HPV vaccination in Indonesia
Setiawan, Didik

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CHAPTER 2

Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context

Didik Setiawan
Jos Luttjeboer
Tjalke A Westra
Jan C Wilschut
Auliya A Suwantika
Toos Daemen
Jarir At-thobari
Bob Wilffert
Maarten J Postma

Summary

The Addition of the Human Papillomavirus (HPV) vaccine to available cytological screening has been proposed to increase HPV-related cancer prevention. A comprehensive review of this combined strategy implemented in the Netherlands is lacking. For this review, we, therefore, analyzed all relevant studies on cost-effectiveness of HPV vaccines in combination with cervical screening in the Netherlands. Most of the studies agree that vaccination in pre-sexual-activity periods of life is cost-effective. Based on published sensitivity analyses, the incremental cost-effectiveness ratio was found to be mainly driven by vaccine cost and discount rates. Fewer vaccine doses, the inclusion of additional benefits of these vaccines to prevent HPV-related non-cervical cancers as well, and vaccination of males to further reduce the burden of HPV-induced cancers are three relevant options suggested to be investigated in upcoming economic evaluations.

Keywords

Cost effectiveness, Cervical cancer, HPV vaccination, cervical cancer screening, The Netherlands

Introduction

Infection with Human Papillomavirus (HPV) is the primary cause of cervical cancer. HPV infection has been reported to be responsible for 250,000 deaths related to cervical cancer in the world annually. The World Health Organization (WHO) reported that cervical cancer is the fourth most common cancer in women (1). Within the many types of HPV known, several types of HPV (e.g., type 16, 18, 31, 33, and 45) are categorized into high-risk HPV (hrHPV) or carcinogenic types (2) and other types of HPV (e.g., type 6 and 11) are categorized into low-risk HPV (lrHPV) or non-carcinogenic types (3,4). Prevention of hrHPV infection will, therefore, provide protection against cervical cancer development.

In order to reduce the burden of cervical cancer, prevention strategies (primary and/or secondary strategies) have been introduced in both developed and developing countries (5). In developed countries, prevention strategies are done through both HPV vaccination (9-13-year-old girls) and cervical cancer screening (with or without hrHPV DNA detection), as primary and secondary prevention strategies (5), respectively. Currently, two commercially available HPV vaccines are on the market; i.e., a bivalent (6-9) and a quadrivalent (10,11) vaccine. Both vaccines have proven to be effective in preventing HPV infection, especially against type 16 and 18. Also, both vaccines have their own specific advantages. For example, cross protection to HPV type 31 and 45 was suggested in the clinical trials for the bivalent HPV vaccine, whereas the quadrivalent HPV vaccine provides protection to the lrHPV types 6 and 11 which are responsible for anogenital warts (10,12). Implementation of one of these vaccines within vaccination programmes may therefore relevantly reduce the burden of cervical cancer. Long term protection of the vaccines however yet has to be proven.
Yet, many countries still face relevant limitations in implementing cervical cancer prevention strategies (13), for example, regarding coverage rates and acceptance. Also, national budget impacts remain an important consideration. In the Netherlands, cervical screening was launched in 1976 for women of 30 years and over and this strategy reduced mortality rates associated with cervical cancer by approximately 50% and has been estimated to be cost-effective. In the context of health economic studies, several studies in the Netherlands confirmed that screening of HPV coupled with vaccination was cost-effective, compared to screening only (14-17). Also, the influence of catch-up vaccination for older women (18), vaccination of young boys, the combination of various screening methods and intervals (19) and reductions in vaccine dosing (20) have been explored.

We systematically reviewed the health economic studies of HPV vaccination in the Netherlands to provide integrated evidence and recommendations on cost-effectiveness in combination with the cervical cancer screening in The Netherlands. Moreover, we examined study results in detail to infer how they might have been influenced by various assumptions and parameters being varied in sensitivity analysis on the base-case. Finally, we come up with some recommendations based on our findings.

**Methods**

**Information sources and eligibility criteria of relevant studies**

In order to obtain all relevant evidence, we searched health economic studies of HPV vaccination and cervical cancer screening in the Netherlands from two major electronic databases (MEDLINE/PubMed and EMBASE), based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (21,22). The evidence was searched until January 2014 and the searching process was performed on January 20th, 2014. The following search terms were used in both databases: (HPV OR human papillomavirus) AND (vaccin* OR immune*) AND (cervical cancer OR cervical neoplasm) AND (economic analysis OR cost utility OR cost-effectiveness OR cost benefit OR cost minimization OR economic evaluation* OR pharmacoeconomics OR economic analysis). Selection criteria for the study were: (i) original study with the full economic analysis in the Netherlands, (ii) including HPV vaccination and screening and (iii) published in the English language. Up to now, a systematic review on HPV vaccination in the Netherlands has not yet been published internationally.

**Data extraction**

Two reviewers evaluated all articles retrieved, independently. If both reviewers did not agree for some reasons, the third reviewer also reviewed the study and conflict was resolved through consensus. We extracted important data from obtained studies based on the CHEERS (consolidated Health Economic Evaluation Reporting Standards) statement (23,24) and other criteria (25,26). From selected articles, we extracted the following information: first author; publication year; model type; perspective; time horizon;
strategies/comparator; discounting; cohort size; gender; age group; vaccine characteristics (coverage, effectiveness, cross protection, booster dose, and duration of protection); screening characteristics (coverage, intensity, adherence, and range of age); cost of treatment; incremental cost-effectiveness ratio (ICER) and sensitivity analysis performed. In order to make the results from each study comparable, the economic results of each study were updated to 2013 using inflation rates from the World Bank annual Consumer Price Index (27). If an article didn’t provide the index year, we assumed that the cost data were derived from the same year as the publication year.

