# Cost-effectiveness analysis of a gender-neutral human papillomavirus vaccination program in the Netherlands

Simons, Joost J. M.; Vida, Nora; Westra, Tjalke A.; Postma, Maarten J.

*Published in:*
Vaccine

*DOI:*
10.1016/j.vaccine.2020.05.031



*Publication date:*
2020

Vaccine 38 (2020) 4687–4694

Contents lists available at ScienceDirect

Vaccine

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

# Cost-effectiveness analysis of a gender-neutral human papillomavirus vaccination program in the Netherlands

Joost J.M. Simons [a,*], Nora Vida [b], Tjalke A. Westra [a], Maarten J. Postma [c,d,e]

[a] Market Access Department, GSK, Huis ter Heideweg 62, 3705 Zeist, the Netherlands
[b] Value Evidence Department, GSK, Avenue Fleming 20, 1300 Wavre, Belgium
[c] Department of Health Sciences, University of Groningen, University Medical Center, Hanzeplein 1, 9713 GZ Groningen, the Netherlands
[d] Unit of Pharmacotherapy, Epidemiology & Economics, University of Groningen, Groningen Research Institute of Pharmacy, A Deusinglaan 1, 9713 AV Groningen, the Netherlands
[e] Department of Economics, Econometrics & Finance, University of Groningen, Faculty of Economics & Business, P.O. Box 800, 9700 AV Groningen, the Netherlands

ARTICLE INFO

*Article history:*
Received 3 September 2019
Received in revised form 7 May 2020
Accepted 11 May 2020
Available online 23 May 2020

*Keywords:*
Human papillomavirus vaccine
Cost-effectiveness analysis
Gender-neutral vaccination
Modelling
Netherlands

ABSTRACT

*Background:* Vaccinating girls against human papillomavirus (HPV) infection is a highly effective and cost-effective intervention to provide protection against HPV-induced cancers. Since vaccination coverage rates among girls is modest in the Netherlands, additional strategies should be implemented to improve the protection against HPV-related cancer. Here we assessed the benefits and cost-effectiveness of gender-neutral vaccination.

*Methods:* We designed a static Markov model with a lifelong time horizon to simulate a cohort of 100,000 12-year-old Dutch boys. The model compares health and economic effects of HPV vaccination taking the current female vaccination coverage into consideration. HPV prevalence in boys was corrected for the predicted herd effects of the female programme in 2017. We extracted transition probabilities from peer-reviewed literature and previously constructed models. The robustness of the model was tested with multiple sensitivity analyses.

*Results:* Vaccinating 30% of 100,000 12-year-old boys prevents 18, 13 and 25 cases of anal, penile, and oropharyngeal cancers in men, respectively. A total of 205 quality-adjusted life-years (QALYs) are saved by preventing cancer-related morbidity and mortality. Assuming a vaccine price of €50 per dose, the incremental cost-effectiveness ratio (ICER) is €17,907 per QALY. In addition, due to vaccine-induced herd effects, we estimated that 110 cases of cancer in females would be additionally prevented and 246 QALYs would be gained in the female cohort, bringing the total to 166 cancers prevented and 451 QALYs gained. Taking these additional benefits of boys' vaccination into account, the overall ICER was estimated at €7310 per QALY gained. The model outcomes are most sensitive to variation in vaccine price, herd immunity from females and vaccine efficacy.

*Conclusions:* Vaccination of boys, additional to girls, will prevent a relevant number of cancers in both boys and girls. Based on the current Dutch situation vaccination of HPV in boys is likely cost-effective.

GSK Study identifier: HO-18-19169. A graphical abstract and supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.05.031.



## 1. Introduction

The human papillomavirus (HPV) is the most prevalent sexually transmittable infection in the Western world, and some types of HPV can cause cancer. Having a persistent oncogenic HPV infection is a known risk factor for ano-genital cancers [1]. Multiple types of cancer such as cervical, vulvar, vaginal, oropharyngeal, anal, and penile cancers are etiologically linked to infection with some oncogenic HPV types [2–4]. Vaccinating individuals against these oncogenic HPV types reduces the risk of developing cancer [2,4–7]. HPV vaccination was initially directed at women to prevent cervical cancer, which is the most prevalent HPV-related cancer. In particular, in women, vaccine efficacies for the AS04-HPV-16/18 vaccine and the 4vHPV vaccine against cervical intraepithelial neoplasia grade 3 or worse (CIN3+) were found to be 93% and 43% respectively, regardless of HPV type [8,9]. For the 9vHPV vaccine an overall efficacy was estimated to be roughly 76% against high grade cervical lesions [10]. In 2008, the Dutch government decided to add the AS04-HPV-16/18 vaccine to the national immunization program. The primary aim of the

* Corresponding author.
*E-mail addresses:* joost.j.simons@gsk.com (J.J.M. Simons), nora.x.vida@gsk.com (N. Vida), tjalke.t.westra@gsk.com (T.A. Westra), m.j.postma@rug.nl (M.J. Postma).

https://doi.org/10.1016/j.vaccine.2020.05.031
0264-410X/

vaccination program was to reduce the burden of cervical cancer in women [11]. Based on current evidence that HPV vaccination also provides protection against noncervical cancers, the potential benefits of the vaccination program are broader than previously anticipated [12].

Men are also at risk for HPV-induced cancers such as penile, anal, and oropharyngeal cancer. HPV is responsible for 86%, 56% and 29% of anal, penile and oropharyngeal cancers, respectively [2,13,14]. Although incidence of HPV-induced cancers in men is lower compared to females, over 300 men still develop HPV-induced cancers in the Netherlands, annually [15]. Over the last couple of years, the incidence of HPV-related cancers in males has been increasing in the Netherlands and internationally [16]. Contrary to women, >90% of HPV-induced cancers in men are caused by HPV-16 or HPV-18 and the HPV vaccines were found to be highly immunogenic and effective in men [17].

Therefore, a gender-neutral HPV vaccination could (or should be expected to) further reduce the burden of HPV-induced cancers in the Netherlands.

