Abstract [First-level Header]

Objectives. Human papillomavirus (HPV) plays a role in the development of benign and malign neoplasms in both sexes. The Italian recommendations for HPV vaccines only consider females. The BEST II study (Bayesian modelling to assess the Effectiveness of a vaccination Strategy to prevent HPV-related diseases) evaluates: 1) the cost-effectiveness of immunization strategies targeting universal vaccination compared to cervical cancer screening and female-only vaccination, and 2) the economic impact of immunization on a variety of HPV-induced diseases.

Methods. We present a dynamic Bayesian Markov model to investigate transmission dynamics in cohorts of females and males in a follow-up of 55 years. We assume that quadrivalent vaccination (against HPV 16, 18, 6 and 11) is available for 12 year old individuals. The model accounts for the progression of subjects across HPV-induced health states (cervical, vaginal, vulvar, anal, penile and head/neck cancer as well as anogenital warts). The sexual mixing is modelled on the basis of age-, sex-, and sexual behavioural-specific matrices to obtain the dynamic force of infection.

Results. In comparison to cervical cancer screening, universal vaccination results in an ICER of €1,500. When universal immunization is compared to female-only vaccination, it is cost-effective with an ICER of €11,600. Probabilistic sensitivity analysis shows a relatively large amount of parameter uncertainty, which interestingly has however no substantial impact on the decision-making process. The intervention being assessed seems to be associated with an attractive cost-effectiveness profile.

Conclusions. Universal HPV vaccination is found to be a cost-effective choice when compared to either cervical cancer screening or female-only vaccination within the Italian context.

Introduction [First-level Header]

Human papillomavirus (HPV) is one of the main factors in both the cause and development of invasive cervical cancer and in other neoplastic malignant and benign lesions, affecting vulva, vagina, anus, penis, head-neck (squamous cell carcinoma - HNSCC), lungs (recurrent respiratory papillomatosis - RRP) and external genital area [1]. HPV places a considerable clinical and economic burden on public health providers; additionally, it has high impact on quality of life and life expectancy of affected patients [2-7]. The most frequent route of infection for HPV is through sexual contact with an infected partner, although other pathways are possible.

Vaccines play an important role in preventing HPV transmission, infection and induced diseases. Currently, a quadrivalent (including HPV genotypes 16, 18, 6 and 11) and a bivalent vaccine (genotypes 16 and 18) are available. In Italy, girls aged 9 to 26 years have the opportunity to routinely receive a HPV vaccine [8]. When compared to the bivalent vaccine, the quadrivalent vaccine shows a higher efficacy, protects against a higher variety of HPV-induced diseases (including anogenital warts) [9], and as a consequence is more cost-effective. The cost-effectiveness of different HPV vaccination schemes (in addition to screening programmes) has been evaluated by a large body of modelling studies [10-12]. The results for universal vaccination strategies, however, have not been conclusive [13, 14], and uncertainty associated with the main parameters of commonly used models has a large influence on results obtained.

Additionally, an important factor in cost-effectiveness analyses of vaccines is the impact of herd immunity [15]. Herd immunity implies that non-vaccinated subjects are protected indirectly as a consequence of decreasing overall prevalence of the infectious disease in the population. Since HPV is highly prevalent in sexually active populations [16-18], universal vaccination (i.e. including males) is highly likely to lead to a more rapid reduction in the burden of HPV-induced disease than sex-specific vaccination [12, 19-23].

Markov models (MMs) are often used in cost-effectiveness analysis to model the disease progression through a set of health states. It is not, however, easy to embed the effects of herd immunity in a standard MM. Furthermore, standard MMs are commonly deterministic and therefore do not address issues relating to uncertainty. In infectious disease transmission modelling, parameters naturally incorporate a large amount of uncertainty, as it is often impractical or even impossible to collect experimental data on most influential

parameters (e.g. the probability of pathogen transmission). As a consequence, only limited evidence is typically available, or clinical experts have to be consulted. A Bayesian statistical approach which formally includes prior information taken from several data sources as well as expert opinion can be used to construct a probabilistic MM in order to characterise the uncertainty associated with the outcomes [24, 25], effectively providing probabilistic sensitivity analysis (PSA) "for free" once the model has been run.

The aim of this study is to evaluate whether female-only or universal vaccination is the most cost-effective intervention against HPV; cervical screening is included in both interventions. To account for the effects of herd immunity, we incorporate dynamic interactions between individuals into a Bayesian MM. Some of the fundamental data (e.g. costs, some of the utility measures and the population structure) are specific to the Italian context. Nevertheless, because many of the basic parameters (e.g. those related to vaccination effectiveness) are taken from the published literature, the model is easily extended to other comparable health care systems, such as the UK and continental European countries.

Methods [First-level Header]

Analytical overview [Second-level Header]

An empirically calibrated static Bayesian MM for the assessment of the cost-effectiveness of a multi-cohort HPV vaccination strategy was presented in [26]. Here, the original model was extended by including: 1) a module for males; 2) population dynamics in an open model structure; 3) a variety of HPV-induced diseases affecting vulva, vagina, anus, penis, head/neck and external genital area; and 4) the dynamic effects of sexual mixing to account for herd immunity. The incidence and prevalence predicted by the model were calibrated using data on age-specific incidence [27] and prevalence [28] obtained from the literature.

In the base-case scenario, we compared universal and female-only vaccination with the quadrivalent vaccine in addition to cervical screening against each other and against the null option of screening-only, which in Italy is

currently offered to females aged 25 to 64 years once every 3 years. Female-only vaccination was offered to 12 year old females and we assumed that universal vaccination was offered to 12 year old females and males.
Risk factors co-promote the development of cancers and other HPV-related diseases by weakening the mucosal barriers of body organs, thus facilitating infection. Whenever possible, we accounted for the impact of risk factors on the transition probabilities [2, 29-33].

All parameters were given suitable probability distributions, reflecting the state of science. Most parameters, however, were subject to a considerable amount of uncertainty, a common feature of pathogenesis in human medicine which requires time-consuming and expensive research. Uncertainty was propagated through the model using Markov Chain Monte Carlo (MCMC) estimation [34].

The model [Second-level Header]

In a MM, the natural progression of a disease is represented by a set of health states that are considered to be mutually exclusive. Individuals are assumed to move across states from one period to the next according to specified transition probabilities, possibly depending on age and sex or other individual characteristics. Figure 1 shows a simplified version of the model structure. The nodes drawn in ellipses represent single health states, whereas the rectangles indicate sets of health states, including pre-cancerous lesions, cancer and post-cancer states. The arrows indicate possible transitions between the states. The complete model includes 36 and 22 health states for the female and male compartments, respectively.

FIGURE 1

At the beginning of the virtual observation period, the model considered 14 cohorts of females and 14 cohorts of males, aged 12-35 years and followed up for a period of 55 years. In addition, the cohorts of females and males aged 0-11 years at the beginning of the follow-up were allowed to sequentially enter the population as soon as they reached 12 years of age (i.e. during the first 10 years of the virtual follow-up). The number of cohorts and

the time period in which new cohorts entered the follow-up was restricted so that real population data could be used to estimate the numbers of new healthy individuals. Overall, 24 cohorts per sex were included.

We assumed that both females and males could be affected by anal cancer. In all cancers but HNSCC, one or several precancerous states were distinguished. Furthermore, the occurrence of anogenital warts in both sexes was integrated into the model. Cancer survivors were considered cured four years after initial diagnosis and were at increased mortality risk during this period. Death could be reached from any other state, with probabilities determined by official life tables [35].

Results obtained in [26] were used to initialise the MM by distributing the cohorts over the health states, while HPV incidence was estimated using data presented in [36]. After sexual debut, healthy individuals move to the state of "Exposure". Once exposed to HPV, the probability of becoming infected with the virus depends on age, sex, and sexual behaviour (categorised as "high-risk" and "average-risk"). Note that there is no transition from "Exposure" to "Healthy" because individuals are assumed to remain sexually active for the rest of their lives. Also, there is no way back from "Clearance" to a pre-infection state ("Exposure"); however, individuals can remain in the "Clearance" state unless they become re-infected and subsequently develop a second HPV-induced disease. An infection with the virus does not necessarily result in disease development; the majority of individuals who are infected with HPV will clear the virus (on average, up to 80-90% within two years [37]) and develop natural immunity. A persisting infection, however, is likely to result in HPV-related disease.

In line with the literature, the risk of re-infection was associated with behavioural factors such as smoking, the long-term (five years or longer) use of oral contraceptives, multi-parity (for females), the overall number of sexual partners, and a history of other sexually transmitted diseases such as chlamydia trachomatis, herpes simplex virus type 2, or syphilis [30-33].

To evaluate our model predictions, we present graphical summaries on the natural history model outcome of HPV infection and disease progression. Figure 2 shows the results of the model calibration in terms of age-specific HPV prevalence, whereas Figure 3 displays the proportions of those affected and unaffected by HPV over time, respectively, separately for the two sexes.

Each model parameter was assigned a suitable probability distribution reflecting current uncertainty, informed by clinical trial data and published literature, when available, or through expert opinion. Table 1 shows the sources and distributional assumptions as well as the mean and 95% credible intervals for the most important parameters. The model was calibrated using age-specific incidence of cervical, anal, vaginal, vulvar, penile cancers and HPV-induced HNSCC as well as the age-specific prevalence of the virus. Finally, each health state was associated with a utility value in terms of QALYs.

