Novel Health Economic Evaluation of a Vaccination Strategy to Prevent HPV-related Diseases

The BEST Study

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Background: The development of human papillomavirus (HPV)-related diseases is not understood perfectly and uncertainties associated with commonly utilized probabilistic models must be considered. The study assessed the cost-effectiveness of a quadrivalent-based multicohort HPV vaccination strategy within a Bayesian framework.

Methods: A full Bayesian multicohort Markov model was used, in which all unknown quantities were associated with suitable probability distributions reflecting the state of currently available knowledge. These distributions were informed by observed data or expert opinion. The model cycle lasted 1 year, whereas the follow-up time horizon was 90 years. Precancerous cervical lesions, cervical cancers, and anogenital warts were considered as outcomes.

Results: The base case scenario (2 cohorts of girls aged 12 and 15 y) and other multicohort vaccination strategies (additional cohorts aged 18 and 25 y) were cost-effective, with a discounted cost per quality-adjusted life-year gained that corresponded to €12,013, €13,232, and €15,890 for vaccination programs based on 2, 3, and 4 cohorts, respectively. With multicohort vaccination strategies, the reduction in the number of HPV-related events occurred earlier (range, 3.8–6.4 y) when compared with a single cohort. The analysis of the expected value of information showed that the results of the model were subject to limited uncertainty (cost per patient = €12.6).

Conclusions: This methodological approach is designed to incorporate the uncertainty associated with HPV vaccination. Modeling the cost-effectiveness of a multicohort vaccination program with Bayesian statistics confirmed the value for money of quadrivalent-based HPV vaccination. The expected value of information gave the most appropriate and feasible representation of the true value of this program.

Key Words: HPV vaccination, multicohort strategy, Bayesian modeling, uncertainty, cost-effectiveness

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The BEST study: Bayesian modeling assessing the Effectiveness of a vaccination Strategy To prevent HPV-related diseases.

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Human papillomavirus (HPV) is the primum movens in the etiopathogenesis of both invasive cervical cancer and other malignant and benign neoplastic lesions that affect the vulva, vagina, anus, penis, head/neck, lungs (recurrent respiratory papillomatosis), and external genital area (condyloma acuminata).[1,2] Genotypes 16 and 18, which are high-risk (oncogenic) variants of HPV, are the most common causes of anogenital carcinomas and account for approximately 75% of all cervical cancers.[3] The low-risk HPV genotypes 6 and 11 are responsible for approximately 90%–95% of anogenital warts,[4] but are not associated commonly with cancer.

Although estimates vary depending on the assumptions made, the cost-effectiveness of vaccination with the quadrivalent vaccine against HPV has been confirmed by a large body of modeling studies, which have been designed to evaluate different vaccination strategies.[5–8] In general, these

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studies compared a single cohort of women who underwent vaccination, plus optional catch-up cohorts, with women who underwent screening alone; the cohorts varied in age of immunization among studies. Only 1 study evaluated the implementation and economic consequences of a multicohort vaccination strategy.[9]

Given that, in general, new vaccines are more expensive than older vaccines; the cost-effectiveness of vaccination strategies should be evaluated appropriately to provide information about the value for money of a selected immunization plan before and during its implementation. Standard models of economic evaluation might not assess the true cost-effectiveness of vaccines adequately, which could result in unintended undervaccination.[10] Moreover, such economic models have become remarkably complex, not only in terms of their development, but also because of the demand for accurate epidemiological data on the natural history and evolution of diseases. Vaccination against HPV has 3 main goals: (1) to prevent transmission, (2) to prevent infection, and (3) to prevent disease. Unfortunately, not all the sequential phases of these processes have been characterized and fully understood. As a result, substantial uncertainty remains concerning the main parameters of economic models with regard to HPV vaccination. Standard frequentist statistics and deterministic sensitivity analyses might not be able to provide a meaningful assessment due to their excess of uncertainty.[11] In the frequentist theory, the concept of probability is linked uniquely to repeatable trials whose uncertainty is related to the intrinsic variability of sampling. In contrast, from the Bayesian perspective, probability describes the (possibly subjective) level of uncertainty with which a particular outcome of a trial is predicted. This uncertainty might be due to the intrinsic variability of the trial, or alternatively to a low level of knowledge about the trial itself.[12]

This study was designed to assess, using a Bayesian approach, the cost-effectiveness of a quadrivalent-based multicohort HPV vaccination strategy. In previous empirical investigations, a multicohort approach has proved to be the most promising alternative in terms of both clinical and economic outcomes.[13]

METHODS

Analytical Overview

After the collection and integration of epidemiological, clinical, demographic, and economic data (details are provided in the Supplementary Appendix, http://links.lww.com/MLR/A330), we designed an empirically calibrated probabilistic model to assess the cost-effectiveness of a multicohort HPV vaccination strategy in the context of the current screening program for cervical cancer in Italy. A Markov model[12] that was capable of simulating the probability of proceeding from one pathological stage to the next was developed. The clinical benefits of vaccination were related to the prevention of HPV-related events such as abnormal Pap smears, precancerous cervical lesions, cervical cancers, and anogenital warts. All direct medical costs that were associated with each vaccinated cohort were compared with exactly the same costs for identical cohorts of girls who were not vaccinated. Whenever possible, risk factors that copromote the development of cervical cancer and other HPV-related diseases were taken into account. A full Bayesian model was used to assess the cost-effectiveness of a multicohort HPV vaccination strategy. All unknown quantities that reflected the state of science currently available were associated with plausible probability distributions. These distributions were updated with the available data, and uncertainty was propagated through the entire model with a Markov Chain Monte Carlo procedure, implemented using R and JAGS (see the Supplementary Appendix, http://links.lww.com/MLR/A330).