Results

Literature search

From our systematic search, we found 358 and 33 articles from PubMed and EMBASE, respectively. We screened 370 articles after removing 21 duplicate articles. There were 358 articles excluded in the screening process, of which 165 articles were not health economic studies, 172 articles were studies outside the Netherlands and 21 articles were not written in English. Furthermore, in the assessment of full-text articles, we excluded two further studies since the first study was cervical cancer screening only and another study was methodologically focused on discounting in health economic analysis of HPV vaccination. Thus, a total of 10 articles were included in this study (Figure 1).

Figure 1. PRISMA Flow Diagram for selection of studies included in the study.

Subsequent tables present the comparison of base-case assumptions (Table 1), cost characteristics (Table 2), study results (Table 3) and sensitivity analysis (Table 4) from
Chapter 2

each study. Publication years range from 2009 to 2013 and six first authors from three different research groups were involved.

**Base-case assumptions**

**Scope of the study**

In health economics studies, the perspective and the time horizon that have been can be conceived as related subjects. To comprise the full impact of HPV vaccination, the implementation of the program should be considered from a broad perspective (e.g., societal perspective) within a long-term time frame. Moreover, the perspective chosen for a model should reflect the core considerations of the relevant decision makers involved. Societal perspective has been recommended to cover all costs, savings and outcomes of the disease and intervention involved. In this review, almost all studies (90%) applied this societal perspective, in line with Dutch overall recommendations for cost-effectiveness. To cover all possible costs, savings and outcomes of both HPV vaccination and cervical cancer screening, a lifetime horizon is crucial (28,29) and indeed most of the studies (80%) applied a lifetime horizon in their models (14,16-19,30-32).

Most of the studies (8) examined the cost-effectiveness of HPV vaccination for young girls aged 10-12 (14-17,19,30,32,33). Almost half of the studies (4) investigated the influence of adding HPV vaccination to cervical screening only (14-17). Moreover, two studies explored various strategies, either the addition of specific screening techniques to vaccination (16,19) or explicit comparisons between the quadri- and the bivalent vaccine (32). Coupe *et al.* also explored the influence of various screening strategies (HPV DNA versus cytology and 4-7 screenings during specific age periods) and cross-protection in addition to direct protection (19,30). Westra *et al.* and Bogaards *et al.* both explored various cut-off ages for catch-up strategies in addition to the recently introduced vaccination program(18,31).
Reviewing cost-effectiveness of HPV vaccination on top of screening in the specific Dutch context

Table 1. Comparison of base-case assumption on perspective, type of model, cohort number, strategies, time horizon, cycle length, gender, age group, vaccine characteristics, screening characteristics and annual discount rate used in cost-effectiveness study of HPV vaccination in the Netherlands

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Perspective</th>
<th>Type of model</th>
<th>Cohort Number</th>
<th>Strategies comparator</th>
<th>Time horizon</th>
<th>Gender Age Group</th>
<th>Vaccine characteristics</th>
<th>Screening Characteristics</th>
<th>Annual Discount Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coupé et al. 2009 (16)</td>
<td>Societal</td>
<td>Markov</td>
<td>100,000</td>
<td>no-Cs + no-Vacc Cs only Cs + Vacc</td>
<td>Lifetime 6 month</td>
<td>F 12</td>
<td>95 85 NS</td>
<td>Lifelong No</td>
<td>85 5 years 80 30-60</td>
</tr>
<tr>
<td>De Kok et al. 2009 (15)</td>
<td>Societal</td>
<td>MISCAN Model</td>
<td>100,000</td>
<td>Cs + Vacc only Cs only</td>
<td>NS NS</td>
<td>F 12</td>
<td>1.5 (HPV Inf) 35 (CIN) 70 (CC)</td>
<td>NS 85 NS</td>
<td>Lifelong Yes</td>
</tr>
<tr>
<td>Rogoza et al. 2009 (14)</td>
<td>Societal</td>
<td>Markov</td>
<td>100,000</td>
<td>Cs + Vacc only Cs only</td>
<td>Lifetime NS</td>
<td>F 12</td>
<td>95 100 Yes</td>
<td>Lifelong NS</td>
<td>90 5 years 80 30-60</td>
</tr>
<tr>
<td>Coupé et al. 2009 (19)</td>
<td>Societal</td>
<td>Markov</td>
<td>100,000</td>
<td>Vacc only Vacc + Cs*</td>
<td>Lifetime NS</td>
<td>F 12</td>
<td>95 100 NS</td>
<td>Lifelong Yes</td>
<td>90 5 years 80 30-60</td>
</tr>
<tr>
<td>Bogaards et al. 2011 (31)</td>
<td>Societal</td>
<td>Dynamic</td>
<td>NS</td>
<td>Vacc and Cs for 17-25 years old girls</td>
<td>Lifetime NS</td>
<td>F 17-25</td>
<td>100 50 NS NS NS NS</td>
<td>NS 90 5 years 80 30-60</td>
<td>4 1.5</td>
</tr>
<tr>
<td>Westra et al. 2011 (18)</td>
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<td>Markov</td>
<td>100,000</td>
<td>Cs + Vacc only Cs only</td>
<td>Lifetime 1 year</td>
<td>F 12-50</td>
<td>95 NS NS NS</td>
<td>Lifelong No</td>
<td>80 NS NS NS</td>
</tr>
<tr>
<td>De Kok et al. 2011 (33)</td>
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<td>Mathematical equation</td>
<td>100,000</td>
<td>Cs + Vacc only Cs only</td>
<td>NS NS</td>
<td>F** 12</td>
<td>100 100 NS NS NS NS NS NS NS</td>
<td>NS 90 5 years 80 30-60</td>
<td>4 1.5</td>
</tr>
<tr>
<td>Coupé et al. 2012 (30)</td>
<td>Societal</td>
<td>Markov</td>
<td>NS</td>
<td>Vacc only Vacc + CBPT Vacc + HPV DNA</td>
<td>Lifetime NS</td>
<td>F 10</td>
<td>95 NS NS NS</td>
<td>Lifelong NS NS</td>
<td>NS 8 strategies</td>
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<td>Westra et al. 2013 (32)</td>
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<td>Markov</td>
<td>100,000</td>
<td>QuadrivalentVA cc Bivalent vac</td>
<td>Lifetime 6 month</td>
<td>F 12</td>
<td>95 50 Yes NS NS</td>
<td>NS 90 5 years 80 NS</td>
<td>4 1.5</td>
</tr>
<tr>
<td>Lutjeboer et al. 2013 (17)</td>
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<td>Markov</td>
<td>NS</td>
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<td>F 12</td>
<td>92.9 100 Yes NS NS NS NS NS NS NS</td>
<td>NS NS NS</td>
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</tbody>
</table>

