Vaccine 27 (2009) 5111–5119

Contents lists available at ScienceDirect

Vaccine

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

How to screen for cervical cancer after HPV16/18 vaccination in The Netherlands

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ARTICLE INFO

Article history:
Received 12 December 2008
Received in revised form 5 June 2009
Accepted 10 June 2009
Available online 28 June 2009

Keywords:
Simulation model
Cervical cancer screening
HPV vaccination

ABSTRACT

In The Netherlands, vaccination against HPV16/18 has been recommended for all 12-year-old girls. Because screening of vaccinated women remains important, we evaluated the model-based cost-effectiveness of cervical cancer screening strategies. We considered cytology and the HPV DNA test as primary screening instrument, varied the number of screening rounds from 7 to 4, and set the screening starting age at 30 and 35 years. Our model predicted reductions in cervical cancer mortality between 60 and 81% (from 199 deaths to 37–79) when adding screening to vaccination (assumptions for vaccination: 95% efficacy, 100% compliance, lifelong protection). Screening 5 times with HPV DNA (€11,133/QALY) or 7 times with cytology (€17,627/QALY) were scenarios with comparable costs and effects and incremental cost-effectiveness ratios below the threshold in The Netherlands (€20,000 per QALY).

1. Introduction

The possibilities for cervical cancer prevention have improved considerably since the recognition that infection with high-risk human papillomavirus (hrHPV) is the necessary cause of cervical cancer [1]. The most important development is the recent availability of prophylactic vaccines that protect against infection of HPV types 16 and 18 [2,3].

Because HPV vaccination is costly and health systems and resources differ among countries, country-specific differences are expected in the way HPV vaccination will be implemented. In The Netherlands, The Dutch Health Council has recently recommended universal vaccination of all 12-year-old girls to be carried out via the national immunization program [4].

Although HPV vaccination can be expected to substantially reduce cervical cancer incidence and mortality [5–7], it is generally agreed upon that cervical cancer screening will need to continue even for vaccinated women. The two available vaccines have shown to be highly effective against cervical intraepithelial neoplasia grade 2/3 (CIN2/3) and are expected to prevent about 70% of the cervical cancer cases. For the remaining 30%, screening remains necessary. Moreover, from the available data, it cannot be excluded that the immunity induced by the vaccine starts waning after 10 or 20 years.

Though there is consensus that cervical cancer screening remains important in a vaccinated population, the best way to screen women after vaccination still needs to be determined. In The Netherlands, women are invited for cytological screening between 30 and 60 years of age with five year intervals. This strategy may not optimize the allocation of health resources when women are vaccinated and the risk of CIN2/3 and cancer has decreased. Besides, the task of cytological reading may become more difficult when the positive predictive value of testing decreases because of lower disease prevalence [8,9].

The HPV DNA test has been suggested as an alternative primary screening instrument. Its performance in screening has been compared to cytology in several studies [10,11], including a number of large population-based screening trials [12–14]. These studies have shown that HPV testing has a higher sensitivity with lower variability than cytology for detecting high-grade lesions, but a slightly lower specificity [10,11]. Therefore, there is a concern that HPV DNA screening may lead to a large number of referrals for colposcopy. In particular in younger women (<30 years), the HPV DNA test may detect lesions that would also have regressed spontaneously [14].

We explored the best way to screen women after vaccination by evaluating the cost-effectiveness of different cervical cancer screening strategies when added to HPV16/18 vaccination. We considered cytology and the HPV DNA test as primary screening instrument, varied the number of screening rounds from 7 to 4, and set the screening starting age at 30 and 35 years. For this purpose, a Dutch Markov simulation model was used that describes the relation between fourteen high-risk HPV types and cervical disease [15]. The most cost-effective screening scenarios for The Netherlands were identified. In addition, the effect of varying assumptions with respect to the compliance to vaccination and screening and the accuracies of cytology and HPV DNA testing was explored.

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doi:10.1016/j.vaccine.2009.06.043

