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Threshold cost-effectiveness analysis for a therapeutic vaccine against HPV-16/18-positive cervical intraepithelial neoplasia in the Netherlands

Jos Luttjeboer [a,*], Didik Setiawan [a], Qi Cao [a], Toos CAHH Daemen [b,1], Maarten J. Postma [a,c,d,1]

[a] Department of Pharmacy, Unit of PharmacoEpidemiology & PharmacoEconomics (PE2), University of Groningen, Groningen, The Netherlands
[b] Department of Medical Microbiology, Tumor Virology and Cancer Immunotherapy, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[c] Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[d] Institute of Science in Healthy Aging & healthcaRE (SHARE), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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ABSTRACT

In this study, the potential price for a therapeutic vaccine against Human Papilloma Virus (HPV)-16 & 18 (pre)-malignant cervical lesions is examined. A decision tree model was built in the context of the new Dutch cervical cancer-screening program and includes a primary test for the presence of HPV. Based on data of cervical cancer screening and HPV prevalence in the Netherlands, cohorts were created with HPV-16 or 18 positive women with cervical intraepithelial neoplasia (CIN) 2 or 3 or cervical cancer stage 1A (FIGO 1A). In the base case, the vaccine price was based on equal numbers of effective treatments in the vaccine branch and the current treatments branch of the model, and parity in cost, i.e. total cost in both branches are the same. The vaccine price is calculated by subtracting the cost of the vaccine branch from cost in the standard treatment branch and divided by the total number of women in the cohort, thereby equalizing costs in both strategies. Scenario analyses were performed taking quality adjusted life years (QALYs) into account with €20,000/QALY, €50,000/QALY and €80,000/QALY as corresponding thresholds. Sensitivity analyses were specifically targeted at the characteristics of the type-specific HPV test in the screening practice and vaccine efficacy. A probabilistic sensitivity analysis (PSA) was performed to quantify the level of uncertainty of the results found in the base case. In the base case, break-even vaccine prices of €381, €568 and €1697 were found for CIN 2, CIN 3 and FIGO 1A, respectively. The PSA showed vaccine pricing below €310, €490 and €1660 will be cost saving with a likelihood of 95% for CIN 2, CIN 3 and FIGO 1A, respectively. The vaccine price proved to be very sensitive for inclusion of QALY gains, including the HPV-type specific test into the Dutch screening practice and vaccine efficacy.

1. Introduction

Screening for (pre)-malignant lesions of the cervix has lowered the number of cervical cancers in the Netherlands. Despite that, approximately 700 women are still diagnosed with cervical cancer and about 200 women die of cervical cancer in the Netherlands every year [1]. To further reduce the incidence of cervical cancers the prophylactic bivalent vaccine against infection with human papillomavirus (HPV) type 16 and 18 was implemented in the national immunization program in 2009, offering vaccination to twelve-year-old girls. The HPV high risk (HR) types are considered the cause of cervical cancers, with HR-HPV types 16 and 18 being responsible for about 70% of all cervical cancers [1,2]. The first significant effects of vaccination on cervical cancers numbers can only be expected and being measured in more than a decade, when the first cohort of vaccinated women enters cervical screening. However, the results of the prophylactic vaccination can be expected far from optimal given the low vaccination coverage of 59% in the Netherlands in 2014 [3].

In 2017, the Dutch cervical screening program is intended to change. Instead of the usage as primary test, which will be replaced by an HR HPV-test, cytology will be used as a triage test in case of a positive HR-HPV-test [4]. The HR-HPV test is more sensitive than cytology for detection of cervical intraepithelial neoplasia (CIN) grade 2 or worse (grade 3 and cancer) 96.1% (CI 95%: 94.2–97.4%) and 53.0% (CI 95%: 48.6–57.4%), respectively [5] and [6]. It is expected that the new screening program will detect an extra of 75 women with CIN or cervical cancer and prevent 18 deaths in contrast with the current screening in the Netherlands, annually. The specificity of the HR-HPV-test is however lower than cytology 90.7% (90.4–91.1%) and 96.3% (96.1–96.5%), respectively [6]. The test provides information about whether or not a woman has an

* Corresponding author.
E-mail address: josluttjeboer@gmail.com (J. Luttjeboer).
[1] These authors contributed equally to this work.

