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Cost-Effectiveness Analysis of Universal Human Papillomavirus Vaccination Using a Dynamic Bayesian Methodology: The BEST II Study

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ABSTRACT

Background: Human papillomavirus (HPV) plays a role in the development of benign and malign neoplasms in both sexes. The Italian recommendations for HPV vaccines consider only 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 with cervical cancer screening and female-only vaccination and 2) the economic impact of immunization on various HPV-induced diseases. **Objective:** The objective of this study was to evaluate whether female-only vaccination or universal vaccination is the most cost-effective intervention against HPV. **Methods:** We present a dynamic Bayesian Markov model to investigate transmission dynamics in cohorts of females and males in a follow-up period of 55 years. We assumed 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 modeled on the basis of age-, sex-, and sexual behavioral-specific matrices to obtain the dynamic force of infection. **Results:** In comparison to cervical cancer screening, universal vaccination results in an incremental cost-effectiveness ratio of €1,500. When universal immunization is compared with female-only vaccination, it is cost-effective with an incremental cost-effectiveness ratio 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 with either cervical cancer screening or female-only vaccination within the Italian context.

Keywords: dynamic Bayesian model, cost-effectiveness analysis, herd immunity, HPV, vaccination programs.

Introduction

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 the vulva, vagina, anus, penis, head-neck (head neck squamous cell carcinoma [HNSCC]), lungs (recurrent respiratory papillomatosis), and external genital area [1]. HPV places a considerable clinical and economic burden on public health providers. In addition, 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 vaccine (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 an

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HPV vaccine [8]. When compared with 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 programs) has been evaluated by a large body of modeling 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.

In addition, an important factor in cost-effectiveness analyses of vaccines is the impact of herd immunity [15]. Herd immunity implies that nonvaccinated subjects are protected indirectly as a consequence of decreasing overall prevalence of the infectious disease in the population. Because 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 modeling, parameters naturally incorporate a large amount of uncertainty because 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 that formally includes previous information taken from several data sources as well as expert opinion can be used to construct a probabilistic MM to characterize 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 was to evaluate whether female-only vaccination or universal vaccination is the most cost-effective intervention against HPV; cervical screening was included in both interventions. To account for the effects of herd immunity, we incorporated 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 United Kingdom and continental European countries.

Methods

Analytical Overview

An empirically calibrated static Bayesian MM for the assessment of the cost-effectiveness of a multicohort HPV vaccination strategy was presented by Favato et al. [26]. Here, the original model was extended by including 1) a module for males; 2) population dynamics in an open model structure; 3) various HPV-induced diseases affecting the 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 women 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 copromote 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 that requires time-consuming and expensive research. Uncertainty was propagated through the model using Markov chain Monte-Carlo estimation [34].

The Model

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

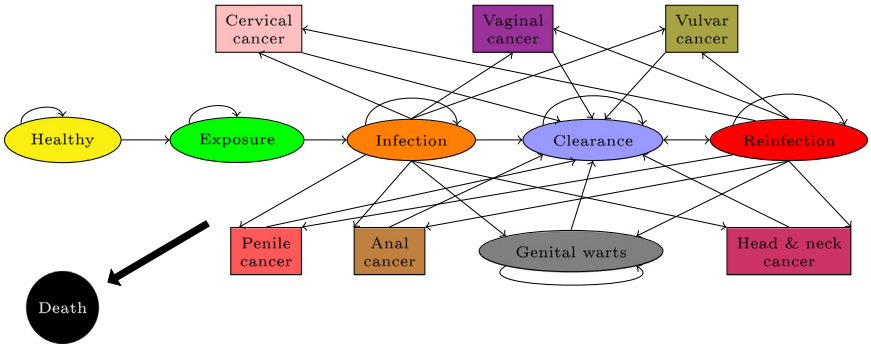

Fig. 1 – Overview of the health states included in the model. Diseases of the cervix, vagina, and vulva can affect only females, and penile cancer is a male-specific disease. Ellipses represent a single health state, whereas rectangles are a whole set of cancer-related health states, including precancerous states, cancer, and the tunnel postcancer 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.