2. Material and methods

2.1. Model

We used a simulation model that describes the natural history of a high-risk HPV infection and the progression into cervical abnormalities and cervical cancer. The model and the estimation of the model parameters have been described previously [15]. The model predictions of the incidence of cervical cancer, the detection of high-grade CIN and the prevalence of high-risk HPV in the current situation of cervical cancer screening agree well with Dutch registry data (www.ikcnet.nl) and population-based figures [12]. The model simulates health trajectories of a cohort of 12-year-old girls until they are deceased. The pre-invasive part of the model consists of 14 parallel Markov chains corresponding to an infection with HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. This allows the occurrence of any multiple infection as part of the model. The model assumes that infection with one of these high-risk HPV types is a prerequisite for the development of CIN2/3 and cervical cancer. Women in the model are categorized as either healthy (Table 1; "No HPV Infection"), infected with high-risk HPV (Table 1; "CIN0, HPV+"), infected with high-risk HPV and having developed a CIN lesion (Table 1; "CIN1-3, HPV+"), or having developed an invasive lesion (Table 1; "FIGO stage 1/2+"). In addition, there is a separate category of women who have developed a CIN1 lesion without a high-risk HPV infection (Table 1; "CIN1, HPV−"). Until state CIN3, spontaneous clearance of an HPV infection and regression of cervical lesions is possible. After HPV clearance, women are again susceptible for infection. The probability to progress from state CIN3 to cervical cancer is assumed to increase with the duration of CIN3 [16]. The model parameters and the data used for their estimation are shown in Table 1. The HPV type-specific incidences and the development of pre-invasive lesions were estimated from data collected in a large screening trial [8,12] and clinical cohort studies [17–20]. Progression probabilities from CIN1 to CIN3 and from CIN3 to cancer were type-specific [21–23]. The progression rate from HPV infection to CIN3 was age-dependent and assumed to be 2.5-fold higher above age 30 than at young age [24]. The progression probabilities from CIN3 to cervical cancer were calibrated on registry data (www.ikcnet.nl) and on historical data [25]. The mean duration from CIN3 to micro-invasive cervical cancer was set at 14 years [26]. To accurately model this long duration, two intermediate tunnel states were included in the model (Persistent CIN3 and Non-regressive CIN3) [27]. The progression between cervical cancer states was estimated from hospital data on clinical cancer cases [28].

2.2. Vaccination

We assumed for the base-case scenario that 100% of all 12-year-old girls would receive the 3 vaccination doses. Furthermore, we assumed a vaccine efficacy of 95% against incident infection with types 16 and 18 [2,42–45] and lifelong protection of the vaccine.

We chose these optimistic assumptions of 100% vaccination compliance and lifelong protection in order to have a conservative estimate of the benefits and costs of screening in a vaccinated population.

2.3. Screening instruments

The two screening instruments considered were cytology and the HPV DNA test. The performance of cytology was estimated from a large Dutch screening trial [12] in which cytological follow-up was based on the conventional Papanicolaou (Pap) smear. Cervical smears were read according to the CISOE-A classification [46], and interpreted as normal (Pap1), borderline or mild dyskaryosis (Pap2 or Pap3a1), and moderate dyskaryosis or worse (>Pap3a2). A translation into the Bethesda 2001 classification is available [46]. The HPV DNA test used in the screening trial was the high-risk GP5+6+ PCR-EIA test [37,47]. The performance of this test is comparable to the performance of the HCII test [11]. Notably, the sensitivity and specificity set for the HPV test (Table 1) refer to the sensitivity and specificity for detecting presence of the virus in the cervix with a clinically validated test [38,48].

2.4. Scenarios for cervical screening

Twenty screening scenarios were evaluated, differing in the choice of screening instrument(s), the length of the screening interval, and the starting age of screening (see Table 2). In all screening scenarios, women were considered vaccinated. With respect to screening instruments, we considered: (1) cytological screening only, (2) cytological screening followed by immediate HPV triage for women with borderline/mild dyskaryosis, (3) HPV DNA screening with immediate cytological triage for HPV positive women, and (4) combined cytology and HPV DNA screening. In cytological screening only (1), a woman is referred for colposcopy if the cytological result is at least moderate dyskaryosis. If the cytological result is borderline/mild dyskaryosis, a woman is retested with cytology after 6 and 18 months and referred for colposcopy if cytology is abnormal. In cytological screening with HPV DNA triage (2), a woman is referred for colposcopy if the cytological result is at least moderate dyskaryosis or if the cytological result is borderline/mild dyskaryosis and the sample is HPV positive. In HPV DNA screening (3), a woman is referred for colposcopy if the sample is HPV positive and cytologically abnormal. If the sample is HPV positive and cytologically normal, a woman is retested with cytology after 6 and 18 months and referred for colposcopy if cytology is abnormal. In combined cytology and HPV DNA screening (4), a woman is referred for colposcopy if the cytological result is at least moderate dyskaryosis or if the sample is HPV positive and cytologically borderline/mild dyskaryosis. If the sample is HPV positive and cytologically normal or if the sample is HPV negative and the cytological result is borderline/mild dyskaryosis, a woman is retested with cytology after 6 and 18 months and referred for colposcopy if cytology is abnormal. For each choice of screening instrument(s), we set the number of screening rounds to 7, 6, 5, and 4 (corresponding to screening intervals of 5, 6, 7.5 and 10 years, respectively). The starting age was set at 30 years and screening was continued until age 60 years. In addition, we evaluated the effect of delaying the starting age of screening to 35 years in combination with five-yearly screening between 35 and 60 years.

2.5. Costs and quality-adjusted life-years

The cost-effectiveness evaluation was carried out from a societal perspective, including both direct health care costs as well as the indirect costs of productivity loss and travel expenses. The costs per unit of health care resource utilization are presented in Table 1. All costs were indexed at year 2006. The costs of screening and treatment were published previously and were updated to 2006 using the consumer price index [40,41,49]. The utilities for different health states (Table 1) were based on international publications [6,39]. Following the Dutch guidelines, the discounting rate per year for costs and health effects were set at 4 and 1.5%, respectively. Discounting started at the age of vaccination (12 years old).