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infection with a HR-HPV type, but it does not provide information on the degree of transformation of cervical cells [7]. If a woman has a PAP3A2 or worse, she will be referred to a gynecologist [8]. A colposcopy is performed and an additional biopsy is taken to assess the state of the lesion. Although, cervical cancer screening will be improved and vaccination is introduced in the Netherlands, this will not eliminate HPV-related pre-cancer and cancer. Notably, despite the introduction of vaccination and an improved screening program, (pre)malignant cervical neoplasia will remain to exist and better treatment options are needed.

Therapeutic HPV-vaccines may improve the treatment of (pre)-malignant cervical neoplasia as no surgical treatment is needed [9]. It can trigger the immune system to recognize HPV-infected cells and enhance the immune system eliminating these cells. A major difference between a therapeutic HPV-vaccine and a prophylactic HPV-vaccine concerns the specific immune response that is evoked against different HPV proteins. The prophylactic vaccines induce antibodies against a viral capsid protein, which can neutralize the virus and thus inhibit infection of cells. The current prophylactic vaccines are however not capable of clearing already existing infections. Upon infection of cells with HPV, the cells express non-structural proteins of HPV, i.e. E1, E2, E6 and E7. Notably, therapeutic HPV vaccines that have entered clinical trials mostly target HPV E6 and E7 [9]. A microencapsulated DNA vaccine has shown promising results; in younger patients a 70% resolution of CIN 2/3 histology was detected, compared to 23% in the placebo group [10]. Noteworthy, the women in this study were younger than 25 years, whereas the starting age for screening women in the Netherlands is 30 years.

Another therapeutic DNA vaccine was studied in CIN 2/3 positive women. Regression of the lesion to either CIN 1 or normal pathology was shown in 53 (49.5%) of 107 vaccinated women and 11 (30.6%) of the 36 placebo recipients. A significant difference of 19.0% (95% CI: 1.4–36.6%) percentage points, in favor of the vaccine group [11].

Other kinds of therapeutic vaccines are also tested in clinical trials. A therapeutic vaccine consisting of a bacterial heat shock protein covalently linked to a HPV E7 protein was studied to determine the effects of vaccination in 20 women with high-grade cervical intraepithelial lesions (HSIL). Seven (35%) women showed complete regression and one (5%) woman regressed to CIN 1 [12].

A therapeutic vaccine consisting of an attenuated recombinant vaccinia virus was tested in 21 CIN 2/3 women. In 24% (95% CI: 8–47%) of the women full eradication of HSIL and HPV was obtained. In 10 (48%, 95% CI: 28–70%) no CIN 2/3 was found [13].

Another vaccinia virus based therapeutic vaccine showed also regression of CIN 2/3 women. In a phase 2 clinical trial 34 females with HSIL received the vaccine. 19 of the 34 women showed no lesion after treatment, in three patients the lesions were reduced by 85–90%, in eight others the lesions reduced by 60%. In the other four females lesions were reduced with 25% [14].

Economic aspects are becoming increasingly important in the assessment of any health-care technology, with (therapeutic) vaccines being an important component. Economic evaluation of a therapeutic of a therapeutic HPV-vaccine is still lacking. Therefore, the aim of this study was to explore potential pricing of a therapeutic HPV vaccine for women identified with HPV-induced cervical lesions in the Netherlands.

2. Methods

We analyzed three cohorts of women with detected HPV-16/18 positive CIN 2, CIN 3 and cancer (notably, early stage FIGO 1A), respectively. It was assumed that therapeutic vaccines are of less use in later stages of cancer. The sizes of the CIN cohorts were estimated for the whole of the Netherlands based on the detected numbers of CIN 2 and CIN 3 in 2010 [15]. With data on the prevalence of HR-HPV in CIN 2 and CIN 3 in the Netherlands, the number of HR-positive women detected in the new screening practice could be calculated [16]. The cohort size for HPV-16/18 positive CIN 2 and CIN 3 was calculated using the prevalence of HPV-16/18 in CIN 2 and CIN 3, assuming all HR-positive CINs are detected in the new screening settings, with a primary HPV-test. For the detection of HPV-16/18 an HPV-type specific test was modeled on top of the screening program. The tissue for the HPV-16/18 test was assumed to be co-collected during regular screening, namely no additional moment for tissue collection is needed. Therefore, the loss to follow-up did not change compared to regular screening. Due to the specificity of the modeled test, some HR-postive-HPV-16/18-negative women would test positive for HPV-16/18. These HPV-16/18 false-positive women were included in the cohort as well [17]. The false positive HPV-16/18 women were kept in the cohort and treated as positives. The cohort size for FIGO 1A was based on a Dutch report on the national cervical screening program [15], the prevalence of HPV-16/18 in cervical cancer [16] and the number of malignancies [18]. In total, 408, 1052 and 16 women were respectively included for HPV-16/18 positive CIN 2, CIN 3 and FIGO 1A in the base case. The cohort sizes reflect estimates of the total number of women with CIN 2, CIN 3 and FIGO 1A in the Netherlands.