*From referenced paper; **based on Dutch guideline; *various strategy of cancer screening; **only evaluate cervical cancer

NS= not stated; CS = cancer screening; Vacc = vaccination; F = female; MISCAN = Microsimulation Screening Analysis; HPV = Human Papilloma Virus; CIN = Cervical Intraepithelial Neoplasia; CC = Cervical Cancer; CBPT = Cytology-Based Pap Test; HPV DNA = Human Papilloma Virus Deoxyribonucleic Acid.
Chapter 2

Type of model

Different types of models (static Markov, micro-simulation or dynamic) were used to measure the cost-effectiveness of HPV vaccination and cervical screening in the Netherlands, which was in line with international studies on the same topic (34-38). Static Markov models were used in most of the studies (n=7), with herd protection (decreased the risk of infection for unvaccinated individuals due to indirect protection) not being included in the model and probabilities, distributions and economic variables generally remaining stable over time (14,16-19,30,32). In particular, four studies used a previously developed static Markov model, with the advantage of requiring less complex modeling techniques (14,18,19,32). Two studies (15,30) used complex micro-simulation for the analysis of screening (MISCAN-model), providing results based on age- and time-specific parameters and distributions, and considering modeled cross-protection. Two further studies applied dynamic (31) and mathematical calculation (33) models. Dynamic models are generally most appropriate to describe the natural spread of infectious diseases since it is possible to take herd immunity into account. Nevertheless, the need for the amount of data is one of the limitations of such dynamic models. Obviously, the choice for static or dynamic models involves a trade-off of complexity versus data needs.

Vaccine characteristics

A cost-effectiveness study usually extrapolates future effects of the vaccine from available clinical trial data (e.g., short-term efficacy, cross protection, and duration of protection), in addition to several types of information related to vaccine application (e.g., coverage and booster dose) and potential real-life herd protective effects. Almost all of the studies (n=9) applied an efficacy of the vaccine from >90% and for those types included in the vaccine based on randomized clinical trials (14,16-19,30-33). One study specified vaccine effectiveness into three categories, which are 1.5% for HPV infection, 35% for development of CIN (pre-invasive lesions), and 70% for cervical cancer cases (15). Two studies (18,30) did not specify the vaccine coverage and two other studies (31,32) applied a coverage of 50% in their studies. Notably, for static models vaccine coverage may not (critically) influence cost-effectiveness estimates. Most of the studies did not include cross protection (n=7) or booster dosing (n=8) in their studies, and the majority of the studies (n=6) used lifelong vaccine protection as the core assumption in the base-case analysis.

Screening characteristics

Cervical cancer screening has been implemented in the Netherlands for many years. The information pertaining to its coverage (the ability of the program to reach the population at risk) and adherence (the willingness to undergo the screening) has been extensively reported (39). Seven studies provided the screening coverage information applied in their studies (14-16,18,19,31,32) and most of them (n=6) applied the screening intensity of once in every five years as it has been recommended in the Netherlands (14-
Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context

16,19,31,32). Two studies explored the influence of screening intensity on their results and investigated various combinations between HPV DNA and cytology testing (19,30). Half of the studies (n=5) described the impact of screening adherence in their models and all of them assumed an adherence rate of 80% for cervical screening in the base-case (14,16,19,31,32). Moreover, ranges of screening ages were investigated from 30 until 50 or 60 years old (16,19,30,31).

Discounting

Seven studies used annual discount rates at 4% and 1.5% for costs and health effects, respectively (14,16,18,19,30-32). These rates were explicitly based on the “update of the Dutch manual for costing in economic evaluations” (29). Two studies (15,33) used international recommendations (40,41) to apply discount rates at 3% for both costs and health effects. Only one study did not provide information related to the discount rates (17).