2.6. Analyses

Model predictions were obtained by simulating the health trajectories of a cohort of 5,000,000 women from age 12 until age 100. Results were divided by 50 to obtain predictions for a cohort

Table 1
Model parameters, screening and vaccine characteristics, quality of life and costs.

Natural history parameters		6 month transition probability[a]	References
HPV Incidence (No HPV Infection to CIN0, HPV+)	Type 16	0.000–0.040	[8]
	Type 18	0.000–0.009	
	Type 31	0.000–0.016	
	Type 33	0.000–0.005	
	Type 45	0.000–0.007	
	Other types	0.000–0.009	
Clearance of infection (CIN0, HPV+ to No HPV infection)	All types	0.39	[29]
Progression from HPV+ to CIN1 (CIN0, HPV+ to CIN1, HPV+)	All types		[30]
	<30 years	0.1–0.10	
	≥30 years	0.10	
Progression from CIN1 to CIN2 (CIN1, HPV+ to CIN2, HPV+)	Type 16	0.40	[21,31]
	Type 18/33	0.25	
	Type 31	0.15	
	Other types	0.10	
Progression from CIN2 to CIN3 (CIN2, HPV+ to CIN3, HPV+)	Type 16	0.40	[21,31]
	Type 18/33	0.25	
	Type 31	0.15	
	Other types	0.10	
Direct progression from CIN0 to CIN3 (CIN0, HPV+ to CIN3, HPV+)	Type 16		[32,33]
	<30 years	0.002–0.02	
	≥30 years	0.02	
	Type 18/31/33		
	<30 years	0.0005–0.005	
	≥30 years	0.005	
	Other types	0	
Regression of HPV-positive CIN1 or 2 (CIN1, HPV+ to No HPV Infection) (CIN2, HPV+ to No HPV Infection)	All types	0.25	[17,19,34]
Regression of HPV-positive CIN3 (CIN3, HPV+ to No HPV Infection)	All types	0.30	[17,19,34]
Probability of HPV negative lesions (No HPV Infection to CIN1, HPV-)	All types	0.003	[12]
Regression of HPV-negative lesions (CIN1, HPV- to No HPV Infection)	All types	0.60	[17]
Progression of CIN3 (CIN3, HPV+ to Persistent CIN3)	Type 16	0.20	[22,35]
	Type 18/45	0.40	
	Other types	0.10	
Progression of persistent CIN3 (Persistent CIN3 to Non-regressive CIN3)	All types	0.046	[22,35]
Progression to cancer (Non-regressive CIN3 to FIGO stage 1)	All types	0.0714	[22,35]
Regression of persistent CIN3 (Persistent CIN3 to No HPV Infection)	All types	0.0268	[22,35]
Progression of cancer (FIGO stage 1 to FIGO stage 2+)		0.048	[28]
Probability of detecting FIGO stage 1		0.032	
Probability of detecting FIGO stage 2+		0.30	

Screening and test characteristics	Parameter values	References
Proportion of women who never attend screening	10%	[36]
Compliance per screening round	80%	[12]
Positive smear rate in		
CIN0	0.015	[12]
CIN1	0.40	
CIN2	0.50	
CIN3	0.75	
HPV testing by GP5+/6+		
Analytical sensitivity	94%	[37,38]
Analytical specificity	100%	

Baseline vaccine characteristics	Parameter values	References
Vaccine efficacy	95%	
Age at vaccination	12 years	
Vaccine coverage	100%	

Health state	Duration (years)	Quality of life estimate	
Abnormal smear/HPV positive test	0.5	0.995	[6,39]
CIN1 treatment	0.5	0.97	
CIN2/3 treatment	0.5	0.93	
CIN2/3 residual	0.5	0.93	
Detection of FIGO 1	0.5	0.65	
Detection of FIGO 2+	0.5	0.55	
Follow-up FIGO1	4.5	0.97	
Follow-up FIGO2+	4.5	0.85	

Table 1 (*Continued*)

Procedures		Costs (€) (2006)[b]	References
Conventional cytological screening			[40]
First smear		50.31	
Repeat smear		54.11	
Administrative costs		7.70	
HPV DNA screening			[40]
First smear		62.50	
Administrative costs		7.70	
Vaccination			
Vaccine 3 doses (€125 per dose and €6 administration costs)		393.00	
Booster dose (€125 per dose and €6 delivery costs)		131.00	
Administrative costs (full vaccination course)		22.50	
Diagnosis, treatment, follow-up			[40,41]
CIN0		338.70	
CIN1	≤50 years	1,450.50	
CIN2	50–70 years	1,680.20	
CIN3	≥70 years	1,827.10	
FIGO stage 1		9,046.97	
FIGO stage 2+		10,659.41	
Palliative care		42,428	
		30,242	
		12,873	

[a] The reported ranges reflect variation with age.
[b] The reported cost prices include indirect costs.