Probabilistic sensitivity analysis of the impact of parameter uncertainty on the results of the cost-effectiveness analysis was performed using a simulation approach based on MCMC estimation. The cost-effectiveness plane, cost-effectiveness acceptability curve (CEAC) and the expected value of information (EVI) were computed and analysed.

TABLE 1

Although recent research indicated that two doses of the quadrivalent vaccine are sufficient to prevent HPV infection [94], we assumed full compliance (and hence full effectiveness) corresponding to a course of three shots. For individuals who were not fully compliant (i.e. who received only one or two doses of the HPV vaccine), an average 50% reduction in vaccine efficacy was assumed. We also considered life-time protection for the vaccine, but assessed the impact of this assumption in sensitivity analyses.

Data from published literature suggest that the vaccine is extremely effective in the prevention of HPV-induced clinical outcomes in girls aged between 16 and 26 years, especially in those who have never been exposed to HPV [43, 44, 95]. Given cross-protection against HPV genotypes other than those targeted [96, 97], the MM includes 10 additional HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) which are responsible for the development of 20% of HPV-induced cancers [98]. The duration of cross-protection against cervical infections has been found to be limited to five years [99], accounting for 32.5% [6.0%; 51.9%] vaccine efficacy against these HPV types [96, 97].

The process of sexual mating [Second-level Header]

The main characteristic of our model is that it accounts for interactions between individuals of different sexes in the definition of the transition probabilities from “Exposure” to “Infection”. We estimated HPV transmission by means of the dynamic force of infection which is defined as a function of HPV transmission probabilities, partner acquisition rates, and population prevalence [100,101].

While estimates of HPV transmission probabilities were available from the literature, they were not directly comparable. Dunne et al. [102] estimated a HPV transmission probability per sex act of 40% (ranging from 5% to 100%); on the other hand, Burchell et al. [103] estimated a probability of 42% [36%; 47%] per partnership. In line with van de Velde et al. [104], we split the population into two groups (termed “average-risk” and “high-risk”, respectively, defined by the number of lifetime sexual partners); we assumed 80% in the former group (1-10 lifetime sexual partners) and modelled the risk of HPV infection also as a function of smoking, education level, and age at sexual debut. The per-partnership HPV transmission probabilities were assumed to range from 17% to 36% in the average-risk and from 29% to 74% in the high-risk group, respectively, using information found in the literature [102, 103].

Data presented in [104] were used to model sex-, age- and behavioural-specific partner acquisition rates, describing the annual numbers of partners an individual had sexual contact with. In particular, sexual mixing was made to depend on age, with younger females generally more likely to select older male partners and vice versa. On average, males tended to have a higher number of partners than females.

Finally, the HPV population prevalence was estimated dynamically by considering the proportion of infected individuals in the population available for mating at a given time period and under the three alternative interventions.

The force of infection was then computed as the product of these three terms and resulted in rates which were rescaled into probabilities [105]. As a consequence, the transition probabilities from the state “Exposure” to the state “Infection” were dependent on the population dynamics and were in turn directly integrated into the health state allocation algorithm of the MM. This allowed us to take the effects of herd immunity into account.

Economic parameters [Second-level Header]

We considered sex-specific utilities, where available, ranging between 0 and 1 (0 representing death and 1 perfect health). In asymptomatic health conditions such as HPV-induced precancerous stages, we assumed that a utility loss occurred after the diagnosis of the corresponding disease.

Only direct medical costs associated with screening, diagnosis and management of HPV-related diseases were included in the model. We assumed that two Pap smears and two colposcopies were conducted in females affected by CIN I-III, and a HPV DNA typing was performed in those suffering from CIN II-III or cervical cancer. According to [76, 106], an anoscopy with corresponding biopsy was conducted, in addition to anal cytology in individuals with precancerous stages of anal cancer. For the other HPV-induced diseases, we did not specifically account for diagnostic costs since the information in the literature was not sufficient; we only included the related treatment costs.

In Italy, the vaccination programme is financed at the Regional level and can therefore largely differ in terms of age and number of the target cohorts, catch-up programmes, and access procedure. The follow-up procedures and monitoring of vaccinated individuals are different as well. For these reasons, the cost per dose of vaccine is subject to wide variability across Regions as well as over time. To formally account for this fact, we modelled the vaccine costs using a distribution ranging from a potential minimum price (i.e. €40) to the maximum price for local health units (i.e. €104 which is the ex-factory price per dose negotiated by the Italian agency for medicines) [72-74]. Cost and utility data available from [26] were updated using [2], [83] and [107]. For the remaining parameters, an extensive literature review was performed to identify the treatment cost of anal [55, 82, 108], vaginal [87] and vulvar [87] pre-cancerous lesions, as well as anal [84], vaginal [88], vulvar [88], penile [90, 91] cancer and HNSCC [4, 85, 86].

Overall costs and utilities were calculated by multiplying the unit costs and unit utilities associated with each health state by the estimated number of individuals for each year of the observation period and each intervention. Because of the model's long-term horizon, it was necessary to discount the resulting estimates to present value. Approaches to this differ [109]: In an Italian context, ISPOR guidelines [110] suggested discounting both costs and benefits at a 3% rate, although NICE [111] recommended a slightly higher value of 3.5%, with a 0-6% range

for sensitivity analyses. Rates actually applied varied between countries, ranging from 1.5% to 10% for benefits and 0% to 10% for costs [112]. In line with [110], the annual discount rates were set at 3% for both benefits and costs, combined with extensive sensitivity analyses.

The economic evaluation was performed using the incremental cost-effectiveness ratio (ICER), accounting for the amount of money spent per quality-adjusted life-year (QALY) gained. Costs averted by the implementation of vaccination as well as QALYs gained were additionally estimated. In the absence of an Italian official threshold, a willingness-to-pay value of €25,000-€40,000 per QALY gained [113, 114] was used. This benchmark of value for money [113] roughly corresponds to the value of £20,000-£30,000 adopted by NICE in the UK [115].

Results [First-level Header]

Natural disease history [Second-level Header]

Figure 2 presents the calibration results for the predicted age-dependent HPV prevalence to data from [28]. For screening-only, our model estimates HPV prevalence in a realistic way; the predictions show a good approximation to the data, with peak HPV prevalence in the youngest, decreasing in older individuals. For the interventions female-only and universal vaccination, our model predicts prevalence reductions by factors around 1.4 and 1.65, respectively. Male HPV prevalence is higher than female as a consequence of more frequent partner change in males [104]. Due to non-existing diagnostic procedures on HPV infection in males [116], we calibrated the model output for both sexes to data on females.

FIGURE 2

Figure 3 shows the cumulative proportions of individuals in the health states over the observation period, separately for the two sexes and diseased and unaffected individuals, respectively. The vast majority remains unaffected by HPV-induced diseases. A small proportion (up to 4% of females and 2.5% of males), however,

acquires a disease at a particular time point of the follow-up. Anogenital warts and early precancerous stages mainly affect younger individuals, whereas more severe precancerous lesions and HPV-induced cancers commonly occur at a later stage in life. We do not display extremely rare cases of cancers of the anus, vulva, vagina, and penis.

FIGURE 3

Overview tables on population size, overall costs and QALYs [Second-level Header]

Table 2 shows the mean population size, mean and median costs, and mean QALYs per intervention over the whole observation period along with the corresponding 95% credible intervals. The cost distribution in the screening-only scenario is highly right-skewed, resulting in a median that is ten times lower than the mean. In contrast, the costs in the interventions female-only and universal vaccination scenarios are symmetrically distributed; as a consequence, their mean and median are similar. Costs and QALYs are reported for the population as a whole. With screening-only, population size is the lowest since more individuals die due to the higher incidence of HPV-induced cancers.

TABLE 2

Mean overall cost differed by a factor of five between screening-only and universal vaccination, reflecting the larger population to which the vaccine is made available in the latter case. Interestingly, QALYs were also highest under universal vaccination. When comparing universal vaccination to the other two alternatives in the base case, the ICER was about €1,500 in comparison to screening-only and about €11,600 in comparison to female-only vaccination.

Probabilistic sensitivity analysis [Second-level Header]

The uncertainty around the cost-effectiveness estimates is analysed by means of cost-effectiveness planes, cost-effectiveness acceptability curves (CEACs) and expected value of information (EVI) analysis.

Universal versus female-only vaccination [Third-level Header]

Figure 4 shows a cost-effectiveness plane comparing universal to female-only vaccination, with the effectiveness differential on the x-axis and the cost-differential on the y-axis. Each point represents the result of a simulation. The grey portion of the plane indicates the "sustainability area" corresponding to a cost-effectiveness threshold of €25,000 [115]. Points in the sustainability area portray "possible futures" in which universal vaccination turns out to be a cost-effective strategy, in comparison to female-only vaccination. Points outside the sustainability area indicate cost-ineffectiveness for the reference intervention, regardless of distance from the threshold. The majority of points lie at the limit of the sustainability area, with low CEAC values as a consequence (see Figure 5). Mean cost- and effectiveness differentials, however, do indicate cost-effectiveness, resulting in an ICER of around €11,600, well below the cost-effectiveness thresholds set above. This is substantially due to herd immunity. As a consequence, the higher overall cost of the universal vaccination strategy is clearly compensated by the gain in utilities.

