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Cost-effectiveness analysis of the introduction of a quadrivalent human papillomavirus vaccine in France

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Objectives: A vaccine to prevent diseases due to human papillomavirus (HPV) types 6, 11, 16, and 18 is now available in France. The objective of this study was to assess the health and economic impact in France of implementing a quadrivalent HPV vaccine alongside existing screening practices versus screening alone.
Methods: A Markov model of the natural history of HPV infection incorporating screening and vaccination, was adapted to the French context. A vaccine that would prevent 100 percent of HPV 6, 11, 16, and 18-associated diseases, with lifetime duration and 80 percent coverage, given to girls at age 14 in conjunction with current screening was compared with screening alone. Results were analyzed from both a direct healthcare cost perspective (DCP) and a third-party payer perspective (TPP). Indirect costs such as productivity loss were not taken into account in this analysis.
Results: The incremental cost per life-year gained from vaccination was €12,429 (TPP) and €20,455 (DCP). The incremental cost per quality-adjusted life-year (QALY) for the introduction of HPV vaccination alongside the French cervical cancer screening program was €8,408 (TPP) and €13,809 (DCP). Sensitivity analyses demonstrated that cost-effectiveness was stable, but was most sensitive to the discount rate used for costs and benefits.
Conclusions: Considering the commonly accepted threshold of €50,000 per QALY, these analyses support the fact that adding a quadrivalent HPV vaccine to the current screening program in France is a cost-effective strategy for reducing the burden of cervical cancer, precancerous lesions, and genital warts caused by HPV types 6, 11, 16, and 18.

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Keywords: Cost-effectiveness, Human papillomavirus, Vaccination, Cervical cancer screening

Every year, there are approximately 33,500 new cases of cervical cancer in Europe and almost 15,000 deaths due to the disease (18). In France, 3,387 French women were diagnosed with cervical cancer and approximately 1,000 women died from this disease in 2000 (16). Cervical cancer has the eighth highest incidence of all female cancers and is ranked fifth among all female cancer mortality in France (16).

The human papillomavirus (HPV) has been identified as the primary cause of cervical cancer and has been detected in over 99 percent of cases worldwide (41;50). Epidemiological studies conducted during the past 30 years have consistently indicated that HPV infection is strongly influenced by sexual activity, with at least 70 percent of sexually active adults becoming infected with HPV during their lifetime (24). Although the majority of HPV infections are cleared spontaneously within 1 year (41), in a small percentage of women, HPV infection persists and leads to lesions, defined as cervical intraepithelial neoplasia (CIN), and in some cases, cervical cancer (CC). Epidemiological studies show that approximately 75 percent of cervical cancer cases in Europe are related to two HPV types: HPV16 and HPV18, 55 percent of precancerous lesions (CIN 2/3) are linked to types 16,18, approximately 35 percent of potentially precancerous lesions (CIN 1) are linked to types 6,11,16,18, and 90 percent of genital wart cases are associated with HPV types 6 and 11 (11;12;49).

Although the incidence and mortality rates of CC have decreased since the introduction of organized cervical cancer screening programs in the past years in Europe, CC remains a public health problem (9). No national organized screening program has been implemented in France. The National Agency for Accreditation and Evaluation of Health (ANAES) recommends screening women for cervical cancer between the ages of 25 and 65 every 3 years (2;39) and the French Health Care payer covers most of the screening costs. However, in reality, screening usually starts before 25 years of age and is extended beyond age 65. The recommended 3-year interval is also often reduced to 2 years in regularly screened women. Presently, approximately 55 percent of females in France undergo a regular cytological test (44). However, although an important initiative, screening alone will not prevent all cases of cervical cancer due to less than 100 percent sensitivity in the diagnostic tests used (risk of false negatives) and limited coverage rate. Approximately 70 percent of new cervical cancer cases happen in nonscreened women (35).

The first prophylactic quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine (GARDASIL®) is designed for the prevention of cervical cancer, precancerous lesions, and genital warts, as well as other HPV-related cancers, including vulval and vaginal cancer. This vaccine has shown 100 percent efficacy in reducing the incidence of cervical cancers, CIN (CIN 2/3, adenocarcinoma in situ), and external genital lesions, including genital warts and vulval dysplasia, related to HPV types 6, 11, 16, and 18 (20;46).