Vaccinating boys would not only decrease the incidence of male cancers, but also reduce the burden in the female population due to herd protection [18]. In the Netherlands, vaccination coverage among girls has varied over the years from a maximum of 65% to a recent estimate of 45% [11]. Due to this modest vaccination coverage, a substantial group of women and men are still at risk of being infected with HPV and developing HPV-induced cancers later in life. Previous cost-effectiveness analyses assessed the cost-effectiveness of a male vaccination program internationally [19], and nationally [20]. Moreover, there have been many models developed in the past looking at female and gender-neutral vaccination [6].

However, not all studies included all types of HPV-induced cancers that could potentially be prevented by vaccination. The clinical and economic benefits of male vaccination against HPV in some of these studies could have been underestimated.

Here, we aim to assess the cost-effectiveness of a gender-neutral HPV vaccination program in the Netherlands. In particular, we estimate the long-term effects of adding boys to the current female-only HPV vaccination program, without taking the positive effects of the female program into account and thus estimating the added benefit of boys' vaccination rather than the combined benefit. Although these analyses are specific for the situation in the Netherlands, results are also relevant for other countries with a modest vaccine uptake with a female-only HPV vaccination program.

## 2. Material and methods

### 2.1. Model overview

The model developed reflects a lifetime multi-stage static Markov approach with time cycles of one year, comparing boys' HPV vaccination with the current situation of the female-only strategy. The simulated boys/men will move from one health state to the other. For every one-year cycle, multiple transition probabilities are set with age dependency were data was available. An overview of the model structure is shown in Fig. 1. Markov models have been used in the past extensively for health-economic modelling [21]. The model was developed in Microsoft Excel 2016 with developer visual basic analysis (VBA) 2016. We simulated a cohort of 100,000 boys from an age of 12 years onwards. In the base case, we assumed that 30% of these boys were vaccinated at the age of 12 years with two doses of the AS04-HPV-16/18 vaccine. Model input parameters, including HPV prevalence, cancer incidence and natural mortality are based on Dutch data sources [22]. According to Dutch pharmacoeconomic guidelines, all future costs and quality-adjusted life-years (QALYs) were discounted at 4% and 1.5%, annually, respectively [23]. The analyses all have a healthcare-payer's perspective.

### 2.2. Utilities

Health-state specific utilities used in the model are shown in Supplementary Table 1. Utilities of healthy states (i.e., in the absence of HPV disease) are assumed as "perfect health" with a utility corresponding to that specific age, ranging from 0.96 to 0.81 for 12 years old and >85+ years old, respectively. Also, the cancer pre-stages (i.e. anal intraepithelial neoplasia, oral intraepithelial neoplasia and penile intraepithelial neoplasia) were assumed to be "perfect health" as generally most of the pre-stages of male HPV cancers are asymptomatic and remain undiagnosed. However, for some pre-stages, symptoms could occur [24]. The perfect health utility was applied in the model as an age-dependent variable, decreasing it as age increases [25].

Cancer utilities were adapted from a utility estimation study by Conway et al. [3]. By using a standard gamble questionnaire with 10 true/false questions, they estimated utilities for anal cancer, penile cancer and oropharyngeal cancer of 0.57 (0.52–0.62), 0.79 (0.74–0.85) and 0.58 (0.53–0.63), respectively.

Utilities after cancer survival were adapted from a systematic review, which reported utilities for anal cancer, penile cancer and oropharyngeal cancer of 0.866, 0.85 and 0.752, respectively [26]. Life-years gained were estimated using the cancer-specific survival rates derived from the Dutch Cancer Registry [15].

### 2.3. Costs

Supplementary Table 2 provides an overview of all costs used in the model. Costs used in the model were updated to 2018 price levels using the price indices provided by the Central Bureau of Statistics (CBS) to correct for inflation [27].

Vaccination costs were set at €50 per dose with an added €13.81 for administration costs with every dose [23,28]. With 2 doses provided, the base-case cost adds up to €127.62 per vaccinated boy. The vaccine costs are varied between €50 to €105 (list price) per dose in the scenario analysis to evaluate their effect on the incremental cost-effectiveness ratio (ICER).

Costs for cancer treatment and care are considered to comprise of those costs during survival, as well as the costs for a cancer death [29]. Costs for cancer death were set to €22,051 per case, taking into account the final year of treatment. The costs per case of cancer were €5460, €4368 and €6552 for anal, penile and oropharyngeal cancer, respectively. These costs were estimated by using Dutch administrative "diagnosis treatment combinations" (DBCs in Dutch). The fixed prices for reimbursement per DBC were based on information about unit costs of healthcare services and the average number of healthcare services applied per cancer treatment, thus taking into account the different gradings of cancer and averaging them [29].

### 2.4. Vaccine characteristics

In line with the current vaccination scheme for adolescent girls and the AS04-HPV-16/18 vaccine summary of product characteristics [30], a two-dose scheme was assumed for 12-year-old boys. Vaccine efficacy used in this model was derived from a clinical study in girls by Lehtinen et al. 2012 [8]. They found that the efficacy of the AS04-HPV-16/18 vaccine for CIN3+ is 100% for HPV-16 and HPV-18 after 4 years.