FIGURE 4

Figure 5 presents a graphical summary of probabilistic sensitivity analysis. The left panel contains the CEAC. Typically, low values of the CEAC indicate the presence of a large amount of parameter uncertainty [25]. In Figure 5, the values are below 80% for the whole range of choices for the willingness-to-pay displayed. Yet, the CEAC only measures the probability of cost-effectiveness, but fails to reflect the impact of uncertainty on the consequences of a "wrong" decision. The panel on the right shows the EVI, again as a function of willingness-to-pay. The EVI is a decision-theoretic measure that quantifies how much the decision maker should be willing to pay to buy new information (i.e. in the form of additional research) that would reduce parameter uncertainty to zero [25]. In the present case, EVI was at most €2.1 per subject and €320,030,305 for the overall population, representing the extremely low future financial investment necessary to resolve parameter uncertainty. These values indicate that the impact of parameter uncertainty on the results of the model is extremely low, despite the low CEAC values, which are induced by a markedly skewed distribution for the underlying cost- and

effectiveness-differentials. Under these circumstances, the results of the cost-effectiveness analysis are rather stable, despite the underlying parameter uncertainty.

FIGURE 5

Universal vaccination versus screening-only [Third-level Header]

The incremental cost of applying universal vaccination compared to screening-only is higher than in the preceding section, since fewer individuals were potentially vaccinated. Incremental QALYs, however, are higher, too, as a consequence of the reduced effects of herd immunity. Figure 6 shows the corresponding cost-effectiveness plane. In comparison to the former analysis, a higher number of points lie within the sustainability area, and the joint distribution of cost- and effectiveness differentials is less right-skewed.

FIGURE 6

Thus, the CEAC exhibited in the left panel of Figure 7 has higher values, nearly reaching 60%. Additionally, EVI indicates a higher value of further research amounting to up to €3.7 per individual and €553,291,173 for the whole population. This is still, however, a comparatively low value, suggesting a low impact of parameter uncertainty. Therefore, one can conclude that despite the low CEAC, universal vaccination is a highly cost-effective alternative when compared to screening-only.

FIGURE 7

Discussion [First-level Header]

In this paper, the standard framework of Markov models is extended to account for dynamic elements such as new individuals entering the population during years of follow-up and the effect of herd immunity, which modifies the rate of infection according to the proportion of individuals who at any given time are infected and exposed to the virus.

Usual methods applied to perform epidemiological and economic evaluations of infectious diseases are based on ordinary differential equations (ODEs) [117].While particularly effective in modelling the dynamic transmission of infectious diseases, these are usually too complex for a stochastic formulation, limiting the possibility of performing extensive probabilistic sensitivity analysis (PSA). As a consequence, they can only be conducted when applying additional retrospective simulation procedures such as the Latin Hypercube Sampling (LHS) [118].

PSA, however, is fundamental in any health economic evaluation [25, 119, 120] and particularly so in the case of infectious disease modelling, where uncertainty surrounding the parameters and assumptions of the model may impact dramatically on cost-effectiveness results. In contrast to most ODE-based models, the Bayesian Markov model developed in this paper is probabilistic in nature, permitting to accommodate PSA in a straightforward way. At the same time, by using discrete time rather than continuous time for modelling the Markov cycle, we are able to include the dynamics of infection and population characteristics. Regulatory bodies such as NICE may benefit from our methodology since it produces a full economic evaluation based on a tool they are familiar with; also, PSA can be directly embedded in the model. In addition to the advantages previously discussed, it considerably reduces the effort on implementation and computation when compared to standard ODE-based methodology.

The use of a Bayesian approach is particularly relevant in the case of infectious disease modelling, since it is likely that many of the fundamental parameters are informed by a combination of evidence, some of which may be based on expert opinion. Thus, it is important to fully account for the underlying uncertainty – failure to do so may result in an under- or overestimation of the economic performance of the interventions being investigated. A full Bayesian analysis also has the advantage of making the conduct of the all-important PSA relatively straightforward, as the uncertainty in the model parameters is directly accounted for in the main model computations. Using tools such as the R package BCEA [121] or the SAVI web app [122]; it is fairly easy to systematically compute the relevant summary assessments such as CEAC and EVI analysis.

The ICER values are sensitive to some of the model parameters. For example, they increase as a consequence of:

- higher vaccine efficacy;

- accounting for cross-protection effects against other HPV types;
- life-long duration of vaccine-induced immunity;
- lower unit cost of vaccination;
- increased sexual activity;
- lower frequency of cervical screening;
- longer observation time period;
- including a higher number of HPV-induced diseases;
- higher rate of discount.

Eight publications [10, 11, 47, 123-127] come to the conclusion that female-only vaccination is superior to universal vaccination. Their ICERs range from €84,750 [11] to €329,680 [47], or even to €623,840 in a sensitivity analysis [10]. They all use a deterministic methodology, with the exception of [11], where sexual mating continues to be modelled in a deterministic way. In all but two publications showing lack of cost-effectiveness [10, 11], the ICERs only account for HPV-induced diseases related to the cervix [47, 127], and in some cases also for anogenital warts [123-126].

In contrast, universal vaccination is estimated to be cost-effective according to seven publications [12, 19-23, 128], with ICER values ranging from €4,470 [128] to €31,240 [19] when compared to screening-only, and €93 [20] to €21,677 [12] when compared to female-only vaccination, respectively (across a large range of scenarios).

This study suggests universal vaccination targeting the same age group (12 years) to be an extremely cost-effective strategy in comparison to screening-only or to a single cohort of females vaccinated at the age of 12 years. The discounted costs per QALY gained correspond to €1,500 (EVI = €3.7 per subject) and €11,600 (EVI = €2.2 per subject), respectively. These values are well below the monetary threshold of sustainability for health interventions.

Moreover, recent research indicates that vaccinating individuals with only two doses of the HPV vaccine is sufficient to prevent HPV infection [94], thus reducing vaccination expenses. The conservative vaccination schedule includes three doses for full protection; it therefore strengthens the evidence that universal vaccination can be a cost-effective intervention.

The present analysis differs from previous studies in six ways: 1) incorporation of the full set of HPV-induced diseases (apart from RRP); 2) a lifelong duration of vaccine-induced immunity without booster application; 3) a comparatively low unit cost of vaccination; 4) a very high vaccine coverage rate; 5) a comparatively low vaccine efficacy; and 6) a shorter follow-up of 55 years. Points i) – iii) contribute to lower ICER values, whereas points iv) - vi) tend to increase them.

The following four aspects seem to drive the results of this study [13, 14]:

- The dynamic force of infection, incorporating sexual mating between females and males, thus automatically considering changes in mixing patterns and population prevalence over time. In contrast, a static force of infection in standard MMs only depends on covariates such as age;
- The inclusion of a high variety of HPV-induced diseases compared to other health economic evaluations which only account for cervical cancer [19, 47, 127];
- The assumption of lifelong immunity following initial HPV-vaccination with three doses, without the necessity of a booster application, in contrast to [19, 21, 47, 127, 129];
- The considerably low unit cost of vaccination compared to the official list price of the vaccine on the Italian market.

While the network model presented in [19] by definition accounts for dynamic effects of sexual mating, it considers only cervical cancer and its precancerous stages. A possible explanation for the higher ICERs presented in [12] could be that vaccination is made available for individuals aged 9-26 years; vaccinating such a high number of age cohorts at a relatively high unit price of around €99 leads to increased vaccination costs. Another network model is presented by [21]; however, an even higher vaccine price of around €138 is assumed. Furthermore, the authors let immunity wane after 15 and 25 years. As for HPV-induced diseases, only anogenital warts and cervical cancer are included. A reason for the higher ICER shown in [23] compared to this study could be the fact that the authors consider only one group of sexual activity without accounting for high-risk sexual behaviour. Yet failure to account for frequent partner change leads one to underestimate the HPV population prevalence, resulting in an underestimate of the cost-effectiveness of HPV vaccination.

In the future, the benefits of HPV vaccination will be further increased since a nonavalent vaccine including genotypes 16, 18, 31, 33, 45, 52, 58, 6 and 11 is being developed. The preliminary results of the corresponding

clinical trials are promising [130]. Therefore, the cost-effectiveness of universal HPV vaccination is likely to further improve, creating added potential to optimise the control of the disease.