The optimal health benefit from an HPV vaccination program is likely to be achieved if it is introduced in girls before sexual activity: as HPV infection is usually acquired in the first years of sexual activity (1), the main benefit of protection from vaccination will occur during this period.

In March 2007, the French Technical Committee for Vaccination (CTV) and the "Conseil Supérieur d'Hygiène Publique de France" (CSHPF) recommended the vaccination with the quadrivalent HPV vaccine for all girls aged 14 years (1). The objective of this study is to determine the cost-effectiveness of adding a HPV vaccination program in adolescent females 14 years of age in addition to the cervical cancer screening program in France.

STUDY METHODOLOGY

Markov Model Structure

A previously published and validated Markov model (25;32;37) used to simulate the natural history of HPV infection and cervical cancer and to estimate the economic consequence of a HPV vaccine in the United States (32;37), was recently adapted to Europe. The original model was revised to separate high-grade squamous intraepithelial lesions into CIN 2 and CIN 3. We used this revised model to assess the cost-effectiveness of adding a quadrivalent HPV vaccine in France.

The Markov model follows a cohort of females from 14 years of age to 85 years through different health states representing the natural history of HPV infection, through to CIN, invasive cervical cancer, and to genital warts. Movement between the health states is based on yearly transition probabilities. Women infected with HPV can return to a "well" state, suffer a persistent infection, progress to CIN 1, or in some cases, progress directly to CIN 2. They may also develop genital warts. It is assumed that the genital warts will be cured within the year and the woman will return to a "well" state. Women who develop CIN 1, CIN 2, or CIN 3 are at risk of developing cervical cancer. It is also assumed that these women return to the "well state" after treatment for their cervical lesions. As women with precancerous lesions are generally asymptomatic, the disease may not be detected until the cancer becomes invasive. Women who are not screened, and, therefore, their cancer not detected, are at risk of cervical cancer death. The severity of cervical cancer is staged according to the FIGO classification system (FIGO

I–IV). Women who underwent hysterectomy were assumed to have their cervix removed and, therefore, were no more at risk for cervical cancer. Each year women face an age-specific risk of dying from other causes.

The main adaptations were to change the model structurally to reflect the screening pattern in France and to populate the model with local epidemiological and economical data. The model was then validated by checking that the predictions for a screened population were similar to the observed epidemiological data for France. The age-specific incidence and mortality rate of cervical cancer for France used for the calibration were derived from a published source (16). The model was programmed using the software TreeAge Pro 2006 (TreeAge Software Inc., Williamstown, MA).

Natural History

Transition probabilities between the different precancerous lesions and cancer health states are presented in Table 1 with cycle length specified as 12 months. Progression between FIGO stages I–II, II–III, and III–IV was assumed to be 90 percent every 48, 36, and 24 months, respectively (37). The age-specific rates of hysterectomy and age-specific incidence of genital warts are shown in Table 2.

Screening Program

In France, cervical screening is recommended every 3 years from age 25 to 65 years (39). However, in reality, screening starts before 25 years and is extended beyond age 65 (44). An extended screening strategy (covering 20–69 years) was, therefore, considered in the model to reflect usual clinical practice. A screening strategy considering the actual 55 percent screening coverage rate and a theoretical 3-year interval between two pap smears was applied to the model. Age-specific coverage rates varied from 23.8 percent in women aged 60–69 and approximately 60 percent in women younger than 50 years (44). With an abnormal Pap result, a colposcopy (with or without biopsy), a repeat Pap test, an HPV DNA test, or no follow-up, dependent on the type of positive smear result, was offered. A repeat Pap screen was offered to women if their Pap test was inadequate (1 percent of cases). The type of follow-up action and the proportion of women receiving each type of follow-up were based on published guidelines, studies, and other sources (6;17;39) (Table 3). The sensitivity of a conventional Pap test for detecting women with CIN 1 or CIN 2/3 was estimated to be 0.63 and 0.61, respectively (39), and the specificity to be 0.957 (38). The sensitivity of the HPV DNA test was 0.958 for CIN 2/3 and specificity was 0.673 (3). The sensitivity of colposcopy and/or biopsy to detect precancerous lesions was estimated to be 0.9 (10;33), and the specificity was assumed to be 1.0 (23;25). Treatment of CIN was assumed to be 100 percent effective, resulting in the patient returning to a HPV-infected state without CIN. The proportion of women treated for CIN 1 in France has been estimated at 75 percent (treatment with laser or exci-