Cost characteristics

The index years and cost components are presented in Table 2. Most of the studies (n=6) clearly specified the index year for the costs ranging from 2006 until 2010 (14,16,17,19,30,31). The price of the vaccine employed in the studies varied from €170 to €368 for 3 doses of vaccine, sometimes including potential price cuts if included in a large-scale programme (14-19,31-33). Most of the studies (n=9) presented the cost for HPV-related cancer treatment (14-19,31-33) and half of them provided vaccine cost items in a detailed description (14-16,18,19). Compared to other studies, two studies obviously implemented higher costs of treatment for all stages of cervical cancer (14,32). In addition, there were only three studies (14,19,30) explicitly specifying direct and indirect non-medical costs on their studies, despite the importance of this specification for health economic studies which apply the societal perspective.
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<td>Conventional cytological screening</td>
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<td>57.73</td>
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<td>55.53</td>
<td>62.09</td>
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<td>8.28</td>
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<td>Colposcopy</td>
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<td>HPV DNA screening</td>
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<td>8.84</td>
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<td>Vaccine 3 doses</td>
<td>450.94</td>
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<td>Booster dose</td>
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<td>vaccine material</td>
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<td>Diagnosis, treatment, follow-up</td>
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<td>CIN0/False positive</td>
<td>350.67</td>
<td>288.52</td>
<td>388.64</td>
<td>382.09</td>
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<td>CIN1</td>
<td>1,520.76</td>
<td>902.58</td>
<td>1,634.01</td>
<td>1,664.37</td>
<td>1,635.83</td>
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<tr>
<td>CIN2</td>
<td>1,749.83</td>
<td>1,329.38</td>
<td>1,892.94</td>
<td>1,927.93</td>
<td>1,895.93</td>
<td>1,718.00</td>
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Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context

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<thead>
<tr>
<th>Condition</th>
<th>Cost (€)</th>
<th>Cost (€)</th>
<th>Cost (€)</th>
<th>Cost (€)</th>
<th>Cost (€)</th>
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<td>1,900.96</td>
<td>1,556.93</td>
<td>2,058.21</td>
<td>2,096.49</td>
<td>2,061.45</td>
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<td>10,380.88</td>
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<td>FIGO Stage 1B</td>
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<tr>
<td>Warts</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$</td>
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<tr>
<td>GPs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>114.00</td>
</tr>
<tr>
<td>STI clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>285.00</td>
</tr>
<tr>
<td>GPs + STI clinic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>338.00</td>
</tr>
<tr>
<td>Terminal care</td>
<td>27,077.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative care ≤50 years</td>
<td>48,683.69</td>
<td>48,683.69</td>
<td>46,125.66</td>
<td>$</td>
<td>$</td>
<td>$</td>
</tr>
<tr>
<td>Palliative care 50-70</td>
<td>34,700.95</td>
<td>34,700.95</td>
<td>32,877.81</td>
<td>$</td>
<td>$</td>
<td>$</td>
</tr>
<tr>
<td>Palliative care ≥70 years</td>
<td>14,771.03</td>
<td>14,771.03</td>
<td>13,994.83</td>
<td>$</td>
<td>$</td>
<td>$</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td></td>
<td></td>
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<tr>
<td>Penis cancer</td>
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<td>Vulva cancer</td>
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<td>Vaginal cancer</td>
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<td>Anal cancer</td>
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<tr>
<td>Oral cavity</td>
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<td></td>
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<tr>
<td>Oro-pharynx</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Direct non medical cost

| Travel expenses            | $                | $                | included         | included         | $                | $                |
| indirect non-medical cost  | $                | $                | included         | included         | $                | $                |

Productivity loss

| $                | $                | included         | included         | $                | $                | $                | $                |

* not included  $ not specified

HPV DNA = Human Papilloma Virus Deoxyribonucleotid Acid, CIN = Cervical intraepithelial Neoplasia, FIGO = The International Federation of Gynecology and Obstetrics, GPs = General Practitioners, STI = Sexually transmitted infections Clinic F = Female, M = Male, IT = Initial treatment, D = Death, LC = Late stage care, CC = Continuous care
**Chapter 2**

**Base-case results**

**Clinical outcome**

Since the effect of HPV vaccination on the prevention of cervical cancer could not be established in the clinical trials, the efficacy of vaccination in the reduction of cervical cancer incidence and mortality was predicted based on the reduction of anogenital warts and CIN lesions upon vaccination (10,11). Clinical and economic outcomes from each study are presented in Table 3. Most of the studies (n=7) expressed the outcome as cervical cancer cases reduction, which resulted from HPV vaccination and/or screening (14-16,18,19,30,32). Only one study provided a clinical outcome in terms of cervical cancer risk reduction ranging from 0.08% to 0.28%(31). A study by Westra et al. presented a full range of outcomes of HPV infection including anogenital warts, CIN, and cervical cancer cases.

**Incremental Cost**

In health economic studies, the incremental cost is the costs difference between two alternative interventions, e.g. costs of vaccination + screening vs. screening alone. Seven studies explicitly provided the incremental costs estimates between strategies (14-16,19,30,31,33). The highest incremental cost estimate (£1,806 per 100,000?) was obtained from a study by Bogaards et al. investigating HPV vaccination for older women. While the most favorable incremental cost (£19 per 100,000 vaccinated persons) was estimated from a study from de Kok et al. (33), which explored the impact of vaccination on all cancers related to HPV infection in both female and male populations. Overall, ranges of incremental cost among all studies are broad, related to different assumptions and parameters in the models. Specifically, the incremental cost attributable to HPV DNA testing (30) and catch up vaccination for older women (31) were estimated at £316-£453 and £347-£1,806 per 100,000 vaccinated women, respectively.
Table 3. Clinical (including life years gain and quality adjusted life-years) and economical outcomes from cost-effectiveness studies of HPV vaccination in the Netherlands