References [First-level Header]

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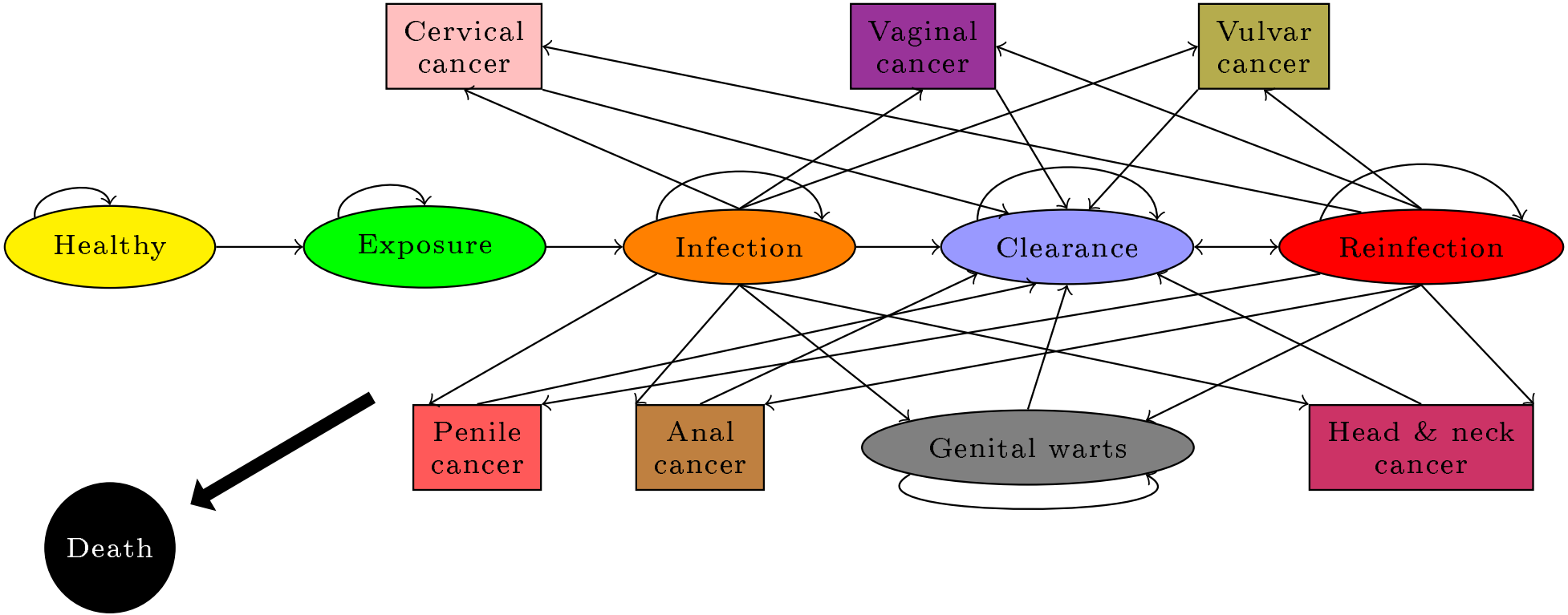

Cervical cancer
Vaginal cancer
Vulvar cancer
Healthy
Exposure
Infection
Clearance
Reinfection
Penile cancer
Anal cancer
Genital warts
Head & neck cancer
Death

Figure 1: Overview of the health states included in the model. Diseases of the cervix, vagina and vulva can only affect females, and penile cancer is a male-specific disease. Ellipses represent a single health state, whereas rectangles are a whole set of cancer-related health states, including precancerous states, cancer and the tunnel post-cancer states. Arrows between nodes represent possible transitions in either one or both directions. Arrows with origin and end at the same node indicate that it is possible to remain in a given health state. Individuals can move to the absorbing state of death from any health state.

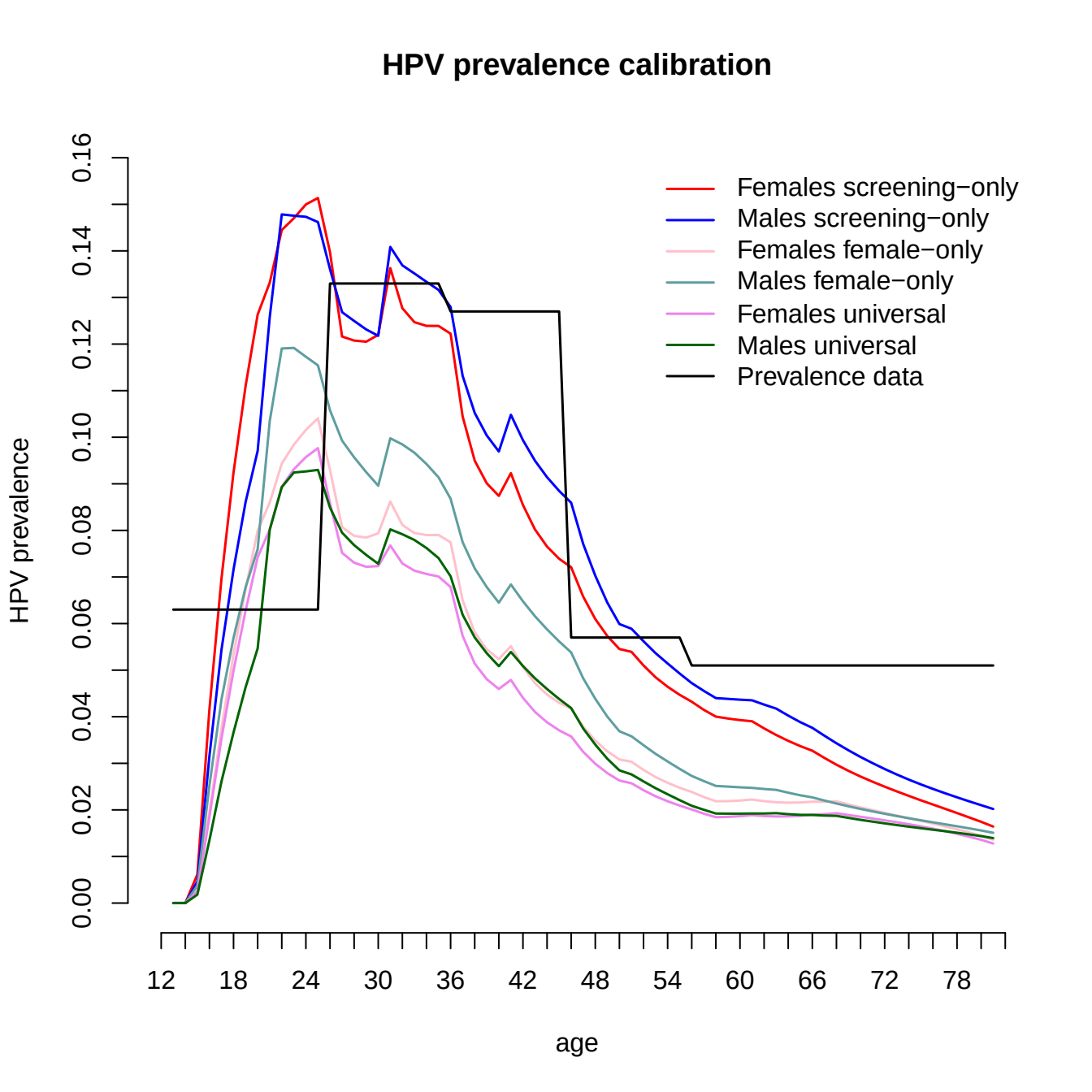
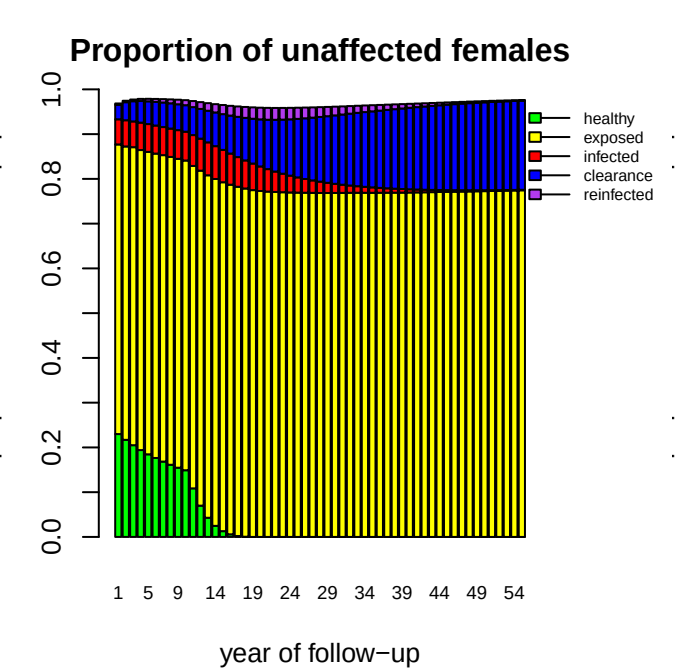
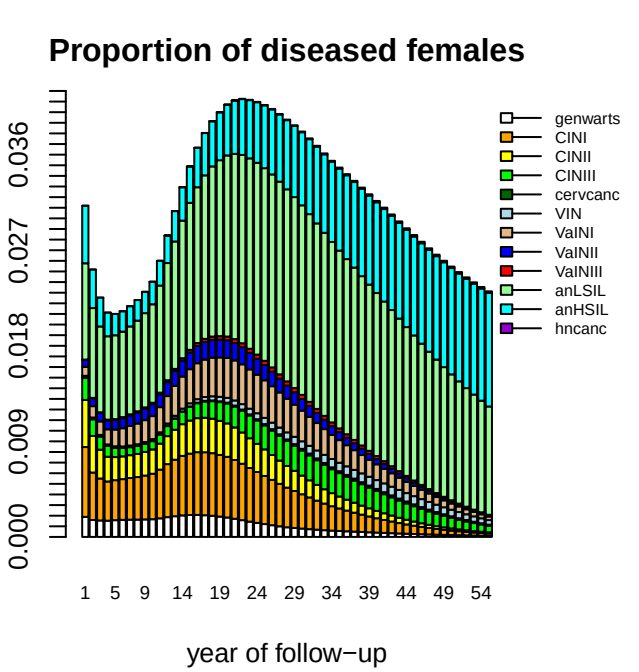
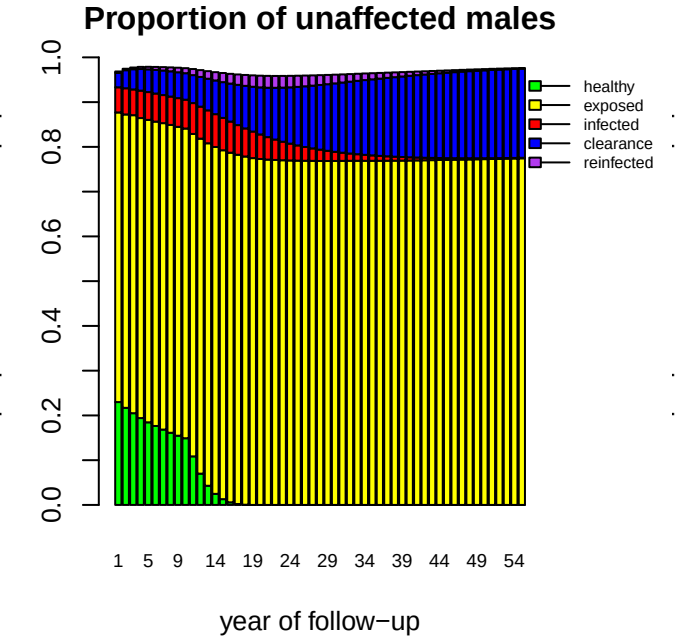