Table 1. Natural History Parameters

Parameter	Age (years)	Annual transition probability
HPV infection		
Well to HPV-infected state[a]	10–12	0
	13	0.01
	14	0.03
	15	0.04
	16	0.06
	17–18	0.085
	19–22	0.25
	23	0.23
	24–29	0.15
	30–33	0.04
	34–49	0.029
	50+	0.008
HPV infection to CIN 1 or CIN 2[a]	All	0.0959
Proportion of HSIL that are CIN 2[b]	All	0.1350
CIN		
CIN 1 to well[b]	12–24	0.4666
	25–29	0.3333
	30–39	0.2666
	40–49	0.1800
	50+	0.0666
CIN 1 to CIN 2[a]	16–34	0.0297
	35+	0.1485
CIN 1 to CIN 3[a]	All	0.0301
CIN 1 to well or HPV-infected state[a]	16–34	0.2248
	35+	0.1124
Proportion CIN 1 regressing directly to well[a]	All	0.90
CIN 2 to CIN 3[a]	16–34	0.0389
	35–44	0.0797
	45+	0.1062
CIN 2 to CIN 1[a]	All	0.2430
CIN 2 to well or HPV-infected state[a]	All	0.1901
Proportion CIN 2 regressing directly to well[a]	All	0.90
CIN 3 to CIN 1[a]	All	0.0000
CIN 3 to CIN 2[a]	All	0.0135
CIN 3 to well or HPV-infected state[a]	16–44	0.0135
	45+	0.0100
Proportion CIN 3 regressing directly to well[a]	All	0.50
CIN 3 to invasive cervical cancer[c]	All	0.0138
Cervical cancer		
Probability of symptoms[b]		
FIGO stage I		0.11
FIGO stage II		0.23
FIGO stage III		0.66
FIGO stage IV		0.90
5-year survival rate after diagnosis[d]		
FIGO stage I		0.9118
FIGO stage II		0.6837
FIGO stage III		0.4398
FIGO stage IV		0.2903

[a] Source: Canfell et al., 2004 (10).
[b] Source: Calibrated based on Myers et al., 2000 (37) and Canfell et al., 2004 (10).
[c] Source: Calibrated from Canfell et al., 2004 (10).
[d] Source: Adapted from Martin, 1997 (31) and Lamblin, 2001 (26).
HSIL, high-grade squamous intraepithelial lesion.

Table 2. Age-Specific Hysterectomy Proportion in the French General Population and Age-Specific Genital Warts Incidence in Women

Age group	Proportion undergoing hysterectomy /100,000[a]	Genital warts incidence /100,000[b]
Less than 16 −	0	238.0
16 to 19	0	701.2
16–24	0	571.2
25–34	84	406.8
35–44	605	179.4
45–54	854	167.4
55–74	204	167.4
75+	98	167.4

[a] Source: Cosson, 1997 (13).
[b] Source: Lukasiewicz et al., 2002 (28;29); Mahe, 2002 (30); Monsonego et al., 2007 (34).

sion); the remaining 25 percent have no treatment, but are followed-up with a repeat Pap smear after 6 months (6).

Vaccination Program

The quadrivalent HPV vaccine is 100 percent effective, as shown in the clinical trials, at preventing precancerous lesions, cervical cancer, and genital warts caused by HPV types 6, 11, 16, and 18 (20;46). The model assumes a reduction of approximately 35 percent for CIN 1, 55 percent for CIN 2/3, 75 percent for cancer, and 90 percent for genital warts. This finding reflects the percentage of cervical cancer, CIN 1–3, and genital warts attributable to HPV types 6, 11, 16, and 18 based on data from the literature (11;12;49).

Duration of protection is likely to be life-long without the need for a booster; this finding is sustained by recent efficacy data seen 5 years poststudy entry (40). This assumption was used in the model as well as in previous economic analyses (15). However, a strategy including the administration of a booster to 50 percent of the initial vaccinated population was tested in sensitivity analyses.

The vaccination strategy assumes all adolescent women would be eligible at age 14. The coverage of the vaccination program in the base case was assumed to be 80 percent of the eligible population.

Costs of Screening, Disease Management, and Vaccination Program

This economic evaluation has been carried out from two perspectives: (i) a direct healthcare cost perspective (DCP), which includes all direct medical costs linked to the vaccination and management of the diseases; and (ii) a third-party payer perspective (TPP; i.e., "Sécurité Sociale"), which includes only direct costs reimbursed by the payers (for instance, 70 percent of consultation costs are reimbursed by the Sécurité Sociale in France). Indirect costs such as loss of productivity are not taken into account in this model.