Cross protection against other types of HPV was not assumed in the base-case analysis. Due to lack of data, in this model we assumed an effectiveness in boys which was comparable to that

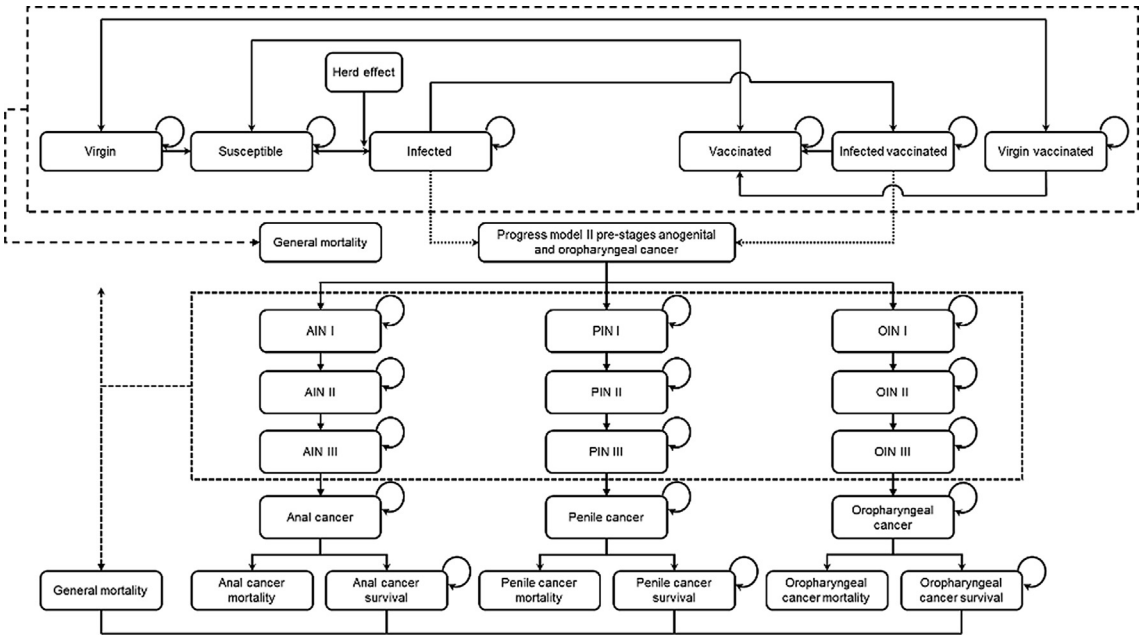


**Fig. 1.** Model overview. AIN, anal intraepithelial neoplasia; OIN, oral intraepithelial neoplasia (fictive, used for calculations); PIN, penile intraepithelial neoplasia.

in girls found in the past. In the scenario analysis, the added value of cross protection against other high-risk types (HPV-31-33-45-52-58) was evaluated. Lehtinen et al found that there was an overall efficacy of 93.2% against CIN3+ infection irrespective of HPV type. When assuming 100% protection for HPV-16/18 and correcting for the number of infections due to HPV-16/18, we calculated a vaccine efficacy of 82.4% against all other high-risk types, resulting in an overall 93.2% protection. The efficacy data is confirmed in real-world data from Scotland, showing an overall reduction in CIN3+ of around 90% [31,32].

No waning of vaccine-induced immunity was assumed since long-term antibody responses are seen in girls, we assume that a comparable immune response will be seen in boys [33].

Approximately 46% of all Dutch girls were vaccinated in 2018, with the coverage rate decreasing in the recent years from 61% in 2015 [11]. A coverage rate for Dutch boys of 30% per year was assumed, meaning that 30,000 boys are vaccinated in addition to girls in the hypothetical cohort.

Important to note is that a static model was used, so that cost-effectiveness is not sensitive to the coverage applied. However, the assumed potential herd effects should of course be conceived as being sensitive to the degrees of coverage among both the 12-year-old girls and boys. Notably, according to Bogaards et al. [5] approximately 37% of all male HPV-related cancers are prevented when 60% of girls would be vaccinated. Based on this, the proportion of male HPV-related cancers prevented for different vaccine coverages was calculated assuming a linear correlation. In the base case, when vaccinating 45.5% of all girls which is similar to the Dutch HPV-vaccination coverage, a correction factor of 28% was applied to correct for the herd immunity of girl vaccination.

In the scenario analyses, the prevented cancer rate due to herd immunity from girls to boys was varied between 10% (vaccinating ±15% girls) and 80% (vaccinating 100% girls), to simulate the effect of increasing/decreasing girls' vaccination coverage on the ICER for boys' vaccination. An overview of all assumptions is shown in Supplementary Table 3.

In the base case analysis, only herd effects from girls to boys were taken into account, in scenario analysis the herd effects from boys to girls were added to simulate the impact on the full cohort.

### 2.5. Univariate deterministic sensitivity analysis

The univariate deterministic sensitivity analysis (DSA) was performed to assess the impact of specific variables on the model predicted outcome. All key parameters were included in the DSA and were varied by ±20% compared with the base case. The impact on the ICER is visualized in a tornado diagram.

### 2.6. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was performed to assess the degree of uncertainty in the outcome measure and the robustness of the results. For the PSA, we used 10,000 simulations for the ICER plane and calculations. A scatterplot in an ICER plane and cost-effectiveness acceptability curve (CEAC) were plotted to visualize the probability of the intervention being cost effective at certain willingness-to-pay thresholds. All transmission probabilities, costs and utilities that are not cycle-/age-dependent were implemented in the PSA. For all costs a Gamma distribution was used, and for all transition probabilities and utilities a Beta distribution (0–1) was used.

### 2.7. Scenario analysis

In the scenario analyses, several scenarios were performed based on different assumptions. In particular, the cost of the vaccine was varied between €50 and €105 per dose, the impact of different coverage rates among females (0–90%), vaccine-induced cross-protection and different discount rates for costs and effects were assumed.

Finally, we estimated the impact of adding boys to the Dutch vaccination program on the incidence of female cancers. The benefit of preventing female HPV-induced cancers was implemented by adding the discounted QALY gains to the QALY gains in men and subtracting the costs prevented in cancer care from the total costs in the male model. Based on previously published literature, we estimated the total discounted QALY loss and discounted costs per cervical cancer case at 3.95 QALYs and €17,800, respectively [26,29].

An overview of all model input variables is shown in Supplementary Table 4. HPV infection rates were included based on a previous HPV model [34,35]. As the risk of HPV infection depends on sexual behavior, the HPV infection rate is the highest in the age group 20–30 years. HPV-type specific disease progression and regression probabilities in male HPV-related disease, were based on cervical cancer disease progression and regression rates [36]. To allow for taking different infection-related parameters into account, the model was split for each HPV type and by each cancer type. Five-year survival rates were derived from Dutch data [15]. Herd effects due to female vaccination on male cancer incidence were set at 28% by decreasing the risk of infection in the male population. Moreover, a 10% herd effect after vaccinating males on female cancer incidence was assumed in the scenario analysis [20].