HPV prevalence calibration
Females screening−only
Males screening−only
Females female−only
Males female−only
Females universal
Males universal
Prevalence data
HPV prevalence
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0.14
0.16
12
18
24
30
36
42
48
54
60
66
72
78
age

Figure 2: Calibration of the HPV prevalence model output to data taken from [28]. The age- and sex-specific prevalence estimates are displayed separately for the three interventions screening-only, female-only and universal vaccination. The figure shows that the model realistically predicts HPV prevalence, peaking in the youngest age groups.


Proportion of unaffected females
healthy
exposed
infected
clearance
reinfected
0.0
0.2
0.4
0.6
0.8
1.0
1 5 9 14 19 24 29 34 39 44 49 54
year of follow−up


Proportion of diseased females
genwarts
CINI
CINII
CINIII
cervcanc
VIN
VaINI
VaINII
VaINIII
anLSIL
anHSIL
hncanc
0.000
0.009
0.018
0.027
0.036
1 5 9 14 19 24 29 34 39 44 49 54
year of follow−up


Proportion of unaffected males
healthy
exposed
infected
clearance
reinfected
0.0
0.2
0.4
0.6
0.8
1.0
1 5 9 14 19 24 29 34 39 44 49 54
year of follow−up

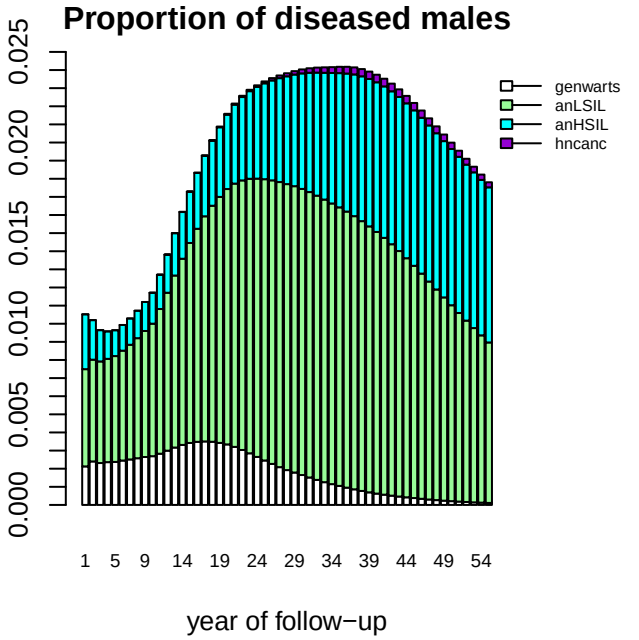

Proportion of diseased males
genwarts
anLSIL
anHSIL
hncanc
0.000
0.005
0.010
0.015
0.020
0.025
1 5 9 14 19 24 29 34 39 44 49 54
year of follow−up

Figure 3: Model outcome of the natural history of HPV infection and disease progression. Cumulative proportions of unaffected and diseased individuals are displayed separately for the two sexes. The vast majority of individuals remain unaffected by the virus, whereas a small age-dependent proportion (up to 4% of females and 2.5% of males) develop a HPV-induced disease.

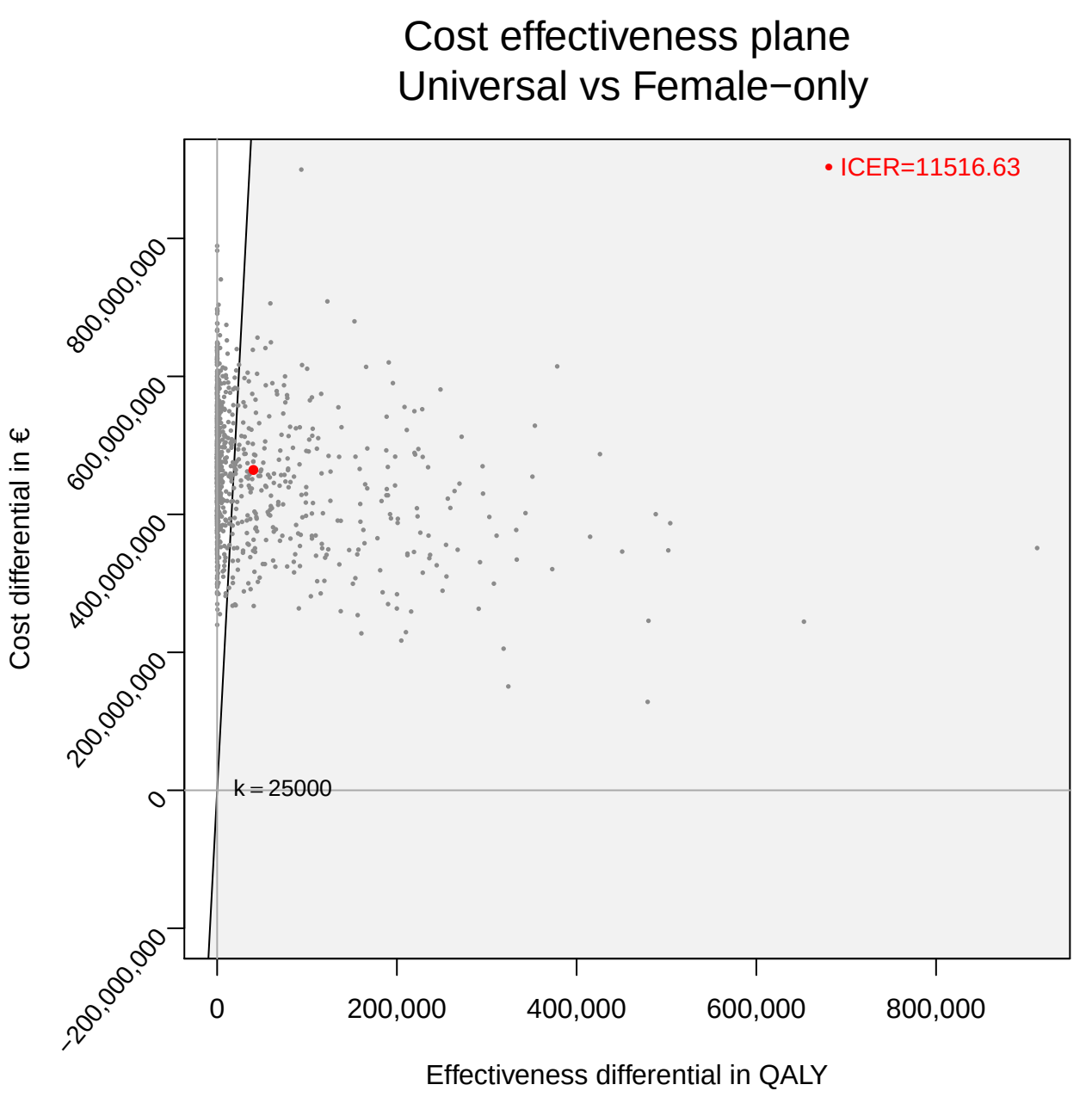
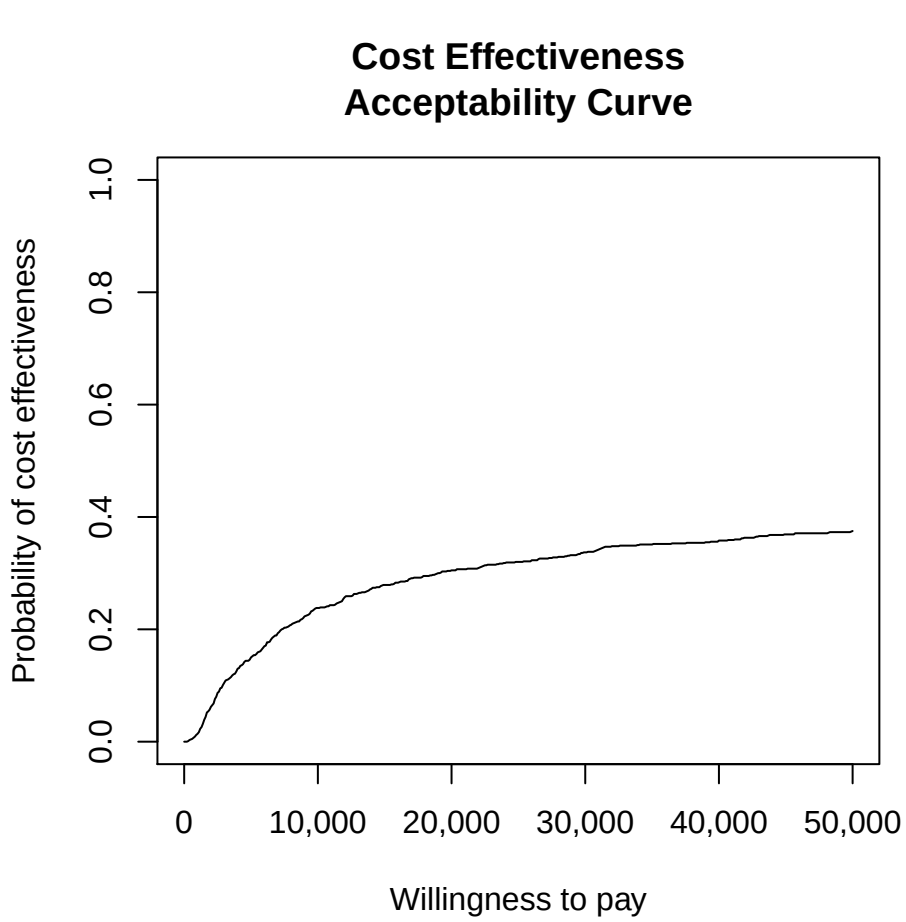