The Model

The model distinguished 16 clinical states that we assumed to be mutually exclusive and exhaustive; we further assumed that subjects can move among these states from one period to the next according to a set of transition probabilities (relevant details are provided in the Supplementary Appendix, http://links.lww.com/MLR/A330). We then produced a "virtual" follow-up of 90 years for a multicohort using a Markov model with annual cycles.

All subjects were in a state of perfect health when observation began. Subjects who have been exposed to HPV can either die, remain in the same asymptomatic state, or progress to being infected by the virus.

The majority of individuals who have been infected with HPV will clear the virus (up to 90% within 2 y[14]) and develop natural immunity to HPV. Women in whom infection persists develop clinical manifestations of disease, such as low-grade or high-grade cervical intraepithelial neoplasia (CIN1 and CIN2–3, respectively). The standard intervention for patients affected by CIN1 is follow-up, and cervical conization is used less frequently. Patients either move subsequently to the state of clearance, in which their quality of life (QoL) returns to its maximum value, or progress toward high-grade lesions. Patients with CIN2–3 usually undergo the surgical procedure of conization. Patients with CIN3 can progress further toward invasive cervical cancer. In all the neoplastic states mentioned, from 1 year to the next, patients can remain in the state of clearance or become reinfected. After reinfection, they can either return to the state of clearance or progress toward a subsequent state. Patients who progress to cervical cancer have an increased mortality (age-specific mortality rates are derived from the population and an additional parameter is used to account for the excess mortality due to cervical cancer).

Subjects without precancerous cervical lesions may be at risk of developing anogenital warts. Anogenital warts can persist over time, or can be cleared (as a result of treatment). After clearance, patients can become reinfected or remain in the state of clearance, in which their QoL returns to the maximum level. However, it is very likely that the QoL of patients with anogenital warts decreases.[15]

When data were directly available, we imposed minimally informative prior distributions and used the data to inform the ensuing posteriors. If data were not directly available, we encoded the information obtained by literature

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review or assumptions based on elicitation of the opinion of clinical specialists in suitable informative prior distributions. Table 1 summarizes all the model parameters that were used to generate the transition probabilities, and shows the distributional assumptions applied, the mean values, and the 95% credible intervals (95% CI). The model was calibrated using data on the age-specific incidence of invasive cervical cancer derived from the Italian female population.[22,37] Given its characteristics, the model can process data from any elective setting.

The Bayesian procedure provides a simulation of a large number of "possible future scenarios" under probabilistic assumptions. These simulations can be used to derive a complete posterior distribution of outcomes. To check convergence, we ran the Markov Chain Monte Carlo algorithm for 2 independent chains of 50,000 iterations, using a burn-in of 5000 iterations and thinning of 90 (to improve convergence). Convergence was evaluated using Gelman–Rubin statistics.[38] A probabilistic sensitivity analysis of the impact of input uncertainty on the results of the cost-effectiveness analysis was performed. Using the simulations, we analyzed the risk that was associated with decisions regarding the health interventions being compared (screening only vs. screening+vaccination). In particular, we computed the cost-effectiveness acceptability curve (CEAC) and the expected value of information (EVI) (see the Supplementary Appendix for additional details http://links.lww.com/MLR/A330).

Vaccination Strategy

To assess the cost-effectiveness of a quadrivalent-based HPV vaccination program, we used the model to project the health benefits and economic consequences generated by the vaccination of girls aged 12, 15, 18, and 25 years. The base case involved the vaccination of 2 cohorts of girls (aged 12 and 15 y). Subsequently, 3-cohort and 4-cohort vaccination strategies were considered, for girls aged 12, 15, and 18 and 12, 15, 18, and 25 years, respectively. In the base case analysis, lifetime duration of protection by vaccination against the targeted HPV genotypes was assumed. However, mean durations of protection that ranged between 15 years and lifelong were also considered.

The vaccination coverage rates were drawn from real data recorded in an Italian vaccination register, which concerns a multicohort vaccination program started in 2007.[19] Although all vaccinated girls included in the register received the recommended 3 doses of the vaccine, in our model a small proportion of girls[19] were assumed to receive only 2 doses, with a resulting reduction in vaccine-induced immunity. We assumed that approximately 50% of the full expected efficacy of the quadrivalent vaccine occurred in vaccinated subjects who received <3 doses (see the Supplementary Appendix, http://links.lww.com/MLR/A330).

The quadrivalent vaccine showed an efficacy of around 100% in the prevention of HPV-induced clinical outcomes in girls aged between 16 and 26 years, especially in those who had never been exposed to HPV.[16,17] In the model, vaccine efficacy was regarded as a preventive intervention against future genotype-specific diseases in subjects with or without previous HPV infections.[39] Furthermore, the cross-protection effect against HPV genotypes other than those targeted in the quadrivalent vaccine was included in the model.[20,21]

Economic Parameters

Only direct medical costs associated with the screening, diagnosis, and management of HPV-related diseases were included in the model. The costs of the quadrivalent vaccine, including those incurred for its administration, were considered. Data on patients' preferences for a full range of health states associated with HPV-related diseases were collected from an Italian female population.[40] Italian utility weights for health state, ranging from 0 (death) to 1 (perfect health), were utilized to estimate the quality-adjusted life expectancy gained. Given that many events are expected to be averted relatively early after vaccination (ie, atypical squamous cells of undetermined significance, CIN1, and anogenital warts), whereas the reduction in invasive cervical cancer is expected to be seen after several years, the annual discount rates were set at 1.5% and 3% for benefits and costs, respectively.[7,41]

The benefits of the multicohort vaccination strategy, compared with those of screening alone, were measured using a single natural health unit (life-year) gained, which was related to costs as the basis for calculations of cost-effectiveness. The assessment was performed by measuring the incremental cost-effectiveness ratio and quality-adjusted life-years (QALYs) gained, adopting the National Health Service perspective. Costs averted by the implementation of vaccination were also estimated. A cutoff point of approximately €30,000–€45,000 per QALY gained[7,8] (which corresponds to the value of £20,000–£30,000 adopted by the National Institute for Health and Clinical Excellence in the United Kingdom)[42] was used as the benchmark of value for money.