## 3. Results

In line with observations from the Netherlands, our model predicts 198 HPV-induced cancers in an unvaccinated cohort of 12-year-old boys during lifetime after vaccinating 45.5% of girls. The incidence decreases to 142 HPV-induced cancers after vaccinating 30% of boys. A total of 56 HPV-induced cancer cases could be prevented (Table 1), resulting in a number needed to vaccinate of 536.

In the univariate DSA, the ICER was found to be most sensitive to the degree of herd immunity from the female population (Fig. 2). Indeed, assuming a higher vaccine coverage among females will reduce the burden of HPV-induced disease in the male population and consequently HPV vaccination of males will become less favorable. Moreover, the ICER was sensitive to the vaccine cost and vaccine efficacy.

The scatterplot with the simulations from the PSA is shown in Fig. 3. The CEAC shows the probability of the vaccination being cost effective with the current parameters and a specific threshold. Whenever the willingness-to-pay threshold exceeds €22,000 there is an estimated 100% likelihood of HPV vaccination boys for being cost effective. At €20,000 this likelihood is 94% (Fig. 4).

To represent a tender-based setting, the vaccine cost was varied between €50 and €105 per dose. This resulted in ICER values of €17,907 (€50 being the vaccine cost in the base-case scenario), €22,295 (€65), €28,145 (€85) and €33,995 (€105).

In males, most cancers are caused by HPV-16 and HPV-18 (>90%) and therefore the expected benefit of cross-protection is small [11, 18, 19, 33]. The ICER became more favorable, shifting from €17,907 to €17,115 per QALY.

In sensitivity analysis, the robustness of model outcomes to the effects of discounting was assessed. In the base case QALYs and costs were discounted at 1.5% and 4% respectively. As a first scenario, we disabled discounting for both effects and costs, which resulted in an ICER of €4539 (Table 2). As a second and third scenario, we discounted the health benefits and costs both by 3% and 4%. These new scenarios resulted in an increase of our base-case ICER, respectively. Finally, we assessed the impact of changing both discounting rates to 1.5% which is according to the discounting rates used in the HPV advice of the Joint Committee on Vaccination and Immunisation, resulting in an ICER of €15,596 (Table 2).

By taking all HPV-induced male cancers into account, HPV vaccination of boys is likely cost-effective in addition to the girls-only program with an estimated ICER of €17,907, as shown in Table 3.

Due to herd immunity from male vaccination to the female population, we conservatively estimate that an additional 10% of female HPV-related cancers would be prevented with male vaccination. This results in a total of 111 cases of HPV-induced female cancer, consisting of vaginal (4 cases), vulvar (1 case), cervical (76 cases), oropharyngeal (19 cases) and anal cancer (11 cases). The total QALY gain increased from 205.11 to 451.38, the incremental costs decreased from €3,672,920 to €3,299,759. Consequently, the ICER was found to be highly sensitive to these additional benefits in girls and improved from €17,907 to €7310 per QALY.

**Table 1**
Impact of AS04-HPV-16/18 vaccination on prevention of HPV-induced cancer cases and by type in 12-year-old Dutch boys.

| | Vaccinated | Unvaccinated | Prevented cases |
|---|---|---|---|
| Anal cancer | 43 | 62 | 18 |
| Penile cancer | 35 | 47 | 13 |
| Oropharyngeal cancer | 64 | 90 | 25 |
| **Total**[a] | **142** | **198** | **56** |

[a] The total of cancer cases could have be affected by the rounding of the types of cancer cases.

## 4. Discussion

The ASO4-HPV-16/18 vaccination program is an effective and cost-effective intervention, providing protection against HPV-induced cancers in males and females. Our results show that by vaccinating 30,000 boys annually in addition to the girls' program

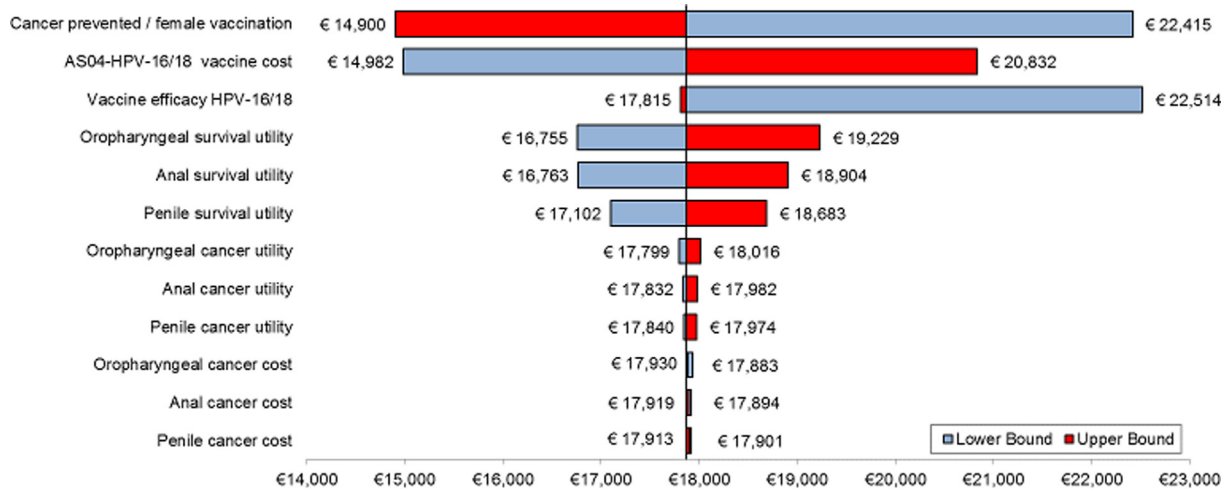


**Fig. 2.** Deterministic sensitivity analysis results of ICER for AS04-HPV-16/18 vaccination. The vertical line represents the base case of €17,907. HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio.