Cost effectiveness plane
Universal vs Female−only
• ICER=11516.63
k = 25000
Cost differential in €
800,000,000
600,000,000
400,000,000
200,000,000
0
−200,000,000
0
200,000
400,000
600,000
800,000
Effectiveness differential in QALY

Figure 4: Cost-effectiveness plane for a comparison of universal to female-only vaccination. The graph shows positive skewness of the joint distribution of cost- and effectiveness differentials, resulting in a CEAC with values below 80% cost-effectiveness for the whole range of the willingness-to-pay.


Cost Effectiveness
Acceptability Curve
Probability of cost effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
10,000
20,000
30,000
40,000
50,000
Willingness to pay

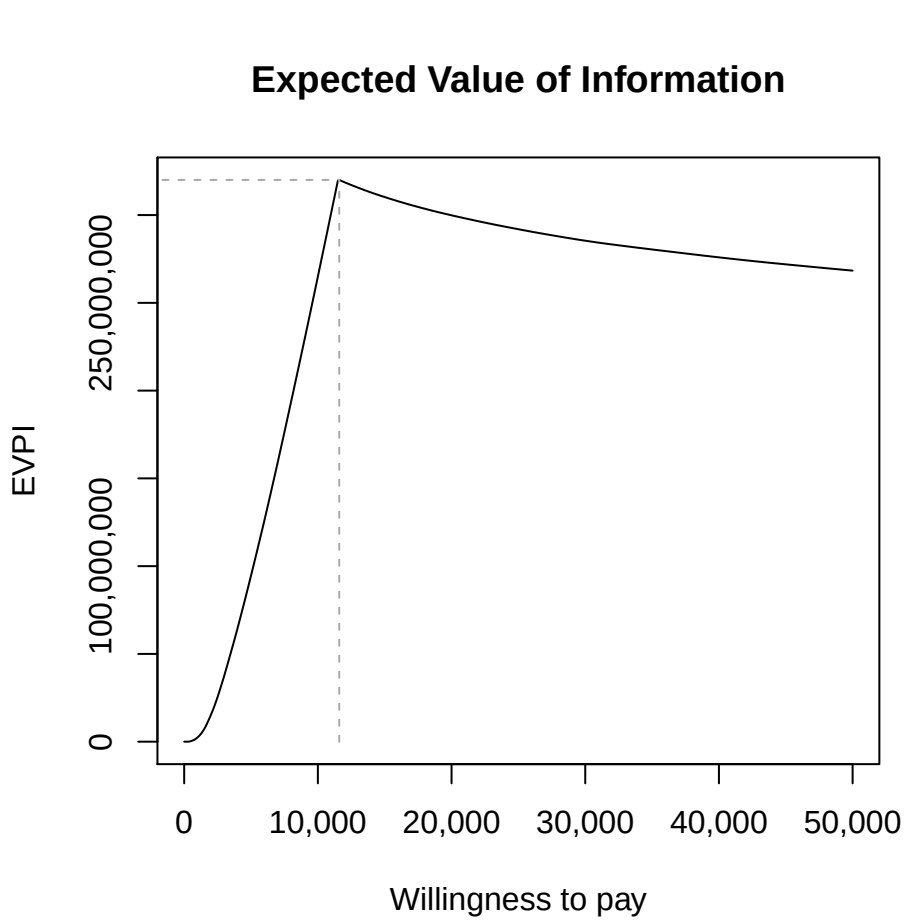

Expected Value of Information
EVPI
0
100,000,000
250,000,000
0
10,000
20,000
30,000
40,000
50,000
Willingness to pay

Figure 5: The figure presents probabilistic sensitivity analysis by means of the cost-effectiveness acceptability curve (CEAC) on the left and the expected value of information (EVI) on the right. The CEAC shows that the probability of cost-effectiveness never reaches 80% (the value defined as reasonable cost-effectiveness [25]) as a consequence of a positively skewed joint distribution of cost- and effectiveness differentials. The EVI indicates that the value of resolving the uncertainty in the model parameters is very much limited, never exceeding €320,030,305 for the overall population.