The estimated costs associated with a screening program alone and a screening plus vaccination program were determined and presented as 2005 costs. The direct costs of resources used for cervical screening, and treatment of precancerous lesions and cervical cancer are summarized in Table 4. Cervical cancer treatment costs are reimbursed in full by the French health insurance system (19).

The total cost of one 0.5-ml dose of a quadrivalent HPV vaccine was estimated at €135.60 (official price of

Table 3. Screening pathway in France

Pap smear results	Follow-up	Proportion (%)
LSIL	Follow-up	62
	Colposcopy and/or biopsy	72
	Repeat pap smear in the next 6 months[a]	28
HSIL	Follow-up	100[b]
	Colposcopy and/or biopsy	100[c]
ASC-US	Follow-up	100
	Repeat pap smear in the next 6 months[a]	38
	Colposcopy alone	19
	Biopsy[a]	17
	HPV test[a]	26
Inadequate (1% of all pap smear)	Repeat screening	80

Note. Source: National Agency for Accreditation and Evaluation of Health (ANAES, 39); Bergeron et al. (6); Fender et al. (17).
[a] "pap smears" refers to women who only have pap smears during the study follow-up. HPV test refers to women who had an HPV test associated or not with pap, but without biopsy during the study follow-up. "Biopsy" refers to women who had a biopsy associated or not with a pap smears and/or an HPV test during the study follow-up.
[b] Bergeron et al. (6) reports a rate of 62% (study period was 6 months) and Fender et al. (17) 80%. A follow-up of 100% was considered to consider women who had a colposcopy alone.
[c] In the study performed by Bergeron et al., 86% of women had a biopsy within during the 6-month follow-up period (unpublished data). The HPV test was not considered as it represented only a few cases.
LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; HPV, human papillomavirus.

Table 4. Costs Parameters (€ 2005)

Parameters	Base case (TPP) (€)	Base case (DCP) (€)	References
Pap smear	28.21	51.76[a]	French Health Insurance (19)
HPV DNA test	47.10	85.10[a]	
Colposcopy	20.52	39.61[a]	
Biopsy	35.00	64.25[a]	
Treatment of CIN 1	247.80	319.40	Bergeron, 2006 (6)
Treatment of CIN 2/CIN 3	759	954	
FIGO I–IV	9,164–26,886	9,164–26,886	Arveux, 2007 (4)
Genital warts	342.40	482.70	Monsonego, 2007 (34)
Vaccine cost (per dose)	88.10	135.60	French official price
Vaccine administration	13.00	20.00	French Health Insurance (19)

[a] Includes visit cost plus an average extra charge for gynecologists (27).
DCP, direct healthcare cost perspective; TCP, third-party payer perspective; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia.

GARDASIL® published in the French Official Journal on July 11, 2007). It is expected that the vaccine will be administered by general practitioners (GPs), and we considered that one visit would be charged for each injection. In France, vaccines are reimbursed at 65 percent and GP visits at 70 percent (19). As three doses of the vaccine are required, the total cost per person vaccinated is €466.80, of which €303.30 would be directly funded by TPP.

Utilities

Utilities used in the model for calculating quality-adjusted life expectancy were derived from a U.S. utility study (15;36). This study used time-tradeoff techniques to elicit utilities in a population of 150 healthy female volunteers. The utilities from this study are presented in Table 5. The expected time in each health state was based on expert opinion (R. Barnabas, Time with disease estimation for utility values, Personal communication, 2005). The utility for those surviving cervical cancer was set as 1.0 (25). In each arm where screening is carried out, the disutility of having a routine Pap smear and the effect of the diagnosis as a result of the smear is taken into account as well as the utility associated with the final outcome of screening in terms of having a CIN result or cervical cancer.

Analysis

Analysis of the adapted Markov model produces estimates of cervical cancer lifetime risks, CIN lifetime risks, genital lifetime risks, lifetime costs, incremental cost per life-year gained (LYG), and incremental cost per quality-adjusted life-year gained (QALY) for a screening plus vaccination strategy, versus screening alone. The analysis has been carried out from both the DCP and TPP perspectives.