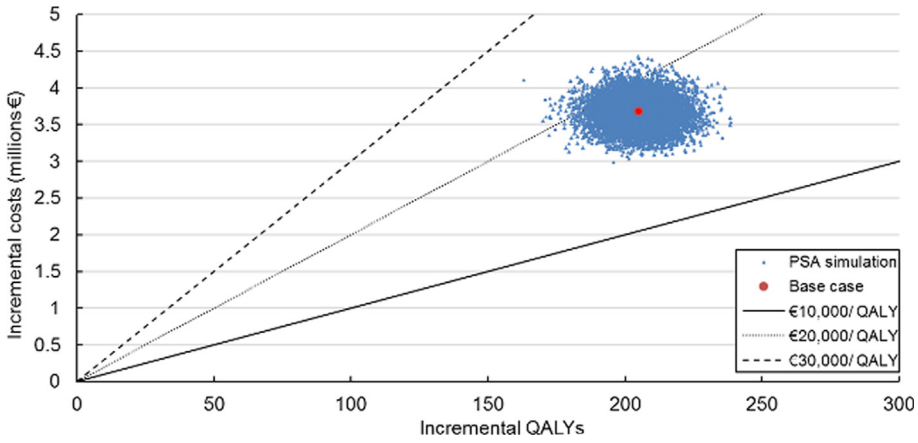


**Fig. 3.** Incremental costs vs. incremental QALYs from 10,000 probabilistic sensitivity analysis simulations. PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

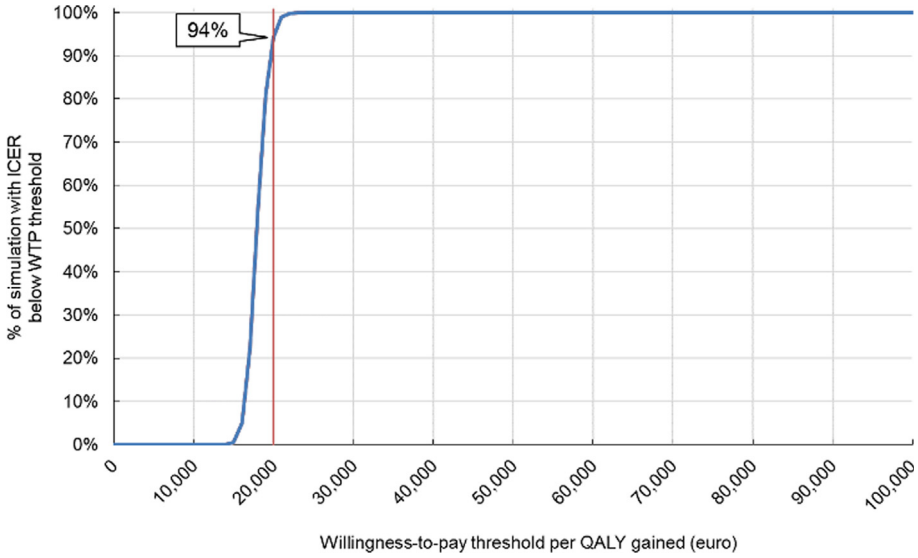


**Fig. 4.** Cost-effectiveness acceptability curve for implementing AS04-HPV-16/18 vaccination for boys. ICER, Incremental Cost effectiveness Ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

**Table 2**
Results of all scenario analysis (discounted).

| Subject | | ICER (€/QALY) | ▲QALY | ▲Costs |
|---|---|---|---|---|
| Base case | | € **17,907**[a] | 205.11 | €3,672,920 |
| Vaccination cost | | | | |
| | € 50[a] | € 17,907[a] | 205.11 | €3,672,920 |
| | € 65 | € 22,295 | 205.11 | €4,572,920 |
| | € 85 | € 28,145 | 205.11 | €5,772,920 |
| | € 105 | € 33,995 | 205.11 | €6,972,920 |
| Male cancers left after girls' vaccination | | | | |
| | 20% (±90% vaccination coverage of girls) | € 64,756 | 58.44 | €3,784,530 |
| | 40% | € 32,329 | 115.72 | €3,741,117 |
| | 63% (±60% vaccination coverage of girls – 2015) | € 20,483 | 180.25 | €3,691,947 |
| | 72%[a] (±45% vaccination coverage of girls – 2017) | € 17,907[a] | 205.11 | €3,672,920 |
| | 100% (No girl vaccination) | € 12,856 | 281.16 | €3,614,471 |
| Cross protection | | € 17,115 | 214.31 | €3.667.912 |
| Discounting | | | | |
| | 4% Costs/1.5% QALYs[a] | € 17,907[a] | 205.11 | €3,672,920 |
| | 4% Costs/4% QALYs | € 79,607 | 46.14 | €3,672,920 |
| | 3% Costs/3% QALYs | € 42,742 | 83.25 | €3,558,346 |
| | 1.5% Costs/1.5% QALYs | € 15,596 | 205.11 | €3,198,955 |
| | 0% Costs/0% QALYs | € 4539 | 513.87 | €2,332,564 |
| Full Scope scenario | | € 7310 | 451.38 | €3,299,759 |

[a] Base case. ▲ Difference between modeled incremental costs and incremental QALY; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

**Table 3**
Discounted and undiscounted ICERs for QALYs and life-years gained.

| Scenario | Incremental cost | Incremental effect | ICER |
|---|---|---|---|
| Incremental cost per QALY (discounted) | € 3,672,920 | 205.11 QALYs | € 17,907/ QALY |
| Incremental cost per life-year gained (discounted) | € 3,672,920 | 178.38 LYs | € 20,591/ LY |
| Incremental cost per QALY (undiscounted) | € 2,332,564 | 513.87 QALYs | € 4539/ QALY |
| Incremental cost per life-year gained (undiscounted) | € 2,332,564 | 454.47 LYs | € 5133/ LY |

ICER, incremental cost-effectiveness ratio; LY, Life Years; QALY, quality-adjusted life-year.

the Netherlands, we could potentially prevent 56 and 111 cases of cancer in boys and girls, respectively, and save a total of 451 QALYs. The incremental costs per QALY gained were estimated at €17,907 for boys and €7310 when the effects of girls were taken into account as well.