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.

At the beginning of the virtual observation period, the model considered 14 cohorts of females and 14 cohorts of males, aged 12 to 35 years and followed up for a period of 55 years. In addition, the cohorts of females and males aged 0 to 11 years at the beginning of the follow-up were allowed to sequentially enter the population as soon as they reached age 12 years (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 were 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 4 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 by Favato et al. [26] were used to initialize the MM by distributing the cohorts over the health states, while HPV incidence was estimated using data presented by Myers et al. [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 behavior (categorized 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 preinfection state ("Exposure"); however, individuals can remain in the "Clearance" state unless they become reinfected and subsequently develop a second HPV-induced disease. An infection with the virus does not necessarily result in disease development; most of the individuals who are infected with HPV will clear the virus (on average, up to 80%–90% within 2 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 reinfection was associated with behavioral factors such as smoking, the long-term (five years or longer) use of oral contraceptives, multiparity (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 presents the distributional assumptions, the means and 95% credible intervals as well as the sources for the most important parameters. The model was calibrated using age-specific incidence of cervical, anal, vaginal, vulvar, and penile cancers, 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 quality-adjusted life years (QALYs).

PSA of the impact of parameter uncertainty on the results of the cost-effectiveness analysis was performed using a simulation

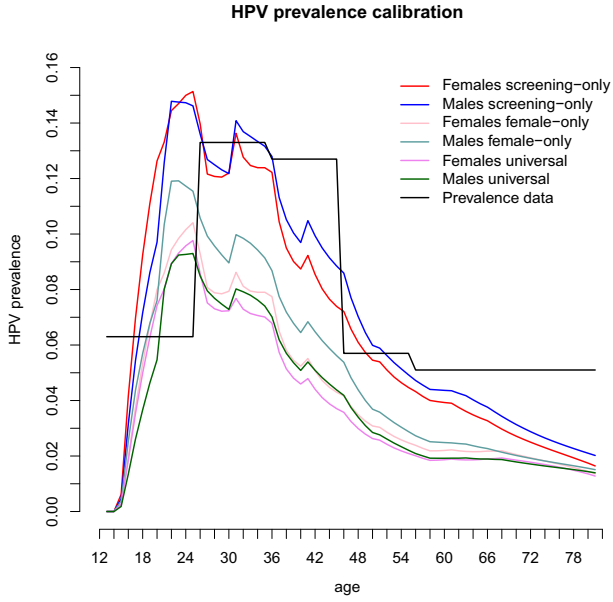

Fig. 2 – Calibration of the HPV prevalence model output to data taken from Baussano et al. [28]. The age- and sex-specific prevalence estimates are displayed separately for the three interventions screening-only, female-only, and universal vaccination. The figure shows that the model realistically predicts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

approach based on Markov Chain Monte Carlo estimation in a Bayesian framework. The cost-effectiveness plane, cost-effectiveness acceptability curve (CEAC), and the expected value of information (EVI) were computed and analyzed.

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 lifetime 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) that 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 5 years [99], accounting for 32.5% (6.0%–51.9%) vaccine efficacy against these HPV types [96,97].

The Process of Sexual Mating

The main characteristic of our dynamic Bayesian model is that it accounts for interactions between individuals of different sex 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].

