons)/(costs of vaccination per 100,000 persons – savings due to the prevention of cervical cancer). For the Dutch situation, the undiscounted costs of vaccination per 100,000 women were estimated at €40,000,000, based on the assumption that all women are vaccinated at age 12 at a cost of €400 for three doses.[21] The undiscounted costs of vaccination per 100,000 persons (both genders) were estimated at €20,000,000, assuming that all women are vaccinated at age 12 at a cost of €400 for three doses[21] and that 50%[22] of the cohort are women (e.g. 50,000 persons). The decrease in the CER of HPV vaccination due to preventing non-cervical HPV-positive cancers was calculated using the proportional increase in number of LYsG and the proportional decrease in total costs.

It is possible to use the data from the Dutch situation to calculate the proportional change in the CER in other countries. The differences between countries in the impact of including the effect on non-cervical HPV-positive cancers on the CER mainly depend on four variables. These are the incidence/mortality of cervical cancer, the incidence/mortality of non-cervical HPV-positive cancers, the clinical cost level and the vaccination costs. Using these variables, the proportional change in CER for other countries, if the vaccine is effective in both genders, can be estimated as

$$1-\frac{\mathrm{WSR_{cc}LYG_{cc}}/5.1}{\mathrm{WSR_{cc}LYG_{cc}}/5.1+\mathrm{WSR_{nc}LYG_{nc}}/6.2}\left(1-\frac{\mathrm{WSR_{nc}S_{nc}}/6.2}{50,000\mathrm{CoV}/\mathrm{CCL}-\mathrm{WSR_{cc}S_{cc}}/5.1}\right),$$

or in case the vaccine is effective in women only

$$1-\frac{\mathrm{WSR_{cc}LYG_{cc}}/5.1}{\mathrm{WSR_{cc}LYG_{cc}}/5.1+\mathrm{WSR_{nc}LYG_{nc}}/5.7}\left(1-\frac{\mathrm{WSR_{nc}S_{nc}}/5.7}{100,000\mathrm{CoV}/\mathrm{CCL}-\mathrm{WSR_{cc}S_{cc}}/5.4}\right),$$

in which CoV is the cost of vaccination in Euros per woman, $\mathrm{WSR_{cc}}$ is the world standardised incidence rate of cervical cancer, $\mathrm{WSR_{nc}}$ is the world standardised incidence rate of non-cervical cancer, CCL is the relative clinical cost level compared to the Dutch clinical cost (Dutch level = 1), $\mathrm{S_{cc}}$ is the savings for preventing cervical cancer in the Dutch situation, $\mathrm{S_{nc}}$ is the savings for preventing non-cervical cancer in the Dutch situation, $\mathrm{LYG_{cc}}$ is the life years gained by preventing cervical cancer in the Dutch situation and $\mathrm{LYG_{nc}}$ is the life years gained by preventing non-cervical cancer in the Dutch situations. The derivation of the equation is given in the appendix. The values of the LYsG and savings in the Dutch situation are given in Table 2. We used the Dutch cervical cancer incidence (world standardised rate (WSR) of 5.1 per 100,000 (rate in 2003)[1]) and the Dutch non-cervical cancer incidence (WSR of

Table 2 – Life years gained (LYsG) and savings by cancer site, in case HPV16/18-positive cancers are eliminated in women only (W), in men only (M) or in both women and men (Both), per 100,000 persons followed from birth till death.

		Cervix	Penis	Vulva/ vagina	Anus	Oral cavity	Oro-pharynx	Total	Total, excluding cervix
Mean number of LYsG per 100,000 persons, undiscounted	W	2812	–	317	138	37	85	3388	576
	M	–	57	–	145	56	165	422	422
	Both	1421	28	160	141	46	124	1921	500
Mean number of LYsG per 100,000 persons, discounted at 3% per year to age 12 years	W	915	–	65	31	9	22	1042	127
	M	–	13	–	38	15	43	109	109
	Both	462	7	33	34	12	32	580	118
Total savings per 100,000 persons, undiscounted (1000 €)	W	5707	–	1071	378	90	136	7382	1674
	M	–	156	–	349	133	296	934	934
	Both	2883	77	541	364	111	189	4165	1282
Total savings per 100,000 persons, Discounted at 3% per year to age 12 years (1000 €)	W	1765	–	192	79	19	29	2084	319
	M	–	32	–	80	32	71	215	215
	Both	892	16	97	68	21	31	1124	232

6.2 or 5.7 per 100,000, if effective in both genders or in women only, respectively). The coefficients in this formula are based on a cohort of 100,000 persons. In the case that the vaccine is effective in both genders 50% of the cohort is female, in the case that the effectiveness is in women only, then 100% of the cohort is female.