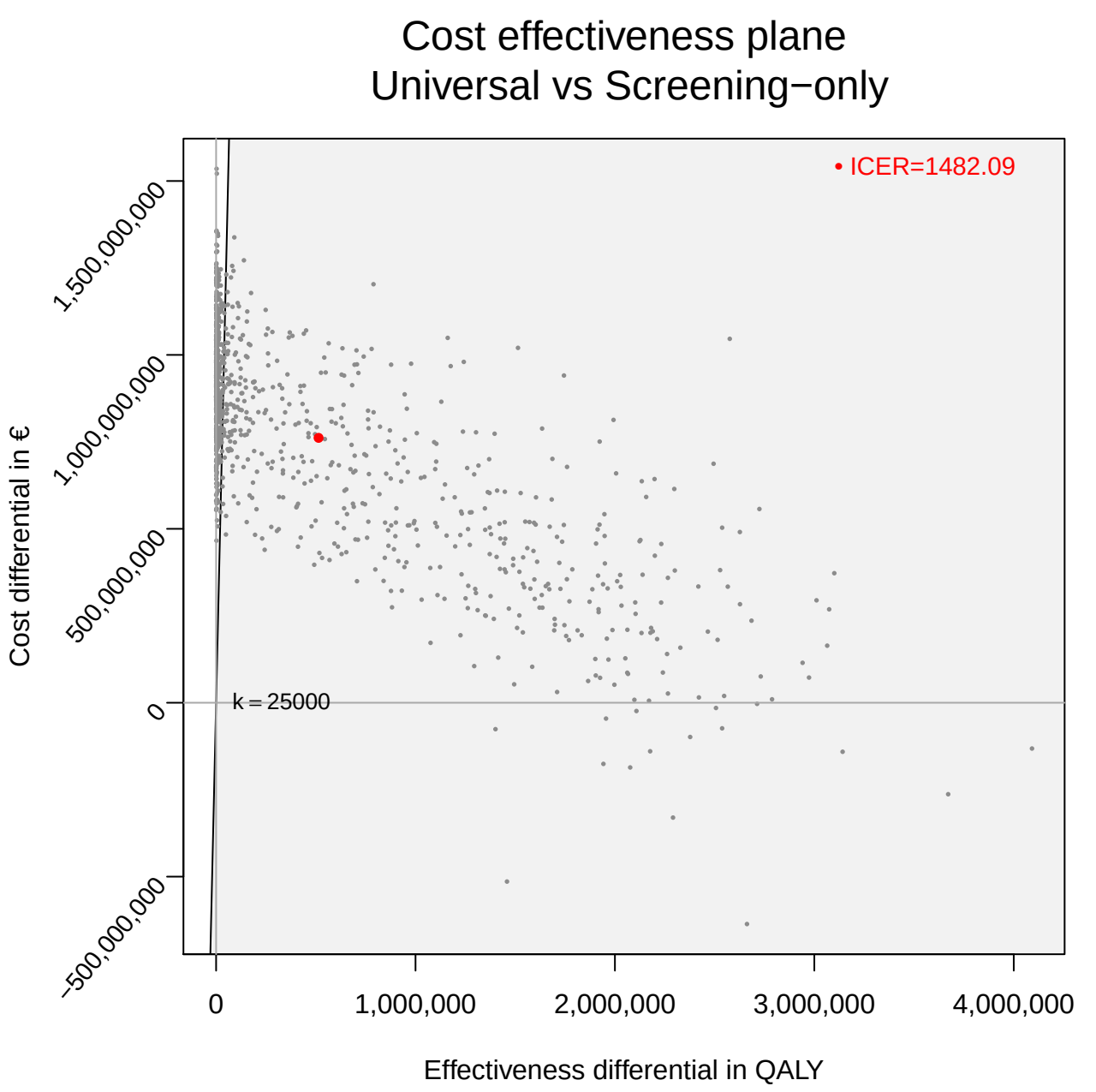
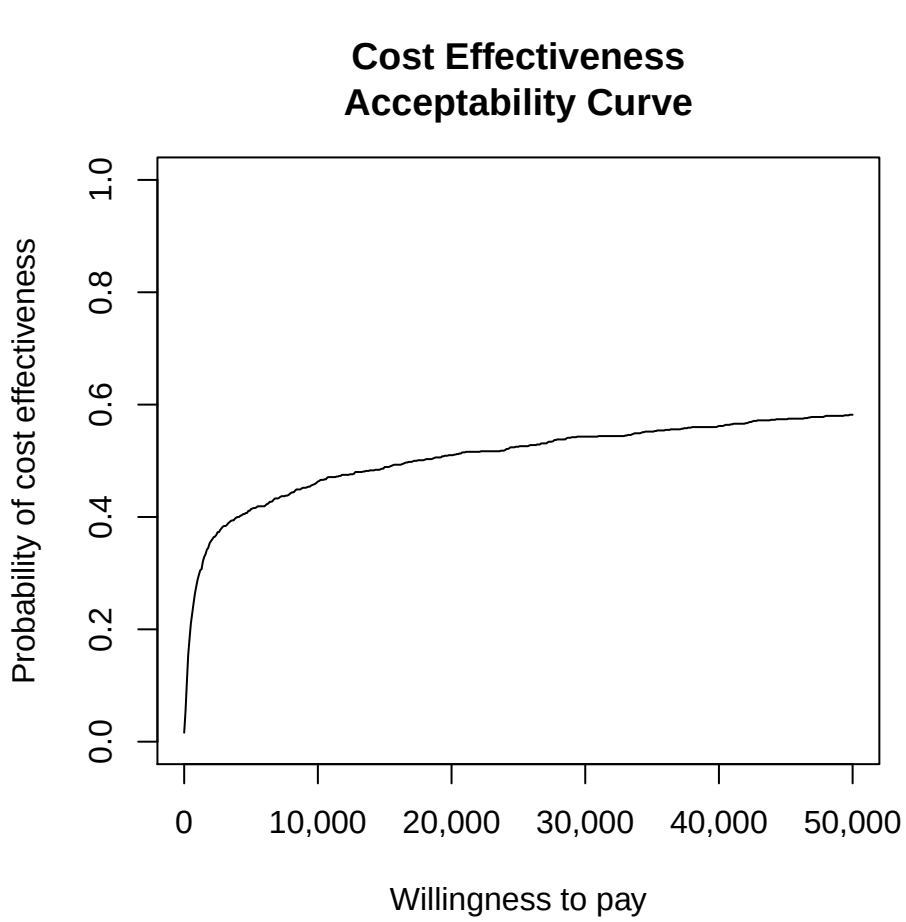

Cost effectiveness plane
Universal vs Screening−only
• ICER=1482.09
k = 25000
1,500,000,000
1,000,000,000
500,000,000
0
−500,000,000
Cost differential in €
0
1,000,000
2,000,000
3,000,000
4,000,000
Effectiveness differential in QALY

Figure 6: Cost-effectiveness plane for a comparison of universal vaccination to screening-only. In comparison to Figure 4, the joint distribution of cost- and effectiveness differentials is less right-skewed, resulting in a CEAC nearly reaching values of 60% cost-effectiveness.


Cost Effectiveness
Acceptability Curve
Probability of cost effectiveness
0.0
0.2
0.4
0.6
0.8
1.0
0
10,000
20,000
30,000
40,000
50,000
Willingness to pay

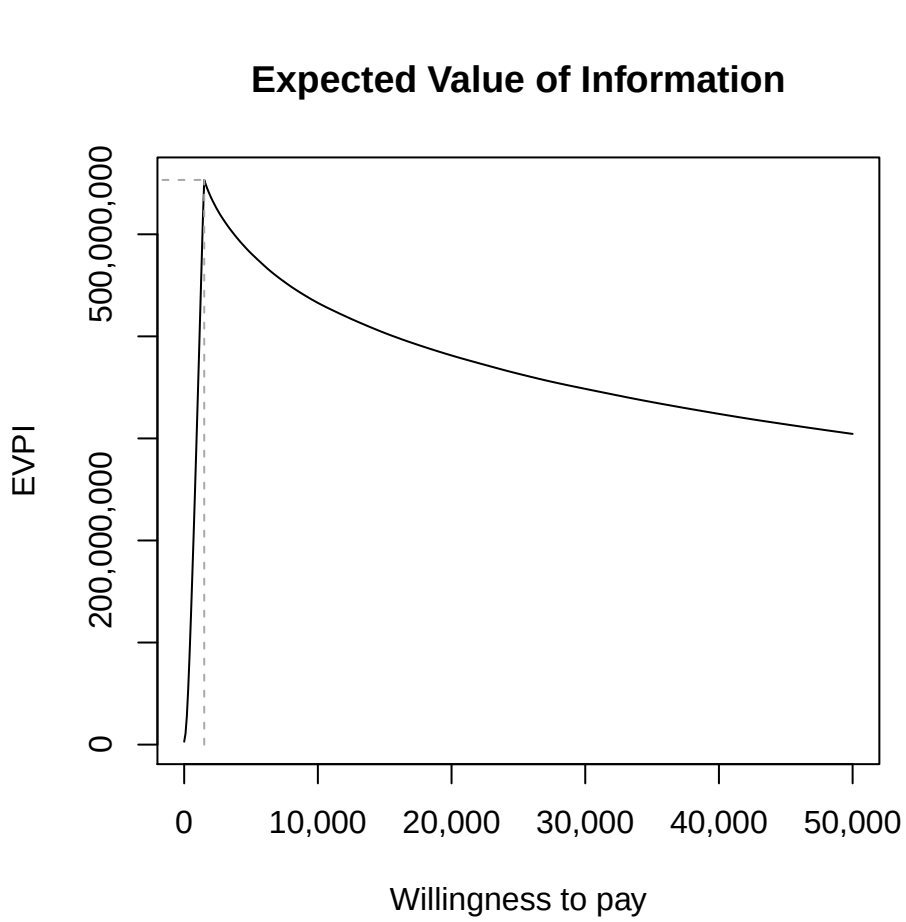

Expected Value of Information
EVPI
0
200,000,000
500,000,000
0
10,000
20,000
30,000
40,000
50,000
Willingness to pay

Figure 7: Probabilistic sensitivity analysis using the cost-effectiveness analysis curve (CEAC) on the left and the expected value of information (EVI) on the right. The CEAC shows that the probability of cost-effectiveness reaches a maximum value of only around 60% at a willingness to pay of €50,000. This is a consequence of the positively skewed distribution of cost and effectiveness differentials. The EVI on the right indicates that the value of resolving parameter uncertainty in the model is very much limited, never exceeding €553,291,173 for the overall population.

Table 1: Distributional assumptions, means and 95% credible intervals as well as literature sources for the most important model parameters.