Although estimates of HPV transmission probabilities were available from the literature, they were not directly comparable. Dunne et al. [102] estimated an HPV transmission probability

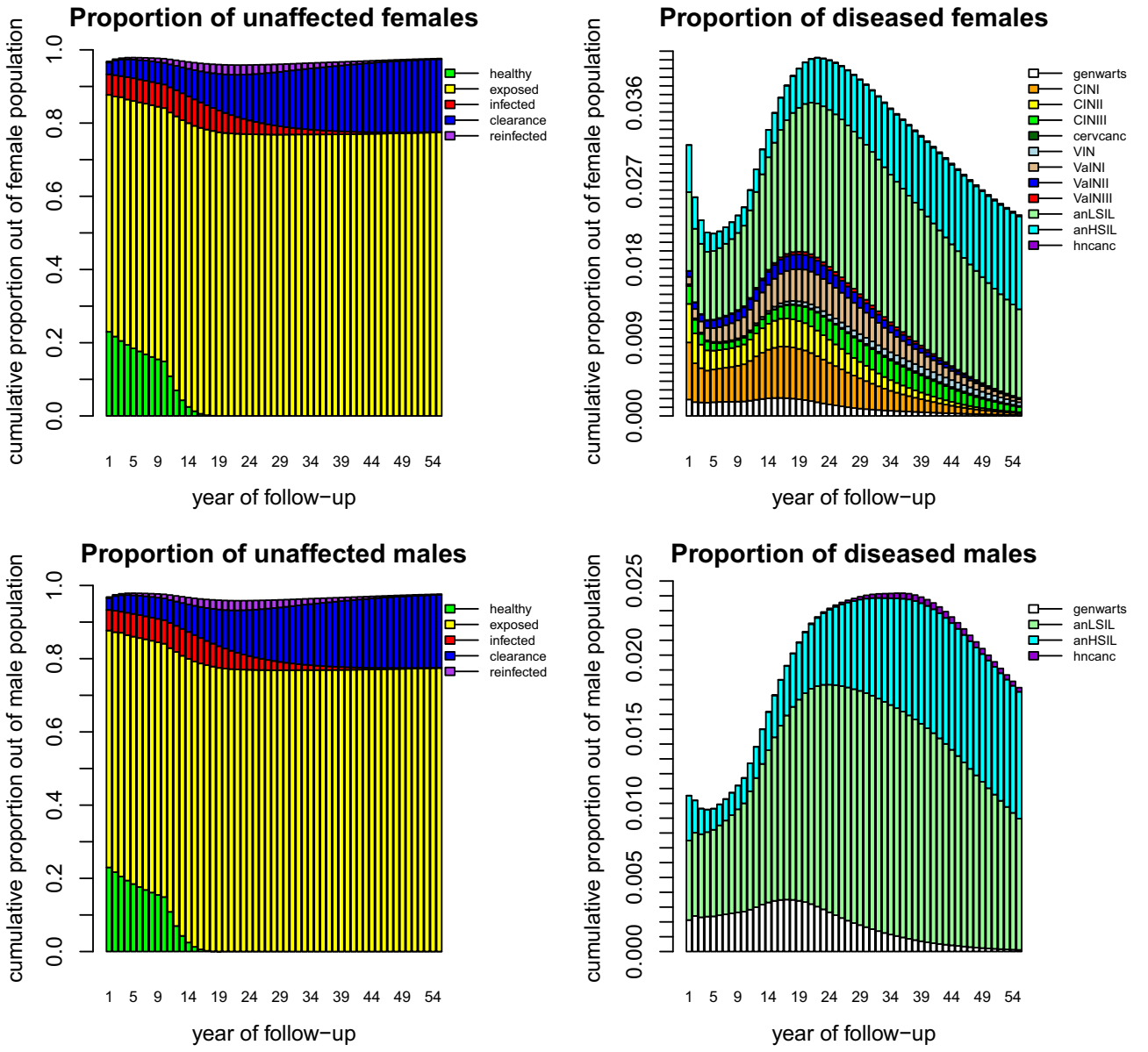

Fig. 3 – Model outcome of the natural history of HPV infection and disease progression. Cumulative proportions of unaffected and diseased individuals are displayed separately for the two sexes. The vast majority of individuals remain unaffected by the virus, whereas a small age-dependent proportion (up to 4% of females and 2.5% of males) develop an HPV-induced disease. anHSIL, anal high-grade squamous intraepithelial lesion; anLSIL, anal low-grade squamous intraepithelial lesion; cervcanc, cervical cancer; CIN, cervical intraepithelial neoplasia; genwarts, anogenital warts; hncanc, HNSCC; HPV, human papillomavirus; VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia.

per sex act of 40% (ranging from 5% to 100%); however, 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 modeled 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 group and from 29% to 74% in the high-risk group, respectively, using information found in the literature [102,103].