In sensitivity analyses, we calculated the proportional decrease of the CER with different values for these variables. In these analyses, the Dutch clinical cost level was multiplied by a factor between 0.1 and 3, based on the mean health expenditure levels per capita worldwide.[23] In the same analyses, the vaccine costs were varied between €100 and €500 for three initial doses, the cervical cancer incidence (WSR) was varied between 2.5 and 50 per 100,000 women years, and the non-cervical cancer with HPV incidence WSR between 0.5 and 36 per 100,000 person years, based on incidence levels worldwide.[2,24,25] The range in non-cervical cancer with HPV incidence is wide, because it was calculated as the two extreme situations in which all individual HPV-positive cancers have the lowest or the highest incidence levels observed worldwide. We also estimated the proportional decrease of the CER for scenarios based on the situation in Finland, Denmark, the United Kingdom (UK) and the United States (US). We calculated the world standardised incidence rates based on the number of incident HPV-positive cancers and the population size in each of these countries.[26–31] We assumed that the age distributions for the cancer incidence and the life tables were similar to those in the Netherlands. For the US, Finland and Denmark, the sub-group of oro-pharynx cancer rates were calculated by multiplying pharynx cancer rates by 54% in males and 67% in women, based on the Dutch NCR data. Also, we assumed the same anal cancer crude incidence rate in Finland and Denmark as in the Netherlands. Vulvar/vaginal cancer incidence data in Finland and Denmark are the data of cancer of 'other female genital organs', excluding cancer of the cervix uteri, corpus uteri, uterus and ovary. The clinical costs level and vaccination costs were based on published cost-effectiveness analyses,[9,10,32] or, in case no cost-effectiveness analyses were published, they were assumed to be the same as in the Netherlands.

3. Results

3.1. Basic data

Table 1 shows the data for the different cancer sites with HPV in the Netherlands. Anal cancer occurs more often in women than in men (53 versus. 39 per 100,000 persons, followed from birth till death). Oro-pharyngeal and oral cancer occurs more often in men than in women (78 versus. 42 and 362 versus. 274 per 100,000 persons, respectively). For anal, oral and oro-pharyngeal cancer, women were slightly older at diagnosis and at death than men. The proportion of cancer cases attributable to HPV16/18 ranged from 3% for oral cancer to 70% for cervical cancer and 83% for anal cancer.

The estimated medical costs per case for treatment ranged from €4000 for penile cancer to €8000 for cervical and vulvar/vaginal cancer. Costs associated with a cancer death ranged from €16,600 for vulvar/vaginal cancer to €19,600 for cervical, oral and oro-pharyngeal cancer.

3.2. Life years gained

If vaccination prevents non-cervical HPV16/18-positive cancers in women only, the number of LYsG will increase by 21% compared to if only cervical cancer is prevented (from 1421 to 1712 per 100,000 persons, Table 2). If cancers are prevented in both men and women, this percentage increases to 35%. If the effects are discounted at a rate of 3% per year, these percentages become 14% and 25%, for prevention in only women and in both men and women, respectively.

3.3. Medical savings and total costs

If as a result of vaccination, non-cervical HPV16/18-positive cancers are prevented in women only, the savings due to