To determine the potential vaccine pricing we developed a decision tree model in Microsoft Excel. As shown in Fig. 1, our model included two comparative strategies for treating HPV-16/18 positive CIN 2, CIN 3 or FIGO 1A: (i) an HPV-16/18 therapeutic vaccine, and (ii) current surgical treatments (Loop Excision of the Transformation Zone (LETZ), conization and hysterectomy). Vaccine pricing was based on (i) parity in costs in both treatment strategies; i.e. costs of the vaccine branch were subtracted from costs in the standard treatment branch and divided by the total number of women in the cohort to estimate the vaccine price, thereby equalizing costs in both strategies and (ii) the number of effective treatments in the vaccine branch of the model was assumed at least the same or higher as in the standard treatments branch. This was modeled by retreating all women who were ineffectively treated by the vaccine and would normally have a hysterectomy and all women who were false positive for HPV-16/18. We also modeled retreatment in the group of women who were positive for HPV-16/18, but were not effectively treated by the vaccine. Note however, that not all retreated women in this last group were taken into account for calculating the vaccine price, due to the equal numbers of effective treatments in both branches of the model.

The efficacy of the vaccine was assumed to be 70% in the base case and the same for all ages. The efficacy was altered in the subsequently conducted sensitivity analysis. The effectiveness of the current treatments, Loop Excision of the Transformation Zone (LETZ), conization and hysterectomy are presented in Table 1 [18].

The average treatments' costs were calculated based on a Dutch report and updated to 2015 price level using the consumer price indices [18] and [22]. The costs in the vaccine branch were made up of HPV-16/18-test costs for all women tested, retreatment costs for HPV-16/18 false-positive women, costs of retreating women who would normally get a hysterectomy and were not effectively treated by the vaccine and costs of retreating women to get to the same number of effective treatments in both the vaccine branch and the standard treatments branch.

2.1. Probabilistic sensitivity analysis

A number of sensitivity analyses and scenario analyses were conducted besides the base case to detect the robustness of our

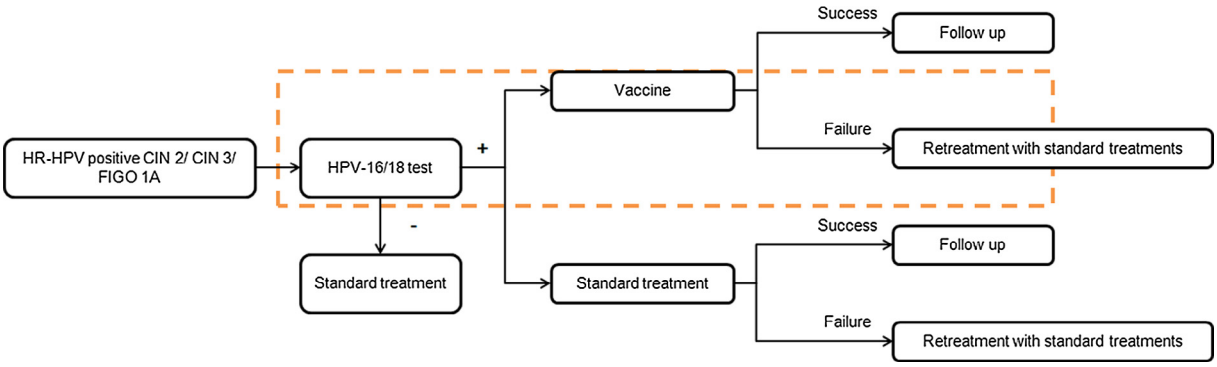

Fig. 1. Decision tree of CIN 2, CIN 3 and FIGO 1A treatment. The field indicated by the orange dashed line shows all parts associated with vaccine treatment in the model. Note that not all women who are retreated with standard treatment options, are part of the vaccine price calculation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

modeled outcomes. A probabilistic sensitivity analysis (PSA) was performed to determine the uncertainty in the vaccine prices. The ranges used in the PSA for the HPV prevalence and the type specific HPV test are presented in Table 1. A beta PERT distribution was used for the varying parameters due to their skewness. The bounds of the confidence intervals were used as minimum and maximum values for creating the beta distributions. For the costs of CIN 2, CIN 3 and FIGO 1A a uniform distribution was chosen with ranges of costs of ±€100. We simulated our model a thousand times to randomly draw values from each distribution and the vaccine prices with those values were calculated.