of 100,000 women. This size roughly corresponds to the age-cohort size of girls in The Netherlands. For each scenario, we determined the number of detected CIN2/3 lesions, the number of cervical cancer cases, the number of cervical cancer deaths, the total (undiscounted and discounted) costs, and quality-adjusted life-years (QALYs). We computed the incremental cost effectiveness ratio (ICER) of each screening scenario when added to vaccination by taking the ratio of the difference in discounted costs and the difference in discounted QALYs. Screening scenarios were also compared in an incremental manner. For that purpose, scenarios were ordered according to increasing costs and, if costs were equal, increasing QALYs. Firstly, we identified the dominated scenarios, that is, scenarios for which another scenario (or a weighed combination of other scenarios) exists that achieves more QALYs at equal costs. These scenarios were removed from the incremental comparison. Subsequently, the ICERs between successive non-dominated scenarios were computed. The ICER of a non-dominated scenario reflects the additional cost that should be invested in order to gain an additional QALY compared to the most effective cheaper (non-dominated) alternative. In The Netherlands, a preventive intervention is considered cost-effective if this additional cost per QALY is less than €20,000. For all screening scenarios, we plotted

Table 2
The number of CIN2/3 lesions detected through screening, lifetime number of cervical cancer cases and cervical cancer deaths per 100,000 women, undiscounted QALYs and lifetime costs per woman. The assumptions for HPV16/18 vaccination are 95% efficacy, 100% compliance and lifelong protection.

	CIN2/3	Cervical cancer cases	Cervical cancer deaths	QALY	Costs (€)
HPV16/18 vaccination	0	533	199	68.7078	559
HPV16/18 vaccination + cytological screening					
Screening 7 times between 30 and 60 years (current programme, 5 years interval)	1595	178	53	68.7465	747
Screening 6 times between 30 and 60 years	1452	199	57	68.7451	710
Screening 5 times between 30 and 60 years	1282	218	65	68.7431	673
Screening 4 times between 30 and 60 years	1113	252	77	68.7394	639
Screening 6 times between 35 and 60 years	1180	229	64	68.7419	703
HPV16/18 vaccination + cytological screening + HPV DNA triage					
Screening 7 times between 30 and 60 years	1604	177	48	68.7479	749
Screening 6 times between 30 and 60 years	1443	191	55	68.7458	711
Screening 5 times between 30 and 60 years	1306	215	63	68.7436	675
Screening 4 times between 30 and 60 years	1120	249	79	68.7394	641
Screening 6 times between 35 and 60 years	1196	229	64	68.7425	704
HPV16/18 vaccination + HPV DNA screening + cytological triage					
Screening 7 times between 30 and 60 years	2254	134	39	68.7500	837
Screening 6 times between 30 and 60 years	2106	143	41	68.7496	785
Screening 5 times between 30 and 60 years	1889	158	46	68.7482	735
Screening 4 times between 30 and 60 years	1668	184	57	68.7453	687
Screening 6 times between 35 and 60 years	1632	186	52	68.7450	766
HPV16/18 vaccination + cytological and HPV DNA screening					
Screening 7 times between 30 and 60 years	2319	127	37	68.7503	934
Screening 6 times between 30 and 60 years	2153	136	40	68.4970	868
Screening 5 times between 30 and 60 years	1951	148	42	68.7489	803
Screening 4 times between 30 and 60 years	1713	174	50	68.7469	741
Screening 6 times between 35 and 60 years	1678	178	50	68.7457	848

the discounted costs per woman against the discounted QALYs in a cost-effectiveness plane and computed the cost-effectiveness frontier, that is, the curve connecting non-dominated scenarios. Note that dominated scenarios lie below the cost-effectiveness frontier on the cost-effectiveness plane.

2.7. Sensitivity analyses

We studied the robustness of the cost-effectiveness of the different screening scenarios with regard to changes in the compliance to vaccination (from 100 to 85%: analysis A), the sensitivity of cytology (from 75 to 65% for CIN3: analysis B), the analytical sensitivity of the HPV DNA test (from 94 to 90%: analysis C), and the attendance per screening round (from 80 to 70%: analysis D). We also investigated the effect of increasing the proportion of women never attending screening (from 10 to 20%) in combination with a low attendance per screening round (from 80 to 70%) (analysis E). Furthermore, under the assumption of 85% vaccination compliance, we studied the cost-effectiveness when screening attendance was lower in vaccinated than in non-vaccinated women (analysis F: 20 and 10% of the vaccinated and non-vaccinated women, respectively, never attend screening; the attendance per round is 70 and 80% in vaccinated and non-vaccinated women, respectively). Likewise, we studied the cost-effectiveness when screening attendance was lower in non-vaccinated than in vaccinated women (analysis G: 20% and 10% of the non-vaccinated and vaccinated women, respectively, never attend screening; the attendance per round is 70 and 80% in non-vaccinated and vaccinated women, respectively). We also studied the effect of decreasing and increasing the costs of HPV DNA testing with €5 (analyses H and I).