Data presented in Van de Velde et al. [104] were used to model sex-, age-, and behavioral-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 did 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 that were rescaled into probabilities [105]. As a consequence, the transition probabilities from the state "Exposure" to the state "Infection" were dependent

Table 1 – Distributional assumptions, means, and 95% CIs 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 y	Informative beta	0.0500 [0.0498; 0.0501]	EO
σ_a	Screening at 25–29 y	Informative beta	0.1530 [0.1480; 0.1590]	EO
σ_a	Screening at 30–34 y	Informative beta	0.2150 [0.2100; 0.2190]	EO
σ_a	Screening at 35–44 y	Informative beta	0.2460 [0.2440; 0.2470]	[38–42]
σ_a	Screening at 45–54 y	Informative beta	0.2600 [0.2540; 0.2660]	[38–42]
σ_a	Screening at 55–64 y	Informative beta	0.2420 [0.2320; 0.2520]	[38–42]
σ_a	Screening at 65–74 y	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 lognormal	0.7816 [0.6847; 0.8888]	[43–45]
γ_2	Vaccine efficacy anus	Informative lognormal	0.7019 [0.6055; 0.7981]	EO
γ_3	Vaccine efficacy head/neck	Informative lognormal	0.5008 [0.4563; 0.5497]	[46], EO
α_1	Vaccine coverage rate	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 with males	Informative gamma	1.6975 [1.5055; 1.9026]	[48], EO
ρ_3	Risk increase in anal cancer in MSM compared with MSF	Informative gamma	17.1880 [0.8714; 53.5615]	[49]
ζ	Proportion of population at increased risk	Informative beta	0.3139 [0.2140; 0.4054]	[29–33]
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 y)	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 HNSCC 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-y survival cervical cancer stage I	Informative beta	0.9782 [0.8931; 0.9999]	[5–7], EO
$\phi_{1,1}^{(an)}$	1-y survival anal cancer stage I/II	Flat normal	0.9900 [0.9800; 1.0000]	[66,67]
$\phi_{1,1}^{(hn)}$	1-y survival HNSCC stage I	Flat beta	0.9839 [0.9334; 1.0000]	[68]
$\phi_{1,1}^{(vag)}$	1-y survival vaginal cancer stage I	Flat beta	0.9531 [0.8014; 0.9999]	[69]

