An Updated Analysis of the Impact of HPV Vaccination Based on Long-term Effectiveness in the Netherlands

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ABSTRACT

Introduction: Vaccination against human papillomavirus (HPV) is considered the most effective strategy to protect women from cervical cancer. Three HPV vaccines are currently licensed in Europe and, although they are generally supported by favorable health economic outcomes, current models fall short in predicting vaccination benefits. Here, we aim to re-evaluate the health benefits of HPV vaccination, using updated long-term effectiveness data and emphasizing quality of life losses related to precancer disease and treatment.

Methods: We used a static Markov model that compared "only screening" (includes unvaccinated girls) and "vaccination" (assumes 100% vaccination coverage with the bivalent HPV vaccine). A lifetime cohort of 100,000 uninfected 12-year-old girls was included, in which the number of cases with cervical intraepithelial neoplasia grade 2 or higher/3 (CIN2+, CIN3), cervical cancer, and cervical cancer deaths per scenario were determined. Furthermore, the reduction in major excisional procedures, the preterm deliveries averted, and the related gain in quality-adjusted life years (QALYs) due to vaccination were estimated.

Results: The bivalent vaccine showed larger reductions in CIN2+, CIN3, cervical cancer cases, cervical cancer deaths, and major excisional treatments, after including long-term efficacy and effectiveness data, compared to previous data. Moreover, we observed an increased amount of QALYs gained due to prevention of major excisional treatment and the negative side effects related to it.

Conclusions: Updated health economic models for HPV vaccination, using updated and long-term effectiveness data and including prevention of treatment-related side effects, demonstrate a substantial additional positive effect on vaccination outcomes. Indeed, extrapolation of the bivalent HPV vaccine's updated long-term effectiveness data against HPV-related cervical diseases shows that the positive effects of vaccination may be more substantial than previously estimated. There is a graphical abstract available for this article.
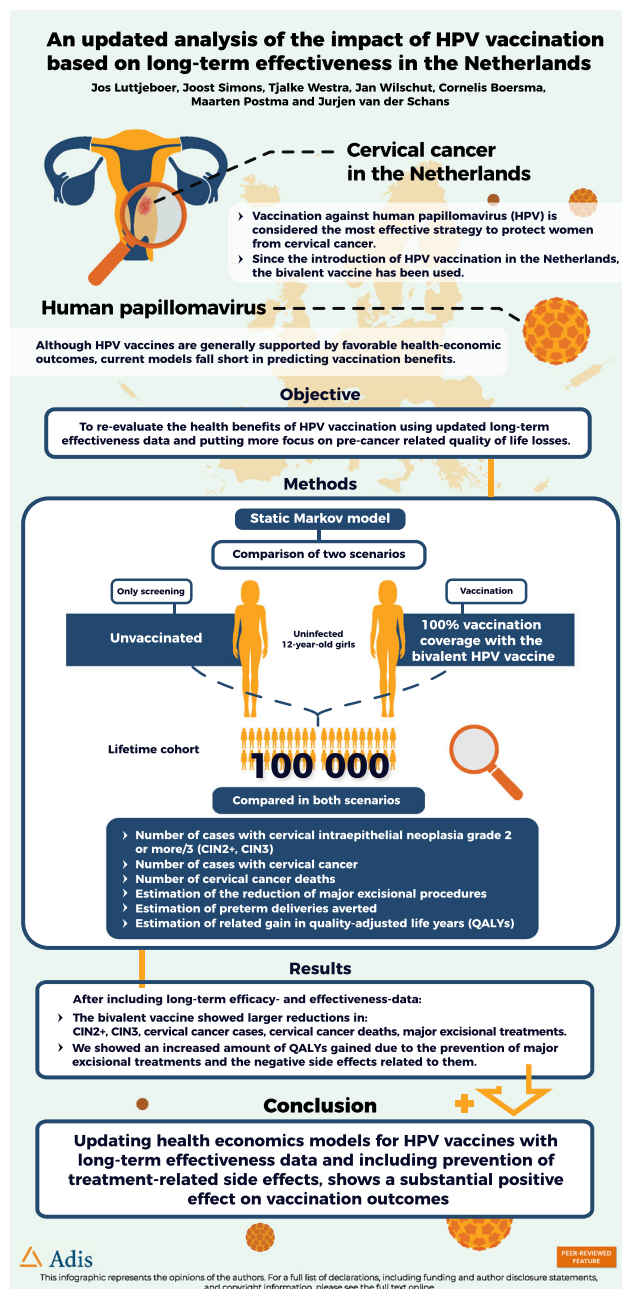
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Graphical Abstract:

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them fall short due to a lack of long-term data and treatment impact. The aim of this study is to re-evaluate the benefits of vaccination with the bivalent vaccine in the Netherlands using updated longer-term data and benefits from preventing treatment.