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Clinical outcome (reduction from previous stages)</th>
<th>Incremental Costs (€)</th>
<th>LYG</th>
<th>QALYs gained</th>
<th>Cost/LYG (€)</th>
<th>Cost/QALY (€)</th>
<th>Funding Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coupe et al. (2009)</td>
<td>CC cases: 61.0% CC-related death: 61.4%</td>
<td>372.31</td>
<td>NR</td>
<td>0.0167</td>
<td>NR</td>
<td>22,294</td>
<td>GSK</td>
</tr>
<tr>
<td>De Kok et al. (2009)*</td>
<td>CIN 2/3 cases: 36% CC cases: 60% CC-related death: 61%</td>
<td>241.20$</td>
<td>370</td>
<td>0.00410$</td>
<td>64,999.07</td>
<td>58,249</td>
<td>GSK</td>
</tr>
<tr>
<td>Rogoza et al. (2009)*</td>
<td>CC cases: 57% CC cases: 74%</td>
<td>31.88$</td>
<td>1,234</td>
<td>NR</td>
<td>25,011.47</td>
<td>20,384</td>
<td>NR</td>
</tr>
<tr>
<td>Coupe et al. (2009)</td>
<td>CC cases: 53%-76% CC-related death: 60%-81%</td>
<td>41.31-149.17</td>
<td>NR</td>
<td>0.0135-0.0182</td>
<td>NR</td>
<td>3,060-8,196</td>
<td>GSK</td>
</tr>
<tr>
<td>Bogaards et al. (2011)**</td>
<td>CC-risk reduction: 0.08%-0.28%</td>
<td>346.49-1,806.33</td>
<td>NR</td>
<td>0.0126-0.0347</td>
<td>NR</td>
<td>27,445-115,858</td>
<td>the 7th Framework Programme of DG Research and GSK</td>
</tr>
<tr>
<td>Westra et al. (2011)**</td>
<td>CC new cases: 50%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>20,907-54,738</td>
<td>GSK</td>
</tr>
<tr>
<td>De Kok et al. (2011)</td>
<td></td>
<td></td>
<td>NR</td>
<td>18.54$</td>
<td>915</td>
<td>NR</td>
<td>1,997.24</td>
</tr>
<tr>
<td>Coupe et al. (2012)</td>
<td>CC cases: 10%-47% CC-related death: 10%-71%</td>
<td>315.74-452.92</td>
<td>NR</td>
<td>0.0104-0.0228</td>
<td>NR</td>
<td>17,469-30,568</td>
<td>GSK</td>
</tr>
<tr>
<td>Westra et al. (2013)</td>
<td>QV AGW: 4,390 CIN-1: 91 CIN-2: 182 CIN-3: 237 CC: 207 BV AGW: 0 CIN-1: 106 CIN-2: 203 CIN-3: 264 CC: 221</td>
<td>NR</td>
<td>QV 606 BV 646</td>
<td>QV AGW: 0.00082 CIN-1: 0.00033 CP: 0.00709 Total: 0.00824 BV</td>
<td>QV 22,700 BV 21,500</td>
<td>QV 16,300 BV 17,600</td>
<td>GSK</td>
</tr>
<tr>
<td>Luttjeboer et al. (2013)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>7,676 (no CP) 6,250 (include CP)</td>
<td>NA</td>
</tr>
</tbody>
</table>

*based on 100,000 simulated women
**depend on age
$original results devided by 100,000
LYG = life year gain; QALYs = quality adjusted life years; CC = cervical cancer; N = not reported; CIN = cervical intraepithelial neoplasia; AGW = anogenital warts; QV = quadrivalent; BV = bivalent; NR = not reported; NA = not applicable; GSK = GlaxoSmithKline
Chapter 2

Life years and quality adjusted life years gained

Two ultimate effects of HPV vaccination and screening programs are Life Years Gained (LYGs) and Quality Adjusted Life Years (QALYs) gained. Four articles described LYGs as the main study outcome (14,15,32,33), with two of them mentioning identical research questions and approaches, but providing completely different LYGs (370 versus 1,234 per 100,000). These differences were primarily caused by the application of different discount rates in both studies (14,15). Generally, the bivalent vaccine yielded slightly higher LYGs but lower QALYs gained compared to the quadrivalent vaccine, with QALYs coming from protection against HPV-induced (pre-)cancer and cross protection as well as genital warts prevention.(32). The highest QALYs gained from HPV vaccination was obtained from a study by Bogaards et al., exploring vaccination for older women (QALYs gained at 0.0347 per vaccinated woman age 17-25) (31). The lowest QALYs gained resulted from a study by De Kok et al., which analyzed additional vaccination onto current screening in the Netherlands, related to specific assumptions and also a higher discount rate applied in the model (15).

Incremental cost-effectiveness ratio

The ICER was obviously often applied as the ultimate comparative outcome of cost-effectiveness analysis. The majority of the studies (n=6) concluded that HPV vaccination could be a cost-effective intervention, compared to the lowest Dutch cost-effectiveness threshold even mentioned (€20,000/QALY) (42). Studies by Luttjeboer et al. (17) and de Kok et al. (33) incorporated all types of cancer into the study, with correspondingly low ICERS (€6,250/QALY and €1,997/LYG, respectively). Another two studies from Coupe et al., which included cross-protective properties and other specific vaccine properties reported cost-effective results at €22,294/QALY and €17,469/QALY. Vaccination for older women (17-25 years old) was investigated by Westra et al. and Bogaards et al. and this strategy seems to be cost-effective as well. These results, however, impedes on the assumption of cross protection in the model, the vaccine price and a threshold for the willingness to pay in the Netherlands above €30,000 per QALY (18,31). Finally, comparison of two available vaccines was investigated by Westra et al., with the ICERS of the bivalent and quadrivalent vaccines estimated at €21,500/LYG or €17,600/QALY and €22,700/LYG or €16,300/QALY, respectively.