2.2. Univariate sensitivity analyses

Besides the PSA, a multiple univariate sensitivity analyses were performed to detect to what extend the potential vaccine price for CIN 2 was sensitive to the specificity of the HPV-16/18-test, the sensitivity of the HPV-16/18 test, the CIN 2 treatment cost and HPV-16/18 prevalence. Meanwhile, the influence of the vaccine efficacy on the potential pricing of such a vaccine was estimated in a one-way sensitivity analysis.

2.3. Scenario analyses

We also performed three scenario analyses. The first scenario investigated the effect of inclusion of quality adjusted life year (QALY) gains into the calculation of the vaccine price, which was not considered in the base case. Quality of life (QOL) obviously decreases when a woman is diagnosed with CIN 2/3 or FIGO 1A, but evidence is still lacking on how much of this decrease is due to surgical treatment [8]. To overcome the lack of insight in the QOL, we calculated the potential vaccine price for scenarios of 10%, 50% and 100% gains in quality adjusted life years (QALYs) for CIN 2, CIN 3 and FIGO 1A for every successfully vaccinated woman, see Table 1. In this calculation, the various suggested Dutch willingness-to-pay thresholds of €20,000, €50,000 and €80,000 per QALY were used as cut-offs [24–26]. The incremental health effects are modeled by a gain in QALYs in the vaccine branch of the model, i.e. for each woman treated successfully with the vaccine a gain in QALY is assigned to this success. The maximum value for the QALY gains are based on the QOL loss multiplied by the duration of the health state [19,20]. This maximum value is then used to calculate the 10% and 50% of the QALY gains. The uncertainty of the found vaccine price was established in a PSA. We also calculated the incremental cost-effectiveness ratio (ICER) for CIN 2 and CIN 3 for a vaccine price of €250, reflecting cost of prophylactic HPV vaccine in the Netherlands. In this calculation the maximum values for QALY gains were used.

The second scenario analyzed a therapeutic vaccine as an alternative for hysterectomy. The price of therapeutic vaccines is unknown since none of these vaccines have entered the market yet. High production costs for a therapeutic vaccine may cause the vaccine to be too expensive to be an alternative for LEEP or conization. Comparison between a therapeutic vaccine and hysterectomy/radical hysterectomy was based on parity in costs between the vaccine branch and the hysterectomy branch. The comparison was extended taking possible QALY gains into account, as was done in scenario 1. In this scenario women, who did not benefit from the vaccine treatment, were retreated in the model with a hysterectomy. Costs of the hysterectomy retreatment were part of the costs in the vaccine branch.

A third scenario analysis was performed, investigating the maximum vaccine price when the primary HPV test in the cervical screening was replaced by an HPV-type specific test, making the cost of testing for HPV-16/18 part of screening.

2.4. Budget-impact analysis

Finally, a budget-impact analysis was conducted in which the vaccine price was varied to calculate the possible cost savings in the Dutch setting. This scenario was divided into two sub-analyses: (i) use of the vaccine against CIN 2 and CIN 3; (ii) use of the vaccine against CIN 2, CIN 3 and FIGO 1A. In this analysis the base case assumptions were used. The incidence of CIN 2, CIN 3 and FIGO 1A may decline due to better screening and the HPV-16/18 vaccination in the coming years. Therefore, we analyzed the result of lowering the numbers of CIN 2, CIN 3 and FIGO 1A with 10% and 20% on the possible savings.

3. Results

The potential vaccine prices for the (pre)malignant cervical lesions increase with severity of the lesions. Maximum vaccine prices were €381, €568 and €1697 for CIN 2, CIN 3 and FIGO 1A respectively. Potential prices of a therapeutic vaccine were very sensitive to whether or not costs of an HPV-test were included in the calculations. In the new screening program the women will be identified as HR-positive. Additional identification of HPV-16/18 is necessary when using a therapeutic HPV-16/18 vaccine. In the future the HR-test may be replaced by a HPV-type specific test. Including the HPV-type-specific test into screening will increase the potential vaccine prices to €584, €724 and €1843 for CIN 2, CIN 3 and FIGO 1A respectively. The potential price goes up with about €200, roughly twice the HPV-test price. Notably, for identifying a HPV-16/18 positive woman approximately two women have to be tested with the HPV-16/18 test.