3. Results

3.1. Health effects of screening in addition to vaccination

The health effects of adding screening to vaccination are shown in Table 2. In the absence of screening, the model predicts 533 cases of cervical cancer and 199 cervical cancer deaths for a cohort of 100,000 women. Compared to vaccination only, our models with both vaccination and screening predict reductions in cervical cancer cases between 53 and 76% (from 533 to 127–252 cases) and reductions in cervical cancer deaths between 60 and 81% (from 199 to 37–77 deaths). Cytological screening with HPV DNA triage and cytological screening with repeat cytological testing give similar numbers of CIN2/3 lesions, cervical cancer cases and cervical cancer deaths. Analogously, HPV DNA screening with cytological triage for HPV positive women and combined cytology and HPV DNA testing (combination testing) give similar health outcomes. Screening scenarios that include HPV DNA testing as (one of the) primary screening instrument(s) are more effective in preventing cervical cancer than scenarios of cytological screening. In order to achieve about the same number of cervical cancer cases and deaths, HPV DNA screening requires two screening rounds less than cytological screening.

3.2. The costs of screening in addition to vaccination

Table 2 also shows the undiscounted costs per woman of adding screening to vaccination. The model predicts a total lifetime cost of €559 per woman if every girl is vaccinated at age twelve but not screened. If the birth cohort size is 100,000 women (current situation in The Netherlands) and the population size is stable, the lifetime costs of €559 per woman can be translated into national yearly costs of €55.9 million. Screening women in addition to vaccination leads to an increase in costs from €55.9 million per year to €63.9–€93.4 million depending on the screening strategy.

3.3. The cost-effectiveness of screening in addition to vaccination

Table 3 shows the discounted QALYs and costs of screening in addition to vaccination.

Compared to vaccination only, the ICERs of the screening scenarios range between €2667 and €7143 per QALY gained. These values lie far below the cost-effectiveness threshold of €20,000/QALY for preventive interventions in The Netherlands. This indicates that according to the Dutch guidelines, any screening scenario evaluated in this study is cost-effective when compared to HPV16/18 vaccination only.

For the incremental analysis, in Table 3, scenarios are ordered according to increasing costs and, if costs are equal, increasing

Table 3
The discounted costs and QALYs per woman for a scenario in which women are vaccinated against HPV16/18 (95% efficacy, 100% compliance, lifelong protection) but not screened and 20 screening scenarios in which women are vaccinated and screened. The scenarios are ordered according to increasing costs and QALYs. For each scenario, the table gives the incremental cost-effectiveness ratio with respect to vaccination only (ICER 1) and the incremental cost-effectiveness ratio (ICER 2) with respect to the nearest cheaper scenario that is not dominated. Non-dominated scenarios are indicated in bold.

Screening and triage modality	Frequency and age interval	Disc costs (€)	Disc QALY	ICER 1	ICER 2
HPV16/18 vaccination		**448**	**42,6937**	Reference	
HPV16/18 vaccination + one of the subsequent screening strategies					
Cytological screening	**4 times, 30–60**	**484**	**42.7072**	**2667**	**2667**
Cytological screening + HPV DNA triage	4 times, 30–60	485	42.7072	2730	Dominated
Cytological screening	6 times, 35–60	494	42,7081	3194	Dominated
Cytological screening	**5 times, 30–60**	**494**	**42.7089**	**3026**	**5882**
Cytological screening + HPV DNA triage	6 times, 35–60	494	42,7084	3155	Dominated
Cytological screening + HPV DNA triage	**5 times, 30–60**	**496**	**42.7091**	**3107**	**9236**
HPV DNA screening + cytological triage	4 times, 30–60	503	42.7097	3438	Dominated
Cytological screening	6 times, 30–60	506	42.7097	3625	Dominated
Cytological screening + HPV DNA triage	6 times, 30–60	507	42.7100	3631	Dominated
HPV DNA screening + cytological triage	6 times, 35–60	513	42,7094	4140	Dominated
Cytological screening	7 times, 30–60	517	42.7103	4157	Dominated
HPV DNA screening + cytological triage	**5 times, 30-60**	**517**	**42.7110**	**3988**	**11,133**
Cytological screening + HPV DNA triage	7 times, 30–60	519	42.7110	4100	Dominated
Cytological and HPV DNA screening	4 times, 30–60	520	42.7104	4285	Dominated
HPV DNA screening + cytological triage	**6 times, 30–60**	**533**	**42.7116**	**4749**	**26,667**
Cytological and HPV DNA screening	6 times, 35–60	534	42,7097	5405	Dominated
Cytological and HPV DNA screening	5 times, 30–60	539	42.7113	5155	Dominated
HPV DNA screening + cytological triage	**7 times, 30–60**	**548**	**42.7117**	**5556**	**150,000**
Cytological and HPV DNA screening	6 times, 30–60	559	42.7116	6176	Dominated
Cytological and HPV DNA screening	**7 times, 30–60**	**578**	**42.7119**	**7143**	**150,000**