Funding

Generally, most studies (n=8) were funded by unrestricted research grants from GlaxoSmithKline (GSK) (15,16,18,19,30-33) and three of them were co-funded by either the 7th Framework Programme of DG Research through the PREHDICT project (30,31) or the Dutch National Institute for Public Health and the Environment (33). Moreover, almost all studies (n=9) clearly defined that the funding had no involvement in study design, data analysis, writing the manuscript or the submission of the study (15-19,30-33).
Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context

**Sensitivity analysis**

With uncertainty being a major issue in health economic modeling (43), sensitivity analysis is used to assess the effect of several assumptions related to costs and QALYs (25,26,44) produced. For policy makers, sensitivity analysis helps to recognize which parameters are the most sensitive for the ICER. Methods and parameters used in sensitivity analysis from all reviewed studies were described in Table 4.

<table>
<thead>
<tr>
<th>Author, (Year)</th>
<th>Methods</th>
<th>Sensitive parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Westra, <em>et al.</em>, (2011)</td>
<td>Univariate</td>
<td>Vaccine efficacy, Duration of vaccine protection, Vaccine price</td>
</tr>
</tbody>
</table>

In this review, all studies apparently performed univariate sensitivity analysis. In addition to univariate sensitivity analysis, two studies carried out probabilistic sensitivity analysis (14,17) by combining probability distributions and analyzing all possible outputs.
Furthermore, most of the studies (n=6) generally showed that ICERs were sensitive to vaccine price (14,15,17,18,31,32).

Coupe et al. (16) performed a one-way sensitivity analysis for vaccine efficacy, screening adherence, waning immunity, cross protection, attendance per screening round, and proportion of vaccinated women. Waning immunity was considered as the most sensitive parameter, it changed the ICER (cost per QALY gained) significantly from €22,294 into €27,539, €32,128, €40,160 for slow-, moderate- and fast waning scenarios, respectively.

Based on univariate sensitivity analysis in the study by De Kok et al. (15), there were three most sensitive parameters for the cost-effectiveness of adding HPV vaccination to the current situation: vaccine price, the incidence of cervical cancer, and the efficacy of HPV vaccination. The ICER would be below €20,000 per QALY gained if the vaccine price was below €44. Furthermore, changes in cervical cancer incidence would affect the ICER significantly, for instance when the incidence of cervical cancer in the Netherlands was changed to 50% of its current level and two times higher, the ICER would become €114,973 and €26,566, respectively. Also, if the effectiveness of the vaccine was reduced and increased by 20%, with the ICERs being €43,115 and €83, respectively.

Corresponding to the probabilistic sensitivity analysis (PSA), a study by Rogoza et al. presented a cost-effectiveness acceptability curve (CEAC) based on 1,000 Markov simulations (14). The result of the PSA showed that to obtain a 95% likelihood, the corresponding Willingness to Pay (WTP) would be €27,325. Therefore, many would consider this as a cost-effective intervention. Additionally, the univariate sensitivity analysis was also performed to investigate the impact of various input parameters (vaccine price, discount rate, duration of vaccine protection and booster dose for older women) on the ICERs. Only vaccine price and discount rate were found as the most influential parameters on the ICERs.

A study by Coupe et al. (19) explored the influence of various screening strategies in their univariate sensitivity analysis. In particular, another study by Coupe et al. (30) demonstrated that the ICERs for both without and with partial cross-protection were sensitive to waning of vaccine-induced immunity, screening adherence and the costs of HPV DNA testing.

Bogaards et al. performed univariate sensitivity analysis for various parameters based on three vaccine prices (€134.35, €69.86, and €37.62) (31). Specifically, introducing HPV vaccination in all 17-25 years old women in the Netherlands could be considered as a cost-effective intervention (€24,211/QALY). When cross-protection was included, the ICER was decreased to €15,836/QALY (31).

A study by De Kok et al. performed a multi-way sensitivity analysis by exploring the influence of World Standardised Rate (WSR), non-cervical HPV-positive cancer incidence, clinical costs level and vaccine price for the cost-effectiveness ratio (33). Based on their
results the authors concluded that the incidence of non-cervical HPV-positive cancer was the most sensitive parameter to the ICER.

From the univariate sensitivity analysis by Westra et al., it can be summarized that the ICER obtained from introducing vaccination in 17-25 years old women in the Netherlands was highly sensitive to the vaccine price (18). With the vaccine price of €68.29/dose and €47.28/dose, vaccination would be cost-effective and highly cost-effective for women <25 years old and women <30 years old, respectively, based on a threshold of WTP at €20,000. An additional study by Westra et al., which took both bivalent and quadrivalent vaccines into account, specifically compared two scenarios in the univariate sensitivity analysis: (i) best case (i.e., vaccine price €45/dose, lifelong protection, herd immunity and 0% discounting for both cost and utility) and (ii) worst case (i.e., vaccine price €105/dose, 20-years protection, no herd immunity, and 4% discount rate for both cost and utility)(32). The best scenario indicates cost-savings. In contrast to the best case scenario, the ICER in the worst scenario was much higher than Dutch WTP for both bivalent (€81,800/QALY) and quadrivalent vaccines (€66,500/QALY) (32).

Luttjeboer et al. performed a univariate and probabilistic sensitivity analysis, inclusive scenario analysis, to illustrate the level of uncertainty of the ICERS (17). Based on one-way deterministic sensitivity and scenario analysis, the discounted costs and QALYs appeared sensitive to vaccine price, discount rate, the cost of cervical cancer and Quality of Life of patients with cervical cancer. Moreover, the CEAC obviously showed that the probability of HPV vaccination being cost-effective is almost 100% if the ICER is below €9,351 per QALY gained.