Table 1
Input parameters relating to costs, treatment effectiveness, QALY loss and HPV-16/18 test characteristics.

Parameter	Value (min-max)[a]	One-way sensitivity/scenario analysis	Source
Surgical treatment of CIN 2	€788[b] (688–888)		[18]
Surgical treatment of CIN 3	€990[b] (890–1090)		[18]
Surgical treatment of FIGO 1A	€3400[b] (3300–3500)		[18]
Hysterectomy	€4976[b]		[18]
Radical hysterectomy	€6951[b]		[18]
Treatment effectiveness LETZ & Conization	90%		[18]
Treatment effectiveness therapeutic vaccine	70%	50–100%[c]	Assumption
Treatment effectiveness hysterectomy	100%		Assumption
QALY gain for CIN 2/3	0[d]	0.007, 0.0375, 0.07[e]	[19]
QALY gain for hysterectomy	0[d]	0.0175, 0.0875, 0.175[e]	[20]
QALY gain for FIGO 1A	0[d]	0.03, 0.15, 0.30[e,f]	[19]
HR-HPV prevalence CIN 2	93.2% (79.55–100%)		[16]
HR-HPV prevalence CIN 3	98.7% (98.3–100%)		[16]
HR-HPV prevalence FIGO 1A	86.7% (61.5–100%)		[16]
HPV-16/18 prevalence CIN 2[g]	54.6% (52.2–56.8%)		[16]
HPV-16/18 prevalence CIN 3[g]	72.1% (69.8–74.4%)		[16]
HPV-16/18 prevalence FIGO 1A[g]	76.9% (69.2–84.6%)		[16]
Specificity HPV test for HPV-16/18	97.8% (95.1–99.2%)		[17]
Sensitivity HPV test for HPV-16/18	73.7% (63.7–78.7%)	80%, 90%, 95% and 100%[c]	[17]
Cost HPV test for HPV-16/18	€83.86		[21]

[a] Minimal and maximal values between parentheses are used in a probabilistic sensitivity analysis.
[b] Updated with the consumer price index to 2015 [22].
[c] Used in a one-way sensitivity analysis.
[d] In the base-case and in the probabilistic sensitivity analysis no QALY gain is assumed when a woman is successfully treated with a HPV-16/18 vaccine.
[e] In a scenario analysis 10%, 50% and 100% of the maximum QALY gain per successful vaccine treatment was used to calculate the vaccine price taking the Dutch willingness-to-pay threshold of €20,000/QALY into account. The vaccine price was further explored using different thresholds. Also a PSA was performed taking the QALY gain into account.
[f] Discounted according to Dutch PharmacoEconomic guidelines [23].
[g] HPV-16/18 prevalence is presented as a proportion of the HR-HPV prevalence.

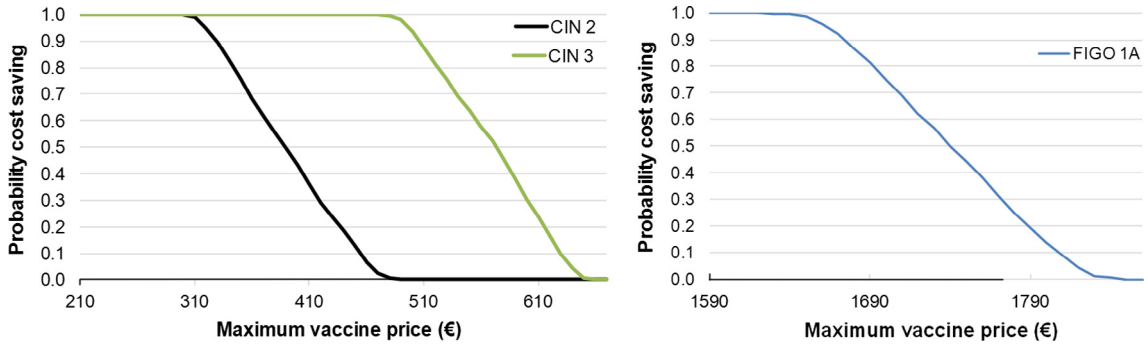

Fig. 2. Results of the PSA indicating the proportion of the simulation falling below a vaccine price threshold (€) for CIN 2, CIN 3 and FIGO 1A.