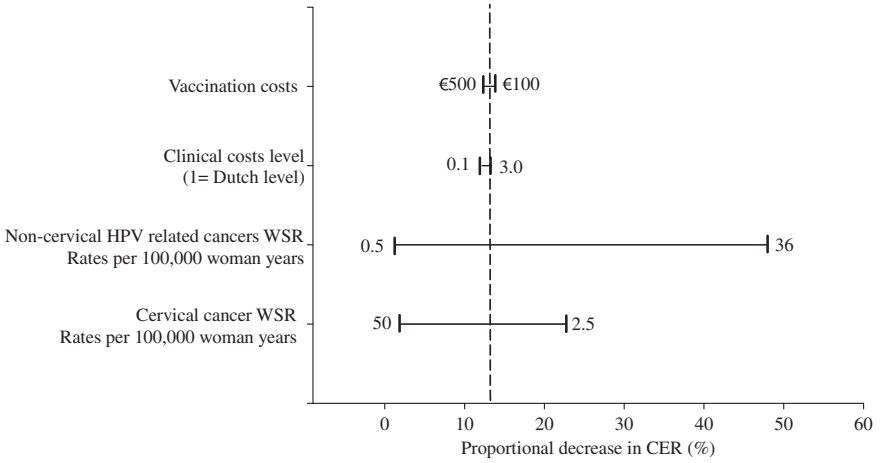

Fig. 1 – One-way sensitivity analysis of the decrease in the cost-effectiveness ratio of HPV vaccination when preventing HPV-positive cancers at extreme values of cervical cancer incidence, of non-cervical HPV-positive cancers incidence, for the clinical costs level and for the vaccine price (price for three initial doses), if HPV infections are prevented in women only (costs and effects are discounted at 3%). Dashed line is the base case result. (WSR = World Standardised Rate, CER = cost-effectiveness ratio)

the avoidance of cancer treatment will increase by 29% compared to the savings from preventing cervical cancer only (from €5,707,000 to €1,674,000 per 100,000 women, Table 2). If non-cervical HPV16/18-positive cancers are prevented in men and women, this percentage increases to 44%. After discounting at a rate of 3% per year, the savings will increase by 18% and 26%, for prevention in only women and in both men and women, respectively. Given these increased savings, the decrease in discounted total costs if the vaccine is effective in women only is 319,000/((100,000 * €400) – 1,765,000) * 100% = 0.8% (Table 2). If the vaccine is effective in both men and women, the decrease in total costs is 232,000/((50,000 * €400)-892,000) * 100% = 1.2%.

3.4. *Impact on the CER*

For the Netherlands, taking the effects of preventing non-cervical HPV16/18-positive cancers into account will, depending on whether these cancers are prevented in only women or in both men and women, increase the number of LYsG by 14% or 25% and decrease the total costs of vaccination by 0.8% or 1.2%, respectively. As a result, the total CER will decrease by 1 – ((1 – 0.008)/(1 + 0.14)) * 100% = 13% if all HPV16/18-positive cancers are prevented in women compared to if only cervical cancer is prevented. If cancers are prevented in both men and women, the CER will decrease by 21%.

Fig. 1 and Table 3 show the decrease of the CER at different levels of cervical cancer incidence, non-cervical cancer incidence, different vaccine prices (price for three initial doses) and clinical costs levels (1 = Dutch clinical costs level). Of the four variables, the variation in the incidence of non-cervical HPV-positive cancers has the largest influence and the clinical costs level has the smallest influence on the decrease in the CER (Fig. 1). Multi-way variation of the four parameters shows a decrease in the CER between 0% and 114% (Table 3). However, the scenarios with the maximum and minimum effect are a combination of low cervical cancer incidence with high non-cervical cancer incidence and vice versa (scenarios 2 and 3), which are unlikely scenarios. Plausible combinations (scenarios 1, 4–9) show a decrease in the CER between 3% and 14% if the vaccine is effective in women only (Table 3). If it is effective in both genders the decrease may vary between 4% and 31%.

4. Discussion

Taking full prevention of non-cervical HPV16/18-positive cancers into account substantially decreases the CER of vaccinating 12-year-old girls. If costs and effects are discounted at a rate of 3%, this maximum approach yields a decrease of 21% for the Dutch situation. However, the CER of HPV vaccination in the Netherlands, without accounting for the effect on the non-cervical HPV-positive cancers, is estimated at €53,500 per Quality Adjusted Life Year (QALY) gained.[21] Thus, even if the effect on all HPV-positive cancers is taken into account, HPV vaccination would still not be cost-effective considering the Dutch cost-effectiveness threshold of €20,000 per QALY gained. The Dutch threshold is, however, very low. If we would consider the threshold of £30,000 per QALY

Table 3 – Multi-way sensitivity analysis of the decrease in the cost-effectiveness ratio (CER) of HPV vaccination when preventing HPV-positive cancers at different levels of (A) cervical cancer incidence, World Standardised Rate (WSR, per 100,000 women years), (B) non-cervical HPV-positive cancers incidence (WSR per 100,000 person years), (C) clinical costs levels (1 = Dutch clinical costs level) and D) vaccine prices (price for three initial doses), if HPV infections are prevented in women only or in both men and women (costs and effects are discounted at 3%).