Discussion and limitation

Cost-effectiveness studies of HPV vaccination in combination with cervical screening were reviewed. In this review, we found that most of the studies reviewed concluded that in the Netherlands vaccination in young girls at various ages would be cost-effective compared to cervical screening alone since the incremental cost-effectiveness per QALY lies below the lowest Dutch cost-effectiveness threshold ever suggested (€20,000/QALY). Our finding is in line with previous reviews from other countries, which confirmed that HPV vaccination is likely a cost-effective intervention (34-38).

We examined 10 published articles on HPV vaccination for young girls; most of the studies (n=8) used previously developed static Markov models to estimate the ICERS (14,16-19,30,32). Two other studies applied microsimulation models (15,30) and only one study applied a dynamic model (31). Since there was only this one dynamic model used among all studies, it was difficult to draw conclusions on the influence of the model chosen for the ICER. The proportions of model types that were used in cost-effectiveness studies have a similar pattern as reported in a review by Kim et al. (47). Nonetheless, the ICERs obtained from a dynamic model seems to be higher than those found in static models, which might be
caused by parameter value choices and the dynamic model also explicitly investigating the effect of HPV vaccination for older women. For infectious diseases such as HPV infections, a dynamic model is generally preferable since it also reveals the full effectiveness of the vaccines inclusive community-based acquired immunity (herd immunity) from such vaccination programs (48-50). Compared to static models, the use of dynamic models would require more complicated data (e.g., data related to sexual contact) but it will likely reduce potential biases in results. Yet, the full impact and mechanism of herd immunity are not fully understood and caution should be warranted when interpreting the results. For countries with a high coverage of vaccination, a static model may be sufficient to describe the cost-effectiveness of the vaccine. For example, for influenza vaccinations, it has been shown that both types of models provide comparable results in such situations where almost all individuals will be vaccinated and consequently no room for herd immunity benefits exists nor can be expected (51).

Some additional variables and assumptions were investigated to optimize the cost-effectiveness of cervical cancer prevention strategies in the Netherlands. Coupe et al. (16,19,30) explored several variables, such as various vaccine efficacies, screening strategies, types of HPV and waning immunity. Vaccination together with 4 times HPV DNA screening provides ICERs of €7,302/QALY with cross protection and €10,881/QALY without cross protection. Also, 7 times cytology screening at €19,192/QALY in addition to HPV vaccination appears to be cost-effective under particular assumptions related to vaccination (efficacy >95%, adherence 100% and lifelong protection). Notably, the assumption on screening coverage used in the model (>80%) was higher than that reported by Rebolj et al. (77% coverage) (39). This might lead an underestimate of the ICER from HPV vaccination compared to screening alone. This touches on an important issue since one of the main problems related to cervical cancer prevention strategy in the Netherlands is a sub-optimal coverage of screening (52). Regarding the cervical screening, Coupe et al. concluded that HPV vaccination could not replace cervical screening since HPV vaccination alone was less effective in preventing cervical cancer cases in women over 40 years of age than screening (16). This recommendation was consistent with that of Thiry et al. (53), who also proposed to implement HPV vaccination if a screening program is successfully performed. They also mentioned that various alternative strategies of screening and the incremental analysis suggested that 5 times HPV DNA detection plus cytological triage could still be a cost-effective intervention at €12,774 (unpublished data) (19).

Theoretically, cross protection will improve the prevention of HPV infection (54). The impact of cross-protection to other HPV types was analyzed by Westra et al. (32), Coupe et al. (30) and Luttjeboer et al. (17). These studies showed that cross protection properties will decrease ICERs far below the cost-effectiveness threshold applied in the Netherlands. In addition, they also took the effectiveness of the two currently available vaccines against non-cervical cancer into account. Both vaccines showed favorable cost-effectiveness in preventing cervical cancer incidence and mortality, however, only the quadrivalent vaccine had an impact on non-cervical disease. Compared to screening alone and considering
cervical cancer only, the ICER of the bivalent vaccine (€17,600/QALY) was slightly better than the ICER of the quadrivalent vaccine (€18,900/QALY). However, the quadrivalent vaccine was more favorable if anogenital warts cases were included in the analysis (ICER €16,300/QALY). These results are in line with the results from various other studies (55,56), which mentioned that mass HPV vaccination with the quadrivalent vaccine was slightly dominated by the bivalent vaccine. However, long-term results on cross-protection yet have to be provided.

Taking the effectiveness for non-cervical HPV-related cancer into account will improve the ICER and it is important to assess the economic impact of the HPV vaccination programs in this respect. In the studies reviewed here, Luttjeboer et al.(17) and de Kok et al.(15) took non-cervical cancer into account. Both authors concluded that this incorporation would decrease the ICER of HPV vaccination by 13% to 19%. Furthermore, various studies (57-60) agreed that one of the main drivers of the economic and epidemiological burden attributable to HPV infection in more-developed countries is non-cervical HPV-related cancer.

One adjacent promising strategy next to routine HPV vaccination is the organization of a catch-up program (38). This strategy offers HPV vaccination in older women (17-25 years old) to increase the effectiveness of the overall vaccination program. Two studies by Bogaards et al.(31) and Westra et al.(18) revealed that a catch-up program will reduce the lifetime risk of treatment for pre-cancerous lesions from 6.12% to 0.45% for the targeted groups in the catch-up program. Also, it will reduce the lifetime cervical cancer risk from 0.52% to 0.24%. Both studies also confirmed that the Dutch cut-off age of HPV vaccination at 16 years old could be a cost-effective choice. Based on the most stringent Dutch willingness to pay threshold at €20,000/QALY gained, vaccination for 12-16 years old girls was proven to be cost-effective, while if the threshold is increased, vaccination for up to 25 years old women was considered as reasonably cost-effective (61). Of course, in general, vaccine price is decisive for cost-effectiveness.