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Table 1 – *continued*

$\phi_{1,1}^{(vulv)}$	1-y survival vulvar cancer stage I	Flat normal	0.7808 [0; 1]	[70]
$\phi_{1,1}^{(pen)}$	1-y 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 lognormal	6.64 [5.05; 8.65]	[72–74]
c^{acq}	Dose of vaccine	Informative lognormal	56.10 [36.48; 77.43]	[72–74], EO
c^{pap}	Papanicolaou test	Informative lognormal	17.07 [14.05; 20.83]	[75]
c^{col}	Colposcopy	Informative lognormal	54.27 [49.63; 59.49]	[75]
c^{cyt}	Anal cytology	Flat lognormal	43.03 [23.59; 83.06]	[76]
c^{dna}	HPV DNA test	Informative lognormal	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 lognormal	309.33 [225.36; 405.64]	[50,79]
c_2^{cin}	CIN II	Informative lognormal	1,342.30 [1,032.51; 1,701.10]	[50]
c_3^{cin}	CIN III	Informative lognormal	1,750.03 [1,381.00; 2,193.80]	[50]
c_1^{cerv}	FIGO I	Informative lognormal	14,782.17 [2,459.13; 44,084.05]	[80]
c^{gw}	Anogenital warts	Informative lognormal	283.48 [242.04; 328.56]	[79,81]
c^{lsil}	LSIL	Informative lognormal	115.46 [76.56; 166.75]	[82]
c^{hsil}	HSIL	Flat lognormal	2,389.34 [1,165.65; 4,360.13]	[55,76]
c_1^{an}	Anal cancer stage I	Flat lognormal	7,618.94 [3,885.66; 12,058.58]	[83,84]
$c_{1,2}^{hn}$	HNSCC stage I/II	Flat lognormal	10,081.71 [5,457.09; 18,036.06]	[4,85,86]
c^{vain}	VaIN I/II/III	Flat lognormal	3,236.98 [1,686.22; 5,376.87]	[87]
c_1^{vag}	Vaginal cancer stage I	Flat lognormal	2,939.32 [1,684.02; 5,029.46]	[83,88]
c^{vin}	VIN	Flat lognormal	3,158.80 [1,920.52; 5,405.63]	[87]
c_1^{vulv}	Vulvar cancer stage I	Flat lognormal	8,304.24 [4,650.56; 14,302.42]	[88]
c^{pein}	PeIN	Flat lognormal	437.13 [63.13; 811.13]	[89]
c^{pen}	Penile cancer	Flat lognormal	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}	Anogenital warts in males	Informative beta	0.6961 [0.1172; 0.9999]	[2]
u_f^{gw}	Anogenital 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]
$u_{1,2,m}^{hn}$	HNSCC stage I/II in males	Informative beta	0.8171 [0.0135; 1]	[2,4]
$u_{1,2,f}^{hn}$	HNSCC 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]

Notes. 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. We assumed that administration costs include costs generated by additional medical consultations induced by mild adverse effects of vaccination. We assumed that approximately 1.8% of the vaccines require an additional visit to a general practitioner. Approximately 75% of Papanicolaou tests are performed using conventional cytology and 25% with liquid-based cytology. A gynecological office visit (at a fee of €20.66) [2] is included in colposcopy costs.

ASCUS, atypical squamous cells of undetermined significance; CI, credible interval; CIN, cervical intraepithelial neoplasia; EO, assumption based on expert opinion; FIGO, International Federation of Gynecology and Obstetrics; HNSCC, head neck squamous cell carcinoma; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; MSF, males who have sex with females; MSM, males who have sex with males; PeIN, penile intraepithelial neoplasia.

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

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 Papanicolaou tests and two colposcopies were conducted in females affected by cervical intraepithelial neoplasia I to III, and an HPV DNA typing was performed in those suffering from cervical intraepithelial neoplasia II and III or cervical cancer. According to Lazenby et al. [76] and Santoso et al. [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 because the information in the literature was not sufficient; we included only the related treatment costs.

In Italy, the vaccination program is financed at the regional level and can therefore largely differ in terms of age and the number of target cohorts, catch-up programs, 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 modeled 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 Favato et al. [26] were updated using Mennini et al. [2], Baio et al. [83], and Marcellusi et al. [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] precancerous lesions, as well as anal [84], vaginal [88], vulvar [88], and 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 the National Institute for Health and Care Excellence (NICE) [111] recommended a slightly higher value of 3.5%, with a 0% to 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 Capri et al. [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 QALY gained. Costs averted by the implementation of vaccination as well as QALYs gained were also estimated. In the absence of an Italian official threshold, a willingness-to-pay value of €25,000 to €40,000 per QALY gained [113,114] was used. This benchmark of value for money [113] roughly corresponds to the value of £20,000 to £30,000 adopted by NICE in the United Kingdom [115].

Results

Natural Disease History

Figure 2 presents calibration results for the predicted age-dependent HPV prevalence to data from Baussano et al. [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]. Because of nonexisting diagnostic procedures on HPV infection in males [116], we calibrated the model output for both sexes to data on females.