RESULTS

Assuming that vaccination induced lifelong immunity, the mean cost per QALY gained in the base case of the multicohort vaccination (2 cohorts aged 12 and 15 y) was €12,013 (95% CI, €2,364–€22,481). When additional cohorts were included, the mean cost per QALY gained rose to €13,232 (95% CI, €4,432–€22,939) and €15,890 (95% CI, €7,179–€25,139) for vaccination strategies based on 3 and 4 cohorts, respectively (Table 2).

The overall expected effect of vaccination appeared to be related to the number of cohorts targeted. In comparison with a single cohort vaccination program (girls aged 12 y only), examination of the curves reported in Figure 1 shows that the combined reduction in HPV-related events (ie, abnormal Pap smears, CIN1, CIN2, CIN3, cervical cancer, and anogenital warts) occurred on average 3.8, 5.5, and 6.4 years earlier with 2, 3, and 4 cohorts, respectively.

However, with a 4-cohort vaccination strategy, the quicker reduction and the shorter time required for the occurrence of the expected results could not compensate for the greater relative decrease in HPV-related events that was observed with the base case (61.3% reduction with 4 cohorts vs. 71.1% with the base case).

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TABLE 1. Distribution of Variables Used in the Model

Variable description	Distribution	Mean	95% CI		References
Vaccine-related Parameters					
Vaccine efficacy	Informative LogNorm	0.7830	0.6830	0.8960	Maw and colleagues[15–17]
Vaccine compliance	Flat Beta	1.0000	0.9990	1.0000	La Torre et al[18]
Vaccine coverage rate	Flat Beta	0.8470*	0.8340	0.8600	La Torre et al[18]
Cross-protection effect	Informative LogNorm	0.0740	0.0410	0.1290	Mennini and colleagues[19,20]
Efficacy decrease due to noncompliance	Informative Beta	0.5040	0.3110	0.7020	Maw et al[15]
Probability of the level of compliance with vaccination program					
1 dose	Flat Dirichlet	0.0000	0.0000	0.0010	La Torre et al[18]
2 doses	Flat Dirichlet	0.0000	0.0000	0.0010	
3 doses	Flat Dirichlet	1.0000	0.9999	1.0000	
Clinical Parameters					
Exposure → Infection (y)					
12–15	Informative LogNorm	0.0020	0.0000	0.0180	Wheeler and colleagues,[21–25] EC
16	Informative LogNorm	0.0240	0.0060	0.0610	
17–18	Informative LogNorm	0.0750	0.0620	0.0900	
19–22	Informative LogNorm	0.1540	0.1260	0.1850	
23–29	Informative LogNorm	0.1210	0.1030	0.1410	
30–33	Informative LogNorm	0.0600	0.0560	0.0650	
34–49	Informative LogNorm	0.0370	0.0350	0.0390	
≥ 50	Informative LogNorm	0.0120	0.0120	0.0120	
Infection → Exposure (y)					
12–24	Informative Beta	0.7190	0.6480	0.7860	Wheeler and colleagues,[21–23,25] EC
25–29	Informative Beta	0.6990	0.5940	0.7940	
30–39	Informative Beta	0.3500	0.2820	0.4170	
40–49	Informative Beta	0.2010	0.1110	0.3010	
≥ 50	Informative Beta	0.0990	0.0570	0.1510	
Infection → CIN1	Informative Beta	0.1100	0.0660	0.1640	Wheeler and colleagues,[21–24]
Infection → CIN2	Informative Beta	0.0220	0.0140	0.0330	Wheeler and colleagues,[21,22,24,25]
Subject to conization					
CIN1 → CIN2	Informative Beta	0.1200	0.0420	0.2430	Wheeler and colleagues,[21,22,25] EC
CIN1 → CIN3	Informative Beta	0.0400	0.0230	0.0610	Wheeler and colleagues,[21–26] EC
CIN2 → CIN3	Informative Beta	0.1400	0.1040	0.1820	Wheeler and colleagues,[21–27] EC
CIN3 → Cancer	Informative Beta	0.0150	0.0070	0.0260	Wheeler and colleagues,[21–27] EC
CIN1 → Clearance	Informative Beta	0.8990	0.8350	0.9520	Wheeler and colleagues,[21–26] EC
CIN2 → Clearance	Informative Beta	0.8600	0.8160	0.9000	Wheeler and colleagues,[21–27] EC
CIN3 → Clearance	Informative Beta	0.8610	0.8190	0.9000	Wheeler and colleagues,[21–27] EC
Not subject to conization					
CIN1 → CIN2	Informative Beta	0.2240	0.1570	0.2950	Wheeler and colleagues,[21,22,25] EC
CIN1 → CIN3	Informative Beta	0.0750	0.0570	0.0950	Wheeler and colleagues,[21–26] EC
CIN2 → CIN1	Informative Beta	0.2500	0.2040	0.3020	Wheeler and colleagues,[22,24] EC
CIN2 → CIN3	Informative Beta	0.3500	0.3010	0.4020	Wheeler and colleagues,[21–27] EC
CIN3 → CIN1	Informative Beta	0.0200	0.0050	0.0420	Wheeler and colleagues,[21–27] EC
CIN3 → CIN2	Informative Beta	0.0300	0.0070	0.0670	Wheeler and colleagues,[21–27] EC
CIN3 → Cancer	Informative Beta	0.0500	0.0240	0.0830	Wheeler and colleagues,[21–27] EC
CIN1 → Clearance	Informative Beta	0.710	0.6000	0.7890	Wheeler and colleagues,[21–27] EC
CIN2 → Clearance	Informative Beta	0.3550	0.2040	0.5300	Wheeler and colleagues,[21–27] EC
CIN3 → Clearance	Informative Beta	0.2850	0.1620	0.4340	Wheeler and colleagues,[21–27] EC
Probability of conization in CIN1					
Immediate	Informative Beta	0.3020	0.2090	0.4010	Ronco et al[26]
Delayed	Informative Beta	0.1700	0.1500	0.1890	EC