We used a cost-effectiveness model to compare two scenarios: only screening and vaccination plus screening. We included 100,000 12-year-old girls in the model and compared the following outcomes: number of individuals with benign cervical lesions, number of individuals with cervical cancer, number of deaths, reduction in treatment after vaccination, premature births avoided after vaccination, and quality of life gains.

We found that the bivalent vaccine showed larger reductions in pre-cancerous lesions (CIN2+, CIN3), cervical cancer cases, cervical cancer deaths, and major excisional treatments, compared to the results of previously published cost-effectiveness analyses when new longer-term data were included. The prevention of treatment for the lesions represents a significant added value for vaccination.

Our modeling study confirms the protective effect of the bivalent vaccine on cervical cancer. Moreover, it reflects a substantial additional value of vaccination compared to the benefits of vaccination that have been shown before.

Keywords: HPV; Netherlands; Cervical cancer; HPV vaccination

PLAIN LANGUAGE SUMMARY

Cervical cancer is one of the most common cancers among women, and the most effective strategy for its prevention is vaccination against HPV infection. Several studies have predicted the benefits of vaccination; however, most of

Key Summary Points

Why carry out this study?

Cervical cancer is one of the most common cancers among women, the most effective strategy for its prevention is vaccination against HPV infection. Several studies have predicted the benefits of vaccination; however, most of them fall short due to a lack of long-term data and treatment impact.

The aim of this study is to re-evaluate the benefits of vaccination with the bivalent vaccine in the Netherlands using updated longer-term data and benefits from preventing treatment.

What was learned from this study?

Using updated efficacy and effectiveness data, modeling of HPV vaccination with the bivalent vaccine showed increased reductions in CIN, excisional treatment, cervical cancer, and cervical cancer deaths compared to previously estimated outcomes of vaccination.

In future models, more focus should be put on using longer term effectiveness data and the prevention of treatment-related side effects to make sure the assessment is holistic and realistic.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to.https://doi.org/10.6084/m9.figshare.23703072.

INTRODUCTION

Cervical cancer is one of the most incident forms of cancer among women. In 2018, an estimated 570,000 women worldwide were diagnosed with cervical cancer, of whom 311,000 died, most of them from low- and middle-income countries [1, 2]. Persistent infection with certain types of human papillomavirus (HPV) is the main cause of cervical cancer [3, 4]. Among these, HPV 16, 18, 31, 33, 35, 39, 45, 52, and 58 are known as high-risk types and are responsible for the development of premalignant cervical lesions [i.e., cervical intraepithelial neoplasia (CIN)] and later, cervical cancer [3, 4].

Currently, the most effective strategy for the prevention of HPV infection, and thus cervical cancer, is the vaccination of preadolescent girls against the most common cancer-causing HPV types before sexual initiation. By 2019, most European countries had introduced HPV vaccination in their national immunization programs [5]. There are three HPV vaccines licensed in Europe: the AS04-adjuvanted bivalent vaccine (Cervarix, GSK) that contains types HPV 16 and 18; the quadrivalent vaccine (Gardasil, MSD) that contains types HPV 6, 11, 16 and 18; and the nonavalent vaccine (Gardasil 9, MSD) that contains types HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 [6]. The Netherlands introduced the bivalent vaccine in 2009 [7].

At the time of their introduction, several health economic studies were conducted to predict the long-term effectiveness of HPV vaccination. However, these evaluations were based on short-term clinical data due to the limited number of years after the introduction of the vaccination [8–10].

New data on the longer-term effectiveness of HPV vaccination have now become available with a focus on late-stage CIN (i.e., CIN2+ and CIN3), which represents the immediate precursor of cervical cancer. Further, the decrease in the incidence of CIN2+/CIN3 was found to be a better predictor of the effectiveness of HPV vaccination against cervical cancer prevention than the reduction in the incidence of (persistent) HPV infection [11]. Current models still fall short in adequately predicting the reduction in CIN2+/CIN3 cases after HPV vaccination and forecast a lower reduction than real-world long-term data show. For example, the bivalent vaccine has been estimated to reduce the number

of CIN2+/CIN3 cases by 37–76% (with a mean of 56%) [12–18], whereas long-term data of randomized controlled trials and real-world evidence show a reduction of 81.5%–100% [8, 19–22]. By including factors such as herd immunity and potential cross-protection to other HPV types, these models could better capture the real-world effectiveness of HPV vaccines when it comes to long-term outcomes, such as prevention of CIN and cervical cancer. Moreover, current cost-effectiveness models often focus only on the benefits of cancer prevention [8–10], whereas CIN and corresponding treatment are also often associated with costs, negative side effects, and reduction in the quality of life.

