Major Article

Until Which Age Should Women Be Vaccinated Against HPV Infection? Recommendation Based on Cost-effectiveness Analyses

Tjalk A. Westra,1 Mark H. Rozenbaum,2 Raina M. Rogoza,3 Hans W. Nijman,3 Toos Daemen,1 Maarten J. Postma,2,4,a and Jan C. Wilschut1,a

1Department of Medical Microbiology–Molecular Virology, University Medical Center Groningen, 2Department of Pharmacy, Unit of Pharmacoepidemiology and PharmacoEconomics (FE2), 3Department of Gynaecology, University Medical Center Groningen, and 4Department of Epidemiology, University Medical Center Groningen, University of Groningen, the Netherlands; and 5Health Economics and Outcomes Research, i3 Innovus, Burlington, Ontario, Canada

Introduction. Cervical cancer is caused by infection with human papillomavirus (HPV). Several countries have implemented vaccination programs against HPV for teenage girls before sexual debut. However, recent clinical trials have demonstrated that vaccination of older women is highly effective as well. Accordingly, it has been suggested that these older women should also be offered vaccination. Here, the cost-effectiveness of HPV vaccination for older women was assessed.

Methods. A Markov model was used to estimate age-specific health benefits and cost savings of HPV vaccination for women 12–50 years of age, in the Netherlands. Sensitivity analyses were performed to test the robustness of the outcomes. State-of-the-art health-economic methods were used, and international health-economic guidelines were followed.

Results. HPV vaccination is highly cost-effective for girls aged 12–16 years. Remarkably, cost-effectiveness only slowly declines with increasing age of the vaccinees up to 25 years. Indeed, substantial health benefits can be obtained by vaccinating women in this age group at acceptable costs. Beyond this age, cost-effectiveness of HPV-vaccination rapidly declines.

Conclusions. Not only HPV vaccination of girls before sexual debut is a highly effective and cost-effective strategy for prevention of cervical cancer, but also vaccination of women until the age of 25 years is generally cost-effective.
hoc catch-up programs covering older teenage girls up to ~18 years [4]. For example, in the Netherlands and the United Kingdom, routine HPV vaccination was introduced for 12- and 13-year-old girls. Furthermore, catch-up programs including teenage girls up to 16 or 18 years, respectively, were implemented in 2008. A few countries have offered HPV vaccination to women at older age in catch-up programs or on an individual basis. For example, the United States and France offer HPV vaccination to women up to 26 years of age [4, 5].

Unfortunately, despite the severity of the disease and the high vaccine efficacy, generally catch-up HPV vaccination did not reach a high coverage [6–9]. For example, in the Netherlands and the United Kingdom, vaccine uptake in the catch-up programs was <50% [9, 10]. As a result, many of these teenage girls are still at risk of acquiring an HPV-16 or -18 infection later on in life.

Recently, several clinical trials have shown that not only HPV vaccination of young teenage girls but also vaccination of older girls and women induces high virus-neutralizing antibody titers [11–13]. Consequently, in addition to vaccination of young teenage girls, implementation of vaccination programs for older girls and women could potentially prevent a significant burden of disease. Especially women in the age range of 18–30 years could benefit, as the risk of infection is highest in this group [14]. Clearly, only HPV-16- and HPV-18-negative women would benefit from the vaccination, as both HPV vaccines are prophylactic vaccines [15].

An advantage of vaccinating women against HPV-16 and -18 at older ages would be that it might weaken concerns about a possibly limited duration of protection, since the women would be vaccinated at or close to the moment they are at highest risk of becoming infected [14]. Indeed, there is uncertainty about the duration of protection of HPV vaccination, due to the as yet relatively short periods of follow-up after vaccination. Protection is now formally proven to be 7.3 and 9 years for Cervarix and Gardasil, respectively [16–18]. Therefore, it may be validly questioned if the vaccination at 12 years would still provide protection 1 or more decades after the initial vaccination, when sexual activity may be highest.