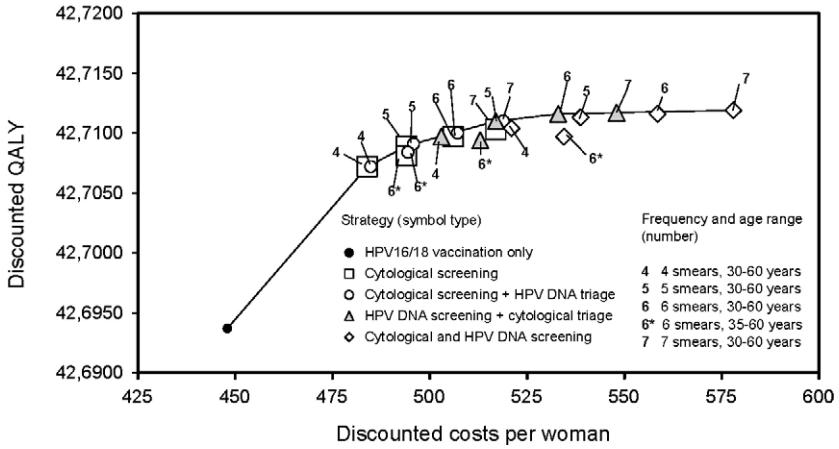

Fig. 1. Cost-effectiveness plane showing the discounted QALYs and costs of a scenario in which women are vaccinated against HPV16/18 (95% efficacy, 100% compliance) but not screened and 20 screening scenarios in which women are vaccinated and screened. The black line represents the cost-effectiveness frontier that connects non-dominated scenarios.

QALYs. The discounted ICER of each non-dominated scenario relative to the most effective cheaper (non-dominated) scenario is given. Non-dominated scenarios are shown in bold face. In addition, in Fig. 1, the discounted QALYs and costs of the screening scenarios are depicted in a cost-effectiveness plane. The figure also shows the cost-effectiveness frontier that connects non-dominated scenarios.

Using €20,000 per QALY as the threshold for cost-effectiveness, 5 times HPV DNA screening between 30 and 60 years is selected as a cost-effective screening scenario (€11,133 per QALY). Costs and effects of this strategy are, however, close to those of 7 times cytological screening (with and without HPV DNA triage). This can also be seen in Fig. 1 where these scenarios largely overlap.

If one is not willing to spend more than €10,000 per QALY, alternative cost-effective screening scenarios are 5 times cytological screening between 30 and 60 years (€5882 per QALY) and 5 times cytological screening with HPV DNA triage between 30 and 60 years (€9236 per QALY).

Delaying the screening age from 30 to 35 is not cost-effective. In Table 3, the scenarios with delayed screening starting age are less effective than other equally costly scenarios and therefore lie below the cost-effectiveness frontier in Fig. 1. Combined cytology and HPV DNA testing is not cost-effective either. Although combination testing is slightly more effective then HPV DNA screening, it is also much more expensive.

Discount rates in The Netherlands differ from those in other countries. Therefore, we investigated whether the use of 3% discount rates for both costs and effects, such as used in the US, would have affected our cost-effectiveness results for The Netherlands. The ordering of the screening scenarios remained the same as presented above. The ICER of 5 times HPV DNA screening was €32,000 per QALY which lies below the cost-effectiveness threshold that is used in the US ($50,000 or €35,000 per QALY).

3.4. Sensitivity analyses

For all screening scenarios, we studied the impact of changes in the model parameters on discounted QALYs and discounted costs. In Fig. 2A and B the results are shown for the scenarios of cytological screening with cytological follow-up and for the scenarios of HPV DNA screening with cytological triage. The lines that correspond to the different screening scenarios are approximately parallel. The same pattern was observed for the remaining screening scenarios that are not depicted in the figure. This means that changing a model parameter affects discounted QALYs and costs in a similar way for all screening scenarios. Therefore, the orderings of the screening scenarios on the basis of both QALYs and costs are robust against changes in model parameters.

However, the absolute value of the ICER may vary. Therefore, we also studied the impact of changes in the model parameters on the cost-effectiveness of screening. Except for analysis I (increased cost of HPV testing), either 5 or 6 times HPV DNA screening is cost-effective in all analyses. This means that the ICERs of these scenarios lie below €20,000/QALY. Compared to vaccination only, the cost-effectiveness varies between €2200 and €4300 per QALY for 5 times HPV DNA and between €2700 and €5100 per QALY for 6 times HPV DNA. In the incremental analysis, 5 times HPV DNA screening is cost-effective in analysis B (low sensitivity of cytology, €15,000/QALY), analysis E (high proportion of women never attending screening in combination with a low attendance per round, €8500/QALY), and analysis H (low cost of HPV test, €10,500/QALY). The scenario of 6 times HPV DNA screening is cost-effective in all analyses in which the vaccination compliance is 85% (A: €17,500/QALY, F: €16,000/QALY and G: €16,500/QALY) as well as in analysis C with a low sensitivity of the HPV DNA test (C: €19,000/QALY) and analysis D with a low attendance per screening round (D: €16,500/QALY). For most sensitivity analyses, costs and effects of 5 times HPV DNA screening are close to those of 7 times cytological screening. However, if the sensitivity of cytology is 65% (analysis B), when a high proportion of women never attend screening (analysis E), or when the cost of the HPV DNA test is low (analyses H), 7 times cytological screening is not cost-effective. When the cost of the HPV DNA test is high (analyses I), HPV DNA screening is not cost-effective, whereas 7 times cytological screening is cost-effective with or without HPV DNA triage.