Currently, the AS04-HPV-16/18 vaccine is licensed for the prevention of anal cancer in males [30]. However, it is likely that the vaccine also provides protection against other HPV-related cancers, such as penile cancer and oropharyngeal cancer, which are taken into account in the base case resulting in an ICER of €17,907. Moreover, considering benefits in the female cohort due to the herd effects, the ICER improved to €7310 which is considered very cost-effective. This is far below the cost-effectiveness threshold of €80,000/QALY which is generally applied for therapeutic oncology interventions and below the threshold of €20,000/QALY for preventive interventions [23]. The ICER was most sensitive to assumptions on indirect effects of the female-only vaccination strategy, vaccine price and vaccine efficacy versus HPV-16/18.

Obviously, the benefits in the male population depend on the degree of herd immunity in the Dutch population due to the current female vaccination program. If vaccination coverage in females increased, and thus more male cancers were prevented due to herd immunity, the male vaccination program would become less cost effective, as seen in the scenario analysis with variating vaccination coverage in females. This has already been shown in previously published literature [37,38]. If vaccination coverage in females increased to 90% (comparable to paediatric vaccination coverage), Bogaards et al. [5] estimated that the HPV-induced cancers in males would be reduced by 66%. Consequently, taking this reduction into account, the ICER was estimated to be €36,422 when considering all remaining HPV-induced male cancers. However, it is unlikely that the vaccination coverage rate would increase to this extend in the short term as the vaccination coverage has been around 60% since the start of the program in 2009 and even lower in more recent years [11].

There are no efficacy data in males currently available for the AS04-HPV-16/18 vaccine. However, based in a clinical trial the immunogenicity of the AS04-HPV-16/18 vaccine in males was shown to be equal to that of the female population [17].

Almost all HPV-related cancers in men are caused by HPV-16 and HPV-18 which means that the ICER is most sensitive to the efficacy against these types. Considering the benefits of cross-protection against additional high-risk HPV-types resulted in a slightly more favorable ICER.

HPV infection and disease prevalence in females have intensively been investigated in the Netherlands [33,39]. However, less is known about the HPV-related disease impact among males. For example, limited prevalence data on pre-malignancies are available. To simulate the progression from HPV infection to cancer in males in the model, we needed to include these premalignancies in our model. However, no costs and QALY losses were assumed. Therefore, the predicted economic and clinical saving can be considered as conservative [24]. No dynamic cost-effectiveness model was developed to simulate the transmission of the HPV between males and females due to data limitations. To correct for the female strategy, we applied a fixed reduction on the male infection probabilities as previously described, which was varied in scenario analyses to simulate a changing vaccination coverage in the female population [5]. This assumption reduced model complexity and uncertainty and improved model transparency. Once more data become available on HPV disease characteristics in males, vaccination coverage in males is known, and the vaccination coverage is stable among females, a dynamic model design is recommended [37,40].

The low vaccination coverage in females does not provide enough herd immunity to protect men from developing preventable HPV-induced cancers. Over the last couple of years more has been discovered about the attribution of HPV to anogenital and oropharyngeal cancers in males and females. The contribution of HPV in oropharyngeal cancers in men is rising rapidly and more different cancer types are being linked to an HPV infection [41].

We did not assume any waning of vaccine effectiveness in our model. For instance, adding vaccine waning after 20 years would not have a big impact on the disease burden. The reason for this is the fact that most of the infections will already take place before the 32th life year and thus the vaccine would have already proven its worth [35].

Published research shows that increasing vaccination coverage in girls is the most cost-effective way of improving prevention of HPV cancer types [5,42]. However, even a high vaccination coverage of over 90% in girls does not provide enough protection to eradicate all HPV-related cancers in men and women. Countries like the United States, Australia and the United Kingdom have already started with gender-neutral vaccination to optimally protect men and women and move closer to eradicating HPV-related cancers [43,44]. As of 2019 there is a positive recommendation in the Netherlands to add boys to the current girls-only vaccination program. Boys are expected to be vaccinated starting 2021.

With the relatively low vaccination coverage in girls and tender-based pricing, a male vaccination program will likely be cost effective, assuming a threshold value of €20,000 per QALY used for preventive interventions.

Finally, our modeling exercises and cost-effectiveness analysis show that vaccination for boys is a cost-effective addition to the current girls-only HPV vaccination program. Over 150 cancer cases could additionally be prevented and a considerable number of QALYs could be gained by implementing gender-neutral vaccination and thus better protecting males and females against HPV-induced ano-genital and oropharyngeal cancers.

## 5. Authors' contributions

All authors attest they meet the ICMJE criteria for authorship; specific contributions are included below. All authors reviewed the version of the manuscript to be submitted and agreed with its content and submission.

J.J.M. Simons: Conception, design of the study, model construction, data collection, data interpretation, conduct of the study, critically reviewing or revising the manuscript for important intellectual content, manuscript writing.

N. Vida: Conception, design of the study, data collection, data interpretation, critically reviewing or revising the manuscript for important intellectual content.

T.A. Westra: Conception, design of the study, data collection, data interpretation, conduct of the study, critically reviewing or revising the manuscript for important intellectual content.