While it has been shown that the HPV vaccines are effective in the older age groups, it remains unclear how all above aspects impact on the cost-effectiveness of vaccinating women at older ages. In particular, as the HPV vaccines, at approximately €100/dose (with 3 doses required), are relatively expensive vaccines compared with other vaccines currently in use, health-economic considerations have played an important role in the decision-making process. For example, in the United Kingdom, the Department of Health decided to include girls up to 18 years of age in a catch-up program based on the cost-effectiveness results of Jit et al [19]. Previously, we have shown that HPV vaccination at 12 years of age is cost-effective in the Netherlands [20]. However, as the vaccine coverage of the catch-up programs is relatively low (<50%) and new data have become available on the vaccines’ efficacy in older women, the question arises if it is worthwhile to vaccinate women at an age beyond the age range of the current catch-up program. Using recent data on the efficacy of vaccination of women in general and at older ages in particular, we have now adjusted our economic model and present the health benefits and cost-effectiveness of HPV vaccination of women 12–50 years of age in the Netherlands, in the context of the current cervical cancer screening program.

METHODS

Model
We adjusted and modified our previous Markov model for HPV infection to estimate the age-specific health benefits and cost-effectiveness of first-time HPV vaccination in the Netherlands, with a focus on ages beyond the coverage of the current vaccination program. The model structure is shown in Figure 1, and specific details of the model can be found in 3 recent papers. For example, assumptions on disease-related costs and QALY losses were adapted from these papers [20–22]. Briefly, the model simulates the progression of HPV infection through cervical intra-epithelial neoplasia (CIN) stages 1–3 on to cervical cancer stages 1–4 for 7 different HPV types [16, 18, 31, 33, 45, “other high-risk types,” and “low-risk types”). The model contains 10 different HPV type-specific health states, specifically “HPV-susceptible,” “HPV-infected,” “CIN 1-3,” “cancer stages 1–4,”

![Figure 1. Schematic representation of the model. The model specifies between 7 types of HPV infection (16, 18, 31, 33, 45, other oncogenic serotypes, and other nononcogenic serotypes).](https://academic.oup.com/jid/article-abstract/204/3/377/2192434)
and “death.” The transition probabilities between “HPV-susceptible” and “HPV-infected” reflect the forces of infection for the different types. In the model, HPV vaccination reduces the force of infection by a constant according to the observed clinical vaccine efficacy. Thus, women who are in the health state of “HPV-susceptible” directly benefit from the vaccination. Women in other health states, who have experienced a prior HPV infection, will only benefit from the vaccination after natural clearance or treatment of the infection, given the assumed absence of therapeutic efficacy of the vaccination. In the model, it is assumed that women do not develop natural immunity against HPV infection and may return to “HPV-susceptible” after leaving the compartment of “HPV-infected.”

The model was calibrated to age- and type-specific HPV prevalence [23], cervical cancer incidence, and cervical cancer mortality [24], taking into account the Dutch national cervical cancer screening program; for example, women 30–60 years are screened at a 5-year interval. The calibration process has been extensively described elsewhere [21, 22]. In short, based on a literature search, the transition probabilities between different health states were estimated. The transition probabilities were varied within their 95% confidence intervals to obtain the optimal goodness-of-fit for HPV prevalence, cervical cancer incidence, and mortality, determined by calculating the average percentage of deviation. Note that we calibrated our model to epidemiological data in the Netherlands from the period before HPV vaccination was introduced. Obviously, our current model refers to the present situation in the Netherlands with vaccination now going on for a few years. Although in the meantime ~50% of Dutch teenage girls of 12–16 years of age are vaccinated against HPV-16 and -18, we considered it plausible to assume that this has not yet substantially influenced the force of infection.

**Vaccine Characteristics**

In the initial clinical trials, it has been shown that both HPV vaccines are highly effective (95%) against HPV16 and -18 infections, until the age of 26 [17, 25–28]. Furthermore, cross-protection against HPV31, -33, and -45 has also been demonstrated [28, 29]. For older women (eg, >26 years of age) less clinical data are available regarding the vaccines’ efficacies.

For both vaccines, it has been shown that the vaccine-induced virus-neutralizing antibody titers decrease with age of vaccination [11, 12]. However, antibody levels after vaccination remain much higher than the levels after a natural infection. It has also been shown that the vaccines’ efficacy against a 6-month persistent infection is somewhat lower in women 24–45 years of age at the time of vaccination (83.1%, 95% CI, 50.6%–95.8%) compared with that in adolescents (95%), but nevertheless, protective efficacy remains very high [11, 30].