	Scenario	(A) Cervical cancer WSR	(B1) Non-cervical HPV-positive cancers WSR, women only	(B2) Non-cervical HPV-positive cancers WSR, both genders	(C) Clinical costs level	(D) Vaccination costs (€)	Decrease in CER if effective in women (%)	Decrease in CER if effective in both (%)
1	Base Case (Dutch situation)	5.1	5.7	6.2	1	400	−13	−21
2	(A) ↑, (B) ↓, (C) ↑, (D) ↓[a]	50	0.5	0.5	3	100	0	0
3	(A) ↓, (B) ↑, (C) ↑, (D) ↓[a]	2.5	36	36	3	100	−78	−114[b]
4	(A) ↓, (B) ↓, (C) ↑, (D) ↑[a]	2.5	0.5	0.5	3	500	−3	−4
5	(A) ↑, (B) ↑, (C) ↓, (D) ↓[a]	50	36	36	0.1	100	−9	−17
6	Scenario based on United Kingdom	6.2	5.5	6.4	2	300	−11	−22
7	Scenario based on United States	5.3	5.9	7.7	3	300	−14	−31
8	Scenario based on Denmark	16.3	5.6	6.9	1	400	−5	−10
9	Scenario based on Finland	3.2	4.4	4.2	1	400	−15	−23

Scenarios 2 and 3 are the contrasting (in terms of influence on the CER) but not necessarily realistic combinations and scenarios 4 and 5 the two contrasting realistic combinations of the extreme parameter values.

[a] ↓, smallest value considered; ↑, largest value considered (see Fig. 1 for the extremes considered).

[b] i.e. Cost saving.

gained (approximately €36,000) the National Institute for Health and Clinical Excellence (NICE) stated as acceptable, HPV vaccination would be just above the cost-effectiveness threshold if the effect on all HPV-positive cancers is taken into account. Moreover, the estimated CER of €53,500 was based on the 2009 over-the-counter price in the Netherlands of approximately €400 for three doses. Currently the price of the vaccine already started to decrease significantly. This means that the vaccination is more likely to become cost-effective.

The results for various levels of cancer incidence, clinical costs and vaccination costs show that the decrease can differ in other countries. Several cost-effectiveness analyses of vaccination against HPV, without accounting for the effect on the non-cervical HPV-positive cancers, have been published.[3–7] For example, Kulasingam and colleagues[32] found that vaccination with screening, compared to screening alone, was associated with an incremental cost-effectiveness ratio of €26,600 per QALY gained.[21] Compared to the Dutch situation, they assumed lower vaccination costs (€309)[21] and two times higher cancer treatment costs. If the effect on non-cervical HPV-positive cancers in women only is taken into account, the cost-effectiveness ratio decreases by 11% (Table 3) to €23,700 per QALY gained.

We assumed a lifelong 100% protection of the vaccine against HPV16/18-positive cancers. Trials to evaluate the effect of HPV vaccination on cervical cancer show protection of the vaccine against HPV16/18-positive pre-invasive lesions of 98%, in HPV16/18 naive women.[33] Although the effect of the vaccine against invasive cervical cancer can tentatively be estimated from the effect against pre-invasive lesions, it is not yet established. In addition, the duration of the protection is still unknown. A lower or shorter effectiveness in preventing cervical cancer would substantially increase the CER, either by a decreased number of life years gained, or by the addition of the costs of booster vaccinations. In both cases, assuming that the efficacy of the prevention of non-cervical HPV-positive cancers follows that of cervical cancer, the relative impact on the CER of preventing these cancers would basically not change.