4. Discussion

To optimize cervical cancer screening for girls vaccinated against HPV16/18, we have evaluated the cost-effectiveness of twenty different screening scenarios by means of simulation modeling. All screening scenarios were cost-effective when compared to vaccination only (ICERs between €2500 and €7000 per QALY). An incremental analysis identified 5 times HPV DNA screening with cytological triage or 7 times cytological screening as cost-effective screening scenarios. Delaying the starting age of (five-yearly) screening from 30 to 35 years old was not cost-effective and neither was combined HPV DNA and cytology testing. Although combination testing was slightly more effective than HPV DNA screening with cytological triage for HPV positive women, it was also much more expensive.

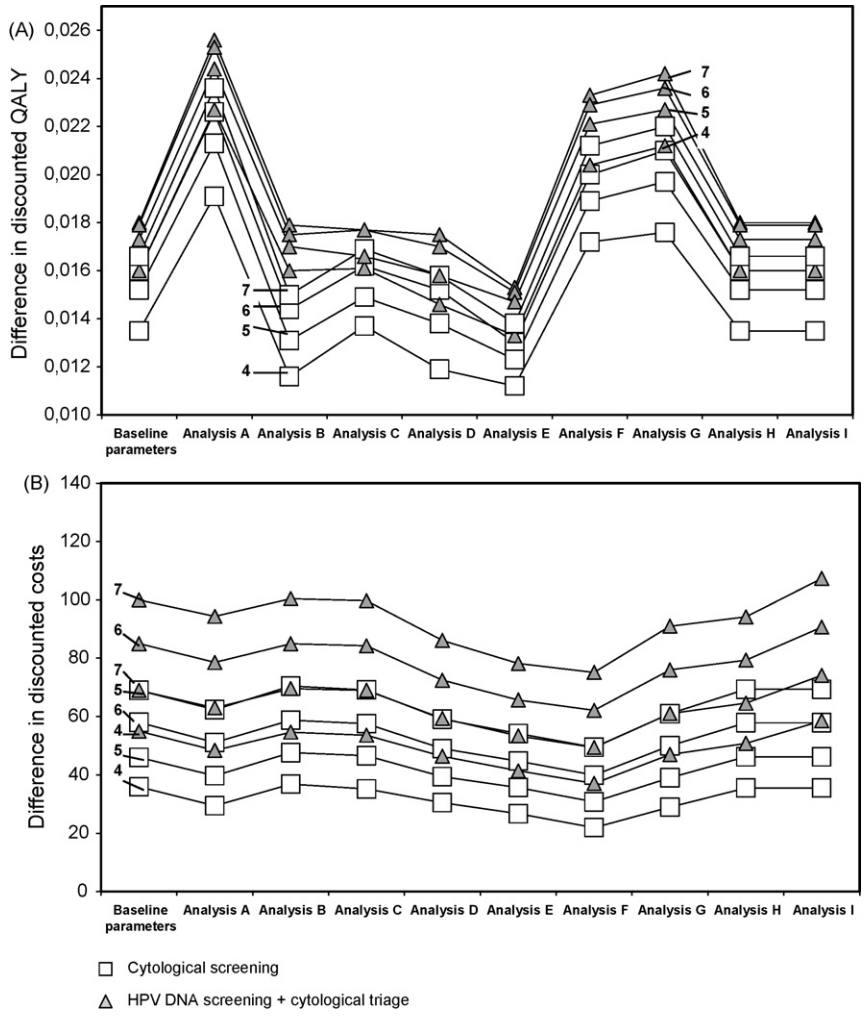

Fig. 2. The difference in discounted QALYs and discounted costs compared to vaccination only for the model with baseline parameter values and the nine sensitivity analyses A–I. Analysis A: compliance to vaccination from 100 to 85%, analysis B: sensitivity of cytology from 75 to 65% in CIN3, analysis C: sensitivity of the HPV DNA test from 94 to 90%, analysis D: attendance per screening round from 80 to 70%, analysis E: the proportion of women who never attend screening from 10 to 20% and attendance per screening round from 80 to 70%, analysis F: 85% compliance to vaccination, among vaccinated women 20% never attends screening and attendance per round is 70%, analysis G: 85% compliance to vaccination, among non-vaccinated women 20% never attends screening and attendance per round is 70%, analysis H: cost of HPV DNA testing −€5, and analysis I: cost of HPV DNA testing +€5.