Here, we aim to re-evaluate the health benefits of HPV vaccination based on longer-term effectiveness data of the bivalent vaccine in the Netherlands. In addition, we compare the reduction in CIN2+ and cervical cancer cases between model simulations using random clinical trials-based vaccine efficacy and longer-term effectiveness data. Key study findings are summarized in the associated Graphical Abstract.

METHODS

Model Design

A previously published static Markov model was used to assess the impact of the bivalent HPV vaccine. The Markov model simulates the progression from HPV infection through CIN stages 1–3 to cervical cancer. Notably, women progress through the model according to transition probabilities that were estimated from the literature. The model version we applied distinguishes seven categories of HPV types: 16, 18, 31, 45, 52, other oncogenic subtypes, and low-risk HPV [23]. In the model, it was assumed that concomitant infections with different HPV types were not possible. Further, a subdivision between histology-identifiable health states was made: normal histology, CIN1, CIN2, CIN3, and four sub-stages for cervical cancer, as defined by the Federation of Gynaecology and Obstetrics (FIGO), stages 1–4. The model was

calibrated by varying parameter estimates over the ranges specified in a literature review, taking the Dutch Cervical Cancer Screening Program (DCCSP) explicitly into account. The screening component in the model involves inviting women between 30 and 60 years old once every 5 years to get a Pap smear test. Although the current DCCSP invites women for an HPV-test instead of a Pap smear, for sake of comparability with previous analyses with the model in the Netherlands, we did not update the screening component in that respect. For calibration of the model, age and type-specific HPV prevalence, HPV-type distribution in normal and disease states, CIN stage-specific prevalence, cervical cancer incidence, and cervical cancer mortality were used to parameterize the model [23].

Population and Vaccine Effectiveness

A cohort of 100,000 uninfected 12-year-old girls (i.e., approximately the number of 12-year-old girls in the Netherlands) has been modeled twice with a lifetime horizon, evaluating the difference between the "only screening" and the "vaccination" scenario [23]. The "only screening" scenario includes girls in the absence of vaccination. The "vaccination" scenario assumed 100% vaccination coverage in a two-dose vaccination schedule, which is in accordance to current recommendations and registrations (no one-dose vaccination schedule was used as this is currently not registered).

Also, due to differences in study populations, vaccine coverage, follow-up, and single/multi-cohort vaccination, differences in long-term impact between HPV vaccines are difficult to assess. Available long-term vaccine effectiveness data come from studies with differences in study populations, vaccine coverage, follow-up time, and single/multi-cohort vaccination. To adjust for these differences, the vaccine effectiveness data were retrieved from a manuscript by Drolet et al. that describes a systematic review and meta-analysis of the population-level impact of vaccinating girls and women against HPV on, among other outcomes, HPV infection and CIN2+. The bivalent vaccine's

effectiveness against HPV 16/18 infection among women 15–19 years old, 5–8 years post-vaccination, was set at 86% (82–89%). Cross-protection against HPV 31/33/45 was set at 71% (0–94%) [24]. The bounds of the confidence intervals were used to explore the uncertainty in the base case that uses the mean effectiveness.

Outcomes: Effectiveness, Reduction of Cases and Major Excisional Treatments

To assess the effectiveness, the model determined the number of cases with CIN2+, CIN3, cervical cancer, and cervical cancer deaths averted per scenario, and compared both scenarios ("vaccination" and "only screening"). In addition, we estimated the reduction in major excisional procedures and preterm deliveries averted, and the related gain in quality-adjusted life years (QALYs) due to vaccination.

The treatment and management of CIN cases are detailed in the study published by Aitken et al. in 2019 [25]. Of all the referrals, 26.4% of patients with CIN1-, 68.0% of those with CIN2-, and 81.8% of those with CIN3-diagnosed lesions underwent excisional treatment (i.e., cone biopsy, large loop excision of the transformation zone, and other excisional therapies).

Valuation of QALYs (in terms of health-related quality of life and time spent in this health state), was based on two studies: (1) the first assessed the effects of therapy on the psychosocial well-being of patients with CIN and estimated a significant difference in physical health-related quality of life between conservative therapy and conization of CIN [26], and (2) the second determined the long-term complications and the impact on QALYs among women after cervical conization, present in 27.6% of the study population over 2.5 years after surgery [27]. These estimates were used to assess the impact of CIN-related treatment.