There is some evidence of cross-protection of the vaccine against HPV 31 and HPV 45, which are closely related to HPV 16 and 18, respectively.[34] On the other hand, there is a possibility that other oncogenic HPV types will eventually fill the biologic niche left behind after the elimination of HPV types 16 and 18. In both cases, the relative impact on the CER of preventing non-cervical HPV-positive cancers could change, if HPV types 31/45 (or the types that fill the niche) have a different prevalence in non-cervical HPV-positive cancers than in cervical cancer. It is reported that the prevalence of HPV types 31/45 is comparable for cervical and penile cancer but less prevalent in the other non-cervical HPV-positive cancers.[35–40] Thus, the relative impact on the CER of preventing non-cervical cancers could be somewhat smaller in case of cross-protection.

In addition to the uncertainty about the effectiveness of the vaccine against cervical cancer, the effectiveness may be less in preventing non-cervical HPV16/18-positive cancers than in preventing cervical cancers. The effect of HPV vaccination on non-cervical HPV-positive cancers is not known. Nevertheless, one trial showed that in women not infected with HPV16/18, the vaccine was 100% effective in preventing HPV16/18 positive vulval/vaginal intraepithelial neoplasias grade 2–3.[8] Moreover, compared to cervical cancer, HPV is less prevalent in these cancers. This could indicate that HPV infection is not a necessary condition for these cancer cases in which HPV was found[2] and, therefore that these HPV-positive cancers could not be prevented as effectively by HPV vaccination. A lower effectiveness against the non-cervical HPV-positive cancers compared to the effect against cervical cancer would result in a smaller decrease of the CER.

The effect of vaccination is maximal if HPV-positive cancers are prevented in both men and women. In the best case, the protection in men would totally result from herd immunity. Nevertheless, since it is unlikely that all women will be vaccinated, and since men may have sex with men, it is also unlikely that all men will be protected due to reduced transmission. In case the effect of the vaccine in men required the vaccination of boys, the presented costs of the vaccination programme would approximately double. If both men and women are vaccinated, the proportional decrease in CER as a result of the effect against all HPV-positive cancers is still 21%.

We estimated costs per LYG and not costs per QALY gained. By lack of evidence-based utility data for the relatively rare cancers described in the present study, we could have assumed similar disability weights for the non-cervical HPV-positive cancers as for cervical cancer. This would however lead to approximately the same proportional decrease in the CER of HPV vaccination. On the other hand, some analyses of the cost-effectiveness of HPV vaccination include the impact of vaccination on the quality of life and costs due to the prevention of non-lethal HPV-related diseases, such as genital warts and cervical intraepithelial neoplasia. For these analyses, our resulting proportional effect on the CE of vaccination of including other cancers is slightly overestimated. The reason is that the proportional decrease in the CER due to the prevention of non-cervical HPV positive cancers in that case would be smaller, since the relative extra benefits of preventing these cancers would be smaller. The impact on the quality-of-life of different HPV-related diseases needs further investigation.

We computed the influence of differences in the cervical and non-cervical HPV-positive cancers background level. In this way, we show the impact of preventing non-cervical HPV-positive cancers in different countries, similar to the scenarios based on the situation in Finland, Denmark, the UK and the US. In the present calculations, demographic data, age distributions of cancer incidence and cancer survival data from the Netherlands were used. Variation in these inputs would influence the results. However, since differences in these data would generally affect the prevention of cervical cancer in roughly the same way as for non-cervical cancers, the influence regarding the relative impact of preventing non-cervical cancers on the CER would be limited.

The proportion of cancers that is HPV 16 or 18 positive was estimated from the global burden of HPV-positive cancers[2] and was assumed to be equal in all countries. However, these proportions may vary between countries.[2] The effect of a lower or higher proportion would have the same effect on the

CER as a lower or higher background incidence of non-cervical HPV-positive cancers, whose effect is shown in Fig. 1 and Table 3.

We examined the effect of adding HPV vaccination to the cervical cancer screening situation. We did not consider the costs of screening, because the effects of the screening programme do differ only slightly between the situations with and without vaccination. By doing so, we neglected the fact that with vaccination less CIN lesions are detected by screening than without vaccination. The consequences of this on the results will be small because the total costs of HPV vaccination only decrease with less than 2% due to preventing CIN2/3 lesions.[21] With discounting this effect would even be smaller, since treatment costs for CIN lesions occur later in time than the costs of vaccination.