In our base case, a high vaccine efficacy at 95% was assumed for all age groups [17, 27]. In the base case, we assumed no cross-protection against other HPV types, since the cross-protective efficacy differs between both vaccines, and evidence for cross-protection requires further support despite preliminary results indicating potentials for it [27]. Furthermore, it was initially assumed that the vaccine would provide lifelong protection and that the cost of vaccination would be €105/dose, as listed in the Dutch Drug Reimbursement System [31, 32]. Probabilistic sensitivity analyses (PSA) were performed on the base case, assuming a beta distribution for efficacies (95% confidence intervals from Paavonen et al [28] were used for this purpose) and a gamma distribution for costs, and a beta distribution for disutilities expressed in QALYs [20]. For one PSA, 1000 simulations were completed.

**Outcome Measures and Cost-effectiveness Analyses**

In the model, the clinical and health-economic impact of HPV vaccination is analyzed for women at different ages (12–50 years) in 1-year age cohorts. In the analysis, a 1-year age cohort of women is followed twice over the full lifetime (until death or 100 years): once as a first-time vaccinated cohort and once as an unvaccinated cohort. A 100% vaccine coverage for the complete vaccination schedule (3 doses) was assumed. However, given that our model is a “static” model, results on cost-effectiveness are insensitive to this particular assumption. The model tracks the total number of CIN and cervical cancer cases, deaths, costs, and health effects, the latter expressed as quality-adjusted life years (QALYs) or life years (LYs). By summing all the costs, LYs and QALYs, and by subsequently calculating the differences between the 2 cohorts—1 without and 1 with vaccination—the model provided estimates for net costs, LYs, and QALYs gained. By dividing the net costs by the LYs and QALYs gained, the incremental cost-effectiveness ratio (ICER) was determined. Health effects and costs were differentially discounted according to Dutch guidelines for health-economic research at 1.5% and 4%, respectively. ICERS were calculated for individual 1-year age groups, enabling us to estimate the cost-effectiveness for HPV vaccination at different ages.

In the Netherlands, ICERS below €20 000/QALY are generally labeled as “cost-effective.” In many cases, higher thresholds up to €50 000/QALY are considered acceptable as well; for example, ICERS up to €30 000/QALY are still highly likely to be considered as favorable [33]. On the other hand, ICERS above €80 000/QALY reflect unfavorable cost-effectiveness in the Netherlands [34]. Finally, ICERS in between €50 000/QALY and €80 000/QALY are likely to be considered unfavorable [33].

**Sensitivity and Scenario Analysis**

Because there is uncertainty about the vaccines’ efficacy and the duration of protection, and because the vaccine price may vary, we performed several sensitivity and scenario analyses to evaluate the robustness of our results.
First, assumptions regarding the vaccine efficacy were evaluated in two different subanalyses: (1) Vaccine efficacy was decreased to 83.1% for all age groups, as indicated above [11], and (2) cross-protection against other HPV types was included (Table 1). Cross-protection against nonvaccine HPV types was included as reported for the bivalent vaccine [27].

Next, the impact of waning immunity on the ICER was analyzed. As vaccine efficacy has only been proven for 9/7.3 years after vaccination, in this scenario the duration of protection was reduced from lifelong to 20 years [16, 31]. Such "medium-term" protection can be motivated, since after 9/7.3 years antibody titers remained high and no clinically relevant reduction in protection has been reported [16]. Furthermore, the impact of an additional 1-dose booster, 20 years after the initial vaccination scheme, was analyzed, assuming the booster to provide lifelong protection thereafter.

Finally, the impact of the vaccine price on the ICER was analyzed. When vaccination strategies are implemented in the context of national immunization programs, substantial price reductions are likely to be granted by the vaccine manufacturers. Since the actual price that is paid by the Dutch government for the HPV vaccine is not publicly known, we varied the vaccine price in a range from €45 to €125 per dose. In this range we also included €125 per dose, to consider the contribution of (varying) vaccination costs [35].

**RESULTS**

**Health Benefits**

In the absence of vaccination, but taking the Dutch cervical cancer screening program into account, the model predicted an annual number of 565 cervical cancer cases and 205 cervical cancer-related deaths in a cohort of 100,000 women in the Netherlands, who were followed during their lifetime (Figure 2).

Addition of HPV-vaccination to the current Dutch cervical cancer screening program resulted in a reduction in cervical cancer cases, mortality, LYS lost, and QALYs lost [20]. Although the benefits of HPV vaccination were sensitive to the age of the vaccinee, important health benefits were consistently found for vaccination up to 25 years of age (Figure 2). Obviously, the health benefits of vaccination gradually decline with the age of the vaccinee. Nevertheless, a 50% reduction in cervical cancer incidence can be obtained by vaccination of women until the age of 25. Above 25 years of age, the clinical benefits of HPV vaccination start to decline more rapidly.