Finally, the impact of preventing CIN treatment on the prevention of preterm deliveries and the related gain in QALYs was investigated. Treatments with major excisional procedures (i.e., loop electrosurgical excision procedure, as also used in the Dutch guidelines; Table S1)

have been reported to be associated with an increased risk of preterm birth and abortion [28]. The group size within the reproductive age range (30–45 years), the number of CIN lesions/treatments, and the Dutch conception rates were used to calculate the chance of pregnancy after a major excisional procedure at 13.0% for women 30–35 years of age, 6.9% for women 35–40 years of age, and 1.4% for women 40–45 years of age. Based on these numbers, we assessed the number of preterm deliveries averted based on probability differences between women with (9.7%) and without (5.3%) treatment for cervical lesions before delivery [28]. Preterm deliveries were associated with lower health-related quality of life and higher depressive scores than those without complications [29, 30]. This results in a lower overall utility score of 0.024 compared to term pregnancies, which was used for the valuation of the preterm delivery aversion due to avoidance of CIN treatment ("vaccination" scenario).

Compliance with Ethics Guidelines

There were no human subjects involved in this study; hence, formal ethical approval was not sought, and informed consent was not applicable.

RESULTS

As shown in Table 1, the "only screening" scenario, i.e., that scenario in which girls are not vaccinated against HPV, gathers the highest number of cases in all stages of HPV-related disease (1,527 with CIN2+, 852 with CIN3, 565 with cervical cancer, and 206 deaths). In the "vaccination" scenario, the bivalent vaccine reduced the number of CIN2+ to 443, CIN3 to 243, cervical cancers to 111, and cervical cancer deaths to 41.

Table 2 shows the incidence of the major excisional treatments and the number of preterm deliveries averted among patients with CIN1/2/3 and the impact on QALYs. The bivalent vaccine averts 895 major excisional treatments compared to the "only screening" scenario. The number of preterm deliveries

Table 1 Number of CIN2+, CIN3, cervical cancer, and death cases, and in the "only screening" and "vaccination" scenarios, and percentage of reduction due to vaccination in a lifetime cohort with 100,000 girls/women

	CIN2+		CIN3		Cervical cancer		Cervical cancer deaths	
	Number of cases	% reduction due to vaccine	Number of cases	% reduction due to vaccine	Number of cases	% reduction due to vaccine	Number of cases	% reduction due to vaccine
Only screening	1527	–	852	–	565	–	206	–
Vaccination	443 (283–868)	71.0% (43.2–81.5%)	243 (154–478)	71.5% (43.9–81.9%)	111 (65–225)	80.4% (60.3–88.6%)	41 (24–82)	80.3% (60.2–88.5%)

CIN2+/CIN3 cervical intraepithelial neoplasia grade 2 or higher/3

Table 2 Incidence and reduction (per vaccination cohort of 100,000 girls) of CIN1-, CIN2-, and CIN3-related major excisional procedures, associated preterm delivery averted and related QALYs gained comparing "only screening" and "vaccination" scenarios

Scenario	CIN1				CIN2				CIN3				Total CIN	
	Major excisional treatment		Preterm delivery averted		Major excisional treatment		Preterm delivery averted		Major excisional treatment		Preterm delivery averted		Major excisional treatment	Total QALYs gained
	Incidence n, (%)[a]	QALYs	Cases	QALYs	Incidence n, (%)[a]	QALYs	Cases	QALYs	Incidence n, (%)[a]	QALYs	Cases	QALYs	Incidence n, (%)[a]	
Only screening N	115	–	–	–	459	–	–	–	697	–	–	–	1271	–
Vaccination, n	41 (63.8)	4.19	0.7	0.00	136 (70.4)	18.50	3.2	0.02	199 (71.5)	28.53	4.6	0.03	376 (70.4)	51.27

CIN1/2/3 cervical intraepithelial neoplasia grade 1/2/3, QALYs quality-adjusted life years gained

[a] % = (n/N) × 100, percentage of reduction of prevention treatments due to vaccination; N number of treatments per 100,000 women in the "only screening" scenario, n = number of treatments per 100,000 women in the "vaccination" scenario

averted was higher in the advanced stages of the disease (Table 2). Regarding the gain in QALYs, the effect of vaccination on prevented major excisional treatments is more substantial than the indirect effect of prevention of preterm delivery. The bivalent vaccine gained 51.27 QALYs (QALYs gained as a result of averted preterm deliveries included, 0.05 QALY).