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Probability of diagnosis without screening					
CIN2	Informative Beta	0.0250	0.0000	0.1040	EC
CIN3	Informative Beta	0.0760	0.0570	0.0960	
Anogenital warts					
Recurrence	Informative Beta	0.4250	0.2390	0.6130	De Aloysio et al,[28] EC
Cost Parameters					
Diagnostic procedures					
Pap test†	Informative LogNorm	17.14	14.25	20.78	French and Nashelsky[29]
Colposcopy‡ and biopsy	Informative LogNorm	54.23	49.00	59.41	
HPV DNA test	Informative LogNorm	78.98	77.04	81.03	Ministero della Salute and Nomenclatore Tariffario Regionale 2006[30,31]
Precancerous cervical lesions					
CIN1	Informative LogNorm	303.52	225.87	398.59	Ronco and Costa et al[26,32]
CIN2	Informative LogNorm	1339.36§	1021.73	1718.62	Ronco et al[26]
CIN3	Informative LogNorm	1759.96	1329.54	2244.73	Ronco et al[26]
External genital lesions					
Anogenital warts	Informative LogNorm	283.88	243.83	332.59	Nomenclatore Tariffario Regionale 2006 and Costa et al[32,33]
Cervical cancer					
FIGO I	Informative LogNorm	14,430.32	2644.27	46,689.52	Merito et al[34]
FIGO II	Informative LogNorm	24,499.29	8455.06	52,861.89	
FIGO III	Informative LogNorm	37,808.01	4833.33	129,962.51	
FIGO IV	Informative LogNorm	35,350.52	2719.00	156,840.72	
Vaccination					
Cost per dose‖	Informative LogNorm	69.13	60.16	79.58	
Administration cost¶	Informative LogNorm	6.77	5.07	8.97	Mennini and colleagues[7,35]

Utilities

Variables	Description	Distribution	Mean	95% CI		References
	External genital lesions					
u^{gw}	Anogenital warts	Informative Beta	0.6870	0.3530	09190	Azzari et al[36]
	Precancerous cervical lesions					
u_1^{cin}	CIN1	Informative Beta	0.8220	0.4360	0.9940	Azzari et al[36]
u_2^{cin}	CIN2	Informative Beta	0.8070	0.4710	0.9850	
u_3^{cin}	CIN3	Informative Beta	0.8040	0.4700	0.9820	
	Cervical cancer					
u_1^{cin}	FIGO I	Informative Beta	0.5850	0.2500	0.8800	Azzari et al[36]
u_2^{cin}	FIGO II	Informative Beta	0.5310	0.2330	0.8090	
u_3^{cin}	FIGO III	Informative Beta	0.5660	0.3780	0.7530	
u_4^{cin}	FIGO IV	Informative Beta	0.4510	0.1770	0.7500	

*Coverage rate extracted from the vaccination register of the Basilicata Region.[18]

†Approximately 75% of Pap tests are performed using conventional cytology and 25% with liquid-based cytology.

‡A gynecological office visit (at a fee of €20.66) is included.[29]

§Calculated considering that CIN2 account for 45% of all high-grade cervical lesions (CIN2, CIN3, and adenocarcinoma in situ).[26]

‖The price range is based on Regional tenders that occurred during 2008 and 2009 in Italy.

¶Included in this value are costs generated by additional medical consultations induced by mild adverse effects of vaccination. We assumed that approximately 1.8% of vaccinees require an additional visit to a general practitioner.

The notation A → B indicates the transition from state A to state B; CI, credible interval; EC, assumption based on data provided by expert clinicians; FIGO, International Federation of Gynecology and Obstetrics; HPV, human papillomavirus.

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TABLE 2. Cost per Discounted QALY Gained and Reduction in HPV-related Outcomes for Multicohort Vaccination Programs

	Base Case—2 Cohorts (12, 15 y)		3 Cohorts (12, 15, 18 y)		4 Cohorts (12, 15, 18, 25 y)	
Parameters	**Screening**	**Vaccination**	**Screening**	**Vaccination**	**Screening**	**Vaccination**
Cost (mean)	88,939,920	132,412,500	136,507,700	206,843,600	193,225,800	286,633,300
SD	19,569,808	8,559,054	23,222,940	10,889,690	27,719,200	15,913,800
5.0%	61,288,700	118,068,900	102,863,800	187,940,900	150,149,600	259,890,100
95.0%	136,383,900	151,164,000	194,312,751	229,925,311	261,661,200	320,433,100
Incremental cost (mean)	—	43,472,580	—	70,335,900	—	93,407,500
SD	—	14,411,870	—	16,692,630	—	17,388,300
5.0%	—	10,850,940	—	30,610,480	—	50,567,490
95.0%	—	64,893,140	—	95,209,663	—	119,798,000
QALY (mean)	—	12,013	—	13,232	—	15,890
SD	—	5367	—	4664	—	4559
5.0%	—	2364	—	4432	—	7179
95.0%	—	22,481	—	22,939	—	25,139
Outcomes						
Abnormal Pap tests	213,824	68,796	327,126	113,366	458,249	210,608
CIN1	54,933	17,610	84,561	29,238	120,351	55,800
CIN2	23,741	7,635	36,795	12,766	51,594	23,741
CIN3	20,928	6,780	31,546	10,981	43,079	19,529
Cervical cancer	7,311	2,373	10,662	3,697	14,100	6,234
Deaths from cancer	2,693	882	3,917	1,370	5,130	2,268
Anogenital warts	46,548	13,361	69,175	21,331	79,910	28,930

HPV indicates human papillomavirus; QALY, quality-adjusted life-years.