M.J. Postma: Conception, design of the study, data collection, data interpretation, critically reviewing or revising the manuscript for important intellectual content.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J.J.M. Simons, N. Vida and T.A. Westra are employed by the GSK group of companies. T.A. Westra holds shares in the GSK group of companies. M.J. Postma declares outside of the submitted work grants and personal fees from MSD, GSK group of companies, Pfizer, Boehringer Ingelheim, Novavax, BMS, Astra Zeneca, Sanofi, Asc Academics and IQVIA. M.J. Postma declares outside of the submitted work grant from Bayer and BioMerieux. M.J. Postma declares outside of the submitted work personal fees from Quintiles, Novartis, Pharmerit and Ingress Health. M.J. Postma declares outside of the submitted work to hold shares from Ingress Health (20%) and from PAG Ltd (100%). M.J. Postma declares outside of the submitted work non-financial support from Asc Academics and to be an adviser for this company.

## Acknowledgments

The authors would like to thank GSK reviewers for their support and review. The authors would like to thank Business & Decision Life Sciences platform for editorial assistance and manuscript coordination, on behalf of GSK. Matthieu Depuydt coordinated manuscript development and editing support.

## Funding

GlaxoSmithKline Biologicals SA was the funding source and was involved in all study (GSK study identifier: HO-18-19169) activities and overall data management (collection, analysis and interpretation). GlaxoSmithKline Biologicals SA also funded all costs associated with the development and the publishing of the present manuscript. All authors had full access to the data and the corresponding author was responsible for submission of the publication.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.05.031.

## References

[1] Schiller JT, Day PM, Kines RC. Current understanding of the mechanism of HPV infection. Gynecol Oncol 2010;118(1 Suppl):S12–7. https://doi.org/10.1016/j.ygyno.2010.04.004.
[2] De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124(7):1626–36. https://doi.org/10.1002/ijc.24116.
[3] Conway EL, Farmer KC, Lynch WJ, Rees GL, Wain G, Adams J. Quality of life valuations of HPV-associated cancer health states by the general population. Sex Transm Infect 2012;88(7):517–21. https://doi.org/10.1136/sextrans-2011-050161.
[4] Hartwig S, St Guily JL, Dominiak-Felden G, Alemany L, de Sanjose S. Estimation of the overall burden of cancers, precancerous lesions, and genital warts attributable to 9-valent HPV vaccine types in women and men in Europe. Infect Agent Cancer 2017;12:19. https://doi.org/10.1186/s13027-017-0129-6.
[5] Bogaards JA, Wallinga J, Brakenhoff RH, Meijer CJ, Berkhof J. Direct benefit of vaccinating boys along with girls against oncogenic human papillomavirus: bayesian evidence synthesis. BMJ 2015;350:h2016. https://doi.org/10.1136/bmj.h2016.
[6] Brisson M, Bénard É, Drolet M, Bogaards JA, Baussano I, Vänskä S, et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Lancet Public Health 2016;1(1):e8–e17. https://doi.org/10.1016/S2468-2667(16)30001-9.
[7] Giuliano AR, Palefsky JM, Goldstone S, Moreira Jr ED, Penny ME, Aranda C, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. N Engl J Med 2011;364(5):401–11. https://doi.org/10.1056/NEJMoa0909537.
[8] Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsagué X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13(1):89–99. https://doi.org/10.1016/S1470-2045(11)70286-8.
[9] Di Mario S, Basevi V, Lopalco PL, Balduzzi S, D'Amico R, Magrini N. Are the Two Human Papillomavirus Vaccines Really Similar? A Systematic Review of Available Evidence: Efficacy of the Two Vaccines against HPV. J Immunol Res 2015;2015:435141. https://doi.org/10.1155/2015/435141.
[10] Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372(8):711–23. https://doi.org/10.1056/NEJMoa1405044.
[11] Schurink TM, de Melker HE. HPV vaccination: Background information for the Dutch Health Council. Rijksinstituut voor Volksgezondheid en Milieu RIVM; 2017. https://doi.org/10.21945/RIVM-2017-0020.
[12] de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012;13(6):607–15. https://doi.org/10.1016/S1470-2045(12)70137-7.
[13] Rietbergen MM, Leemans CR, Bloemena E, Heideman DA, Braakhuis BJ, Hesselink AT, et al. Increasing prevalence rates of HPV attributable oropharyngeal squamous cell carcinomas in the Netherlands as assessed by a validated test algorithm. Int J Cancer 2013;132(7):1565–71. https://doi.org/10.1002/ijc.27821.
[14] Heideman DA, Waterboer T, Pawlita M, Delis-van Diemen P, Nindl I, Leijte JA, et al. Human papillomavirus-16 is the predominant type etiologically involved in penile squamous cell carcinoma. J Clin Oncol 2007;25(29):4550–6. https://doi.org/10.1200/JCO.2007.12.3182.
[15] Integraal Kankercentrum Nederland. Cijfers over kanker; 2017. https://www.cijfersoverkanker.nl [accessed 23 August 2019].
[16] Ackerson B, Hechter R, Sidell M, Sy LS, Slezak J, Chao C, et al. Human papillomavirus vaccine series completion in boys before and after recommendation for routine immunization. Vaccine 2017;35(6):897–902. https://doi.org/10.1016/j.vaccine.2017.01.007.
[17] Petaja T, Keranen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10–18 years. J Adolesc Health 2009;44(1):33–40. https://doi.org/10.1016/j.jadohealth.2008.10.002.
[18] Barnabas R. Deterministic compartmental models application: Application: Modeling the Potential Benefit of HPV Vaccines; 2012. http://www.scharp.org/pdf_files/VIDI/meeting/Barnabas_HPV_Model.pdf [accessed 23 August 2019].
[19] Jiang Y, Gauthier A, Postma MJ, Ribassin-Majed L, Largeron N, Bresse X. A critical review of cost-effectiveness analyses of vaccinating males against human papillomavirus. Hum Vaccin Immunother 2013;9(11):2285–95. https://doi.org/10.4161/hv.25754.
[20] Qendri V, Bogaards JA, Berkhof J. Health and economic impact of a tender-based, sex-neutral human papillomavirus 16/18 vaccination program in the Netherlands. J Infect Dis 2017;216(2):210–9. https://doi.org/10.1093/infdis/jix272.
[21] Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making 1993;13(4):322–38. https://doi.org/10.1177/0272989X9301300409.
[22] Centraal Bureau Statistiek. General Mortality Rates for every age; 2017. http://statline.cbs.nl/StatWeb/publication/?PA=70895ned [accessed 23 August 2019].
[23] Hakkart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Institute for Medical Technology Assessment, Erasmus Universiteit Rotterdam; 2016. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg [accessed 23 August 2019].
[24] Weis SE. Current treatment options for management of anal intraepithelial neoplasia. Onco Targets Ther 2013;6:651–65. https://doi.org/10.2147/OTT.S38217.
[25] Heijink R, van Baal P, Oppe M, Koolman X, Westert G. Decomposing cross-country differences in quality adjusted life expectancy: the impact of value sets. Popul Health Metr 2011;9(1):17. https://doi.org/10.1186/1478-7954-9-17.
[26] Suijkerbuijk AW, Donken R, Lugner AK, de Wit GA, Meijer CJ, de Melker HE, et al. The whole story: a systematic review of economic evaluations of HPV vaccination including non-cervical HPV-associated diseases. Expert Rev Vaccines 2017;16(4):361–75. https://doi.org/10.1080/14760584.2017.1256778.
[27] Centraal Bureau Statistiek. Jaarmutatie consumentenprijsindex; 2016. http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=70936NED&D1=0&D2=610,623,636,649,662,675,688&HDR=T&STB=G1&VW=t [accessed 23 August 2019].
[28] Zorginstituut Nederland. Guideline for economic evaluations in healthcare; 2016. https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg [accessed 23 August 2016].