**Cost-Effectiveness**

As the health gains among women above 30 years of age are limited, we only determined the ICER of HPV vaccination for women 12–35 years of age. Figure 3 shows the cost-effectiveness acceptability curves for HPV vaccination at different ages. The ICER of HPV vaccination for 12-year-old girls was €19,900/QALY (95% CI, €19,200–21,600/QALY) and increased to €52,100/QALY (95% CI, €50,400–57,100/QALY) for 30-year-old women. The ICER remained below €30,000/QALY for women <23 years of age.

The ICER of the current catch-up program, that is, the average ICER for girls aged 13-16 year, was estimated at €22,500/QALY. Extension of the age groups in potential catch-up programs resulted in average ICERs of €23,500 and €26,900/QALY for inclusion of all girls/women 12–18 or 12–25 years of age, respectively.

**Sensitivity and Scenario Analyses**

In further sensitivity analyses, the impact of vaccine efficacy, duration of protection, and vaccine price were analyzed (Figures 4–6). Figure 4 shows that including the benefits of cross-protection against HPV31, -33 and -45 resulted in a further improvement of the cost-effectiveness of the vaccination, the ICER now remaining below €30,000/QALY even for

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### Table 1. Parameters Used in the Model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case</th>
<th>Sensitivity analysis</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Cohort size</td>
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<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Screening coverage</td>
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<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Vaccine coverage</td>
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<td></td>
<td>[20]</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
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<td></td>
<td></td>
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<td>HPV-16/18</td>
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<td>83.1–95%</td>
<td>[26]</td>
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<td>0–78.7%</td>
<td>[26]</td>
</tr>
<tr>
<td>HPV-33</td>
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<td>0–45.7%</td>
<td>[26]</td>
</tr>
<tr>
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<td>0–75.7%</td>
<td>[26]</td>
</tr>
<tr>
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<td>€65–€125</td>
<td>[32]</td>
</tr>
<tr>
<td>Duration of protection</td>
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<td>[31]</td>
</tr>
<tr>
<td>Booster dose</td>
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<td>1 dose after 20 y*</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Booster dose was combined into a scenario in which the vaccine induced immunity wanes after 20 years.

€1.00 = $1.29 (November 2010)
women of 25 years of age. Lowering of the vaccines’ efficacy to 83.1% for all age groups resulted in a slight increase of the ICERs (Figure 4).

When the duration of protection was reduced to 20 years, the ICER increased to values above €20,000/QALY for all age groups but remained below €50,000/QALY for women up to the age of 25 (Figure 5). Inclusion of a booster vaccination, 20 years after the original vaccination, resulted in slightly more favorable ICERs, but the values remained above €20,000/QALY for all age groups.

Figure 6 illustrates that the ICERs are highly sensitive to the vaccine price. For example, when the vaccine price was reduced to €65/dose, the ICER was highly cost-effective (<€20,000/QALY) for all women <25 years of age. ICERs remained below €20,000/QALY for women <30 years when the vaccine price was €45/dose.
DISCUSSION

Recently, it has been argued that HPV vaccination should be offered not only to teenage girls but also to older women [11, 12, 36]. The arguments were primarily based on favorable efficacy data from clinical trials [11, 12] rather than on cost-effectiveness considerations. In this study, we show that not only can substantial health benefits be obtained by vaccinating women until the age of 25 years but also that vaccination of these women is generally cost-effective with ICERs below €30,000 per QALY gained. On the other hand, for women of 30 years and older, HPV vaccination becomes less attractive, with ICERs rising above €30,000 or even €50,000 per QALY gained. For women between 25 and 30 years, a potential for favorable cost-effectiveness exists, depending mostly on the vaccine price.

This is the first study that analyses in detail the health benefits and cost-effectiveness of HPV vaccination for women in individual 1-year age groups up to an age of 50 years. Our analysis shows potentials for favorable cost-effectiveness up to ages far beyond the age categories currently implicated in catch-up programs for HPV vaccination in, for example, the UK and the Netherlands. Importantly, the outcomes predicted by our model would appear to be quite robust, based on sensitivity analyses. We note that our sensitivity analyses did not include transition probabilities, since these were used to calibrate the model. Base-case values may therefore be considered as “optimal” values.