Figure 3 shows the cumulative proportions of individuals in the health states over the observation period, separately for the two sexes and for 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.

Overview Tables on Population Size, Overall Costs, and QALYs

Table 2 presents 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 skewed to the right, resulting in a median that is 10 times lower than the mean. In contrast, the costs in the interventions female-only and universal vaccination are symmetrically distributed; as a consequence, their mean and median are similar. Costs and QALYs are reported for the population as a whole. With

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

Intervention	Population size, mean	Overall cost (€)				Overall QALY	
		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 vaccination	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 vaccination	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]

CI, confidence interval; QALY, quality-adjusted life-year.

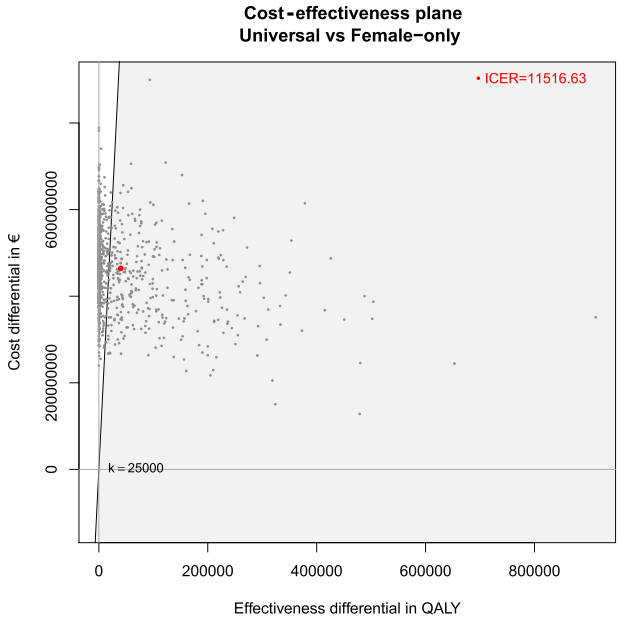

Fig. 4 – Cost-effectiveness plane for a comparison of universal to female-only vaccination. The graph shows positive skewness of the joint distribution of cost and effectiveness differentials, resulting in a cost-effectiveness acceptability curve with values below 80% cost-effectiveness for the whole range of willingness-to-pay values. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

screening-only, population size is the lowest since more individuals die due to the higher incidence of HPV-induced cancers.

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

The uncertainty around the cost-effectiveness estimates is analyzed by means of cost-effectiveness planes, CEACs, and EVI analysis.

Universal versus female-only vaccination

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 gray 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. Most of the points lie at the limit of the sustainability area, with low CEAC values as a consequence (see Fig. 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 5 presents a graphical summary of PSA. 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 values displayed. Yet, the CEAC measures only 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