The base case and all the other vaccination strategies under consideration were cost-effective interventions. The cost per QALY gained remained below the range of threshold values, as shown by the cost-effectiveness acceptability curve (Fig. 2). QALYs were gained primarily through the reduction of HPV-related events such as CIN1 and anogenital warts (which accounted jointly for 65% of the discounted QALY gained), followed by CIN2–3, and finally cervical cancer (Table 3). Given that the cost of vaccination exceeded the expected decrease in costs derived from the prevention of HPV-related outcomes, vaccination is unlikely to be cost saving. However, the base case vaccination strategy resulted in a mean net reduction in cost of €80 million (95% CI, €40.1–€144.7 million) due to the prevention of HPV-related diseases (the net mean cost reduction reached €119 and €138 million with 3 and 4 cohorts, respectively). Analysis of the EVI showed that the uncertainty in the model inputs was irrelevant to the optimal decision-making process: even around the point of maximum uncertainty, the expected value of additional research that could reduce the uncertainty was only €12.6 per patient (Fig. 2).

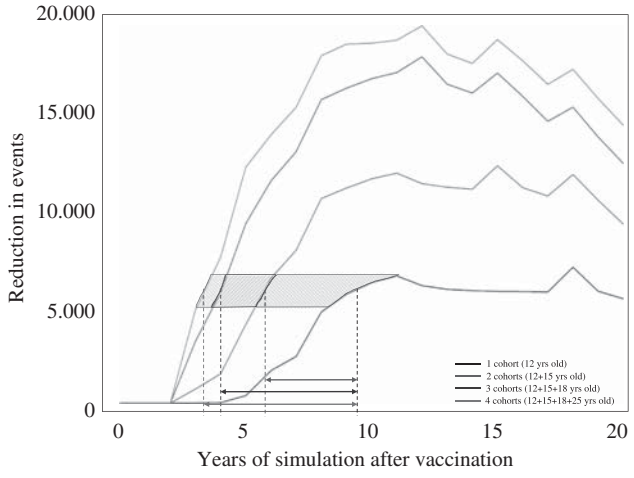

FIGURE 1. Mid-term curves of events averted by vaccination strategy (base case, 3 and 4 cohorts versus a single cohort of girls aged 12 years).

In the base case, the cost per discounted QALY gained almost doubled to €23,525 (95% CI, €11,252–€36,460) when the duration of protection was shorter than expected (15 y) and a subsequent booster was administered. Without a booster, and assuming exponential waning of protection, the cost per QALY tended to the upper limit of the threshold value, amounting to €38,822 (95% CI, €19,570–€62,932). To the extent that a linear relationship exists between the vaccination coverage rate and the reduction in HPV-related events, a coverage rate in excess of 70% did not have a significant impact on the cost-effectiveness of either the base case or the other multicohort strategies. In contrast, for coverage rates <50%, the cost per QALY gained declined to €8,427 (95% CI, €-5,118–€20,041) in the base case. This was probably the result of a nonlinear relationship between coverage rate and expected benefits from vaccination.

DISCUSSION

Models that are used to assess the cost-effectiveness of HPV vaccination programs must account for different levels of uncertainty that surround several of their basic parameters. Current knowledge about the duration of protection from vaccination, the effectiveness of the vaccines, and the effect of cross-protection is not sufficient to determine the cost-effectiveness of HPV vaccination programs with certainty. Moreover, the magnitude of the benefits derived from a vaccination strategy in a given setting is associated directly

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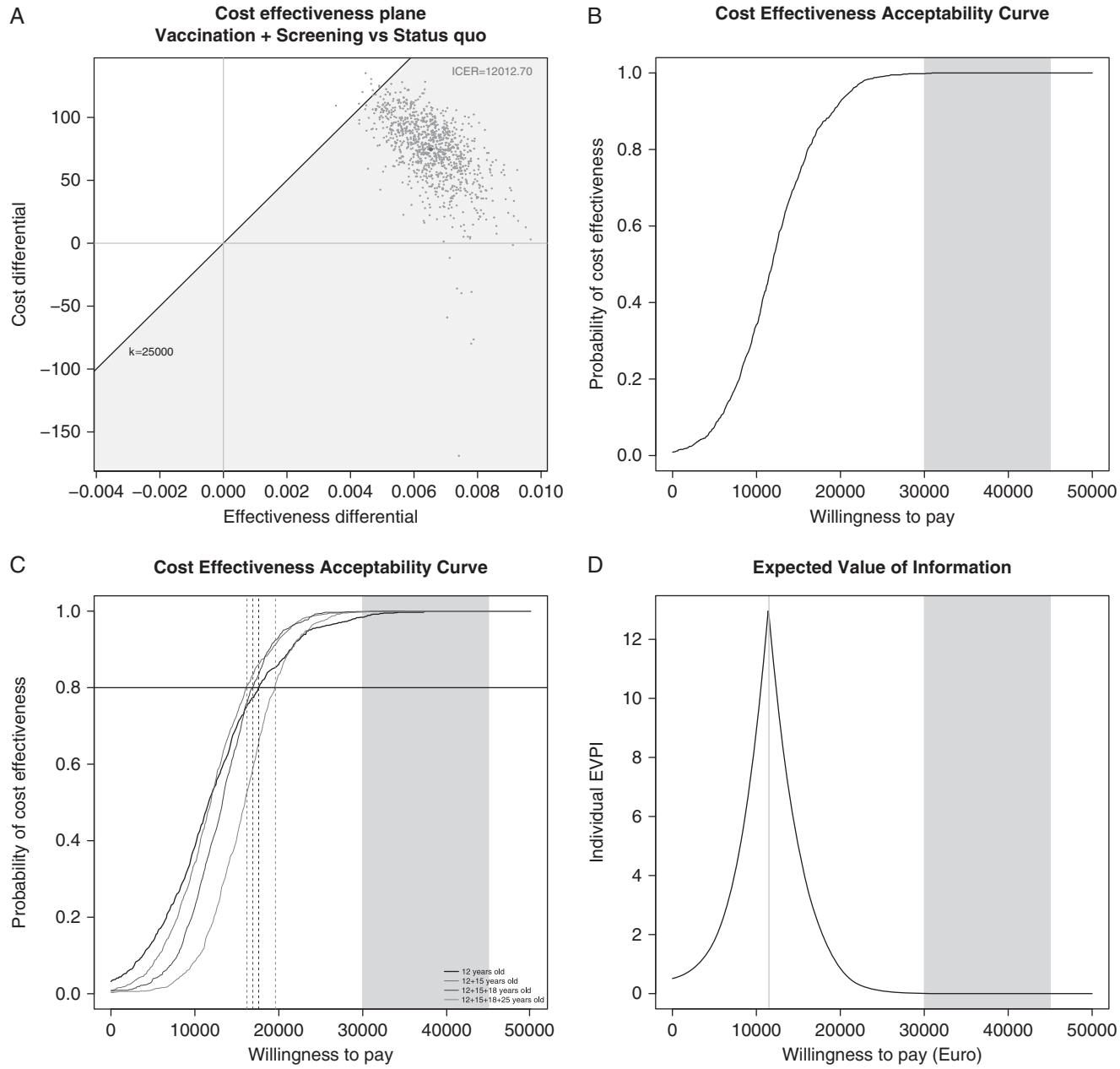