Finally, the Dutch Health Care Insurance Board ('College voor Zorgverzekeringen') recommended in 2006 that costs and effects were to be discounted at 4% and 1.5%, respectively, per year.[41] In this analysis, applying these rates to the Dutch situation would result in a 15% instead of a 13% decrease in the CER, if vaccination prevents HPV-positive cancers in women only. If vaccination prevents cancers in men also, this figure is 24% instead of 21%.

In conclusion, this study shows how a simple calculation can be used to estimate the potential improvement of the cost-effectiveness ratio of HPV vaccination by including the effect of preventing non-cervical HPV-positive cancers. Results are based on the assumption that all cancers attributed to HPV16/18 are prevented lifelong. With this hypothesis, the effect for the Netherlands is estimated as a 21% decrease. For other countries, the impact depends on the incidence of cervical and non-cervical HPV16/18-positive cancer, the vaccine costs and the clinical healthcare price level. The actual effect of HPV vaccination on non-cervical HPV-positive cancers can only be revealed by follow-up of HPV-vaccinated populations.

Conflict of interest statement

None declared.

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Appendix Derivation. of the equation

The equation to estimate the proportional change in the cost-effectiveness ratio if the vaccine is effective in both men and women in other countries can be derived as follows:

$$
\begin{aligned}
&1-\text{CER with other cancers}/\text{CER without other cancers} = \\
&= 1-\frac{\text{costs with other cancers}}{\text{effects with other cancers}}\Big/\frac{\text{costs without other cancers}}{\text{effects without other cancers}} \\
&= 1-\frac{\text{costs of vaccination}-\text{savings with other cancers}}{\text{effects with other cancers}}\Big/\frac{\text{costs of vaccination}-\text{savings without other cancers}}{\text{effects without other cancers}} \\
&= 1-\frac{50,000\text{CoV}-\text{WSR}_{cc}\text{S}_{cc}\text{CCL}/5.1-\text{WSR}_{nc}\text{S}_{nc}\text{CCL}/6.2}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1+\text{WSR}_{nc}\text{LYG}_{nc}/6.2}\Big/\frac{50,000\text{CoV}-\text{WSR}_{cc}\text{S}_{cc}\text{CCL}/5.1}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1} \\
&= 1-\frac{\text{WSR}_{cc}\text{LYG}_{cc}/5.1}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1+\text{WSR}_{nc}\text{LYG}_{nc}/6.2}\,\frac{50,000\text{CoV}-\text{WSR}_{cc}\text{S}_{nc}\text{CCL}/5.1-\text{WSR}_{nc}\text{S}_{nc}\text{CCL}/6.2}{50,000\text{CoV}-\text{WSR}_{cc}\text{S}_{cc}\text{CCL}/5.1} \\
&= 1-\frac{\text{WSR}_{cc}\text{LYG}_{cc}/5.1}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1+\text{WSR}_{nc}\text{LYG}_{nc}/6.2}\left(1-\frac{\text{WSR}_{nc}\text{S}_{nc}\text{CCL}/6.2}{50,000\text{CoV}-\text{WSR}_{cc}\text{S}_{cc}\text{CCL}/5.1}\right) \\
&= 1-\frac{\text{WSR}_{cc}\text{LYG}_{cc}/5.1}{\text{WSR}_{cc}\text{LYG}_{cc}/5.1+\text{WSR}_{nc}\text{LYG}_{nc}/6.2}\left(1-\frac{\text{WSR}_{nc}\text{S}_{nc}/6.2}{50,000\text{CoV}/\text{CCL}-\text{WSR}_{cc}\text{S}_{cc}/5.1}\right),
\end{aligned}
$$

in which CoV is the cost of vaccination in Euros per woman, WSR_{cc} is the world standardised incidence rate of cervical cancer, WSR_{nc} is the world standardised incidence rate of non-cervical cancer, CCL is the relative clinical cost level compared to the Dutch clinical cost (Dutch level = 1), S_{cc} is the savings of preventing cervical cancer in the Dutch situation, S_{nc} is the savings of preventing non-cervical cancer in the Dutch situation, LYG_{cc} is the life years gained by preventing cervical cancer in the Dutch situation and LYG_{nc} is the life years gained by preventing non-cervical cancer in the Dutch situations.

The equation for the case in which the vaccine is effective in women only can be derived in the same way.

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