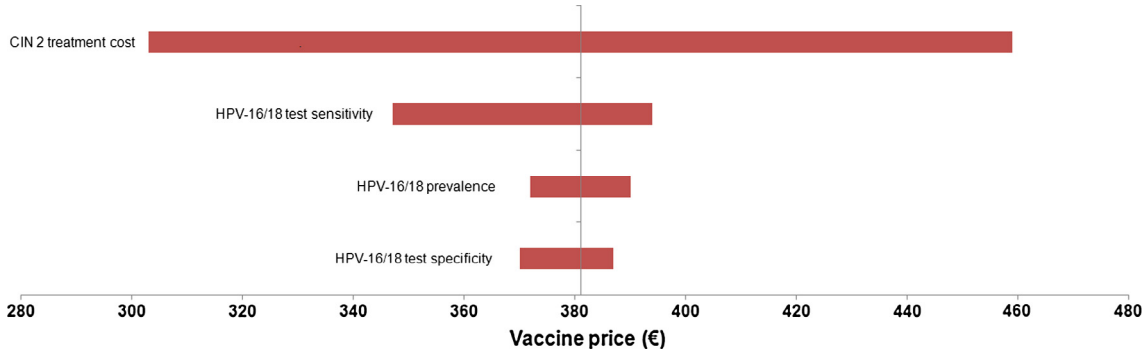

Fig. 3. Tornado diagram showing the sensitivity of the potential vaccine price for changes in parameter values.

Fig. 2 shows the results of the PSA. The figure shows the probability of cost savings per value for the vaccine price. A vaccine price below €310, €490 and €1660 will be cost saving with a likelihood of 95% for CIN 2, CIN 3 and FIGO 1A respectively.

Fig. 3 shows the results of the sensitivity analyses on the HPV-16/18 prevalence, the CIN 2 treatment costs, the sensitivity and the specificity of the HPV-test. Treatment costs for CIN 2 have the highest impact on vaccine pricing, HPV-16/18 test specificity has the

Table 2
Results of sensitivity analyses on vaccine efficacy for CIN 2, CIN 3 and FIGO 1A.

Vaccine efficacy (%)	Vaccine price CIN 2	Vaccine price CIN 3	Vaccine price FIGO 1A
50	€208	€333	€442
55	€251	€392	€753
60	€295	€450	€1063
65	€338	€509	€1374
70	€381	€568	€1684
75	€425	€627	€1995
80	€468	€685	€2305
85	€511	€744	€2616
90	€554	€803	€2926
95	€598	€862	€3237
100	€641	€921	€3547

lowest impact. In Table 2 the results of the one-way sensitivity analysis on the vaccine efficacy is presented. The potential vaccine price was very sensitive to the vaccine efficacy.

Inclusion of QALY-gains for the vaccine over the current treatments led to higher maximum vaccine prices as shown in Table 3. The maximum vaccine price almost doubles, while half of the maximal QALY gain was achieved by vaccinating instead of surgery for the €20,000/QALY threshold. The results of the PSA give the vaccine prices that have 0.95 and 0.05 probability of being cost-effective. The incremental cost-effectiveness ratio for a therapeutic vaccine costing €250 and taking maximum QALY gain into account showed to be €-2744/QALY and €-6562/QALY for CIN 2 and CIN 3, respectively.

The deterministic maximum price for the vaccine as an alternative for hysterectomy and radical hysterectomy were €3399 and €4781 respectively. As an alternative for these expensive treatments pricing of a therapeutic vaccine was found to be high compared to surgical treatment of CIN 2, CIN 3 and FIGO 1A. As shown in Table 4, the potential therapeutic vaccine price was very sensitive when taking QALY gains into account.

In the budget impact analysis, the annual cost savings were calculated for two scenarios (Table 5). A maximal achievable cost saving for a therapeutic HPV-16/18 vaccine against CIN 2&3 and CIN 2, CIN 3 and FIGO 1A was detected. In the base case, vaccine prices of €530 and €540 were breakeven points for the CIN 2&3 and CIN 2, CIN 3 and FIGO 1A scenario respectively. Decreasing cohort sizes have an enormous impact on the possible savings.

4. Discussion

Cervical (pre)cancer is still a major threat for women worldwide and new treatments are necessary to further reduce the number of cervical cancers. In this study, we examined the potential pricing of a therapeutic vaccine against HPV-16/18 positive CIN 2, CIN 3 and FIGO 1A. A conservative approach was chosen to arrive at a

Table 3
Results of probabilistic sensitivity analyses on the potential vaccine price for three cost-effectiveness thresholds. In parentheses the QALY gain per effective treatment.