[29] de Kok IM, Habbema JD, van Rosmalen J, van Ballegooijen M. Would the effect of HPV vaccination on non-cervical HPV-positive cancers make the difference for its cost-effectiveness?. Eur J Cancer 2011;47(3):428–35. https://doi.org/10.1016/j.ejca.2010.09.030.
[30] European Medicines Agency. Summary of product characteristics – Cervarix; 2016. https://www.ema.europa.eu/en/documents/product-information/cervarix-epar-product-information_en.pdf [accessed 23 August 2016].
[31] Cameron RL, Kavanagh K, Pan J, Love J, Cuschieri K, Robertson C, et al. Human papillomavirus prevalence and herd immunity after introduction of vaccination program, Scotland, 2009–2013. Emerg Infect Dis 2016;22(1):56–64. https://doi.org/10.3201/eid2201.150736.
[32] Palmer T, Wallace L, Pollock KG, Cuschieri K, Robertson C, Kavanagh K, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12–13 in Scotland: retrospective population study. BMJ 2019;365:l1161. https://doi.org/10.1136/bmj.l1161.
[33] Donken R, King AJ, Bogaards JA, Woestenberg PJ, Meijer C, de Melker HE. High Effectiveness of the Bivalent Human Papillomavirus (HPV) vaccine against incident and persistent HPV infections up to 6 years after vaccination in Young Dutch Women. J Infect Dis 2018;217(10):1579–89. https://doi.org/10.1093/infdis/jiy067.
[34] Luttjeboer J, Westra TA, Wilschut JC, Nijman HW, Daemen T, Postma MJ. Cost-effectiveness of the prophylactic HPV vaccine: an application to the Netherlands taking non-cervical cancers and cross-protection into account. Vaccine 2013;31(37):3922–7. https://doi.org/10.1016/j.vaccine.2013.06.044.
[35] Westra TA, Stirbu-Wagner I, Dorsman S, Tutuhatunewa ED, de Vrij EL, Nijman HW, et al. Inclusion of the benefits of enhanced cross-protection against cervical cancer and prevention of genital warts in the cost-effectiveness analysis of human papillomavirus vaccination in the Netherlands. BMC Infect Dis 2013;13:75. https://doi.org/10.1186/1471-2334-13-75.
[36] Rogoza RM, Westra TA, Ferko N, Tamminga JJ, Drummond MF, Daemen T, et al. Cost-effectiveness of prophylactic vaccination against human papillomavirus 16/18 for the prevention of cervical cancer: adaptation of an existing cohort model to the situation in the Netherlands. Vaccine 2009;27(35):4776–83. https://doi.org/10.1016/j.vaccine.2009.05.085.
[37] Datta S, Pink J, Medley GF, Petrou S, Staniszewska S, Underwood M, et al. Assessing the cost-effectiveness of HPV vaccination strategies for adolescent girls and boys in the UK. BMC Infect Dis 2019;19(1):552. https://doi.org/10.1186/s12879-019-4108-y.
[38] Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. Br J Cancer 2007;97(9):1322–8. https://doi.org/10.1038/sj.bjc.6604023.
[39] Woestenberg PJ, King AJ, van Benthem BHB, Donken R, Leussink S, van der Klis FRM, et al. Bivalent vaccine effectiveness against type-specific HPV positivity: evidence for cross-protection against oncogenic types among Dutch STI clinic visitors. J Infect Dis 2018;217(2):213–22. https://doi.org/10.1093/infdis/jix582.
[40] Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. BMJ 2008;337:a769. https://doi.org/10.1136/bmj.a769.
[41] Stein AP, Saha S, Kraninger JL, Swick AD, Yu M, Lambert PF, et al. Prevalence of human papillomavirus in oropharyngeal cancer: a systematic review. Cancer J 2015;21(3):138–46. https://doi.org/10.1097/PPO.0000000000000115.
[42] Bogaards JA, Kretzschmar M, Xiridou M, Meijer CJ, Berkhof J, Wallinga J. Sex-specific immunization for sexually transmitted infections such as human papillomavirus: insights from mathematical models. PLoS Med 2011;8(12):e1001147. https://doi.org/10.1371/journal.pmed.1001147.
[43] Paul KT. "Saving lives": Adapting And Adopting Human Papilloma Virus (HPV) vaccination in Austria. Soc Sci Med 2016;153:193–200. https://doi.org/10.1016/j.socscimed.2016.02.006.
[44] Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines djv086. J Natl Cancer Inst. 2015;107(6). https://doi.org/10.1093/jnci/djv086.