There is controversy regarding whether monetary costs and health benefits should be discounted at the same rate or differentially in economic evaluations, particularly when evaluating public health programs such as vaccination (7;8). It is often argued that the benefits of health promotion strategies should be discounted at a lower rate than those of costs, reflecting the likelihood that society has a stronger time preference for money than health (7), and so as to adversely affect the prioritizing of health promotion/disease prevention over curative treatments. In the base case, an annual discount rate of 3.5 percent and 1.5 percent was used for costs and benefits, respectively, and different rates for both costs and benefits

Table 5. Utility Values Used in the Markov Model (15;36)

Health status	Utility value	Duration
Routine screening Pap smear	0.9764	1 month
ASC-US diagnosis from Pap smear	0.9404	2 months
LSIL/HSIL diagnosis from Pap smear	0.9062	2 months
Genital warts	0.9142	85 days
CIN 1	0.9102/0.9551	2 months with 10 months follow-up
CIN 2/3	0.8658	2 months
FIGO I	0.7598	5 years
FIGO II–IV	0.6693	5 years

ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia.

were examined in the sensitivity analysis, as recommended by the French Guidelines for the Economic Evaluation of Health Care Technologies (5).

Sensitivity Analysis

One-way sensitivity analysis was undertaken on key parameters that were considered to be potentially the most important for the robustness of the cost-effectiveness result. The following key parameters were varied: (i) duration of vaccine protection between 10 years to lifetime; (ii) the vaccine efficacy from 80 percent to 100 percent effective, (iii) the discount rate for both costs and benefits (0 percent/0 percent, 3 percent/3 percent, and 5 percent/5 percent), (iv) the proportion of cervical cancer cases linked to HPV types 16 and 18 from 75 percent in the base case to 82 percent (43), (v) treatment costs by ±20 percent, and (vi) the duration of time spent in each state to elicit utilities. In addition, the impact on cost-effectiveness of a scenario whereby a booster vaccine is required to achieve lifetime protection from HPV was explored. The booster vaccine was administered to 50 percent of females originally vaccinated.

RESULTS

Base Case Analysis

Results from the calibration showed that the predicted age-specific annual incidence of invasive cervical cancer in the French screened population was similar to the observed data in France (Figure 1). The adapted Markov model for France predicted a lifetime cervical cancer risk of 0.94 percent and a lifetime cancer mortality risk of 0.22 percent for women undergoing cervical screening in France. With the introduction of a quadrivalent vaccine, that will protect against 75 percent of cervical cancers caused by HPV types 16 and 18 (12), and 90 percent of genital wart cases (49), alongside the screening program, and assuming a vaccination coverage rate of 80 percent, these risks are decreased by approximately 65 percent to 0.33 percent and 0.08 percent, respectively.

Considering a cohort of 370,000 women in France, the model estimates that, with screening alone, 3,465 cervical cancer cases, 821 CC deaths, 18,813, 14,716, and 29,742 cases of detected CIN 1, 2, and 3 cases, respectively, and 34,868 cases of genital warts would occur in France annually. Considering the same cohort, the model estimates that 2,245 cervical cancer cases; 531 CC deaths; 6,278, 6,801, and 8,983 cases of detected CIN 1, 2, and 3 cases, respectively, and 23,105 cases of genital warts could be avoided with vaccination.

The incremental cost-effectiveness of a screening plus vaccination program from a TPP in France versus screening alone was €12,429 per LYG and €8,408 per QALY gained. From a direct healthcare cost perspective (DCP), incremental cost-effectiveness ratios (ICERs) of 20,455€ per LYG and €13,809 per QALY gained were achieved (Table 6). Therefore, a vaccination program with a quadrivalent HPV vaccine alongside current screening program can be considered as a cost-effective strategy if the commonly accepted cost-effectiveness threshold of €50,000 per QALY is used (5).

Sensitivity Analyses

The base case assumes lifetime duration of protection for vaccination consisting of three doses and no booster. The duration of vaccine efficacy was varied between 10 years and lifetime. From the TPP, the incremental cost-effectiveness was sensitive to durations of protection less than 20 years, but not for longer durations. A scenario of requiring a booster vaccination for 50 percent of females originally vaccinated resulted in increased cost-effectiveness ratios compared with the base case program without booster, but still below €50,000 per QALY gained from the TPP (Table 7). The cost-effectiveness ratio was relatively insensitive to changes in vaccine efficacy (Table 7). In general, the model was not sensitive to changes in CIN and cervical cancer treatment costs. The cost-effectiveness ratio was also relatively insensitive to changes to utilities such as length of time in each health state (Table 7).