FIGURE 2. A, B, and D, Cost-effectiveness plan, cost-effectiveness acceptability curve, and expected value of information for the base case scenario (2 cohorts of girls, aged 12 and 15 y). The shaded areas show the range of threshold values for a cost-effective health intervention. C, Comparison of cost-effectiveness acceptability curves for different multicohort strategies. With a probability of cost-effectiveness of 80%, the lowest cost per QALY gained is predicted in the base case scenario (€16,050) and in a 3-cohort vaccination program (€16,850), even when compared with a single-cohort vaccination strategy for girls aged 12 years only (€17,590).

not only with the prevalence and treatment costs of disease attributable to HPV but also with the coverage rate achieved.[6]

To deal with this multitude of uncertainties, a specific Bayesian model was adopted for the assessment of a multicohort vaccination strategy against HPV. Models developed under the Bayesian framework formally combine prior knowledge with current information on the parameters of interest. The prior distributions may be based on subjective judgement, but this is not essential. When data are available from existing evidence, they can be included in the process. Hence, in the Bayesian approach, prior information and clinical results are part of a continual data stream, in which inferences are updated whenever new data become available.

To our knowledge, this is the first study that accomplished an economic evaluation of a multicohort HPV

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TABLE 3. Distribution of Discounted QALY Gained by Main Prevented HPV-related Events

Event	Base Case—2 Cohorts (12, 15 y) (%)	3 Cohorts (12, 15, 18 y) (%)	4 Cohorts (12, 15, 18, 25 y) (%)
CIN1	37.6	38.0	39.1
CIN2	15.7	16.0	16.4
CIN3	13.9	13.7	13.9
Cervical cancer	5.2	5.0	5.0
Anogenital warts	27.6	27.3	25.6
Total	100	100	100

HPV indicates human papillomavirus; QALY, quality-adjusted life-years.

vaccination strategy that is based on a Bayesian modelling approach. Although the results reported in the present study cannot be compared strictly with any cost-effectiveness assessment performed previously, the range of costs per QALY gained for a single cohort of girls aged 12 years is mostly consistent with base case results from other principal studies conducted in the United Kingdom by Jit et al,[43] in the United States by Kim and Goldie,[6] and in an earlier Italian study.[7] All the earlier studies performed several rigorous sensitivity analyses. However, considering the large body of uncertainty that surrounds HPV vaccination, it is likely that our results, which are based on a Bayesian model, are more robust. Moreover, in our study, prior distributions of parameters that influence the impact of vaccination significantly (eg, coverage rates) were derived directly from programs that had already been implemented, rather than from assumptions. In order to improve comparability with the existing literature, we have also run a further sensitivity analysis, in which the discount rates were both set at the level of 3%; in this case, we obtain values for the incremental cost-effectiveness ratio of €27,680, €27,620, €29,000, and €33,100 for the single cohort of 12-year-olds only, and the multicohorts of 12 and 15 years old, 12, 15, 18 years old, and 12, 15, 18, 25 years old, respectively. With respect to the Italian context, these can be considered well within the acceptability threshold.

Less time is required to reduce HPV-related outcomes with a multicohort vaccination program than with vaccination of a single cohort of girls aged 12 years. In particular, the clinical benefits of vaccination (especially the prevention of CIN1 and anogenital warts) are expected to occur 3.8–6.4 years earlier with multicohort vaccination. Indeed, the greater the number of cohorts the more it is possible to compensate for the blunted efficacy of a vaccination program in which a low rate of coverage is achieved.

The EVI is a key parameter in decision analysis because it tests the robustness of results by taking into account several dimensions of uncertainty.[44] The EVI indicates how much a rational decision maker should be willing to spend in order to acquire perfect information (ie, to eliminate uncertainty). An EVI <€13 per patient implies that the uncertainty that is currently present in the model parameters does not have a substantial impact on the decision-making process. Operating in the Bayesian paradigm allowed us to produce this evaluation easily. In contrast, running a study aimed at acquiring such evidence directly would certainly be much more expensive. Thus, it is appropriate for the decision maker to make the decision using only the current knowledge of the results from the model, and no extra information is required.