The weight given to health outcomes and money in the present has been agreed to be higher than their value in the future (26). In health economics studies, especially for cervical cancer prevention, implementing the appropriate discount rates is crucial to obtain accurate calculations. The discount rates for cost-effectiveness studies in the Netherlands are 4% and 1.5% for cost and health outcomes (28,29,62,63), respectively. Only a few countries/studies implement a different discounting for cost-effectiveness, for example, only studies performed in Taiwan (55) and Belgium (64) implemented a 3% annual discount rate for cost and 1.5% for utility. These studies were unique since most countries (65-67) implement equal discount rates for both parameters in their economic studies. Notably, exact recommendations on discounting are still under debate.

In order to maintain the independence of both the author and the study results, it is necessary to clearly specify the funding bodies and the role of the bodies in the study.
process. Although most of the studies supported by unrestricted educational grants from GlaxoSmithKline but all of them obviously defined that the funding body had no role in designing, writing or publishing the study.

From the sensitivity analyses, it can be concluded that vaccine price, discount rate and duration of protection were the most influential parameters on the ICER. These results were in line with the results from previous studies in other countries, which confirmed that the ICER of HPV vaccination has been considered to be sensitive to vaccine price (68,69) and discount rate (70-72). Regarding duration of protection, since most of the long-term effectiveness of the vaccine has not been obtained yet, authors were forced to use assumptions and/or intermediate outcomes for their model. Inappropriate assumptions employed in the model result in an under- or overestimation of ICERs. Therefore, sensitivity analysis ultimately plays an important role in health economic modeling.

It has been highlighted in previous studies that systematic reviews have a number of limitations. In this study, the searching process was performed only in PubMed and EMBASE as most used sources. Knowing the Dutch landscape, we are convinced not to have missed any relevant contributions. Most studies in this review did not include the complete benefit of HPV vaccination. It is known that the benefits of HPV vaccination are not only limited to cervical cancer, CIN and anogenital warts but also refer to recurrent respiratory papillomatosis (RRP) (73), adverse pregnancy outcomes (74), cross protection (54) and other (pre) cancerous lesions (i.e., penile, vaginal, vulvar and oropharyngeal) (75). The results of cost-effectiveness studies will be better when it would additionally include all these vaccine benefits.

Although we did not assess the quality of each study in detail, we found that in most studies – even when using previously developed models - the information related to the model was not always clear and sometimes difficult to assess by the reader. Here gains can be achieved, for example, by using guidelines on performing model-based cost-effectiveness studies (23,76,77), that advise that the model structure should be described, should be consistent and follow a coherent theory.

Generally, various cost-effectiveness studies attempted to predict the best strategy on how to implement HPV vaccination in the Netherlands. Notably, almost all studies agreed that vaccination for young girls is cost-effective. Investigating the influence of fewer doses of vaccination, exploring the advantages of catch-up programs and applying HPV vaccination in males will provide further details on optimal cervical cancer prevention strategies.

**Expert commentary**

Several modeling studies related to HPV vaccination have been explored by various researchers (78). Two-dose HPV vaccination for young girls has been considered as effective as 3-dose schedules (20). Since various studies confirmed that cost-effectiveness of HPV
Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context

vaccination is sensitive to vaccine price, the implementation of two doses of HPV vaccine next to existing screening strategies will be a promising strategy. Furthermore, parameters such as coverage and adherence to both vaccination and screening should be varied in sensitivity analyses in cost-effectiveness studies. Considering the full benefit of HPV vaccination by incorporating the HPV-related non-cervical cancer and using a dynamic model are important issues to provide all information on cost-effectiveness.

Five-year view

Since the natural history of HPV infection has been understood, it is possible to reduce the number of deaths caused by cervical cancer significantly through appropriate HPV vaccination and cervical screening. A new vaccine product has been developed which covers 7 oncogenic types of HPV (79). Moreover, the additional effect of a nine-valent HPV vaccine has been investigated (13,80,81). Both studies revealed a potential further reduction in cervical cancer incidence. New vaccines will enhance the competitiveness in the same market. A further reduction of prices for vaccination can be expected in the future. Since the ICER of HPV vaccination is obviously sensitive to vaccine price, lower vaccine prices of new vaccines will increase the cost-effectiveness ratio of HPV vaccination further. Also, significant reductions in the future national budgets allocated to cervical cancer prevention and therapy are possible even if the current price of the vaccine is relatively high compared to some other vaccines (82).

Key Issues

- The cost-effectiveness of HPV vaccination has been modelled extensively in previous studies and those studies show that vaccination of 12 to 16 years old girls is cost-effective.
- HPV Vaccination of older women in the Netherlands is potentially cost-effective.
- Vaccine price and discount rates are the most sensitive parameters for cost-effectiveness identified in this review.
- Taking cross protection and herd immunity into account will further reduce ICERs. Yet, such models require more complex data.

Acknowledgement

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Chapter 2

Reference

Papers of special note have been highlighted as:

* of interest


Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context


Chapter 2


* A complete example on how to report systematic review and meta analysis


* A comprehensive and easy to use reference on decision analytic modelling


Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context


Reviewing cost-effectiveness of HPV-vaccination on top of screening in the specific Dutch context


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