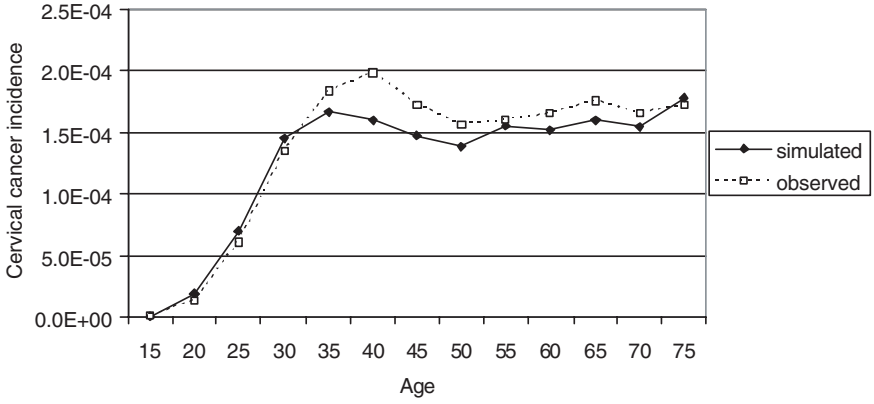

Figure 1. Simulated and observed cervical cancer incidence for the screened population.

Table 6. Cost-Effectiveness Ratios from a Direct Healthcare Cost (DCP) and Third Party-Payer (TPP) Perspectives

	Costs (€)	LYG	Incremental cost (€)/ LYG	QALYs	Incremental cost (€)/ QALY
TPP					
Screening only	177.8	42.4692	—	42.4425	—
Screening + vaccination	369.5	42.4846	12,429	42.4653	8,408
DCP					
Screening only	274.1	42.4695	—	42.4427	—
Screening + vaccination	584.8	42.4847	20,455	42.4652	13,809

LYG, life-year gained; QALY, quality-adjusted life-year.

Cost-effectiveness was sensitive to the discount rate used, with higher joint discount rates for costs and benefits resulting in higher cost-effectiveness ratios (Table 7). With zero discounting of costs and benefits, the ICERs were less than €2,800 per LYG gained for TPP.

Finally, the proportion of cervical cancer cases attributable to HPV types 16 and 18 was estimated at 75 percent in the base case. Considering a proportion of 82 percent (43) led to an ICER of €7,680/QALY (TPP).

DISCUSSION

Current evidence on the cost-effectiveness of HPV vaccines in the United States has shown that vaccination in combination with screening will reduce the incidence of HPV associated with cervical cancer and has, therefore, the potential to be cost-effective in the reduction of CIN and cervical cancer (21;25;45). As far as is known, this analysis provides the first cost-effectiveness analysis of a joint cervical cancer screening and HPV vaccination program in France. When considering the direct healthcare cost perspective, the base case results demonstrated a cost-effectiveness ratio of approximately €20,455 per LYG and of €13,809 per QALY gained for vaccination plus screening program compared with screening alone. By usual benchmarks in Europe interventions, these outcomes would be considered cost-effective, especially if cancer prevention is considered as a national public health priority (as it is in France). With these ratios well below the commonly accepted cost-effectiveness threshold of €50,000 per QALY, a vaccination program with a quadrivalent HPV vaccine alongside current screening program is a cost-effective strategy.

Table 7. Sensitivity Analysis from the TPP Perspective

	TPP perspective	
Parameters	€/LYG	€/QALY
Base case	12,429	8,408
Duration of efficacy		
10 years	55,750	37,228
20 years	22,021	14,935
Lifetime achieved with booster	19,650	13,400
Vaccine efficacy		
80%	15,267	10,444
Discount rate for costs/benefits		
0%/0%	2,758	2,019
3%/3%	19,064	12,430
5%/5%	68,714	35,652
Proportion of cervical cancer linked to HPV types 16 and 18		
82%	10,862	7,680
Treatment costs		
−20%	12,891	8,719
+20%	11,968	8,096
Utilities		
−50% duration	N/A	9,000
+50% duration	N/A	7,547

LYG, life-year gained; QALY, quality-adjusted life-year; N/A, not applicable.