The duration of protection from vaccination has a great impact on the cost-effectiveness of a multicohort strategy. With duration of protection of only 15 years, the cost per QALY gained was increased significantly. However, irrespective of whether a booster was included, the costs per QALY gained did not exceed the threshold value, which indicated that the multicohort approach remained cost-effective.

Coverage rates are also important, especially when levels of only 50% are achieved among females. From this perspective, a vaccination program that includes both boys and girls can be considered to be a multicohort strategy. In such a vaccination program (ie, involving girls and boys aged 12 y), with reduced levels of coverage, cost-effectiveness can be improved as a result of the increased clinical benefits from herd immunity. In general, the vaccination of boys has been reported to exceed conventional thresholds of good value for money.[43,45] However, when the combined clinical benefits for both sexes were considered, the costs per QALY gained were below threshold values.[45,46]

The study has some limitations. First, it did not take herd immunity effects into account. It must be acknowledged that the effects of dynamic transmission should be included in cost-effectiveness analyses because economic evaluations of primary prevention should be driven by societal benefits (ie, indirect effects on people who do not participate in the program) rather than by individual need.[47] Moreover, the use of a static rather than a dynamic model will probably result in an underestimation of cost-effectiveness. If an intervention is estimated to be cost-effective using a static approach, it should be even more cost-effective when dynamic effects are considered. However, there might be exceptions to this rule. For example, when the severity of disease rises with age, a static model might lead to a more favorable estimate of cost-effectiveness than a dynamic model.[48] Second, neither the vaccination of boys nor the efficacy of the vaccine against noncervical HPV-related cancers was included in the model. Finally, although basically correct in the short term, the assumption that the screening interval will remain unchanged over time may be criticized.

The study highlights the features of a methodological approach that is designed to reduce the uncertainty associated with HPV vaccination. The quadrivalent-based multicohort HPV vaccination program can provide excellent value for money invested, and Bayesian analysis provides

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the most appropriate and feasible representation of the true value of this program.

Especially when associated with the EVI, Bayesian models are a suitable approach to provide decision makers not only with a more reliable assessment of cost-effectiveness than other types of model, but also with an estimate of the difference that uncertainty makes. The model described is highly flexible and can be adapted to any elective setting. Moreover, the model can be extended in several directions, for example to investigate the inclusion of a male cohort to account for unobserved factors (eg, herd immunity), or to include confounders that affect the cost-effectiveness of HPV vaccination. A Bayesian analysis of a vaccination program that includes girls and boys (eg, aged 12 y) is relevant to the evaluation of the short-term reduction in early cervical and noncervical HPV-related lesions and equity of access to primary prevention for both sexes.