To choose between 5 times HPV DNA screening and 7 times cytological screening, several arguments are important to mention in addition to our cost-effectiveness results. A clear advantage of 7 times cytology is that this is the current screening strategy in The Netherlands. However, an advantage of HPV DNA screening is the possibility to lengthen the screening interval and in that way to decrease the total number of cervical smears. Another issue that should be taken into account is the expectation that the positive predictive value of cervical screening will be reduced in vaccinated populations because fewer women will develop high-grade cervical lesions. This decrease in positive predictive value plays a role in cytological screening as well as in HPV DNA screening. However, it has been indicated that vaccination has a larger impact on cytological screening than on HPV DNA screening because of an expected decrease in the performance of cytological reading [50]. The reasoning is that the reading performance for cytological slides will deteriorate if the occurrence of an abnormal smear becomes less common. Finally, it has been shown that the sensitivity of cytology is highly variable over countries and laboratories [11,51]. An important reason for this is that cytology is a subjective test that is labour intensive. Therefore, in countries without quality assurance, it is virtually impossible to maintain a high clinical performance of cytology. HPV DNA testing, on the other hand, is both objective and reproducible [11,51]. A particularly attractive feature of HPV DNA testing is that it allows for automated screening.

In our main analysis, we investigated the cost-effectiveness of screening in a cohort consisting of vaccinated women only (compliance to vaccination 100%). Therefore, these cost-effectiveness results provide a conservative estimate of the optimal number of screening rounds in a cohort consisting partly of vaccinated and partly of unvaccinated women. In the sensitivity analyses, we also studied the cost-effectiveness of screening in a population in which 85% of the women are vaccinated and found that, in that situation, 6 times HPV DNA screening is cost-effective as well. We also carried out a number of other sensitivity analyses and consistently found that either 5 or 6 times HPV DNA screening was cost-effective for The Netherlands at a ceiling ratio €20,000/QALY. This was true even if screening attendance was assumed to be lower in non-vaccinated than in vaccinated women. In most sensitivity analyses, we found screening 7 times with cytology to be comparable to 5 times HPV DNA screening in terms of effectiveness, costs and cost-effectiveness. These outcomes are in line with our main analysis. Screening 7 times with cytology was clearly dominated by 5 times DNA screening when the sensitivity of cytology was assumed to be 65% instead of 75% or when lower costs were assumed for HPV

DNA testing. When higher costs were assumed for HPV DNA testing, screening 7 times with cytology dominated over 5 times HPV DNA screening.

It should be mentioned that we did not incorporate the effect of herd immunity in our simulation model. Herd immunity refers to the phenomenon that unvaccinated persons are (partly) protected against infection because vaccinated persons cannot contribute to spreading the virus. In general, including herd immunity in a model leads to more conservative estimates for the cost-effectiveness of screening, because the protection offered by vaccination increases. This phenomenon only plays a role when vaccination coverage in the population is incomplete, and therefore does not affect the results of our main analysis (100% vaccination compliance). Incomplete coverage was studied in the sensitivity analyses by assuming a vaccination compliance of 85%. Incorporating the effect of herd immunity in these analyses basically means that a larger proportion of women are protected against infection than only the 85% of women who are vaccinated, although the magnitude of the increase in protection is unknown. Therefore, predictions with herd immunity lie in between predictions obtained under 100% vaccination compliance and predictions under 85% vaccination compliance (without herd immunity). Because the vaccination compliance itself did not have a substantial effect on the results, including herd immunity in our model would not have led to substantially different results.

Only few studies so far have formally addressed the optimization of cervical cancer prevention by studying the cost-effectiveness of combined vaccination and screening [6,52,53]. The general conclusion from these studies is that it is possible to maintain a cost-effective screening programme in addition to vaccination. For countries with frequent screening, such as the US, the cost-effectiveness of screening can be improved by decreasing the screening frequency [6,53] or by delaying the starting age of screening [6]. Notably, the age at which screening starts in The Netherlands (30 years) is higher than in other countries like the US and the UK (between 20 and 25 years). This may explain why we found unfavourable results for delaying the screening age whereas Goldie et al. [6] reported that a combined vaccination and screening program may be cost-effective provided that screening is initiated at a later age and conducted less frequently (e.g. triennial screening from age 25 onwards). Furthermore, some studies suggest that screening may benefit from more advanced screening tests such as liquid-based cytology [6] or the HPV DNA test [53]. Overall, cost-effectiveness studies published so far support the cost-effectiveness of HPV DNA screening in the vaccinated population if the screening interval is lengthened in comparison to the screening interval in the unvaccinated population. This is in line with our conclusion that 5 times HPV DNA screening is a cost-effective screening scenario for The Netherlands.

To conclude, our model calculations indicate that cervical cancer screening can remain a cost-effective preventive intervention in The Netherlands, also after the introduction of HPV16/18 vaccination. Optimal screening scenarios in vaccinated women were either 5 times HPV DNA screening or 7 times cytological screening between 30 and 60 years of age. These scenarios were equally effective and cost-effective with ICERs below the Dutch threshold of €20,000 per QALY. Arguments in favour of HPV DNA screening are the possibility to reduce the current number of lifetime screening rounds, the use of an objective screening test, and the possibility to monitor the effectiveness of the HPV vaccination programme.

Acknowledgement

This study was funded by an unrestricted grant from GlaxoSmithKline.

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