The cost-effectiveness results are robust to most sensitivity analyses. The base case results assume lifetime protection. To date, all cost-effectiveness analyses of HPV vaccination show that duration of efficacy will be a key to determining how cost-effective the vaccine will be (47). The need for a long duration of vaccine efficacy is consistent with our understanding of the natural history of HPV infection: progression to cervical cancer can take more than 10 years (42). Currently, approximately 5 years of efficacy data are available (48). Long-term monitoring of women currently participating in the vaccine trials will be needed to determine whether and when a booster should be given.

Some limitations on the way the screening strategy was considered in our model should be highlighted. First, it was reported that, among screened French women, 7 percent receive annual screening, 45 percent biannual and 43 percent every 3 years (44). In this analysis, we assumed a 3-year theoretical screening interval, as our model did not allow considering different screening modalities. However, this simplification is likely not to change the conclusion of the analysis.

Furthermore, approximately 70 percent of cervical cancer cases occur in women who were never screened (35). Our model assumed that the vaccine will be given

homogeneously in both populations: those who are regularly screened and those who are never screened.

At least, our analysis is based on the assumption that vaccination will be added to the cervical screening program. If women are less likely to adhere to screening once they are vaccinated, under the assumption that they are protected from cervical cancer, then gains from vaccination will be offset by decreased adherence with screening. An education campaign that highlights the need for continued screening and clarifies the role of the vaccine within the existing program will be key to ensuring that gains from adding vaccination to screening are realized.

One controversial area is the choice of discount rate. We have applied a base rate of 3.5 percent for costs and 1.5 percent for benefits, as there is greater theoretical and policy support for such differential discounting of preventive interventions, including vaccination, relative to that for treatment interventions (7;8). Discounting at the same rate penalizes preventive interventions relative to treatment interventions, and as health policy in most European countries has shifted toward disease prevention, then there is a case for differential discounting to reflect health policy and society preferences. However, in the sensitivity analysis, discounting both costs and benefits at 3 percent resulted in a cost-effectiveness ratio below €50,000 per QALY gained.

Our results suggest that the use of QALYs is important, because it allows inclusion of feelings of anxiety and embarrassment due to abnormal Pap test results as well as genital warts. The utility for those surviving cervical cancer was set as 1.0 (25), which may lead to a potential underestimation in QALY gained. The utilities used were derived from a study conducted among college-aged students in the United States (22;36). Although utilities derived from a French population as well as a study of time spent in a given health state would more accurately reflect the morbidity associated with cancer, CIN, and warts, this information has yet to be published. Furthermore, a sensitivity analysis showed that the cost-effectiveness ratio was relatively insensitive to changes in the utility values entered into the model.

The model used for this analysis is a cohort model—the progression of the disease is simulated for a single cohort over its expected lifetime. Although this has the advantage of being computationally easier to handle, it potentially underestimates the benefit of HPV vaccination at the population level. A key limitation of the cohort model is that it does not take into account the effect of "herd immunity," or changes in the population over time (14). This limitation can be addressed with the use of a transmission dynamic model. A dynamic model analyzing the cost-effectiveness of a quadrivalent HPV vaccine in the United States has been published recently and an adaptation to the United Kingdom is on-going (15;22). Results from this analysis have shown that a routine vaccination (before age 12) plus catch-up vaccination (ages 12–24) of both males and females was the most effective strategy, reducing the annual incidence of HPV 6/11/16/18-related genital warts, CIN, and cervical cancer by 94 percent, 87 percent, and 88 percent, respectively, in the long-term after vaccine introduction. Additionally, this analysis shows that benefits from a quadrivalent HPV vaccine could be achieved quickly after its introduction because of its ability to prevent in the short term genital warts and low-grade squamous intraepithelial lesions.

Finally, the model assumes a reduction of 75 percent of cervical cancer cases. However, vaccine's cross-protection against other HPV types than HPV 6, 11, 16, and 18 will result in a higher reduction in cervical cancer. It is likely that by not including this effect as well as the effect of herd immunity, and other potential preventive benefits (e.g., vulval intraepithelial neoplasia, vaginal intraepithelial neoplasia, vulval cancer, vaginal cancer, or laryngeal papillomas, related to HPV types 6, 11, 16, and 18), the model estimates must be considered conservative. In addition, indirect costs of lost productivity have not been included, which again could improve cost-effectiveness further from a societal perspective. Overall, this study strongly supports a national program of adding HPV vaccination in adolescent females to the existing cervical screening program in France as a cost-effective strategy from a healthcare and public health perspective.

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