		€20,000/QALY			€50,000/QALY			€80,000/QALY		
		Deterministic vaccine price	Probability cost effective		Deterministic vaccine price	Probability cost effective		Deterministic vaccine price	Probability cost effective	
	QALY savings		0.95	0.05		0.95	0.05		0.95	0.05
CIN 2	10% (0.007 QALY)	€477	€402	€544	€620	€544	€690	€764	€686	€781
	50% (0.035 QALY)	€859	€781	€930	€1576	€1492	€1648	€2294	€2201	€2368
	100% (0.07 QALY)	€1337	€1225	€1407	€2772	€2675	€2848	€4206	€4089	€4291
CIN 3	10%(0.007 QALY)	€664	€590	€733	€810	€735	€878	€955	€879	€1023
	50% (0.035 QALY)	€1052	€976	€1119	€1779	€1700	€1846	€2505	€2425	€2573
	100%(0.07 QALY)	€1537	€1459	€1604	€2990	€2906	€3058	€4443	€4351	€4513
FIGO 1A	10% (0.03 QALY)	€2654	€2577	€2746	€4109	€4023	€4205	€5564	€5466	€5663
	50% (0.15 QALY)	€6547	€6426	€6635	€13,821	€13,635	€13,931	€21,096	€20,839	€21,234
	100% (0.30 QALY)	€11,396	€11,235	€11,499	€25,945	€25,638	€26,102	€40,495	€40,039	€40,711

Table 4
Results of calculating the vaccine price as an alternative for (radical) hysterectomies taking QALY gain into account for different willingness-to-pay thresholds. In parentheses the QALY gain per effective treatment.

QALY gains	Hysterectomy			Radical hysterectomy		
	€20,000/QALY	€50,000/QALY	€80,000/QALY	€20,000/QALY	€50,000/QALY	€80,000/QALY
10% (0.0175 QALY)	€3644	€4012	€4379	€5026	€5394	€5761
50% (0.0875 QALY)	€4624	€6462	€8299	€6006	€7844	€9681
100% (0175 QALY)	€5849	€9524	€13,199	€7231	€10,906	€14,581

Table 5
Annual cost savings in the Netherlands for a series of vaccine prices and two scenarios for applying the vaccine (CIN only and FIGO 1A as well as CIN).

Vaccine price	CIN 2 & CIN 3			CIN 2, CIN 3 and FIGO 1A		
	Base-case	90% of cohort sizes	80% of cohort sizes	Base-case	90% of cohort sizes	80% of cohort sizes
€0	€637,569	€506,504	€450,226	€660,340	€524,990	€466,657
€100	€517,896	€408,193	€362,838	€539,340	€425,589	€378,301
€200	€398,223	€309,881	€275,450	€418,340	€326,187	€289,944
€300	€278,550	€211,569	€188,061	€297,340	€226,786	€201,588
€400	€158,876	€113,257	€100,673	€176,340	€127,385	€113,231
€500	€39,203	€14,945	€13,285	€55 5340	€27,984	€24,875
€600	€−80,470	€−83,366	€−74,103	€−65,660	€−71,417	€−63,482

maximum vaccine price for the therapeutic vaccine in the Netherlands. The conservative approach is reflected in the base case by making a cost comparison, as it is uncertain how many QALYs could be gained with a successful vaccination, including an extra HPV-test for detecting HPV-16/18 positive women and not taking prolonged protection against HPV-infections and cross-protections into account. A limitation of our study is the short time horizon of the study. In our study the vaccine price was based on the number CIN 2, CIN 3 and FIGO 1A detected in one year. The calculation of the vaccine price is based on equal costs and at least equal effective treatments in both branches of the model. The authors believe that taking more rounds of treatments into account would make the estimation of the vaccine price unnecessarily complex, whereas this simplification does not invalidate our model.

Notably, the deterministic maximum vaccine price is lower than the average treatment cost for the stages investigated due to retreated false-positive diagnosed women, costs of an additional HPV test, re-treated women who would normally be treated by hysterectomy and are ineffectively treated by the vaccine and retreatment costs of unsuccessfully vaccinated HPV-16/18 positive women. Obviously, a type-specific HPV-test for HPV-16/18 identification is essential for treating women with a therapeutic HPV-16/18 vaccine effectively. The maximum vaccine price is very sensitive to the costs of the additional HPV test. Replacing the primary HR-HPV-test in the cervical cancer screening with a type-specific test would increase the acceptable maximum vaccine price drastically as these costs would no longer be needed in the vaccination strategy. However, it will obviously affect the cost-effectiveness of screening as the ICER of screening is sensitive for the cost of the primary HPV-test [19]. Another solution to the problem of requiring an additional type-specific HPV-test is to broaden the spectrum of a therapeutic vaccine against multiple HR-HPV-types, as is being done for the prophylactic vaccines.