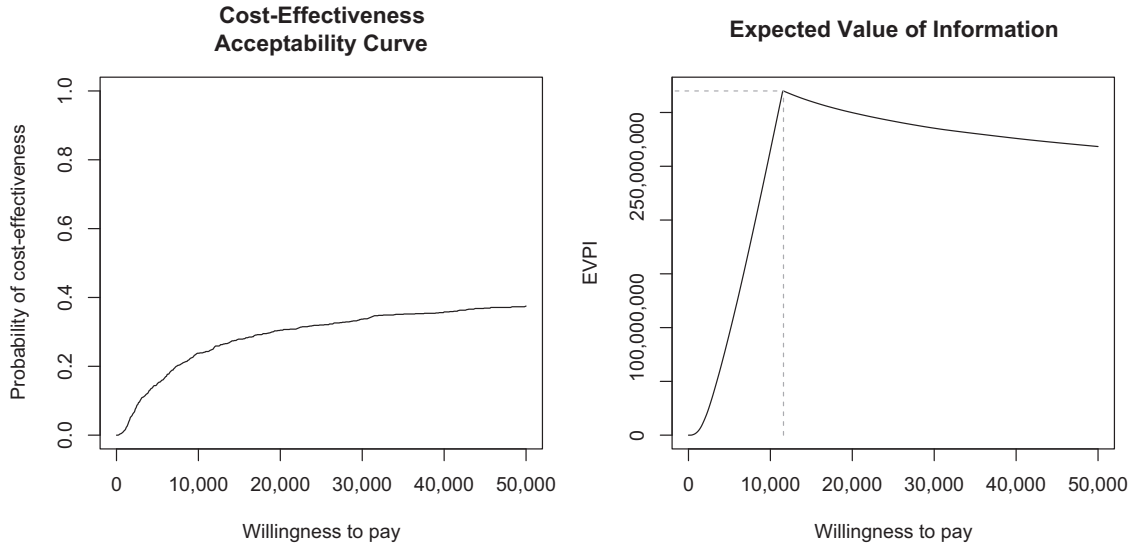

Fig. 5 – The figure presents probabilistic sensitivity analysis by means of the cost-effectiveness acceptability curve (CEAC) on the left and the expected value of information (EVI) on the right. The CEAC shows that the probability of cost-effectiveness never reaches 80% (the value defined as reasonable 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.

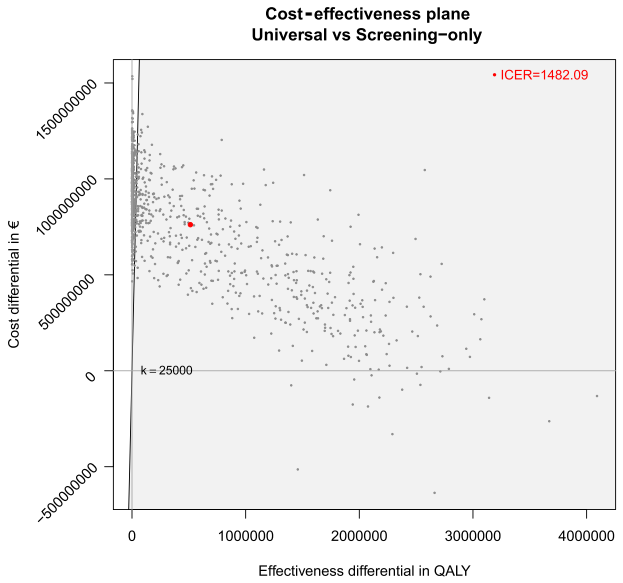

Fig. 6 – Cost-effectiveness plane for a comparison of universal vaccination to screening-only. In comparison to Figure 4, the joint distribution of cost and effectiveness differentials is less skewed to the right, resulting in a cost-effectiveness acceptability curve nearly reaching values of 60% cost-effectiveness. ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

function of willingness-to-pay values. 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.

Universal vaccination versus screening-only

The incremental cost of applying universal vaccination compared with screening-only is higher than in the preceding section because 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 skewed to the right.

Thus, the CEAC exhibited in the left panel of Figure 7 has higher values, nearly reaching 60%. In addition, 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 with screening-only.

Discussion

In this article, 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 [117]. Although particularly effective in modeling the dynamic transmission of infectious diseases, these