In this analysis, we used a static model to predict the outcome of HPV vaccination among different age groups. One might argue that for modeling of infectious diseases, a dynamic approach—in which herd-immunity benefits are taken into account—would be preferable [37]. Clearly, due to widespread introduction of HPV-vaccination programs among teenage girls, herd-immunity benefits will arise. However, as yet, these benefits are likely to be limited, certainly for women above 18–20 years of age, since at this point vaccination coverage in these older age groups will be very low and HPV transmission is likely to occur in a strongly age-assorted fashion. Obviously, as the girls who have been vaccinated thus far grow older, the contribution of herd immunity to protection against HPV in the older age groups will increase and may then warrant the use of dynamic transmission modeling approaches. However, in the current situation, the use of a static model is not only justified but possibly even preferable, since static modeling improves the transparency and robustness of the results. To assess the long-term impact of HPV vaccination and herd immunity.
among unvaccinated girls and older women, we are currently developing a dynamic transmission model.

As shown in sensitivity analysis, the estimated ICERs in this study are strongly dependent on assumptions regarding vaccine price and duration of protection. In the base case, we assumed a price for the vaccine of €105/dose. Under these conditions, using a cutoff of €30 000/QALY, HPV vaccination is cost-effective for individual 1-year age cohorts up to an age of 23 years. However, it is known that significant discounts can be achieved on registered vaccine prices, in particular when the vaccination is implemented in a national immunization program. In our analysis, with discounts of €20 or €40/dose, vaccination remains cost-effective for individual 1-year age cohorts up to an age of 27 or 30 years, respectively.

As the time of follow-up for the 2 registered HPV vaccines is still limited, there is uncertainty about the duration of vaccine-induced protection. However, based on the relatively slow waning of antibody titer after vaccination, David et al. [31]—using extrapolation methods—estimated that at least the bivalent HPV vaccine is likely to induce lifelong protection. Accordingly, in our base case we assumed lifelong protection. If the duration of protection would be limited, HPV vaccination would become less favorable for all age groups.

Even though our study was conducted for the situation in the Netherlands, in general the results also apply for many other Western countries. For example, the results of our study are in line with the conclusions of earlier cost-effectiveness analyses of HPV vaccination indicating that ad hoc catch-up programs including women up to ~24 years is generally cost-effective compared with screening only [19, 38, 39]. Our study adds to this conclusion that, for individual 1-year age cohorts, HPV vaccination remains cost-effective up to an age of ~25 years, or—depending primarily on the vaccine price—even up to 27 or 30 years. Furthermore, our findings are in line with the conclusion of Kim et al [40] that the cost-effectiveness of HPV vaccination of women 30 years and older is unfavorable. Note that our findings are slightly more favorable than those of Kim et al [40], probably due to the lower discount rate applied in the Netherlands to future health outcomes and a lower screening frequency than assumed by Kim et al. Furthermore, Kim et al assumed a higher screening compliance whereby the incremental benefit of HPV vaccination will be reduced. However, despite these differences, the general conclusions are line with each other.

From our study, we conclude that vaccination of 12-year-old girls is a highly (cost-)effective strategy to prevent HPV infection. Furthermore, we also conclude that large-scale catch-up programs including women up to 25 years of age will generally be cost-effective at an average ICER of <$30 000/QALY gained. However, in view of the relatively low vaccination coverage that was achieved in earlier catch-up programs for teenage girls, it is not very likely that many countries will implement new ad hoc large-scale catch-up vaccination programs including age groups up to 25 years, despite their potential cost-effectiveness. Therefore, in this study we analyzed the cost-effectiveness of HPV vaccination of individuals in 1-year age groups rather than large catch-up groups. We demonstrate that even for individual-based vaccination, as has been introduced in the United States, the ICER remains below €30 000/QALY gained for women up to 25 years and ranges between €30 000 and €50 000 for women up to 30 years of age. With a modest reduction in vaccine price of 33%, even vaccination of individual women up to 30 years of age would remain cost-effective at an ICER of €30 000/QALY gained. Individual-based vaccination could readily be implemented, for example, within the context of national drugs reimbursement schemes. For women >30 years of age, addition of HPV vaccination to organized cervical cancer screening programs is unlikely to be cost-effective, and therefore it is probably more beneficial to focus on other interventions to protect them against cervical cancer.

Funding

This work was funded by an unrestricted educational grant from GlaxoSmithKline (Zeist, the Netherlands) to T. A. Westra. GSK, however, had no role whatsoever in the study design, analysis of the data, writing of the manuscript, or the decision to submit this work for publication.

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