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REFERENCES

1. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*. 1999;189:12–19.
2. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine*. 2006;24(suppl 3):S35–S41.
3. Clifford GM, Smith JS, Plummer M, et al. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *Br J Cancer*. 2003;88:63–73.
4. Von Krogh G. Management of anogenital warts (condylomata acuminata). *Eur J Dermatol*. 2001;11:598–603.
5. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis*. 2007;13:28–41.
6. Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. *N Engl J Med*. 2008;359:821–832.
7. Mennini FS, Giorgi Rossi P, Palazzo F, et al. Health and economic impact associated with a quadrivalent HPV vaccine in Italy. *Gynecol Oncol*. 2009;112:370–376.
8. Mennini FS, Costa S, Favato G, et al. Anti-HPV vaccination: a review of recent economic data for Italy. *Vaccine*. 2009;27:A54–A61.
9. Favato G, Pieri V, Mills R. Cost-effective analysis of anti-HPV vaccination programme in Italy: a multi-cohort Markov model. March 2007. Available at: http://www.ssrn.com/abstract=961847. Accessed January 1, 2011.
10. Drummond M, Chevat C, Lothgren M. Do we fully understand the economic value of vaccines? *Vaccine*. 2007;25:5945–5957.
11. Briggs AH, Gray AM. Methods in health care service research—handling uncertainty in economic evaluations of healthcare intervention. *BMJ*. 1999;319:157–177.
12. Spiegelhalter DJ, Best NG. Bayesian approaches to multiple sources of evidence and uncertainty in complex cost-effectiveness modelling. *Stat Med*. 2003;22:3687–3709.
13. Mennini F, Baio G, Montagnano G, et al. Governance of preventive health intervention and on time verification of its efficiency: the GIOVE study. *BMJ Open*. 2012;2:e000736.
14. Moscicki AB, Schiffman M, Kjaer S, et al. Chapter 5: updating the natural history of HPV and anogenital cancer. *Vaccine*. 2006;24: S42–S51.
15. Maw RD, Reitano M, Roy M. An observational survey of patients with genital warts: perception regarding treatment and impact on lifestyle. *Int J STD AIDS*. 1998;9:571–578.
16. The FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *The Lancet*. 2007;369:1861–1868.
17. The FUTURE I Study Group. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007; 356:1928–1943.
18. La Torre G, Chiaradia G, de Waure C, et al. Systematic review and meta-analysis of clinical trials on the efficacy of the quadrivalent HPV vaccine. HTA reports of quadrivalent anti-HPV vaccine, Gardasil. *Ital J Public Health*. 2009;2(suppl 2):S25–S32. [Italian].
19. Mennini FS, Baio G, Montagano G, et al. Governance of preventive health intervention and on time verification of its efficiency in a region of southern Italy. Health Technology Assessment International (HTAi) society, 7th annual meeting. Dublin, Ireland, 6th-9th June 2010. Abstract M5-18; p. 176–177.
20. Brown DR, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16-26 years. *J Infect Dis*. 2009;199:926–935.
21. Wheeler CM, Kjaer SK, Sigurdsson K, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. *J Infect Dis*. 2009;199:936–944.
22. Ronco G, Ghisetti V, Segnan N, et al. Prevalence of human papillomavirus infection in women in Turin, Italy. *Eur J Cancer*. 2005;41:297–305.
23. Canfell K, Barnabas R, Patnick J, et al. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. *Br J Cancer*. 2004;91:530–536.
24. Centurioni MG, Puppo A, Merlo DF, et al. Prevalence of human papillomavirus cervical infection in an Italian asymptomatic population. *BMC Infect Dis*. 2005;27:5–77.
25. Myers ER, McCrory DC, Nanda K, et al. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol*. 2000;151:1158–1171.
26. Ronco G, Giorgi-Rossi P, Carozzi F, et al. New Technologies for Cervical Cancer screening Working Group. Human papillomavirus testing and liquid-based cytology in primary screening of women younger than 35 years: results at recruitment for a randomised controlled trial. *Lancet Oncol*. 2006;7:547–555.
27. Giorgi Rossi P, Ricciardi A, Cohet C, et al. Epidemiology and costs of cervical cancer screening and cervical dysplasia in Italy. *BMC Public Health*. 2009;9:71. Available at: http://www.biomedcentral.com/1471-2458/9/71. Accessed January 1, 2011.
28. De Aloysio D, Miliffi L, Iannicelli T, et al. Intramuscular interferon-beta treatment of cervical intraepithelial neoplasia II associated with human papillomavirus infection. *Acta Obstet Gynecol Scand*. 1994; 73:420–424.
29. French L, Nashelsky J. Clinical inquiries. What is the most effective treatment for external genital warts? *J Fam Pract*. 2002;51:313.
30. Italian Ministry of Health. List of prosthesis and technical aids provided within the framework of the national health service. Specialistic outpatient health care services. Available at: http://www.ministerosalute.it/imgs/C_17_bacheca_6_listaelencodocumenti_elenco0_listadocumenti_documento0_listafile_file0_linkfile.xls. Accessed January 1, 2011. [Italian].
31. List of prosthesis and technical aids provided within the framework of the national health service 2006. Lazio Region. Changes and additions to the DGR n. 439 of 21/07/2006. Available at: http://www.asplazio.it/asp_online/att_territoriale/files/sias/normativa/DGR562_5_09_06.pdf. Accessed January 1, 2011. [Italian].
32. List of prosthesis and technical aids provided within the framework of the national health service 2006 (second version of the ICD-IX). Emilia-Romagna. Available at: http://www.saluter.it/wcm/saluter/sanitaer/ssr/assistenza_territoriale/Dipartimento_cure_primarie/specialistica/linkallegati/nomenclatore/allegati_2/nomencla_ICDIX_nov07.pdf. Accessed January 1, 2011. [Italian].
33. Costa S, Favato G. Evaluation of the economic impact produced by the prevention of events induced by the HPV 6-11virus types contained in the quadrivalent vaccine. January 2008. Available at: http://www.ssrn.com/abstract=1080113. Accessed January 1, 2011.

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34. Merito M, Largeron N, Cohet C, et al. Treatment patterns and associated costs for genital warts in Italy. *Curr Med Res Opin*. 2008;24:3175–3183.
35. Ferrandina G, Marcellusi A, Mennini FS, et al. Hospital costs incurred by the Italian National Health Service for invasive cervical cancer. *Gynecol Oncol*. 2010;119:243–249.
36. Azzari C, Massai C, Poggiolesi C, et al. Cost of varicella-related hospitalizations in an Italian paediatric hospital: comparison with possible vaccination expenses. *Curr Med Res Opin*. 2007;23: 2945–2954.
37. AIRTum: Italian Network of Cancer Registries Work Group. Italian cancer figures-Report 2006. Incidence, mortality and estimates. I dati di incidenza e mortalità dei Registri Tumori generali, 1998-2002. Epidemiol Prev, Suppl 2: 1-148, 2006. Available at: http://www.registri-tumori.it/cms/?q=Indice2006. Accessed January 1, 2011.
38. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Stat Sci*. 1992;7:457–472.
39. The FUTURE II Study Group. Prophylactic efficacy of a quadrivalent human papillomavirus (HPV) vaccine in women with virological evidence of HPV infection. *J Infect Dis*. 2007;196:1438–1446.
40. Mennini FS, Panatto D, Cristoforoni P, et al. The time-trade off approach to measure patients' preferences for health states associated with HPV-related pathologies: a multicenter study performed in Italy. Health Technology Assessment International (HTAi) society, 7th annual meeting. Dublin, Ireland, 6th-9th June 2010. Abstract M5-53; p. 192.
41. Bonneux L, Birnie E. The discount rate in the economic evaluation of prevention: a thought experiment. *J Epidemiol Community Health*. 2001;55:123–125.
42. Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. *BMJ*. 2004;329:224–227.
43. Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. *BMJ*. 2008; 337:a769.
44. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ*. 1996;5:513–524.
45. Kim JJ, Goldie SJ. Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States. BMJ 2009;339:b3884. Available at: http://www.bmj.com/content/339/bmj.b3884.full.pdf. Accessed January 1, 2011.
46. Elbasha EH, Dasbach EJ. Impact of vaccinating boys and men against HPV in the United States. *Vaccine*. 2010;28:6858–6867.
47. Brisson M, Edmunds WJ. Impact of model, methodological, and parameter uncertainty in the economic analysis of vaccination programmes. *Med Decis Making*. 2006;26:434–446.
48. Brisson M, Edmunds WJ. Economic evaluation of vaccination programmes: the impact of herd-immunity. *Med Decis Making*. 2003;23:76–82.

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