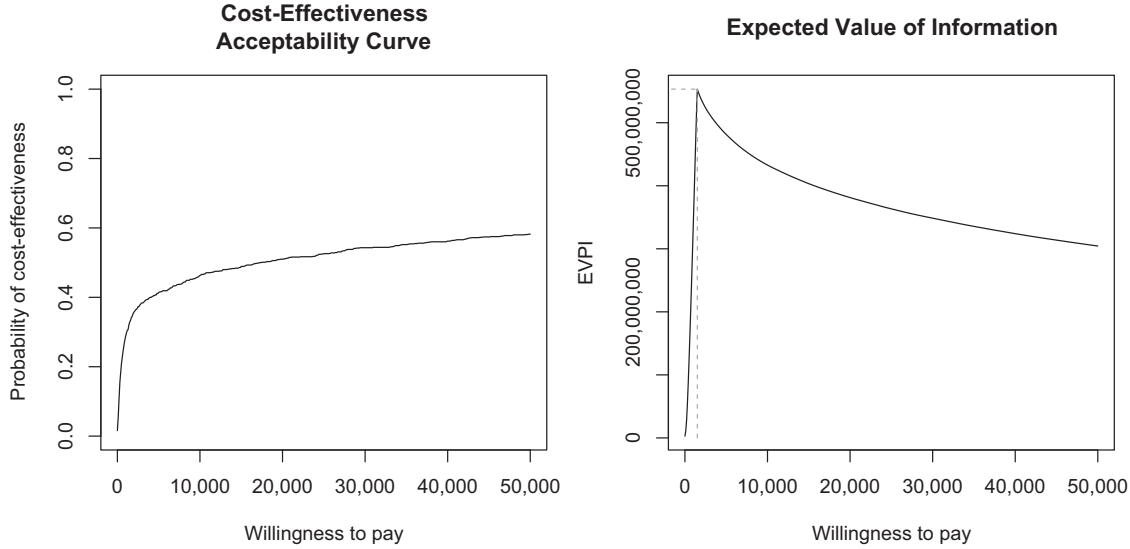

Fig. 7 – Probabilistic sensitivity analysis using the cost-effectiveness analysis curve (CEAC) on the left and the expected value of information (EVI) on the right. The CEAC shows that the probability of cost-effectiveness reaches a maximum value of only around 60% at a willingness-to-pay value of €50,000. 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.

are usually too complex for a stochastic formulation, limiting the possibility of performing extensive PSA. As a consequence, they can be conducted only when applying additional retrospective simulation procedures such as the Latin hypercube sampling [118].

PSA, however, is fundamental in any health economic evaluation [25,119,120] and particularly so in the case of infectious disease modeling, in which uncertainty surrounding the parameters and assumptions of the model may dramatically affect cost-effectiveness results. In contrast to most ordinary differential equation–based models, the dynamic Bayesian Markov model developed in this article 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 modeling 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 because 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 with standard ordinary differential equation–based methodology.

The use of a Bayesian approach is particularly relevant in the case of infectious disease modeling because 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 underestimation 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 because 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

1. higher vaccine efficacy;
2. accounting for cross-protection effects against other HPV types;
3. lifelong duration of vaccine-induced immunity;
4. lower unit cost of vaccination;
5. increased sexual activity;
6. lower frequency of cervical screening;
7. longer observation time period;
8. including a higher number of HPV-induced diseases; and
9. higher rate of discount.

Eight studies [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 Kim and Goldie [11], in which sexual mating continues to be modeled 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 studies [12,19–23,128], with ICER values ranging from €4,470 [128] to €31,240 [19] compared with screening-only and €93 [20] to €21,677 [12] compared with 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 = €2.1 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 recurrent respiratory papillomatosis); 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. The first three points contribute to lower ICER values, whereas the last three points tend to increase them.

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

1. 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 depends only on covariates such as age;
2. The inclusion of a high variety of HPV-induced diseases compared with other health economic evaluations that account only for cervical cancer [19,47,127];
3. The assumption of lifelong immunity following initial HPV vaccination with three doses, without the necessity of a booster application, in contrast to Danish Centre for Health Technology Assessment [19], Olsen and Jepsen [21], Taira et al. [47], Zechmeister et al. [127], and Hughes et al. [129]; and
4. The considerably low unit cost of vaccination compared with the official list price of the vaccine on the Italian market.

Although the network model presented by the Danish Centre for Health Technology Assessment [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 by Elbasha and Dasbach [12] could be that vaccination is made available for individuals aged 9 to 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 Olsen and Jepsen [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 Chesson et al. [23] compared with that in this study could be the fact that the authors consider only one group of sexual activity without accounting for high-risk sexual behavior. 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 because 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 optimize the control of the disease.

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