There are considerable uncertainty of the vaccine price for CIN 2, CIN 3 and FIGO 1A as shown in our PSA. Despite the uncertainty, a vaccine price around €300 will most likely be cost saving for all (pre)-malignant cervical lesions and annually a possible 0.28 million euro can be saved when the vaccine is used against CIN 2 and CIN 3. When the vaccine is also used against FIGO 1A savings can possibly be 0.30 million euro. This saving is of course very sensitive to the total number of HVP-16/18 positive CIN 2, CIN 3 and FIGO 1A. When the incidence and prevalence of these lesions drops, the possible monetary gains also drop.

Women diagnosed with abnormal cervical cells experience a reduced QOL. This reduction is mostly due to the fear of having or getting cancer and not necessarily due to the surgical treatment of abnormal cells. A study in the Netherlands on the QOL of women referred for colposcopy showed that the reduction in QOL is likely irrespective of the CIN-grade [8]. It is likely though, that treating women with a vaccine instead of surgically decreases the QOL loss of these women. Already a small gain in QALYs in comparison to the current treatments leads to a big increase in the maximum vaccine price. Further research into the QOL of (pre)-malignant lesions is needed in order to justify inclusion of exact gains in QOL by the vaccine.

Besides a possible reduction in QOL using a therapeutic HPV-vaccine is likely beneficial when it comes to pre-term births. Studies have shown that excision of the cervix causes an increased risk of pre-term pregnancies. The risk of a pre-term pregnancy after excision is not restricted to the first birth after excision, but the woman may have an increased risk throughout her reproductive years [27,28].

Vaccine efficacy of therapeutic HPV vaccine is only established in small groups. Our sensitivity analysis on the vaccine efficacy showed that this parameter has a big impact on the maximum vaccine price for CIN 2, CIN 3 and FIGO1A. A low vaccine efficacy leads to more women who need to be retreated, reducing the potential vaccine price.

The modeled type-specific HPV-test has a far from ideal sensitivity. Therefore, a sensitivity analysis was performed on the sensitivity of the test. A poor sensitivity leads to high numbers of undetected HPV-16/18 positive women, this leads to relatively high numbers of women tested for HPV-16/18 per vaccinated women, decreasing the maximum vaccine price. A type-specific test with a better sensitivity will lead to more women detected and vaccinated HPV-16/18 CIN 2, CIN 3 or FIGO 1A, therefore reducing the number of true positive women treated surgically. However, a type-specific HPV-test with a higher sensitivity will only slightly increase the vaccine price, but it can offer more women a choice between vaccination and conventional treatments.

Hysterectomies are major procedures leading to a decreased QOL. If therapeutic vaccines can be an alternative for hysterectomies, major cost savings and QALY gains can be expected, allowing a threshold vaccine price at €3399 for this setting. The inclusion of QALYs into the calculation of the vaccine price leads to a profound increase of the vaccine price.

5. Conclusion

In this study, the pricing of a potential therapeutic HPV vaccine against HPV-16/18-positive CIN 2, CIN 3 and FIGO stage 1A cervical cancer was explored in the Dutch setting. If no gain in QALYs was assumed, maximum vaccine prices resulted of €381, €568 and €1697 for CIN 2, CIN 3 and FIGO 1A, respectively. The PSA showed vaccine pricing below €310, €490 and €1660 will be cost saving at 95% likelihood or more. Taking QALY gains into account increases the maximum vaccine price, although for CIN 2 and CIN 3 only small gains in QALYs may be reasonable. The vaccine pricing is also sensitive to the inclusion of a type-specific HPV-test. Treating CIN 2, CIN 3 and FIGO 1A with a therapeutic vaccine costing €300, can save about 0.30 million euro in the Netherlands annually.

Conflict of interest

Prof Maarten J. Postma received grants and honoraria from various pharmaceutical companies, inclusive those developing, producing and marketing (prophylactic HPV) vaccines. Also, Prof Postma holds stocks in Ingress Health (Rotterdam, Netherlands/Wismar, Germany). J. Luttjeboer MSc has no conflicts of interest to report. Prof Toos Daemen is founder of ViciniVax, a spin-off from the UMCG developing cancer vaccines.

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