Screening-related parameters				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
σ_a	Screening at 12-24 yrs	Informative Beta	0.0500 [0.0498;0.0501]	EO
σ_a	Screening at 25-29 yrs	Informative Beta	0.1530 [0.1480;0.1590]	EO
σ_a	Screening at 30-34 yrs	Informative Beta	0.2150 [0.2100;0.2190]	EO
σ_a	Screening at 35-44 yrs	Informative Beta	0.2460 [0.2440;0.2470]	[38-42]
σ_a	Screening at 45-54 yrs	Informative Beta	0.2600 [0.2540;0.2660]	[38-42]
σ_a	Screening at 55-64 yrs	Informative Beta	0.2420 [0.2320;0.2520]	[38-42]
σ_a	Screening at 65-74 yrs	Informative Beta	0.1840 [0.1640;0.2020]	[38-42]
Vaccine-related parameters				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
γ_1	Vaccine efficacy cervix	Informative LogNorm	0.7816 [0.6847;0.8888]	[43-45]
γ_2	Vaccine efficacy anus	Informative LogNorm	0.7019 [0.6055;0.7981]	EO
γ_3	Vaccine efficacy head/neck	Informative LogNorm	0.5008 [0.4563;0.5497]	[46], EO
α_1	Vaccine coverage rate (VCR)	Informative Beta	0.9048 [0.6597;0.9992]	[20, 22, 23, 47], EO
Infection-related parameters				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
ρ_2	Risk increase in anal cancer in females compared to males	Informative Gamma	1.6975 [1.5055; 1.9026]	[48], EO
ρ_3	Risk increase in anal cancer in MSM compared to MSF	Informative Gamma	17.18 80 [0.8714; 53.5615]	[49]
ζ	Proportion of population at increased risk	Informative Beta	0.3139 [0.2140;0.4054]	[29]
τ_1	Probability of conization in CIN I (immediate)	Informative Beta	0.3029 [0.2101;0.4180]	[50]
τ_2	Probability of conization in CIN I (delayed)	Informative Beta	0.1701 [0.1525;0.1909]	EO
μ_1	Probability of HPV transmission (average risk)	Informative Normal	0.2532[0.1707; 0.3607]	EO
μ_2	Probability of HPV transmission (high risk)	Informative Normal	0.5220 [0.2915; 0.7439]	EO
Transition probabilities				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
δ_{0a}	Infection → Exposure (40-49 yrs)	Informative Beta	0.2048 [0.1118;0.3022]	[51-54], EO
δ_1	Infection → CIN I	Informative Beta	0.0450 [0.0279; 0.0661]	[36], EO
δ_2	Infection → CIN II	Informative Beta	0.0115 [0.0034; 0.0234]	[36], EO
δ_3	Infection → LSIL	Informative Beta	0.0286[0.1003; 0.1387]	[49, 55], EO
δ_4	Infection → HSIL	Informative Beta	0.0104[0.0008; 0.0496]	[49, 55, 56], EO
δ_5	Infection → VaIN I/II	Informative Beta	0.0073 [0.0054;0.0069]	[57]
δ_6	Infection → PeIN	Informative Beta	0.0002 [0;0.0014]	[58]
Probabilities of diagnosis				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
η_1	Diagnosis CIN II (without screening)	Informative Beta	0.0247 [0.0001;0.1010]	EO
η_2	Diagnosis CIN III (without screening)	Informative Beta	0.0758 [0.0576;0.0982]	EO
η_3	Diagnosis LSIL	Informative Beta	0.0496 [0.0400;0.0606]	EO

η_4	Diagnosis HSIL	Informative Beta	0.0997 [0.0920;0.1087]	EO
$\beta_1^{(hn)}$	Diagnosis head and neck cancer stage I	Flat Normal	0.2260 [0.1039;0.4043]	[59-62]
η_5	Diagnosis VaIN I/II	Informative Beta	0.1998 [0.1798;0.2190]	EO
$\beta_1^{(vulv)}$	Diagnosis vulvar cancer stage I	Flat Normal	0.3549 [0.0028;0.9926]	[63, 64]
$\beta_1^{(pen)}$	Diagnosis penile cancer stage I	Flat Normal	0.5905 [0.5275;0.6512]	[65]
Probabilities of survival				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
$\phi_{1,1}^{(cerv)}$	1 year survival cervical cancer stage I	Informative Beta	0.9782 [0.8931;0.9999]	[5-7], EO
$\phi_{1,1}^{(an)}$	1 year survival anal cancer stage I/II	Flat Normal	0.9900 [0.9800;1.0000]	[66, 67]
$\phi_{1,1}^{(hn)}$	1 year survival head and neck cancer stage I	Flat Beta	0.9839 [0.9334;1.0000]	[68]
$\phi_{1,1}^{(vag)}$	1 year survival vaginal cancer stage I	Flat Beta	0.9531 [0.8014;0.9999]	[69]
$\phi_{1,1}^{(vulv)}$	1 year survival vulvar cancer stage I	Flat Normal	0.7808 [0;1]	[70]
$\phi_{1,1}^{(pen)}$	1 year survival penile cancer stage I	Flat Beta	0.8933 [0.7584;0.9822]	[71]
Cost of vaccination and diagnostic procedures				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
c^{adm}	Administration	Informative LogNorm	6.64 [5.05;8.65]	[72-74]
c^{acq}	Dose of vaccine	Informative LogNorm	56.10 [36.48;77.43]	[72-74], EO
c^{pap}	Pap test	Informative LogNorm	17.07 [14.05;20.83]	[75]
c^{col}	Colposcopy	Informative LogNorm	54.27 [49.63;59.49]	[75]
c^{cyt}	Anal cytology	Flat LogNorm	43.03 [23.59;83.06]	[76]
c^{dna}	HPV DNA test	Informative LogNorm	79.10 [76.98;81.13]	[77, 78]
Cost of HPV-induced diseases				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
c_1^{cin}	CIN I	Informative LogNorm	309.33 [225.36;405.64]	[50, 79]
c_2^{cin}	CIN II	Informative LogNorm	1,342.30[(4)] [1,032.51;1,701.10]	[50]
c_3^{cin}	CIN III	Informative LogNorm	1,750.03 [1,381.00;2,193.80]	[50]
c_1^{cerv}	FIGO I	Informative LogNorm	14,782.17 [2,459.13;44,084.05]	[80]
c^{gw}	Anogenital warts	Informative LogNorm	283.48 [242.04;328.56]	[79, 81]
c^{lsil}	LSIL	Informative LogNorm	115.46 [76.56;166.75]	[82]
c^{hsil}	HSIL	Flat LogNorm	2,389.34 [1,165.65;4,360.13]	[55, 76]
c_1^{an}	Anal cancer stage I	Flat LogNorm	7618.94 [3885.66;12058.58]	[83, 84]
$c_{1,2}^{hn}$	Head and neck cancer stage I/II	Flat LogNorm	10,081.71 [5,457.09;18,036.06]	[4, 85, 86]
c^{vain}	VaIN I/II/III	Flat LogNorm	3,236.98 [1,686.22;5,376.87]	[87]
c_1^{vag}	Vaginal cancer stage I	Flat LogNorm	2,939.32 [1,684.02;5,029.46]	[83, 88]
c^{vin}	VIN	Flat LogNorm	3,158.80 [1,920.52;5,405.63]	[87]
c_1^{vulv}	Vulvar cancer stage I	Flat LogNorm	8,304.24 [4,650.56;14,302.42]	[88]
c^{pein}	PeIN	Flat LogNorm	437.13 [63.13;811.13]	[89]
c^{pen}	Penile cancer	Flat LogNorm	5,807.15 [3,472.35;9,233.68]	[90, 91]

Utilities of HPV-induced diseases				
Variable	**Description**	**Distribution**	**Mean and 95%-CI**	**Source**
u^{ascus}	ASCUS	Informative Beta	0.8302 [0.5725;0.9767]	[2]
u_1^{cin}	CIN I	Informative Beta	0.8396 [0.2058;0.9999]	[2]
u_2^{cin}	CIN II	Informative Beta	0.7967 [0.0469;0.9999]	[2]
u_3^{cin}	CIN III	Informative Beta	0.8396 [0.1845;0.9999]	[2]
u_1^{cerv}	FIGO I	Informative Beta	0.5769 [0.2766;0.8641]	[2]
u_m^{gw}	Genital warts in males	Informative Beta	0.6961 [0.1172;0.9999]	[2]
u_f^{gw}	Genital warts in females	Informative Beta	0.7761 [0.0520;0.9999]	[2]
u^{lsil}	LSIL	Informative Beta	0.9793 [0.9517;0.9955]	[92]
u^{hsil}	HSIL	Informative Beta	0.9793 [0.9480;0.9959]	[92]
$u_{1,m}^{an}$	Anal cancer stage I in males	Informative Beta	0.6654 [0.1847;0.9850]	[2, 3]
$u_{1,f}^{an}$	Anal cancer stage I in females	Informative Beta	0.7275 [0.0669;0.9999]	[2, 3]
$u_{1,2,m}^{hn}$	Head and neck cancer stage I/II in males	Informative Beta	0.8171 [0.0135;1]	[2, 4]
$u_{1,2,f}^{hn}$	Head and neck cancer stage I/II in females	Informative Beta	0.7413 [0.2500;0.9911]	[2, 4]
u^{pen}	PeIN, Penile cancer all stages	Informative Beta	0.7922 [0.7489;0.8455]	[93]

The notation A → B indicates the transition from state A to state B. This plays a role in context of the transition probabilities between the health states reported. EO = Assumption based on expert opinion. CI = Credible interval. FIGO = International Federation of Gynecology and Obstetrics. MSM = Males who have sex with males. MSF = Males who have sex with females. We assume that administration costs include costs generated by additional medical consultations induced by mild adverse effects of vaccination. We assume that approximately 1.8% of vaccinees require an additional visit to a general practitioner. Approximately 75% of Pap tests are performed using conventional cytology and 25% with liquid-based cytology. A gynaecological office visit (at a fee of €20.66) [2] is included in colposcopy costs.

Table 2: Population size, overall costs in € and QALYs for the three interventions in the total follow-up.

	Population size	**Overall cost**				**Overall QALY**	
Intervention	**Mean**	**Mean**	**95% CI**	**Median**	**95% CI**	**Mean**	**95% CI**
Screening-only	149,652,365	187,189,634	[169,986,589; 204,392,679]	18,279,665	[13,007,644; 28,495,706]	127,935,994	[127,884,948; 127,987,040]
Female-only	149,727,525	484,357,417	[478,212,474; 490,502,360]	478,135,234	[469,493,395; 487,530,520]	128,409,504	[128,399,222; 128,419,785]
Universal	149,736,770	948,732,541	[937,699,221; 959,765,861]	941,748,716	[929,302,951; 951,984,667]	128,449,826	[128,444,388; 128,455,264]