DISCUSSION

This is the first modeling exercise exploring the impact of HPV vaccination using updated long-term vaccine effectiveness data. In our analysis, the bivalent HPV vaccine showed larger reductions in CIN2+, CIN3, and cervical cancer cases, cervical cancer deaths, and major excisional treatments, compared with previously published modeling results based on older shorter-term effectiveness data. Compared with the study of Rogoza et al., our analysis shows a greater reduction in CIN2+/cervical cancer cases (CIN2+ reduction: 76.7% vs. 57%, cervical cancer reduction: 80.4% vs. 74%), demonstrating that previous health economic models fall short in providing predicted clinical outcomes derived from early clinical data [23]. This shows that using longer-term data is beneficial for HPV models to better predict real-world clinical outcomes.

For this study, data on the effectiveness of HPV vaccines were retrieved from the meta-analysis of Drolet et al., as this study provides a generalization of individual studies with different settings and is, therefore, the most reliable source for the effect size of HPV vaccination for our study [24]. However, over the past few years, longer-term studies have shown even higher levels of effectiveness [19, 20, 31]. For instance, a retrospective study conducted in the Scottish population after immunization with the bivalent HPV vaccine showed an 89% reduction in the prevalence of CIN3+ and an 88% reduction in CIN2+ after 10 years [20]. The same study demonstrated evidence of herd protection among unvaccinated women [20]. Since our single-cohort model does not consider herd immunity effects and cross-protection (due to the assumption of 100% vaccination coverage),

it may not reveal the full potential value of HPV vaccination. Higher efficacy rates were presented in the end-of-study analysis PATRICIA trial, reaching over 90% against all CIN3+, irrespective of HPV type and age group [8]. Differences between efficacy and long-term effectiveness rates suggest even higher vaccine effectiveness in the real-world setting, although these variations could also be ascribed to a different surveillance strategy in a trial-based study compared to the real-world situation [32].

Our analysis suggests that previous studies did not fully capture the effectiveness of the bivalent vaccine on CIN2+ [12–15, 33]. Our model included other high-risk HPV types, in addition to HPV 16, 18, 31, 33, and 45, to come closer to the real-world vaccine effectiveness (24). The effectiveness against CIN2+ estimated in this study corresponds with the changes in CIN2+ between the pre- and post-vaccination periods 5–8 years after vaccination among 20- to 24-year-old women as provided in Drolet et al. (24). However, it should be noted that this is based on a single study.

The second part of our analysis evaluated the QALYs gained by averted CIN treatment and averted preterm deliveries, which is, to our knowledge, the first study to take these aspects of HPV vaccination into account. The impact of vaccination on QALYs gained was more substantial when prevention of major excisional treatments was considered, compared to previous models not including these additional benefits, and appeared to be of the same order of magnitude as found in a recently published study on the added value of HPV vaccination of boys (34).

Our study has several limitations. First, in line with Rogoza et al. [23] cross-protection was assumed to be lifelong. Although the bivalent vaccine targets HPV 16 and 18, randomized trials, and post-implementation surveillance have demonstrated cross-protection against other phylogenetically-related HPV types, but the range and longevity of protection against the non-vaccine types has been debated [35, 36]. Recent analyses in the Costa Rica HPV vaccine trial and the associated long-term follow-up show that cross-protection is substantial without signs of waning 11 years post-

vaccination [36]. Second, valuation of the QALYs gained by aversion of preterm delivery was based on two studies which assessed the time spent in a health state and the utility scored separately [26, 27]. Although these data are complementary, the impact of these adverse outcomes is considerable, and should be assessed in a future single study. Finally, we present the potential number of preterm deliveries based on the number of CIN treatments. Based on general Dutch conception rates, we approximated the time to pregnancy and the related negative effect of CIN treatment. In addition, we assumed that women treated for CIN are as likely to become pregnant as untreated women. The negative effects are, however, related to the time since treatment and the amount of tissue excised [37].

These outcomes could be of high importance to decision-makers who assess vaccines to be included in a national immunization program. It shows the importance of including real-world data to make better, more realistic estimates. and shows that additional benefits might be attributed to the vaccine when a more holistic approach of disease prevention is used.

CONCLUSIONS

Our re-evaluation of the health benefits of the bivalent HPV vaccine, based on long-term effectiveness data, more accurately predicts real-world clinical outcomes, suggesting that previous models underestimated the reduction in CIN2+ and cervical cancer cases in the Netherlands. Moreover, preterm deliveries as a result of treatment of a cervical lesion can be averted by HPV vaccination. Although this may prevent grief for those involved, the QALY gain is not substantial, as the frequency of preterm delivery is low compared to the number of CIN lesions. Finally, a substantial amount of QALYs are gained by preventing major excisional treatment. This study underlines the importance of continuous research and a broad understanding of vaccine benefits.

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