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A comparative analysis of the epidemiological impact and disease cost-savings of HPV vaccines in France

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The aim was to compare the epidemiological and economic impact of bivalent HPV 16/18 and quadrivalent HPV 6/11/16/18 vaccinations in France, considering differences in licensed outcomes, protection against non-vaccine HPV types and prevention of HPV-6/11-related diseases.

The differential impact of the two vaccines was evaluated using a published model adapted to the French setting. The target population was females aged 14–23 y and the time horizon was 100 y. A total of eight different scenarios compared vaccination impact in terms of reduction in HPV-16/18-associated carcinomas (cervical, vulvar, vaginal, anal, penile and head and neck), HPV-6/11-related genital warts and recurrent respiratory papillomatosis, and incremental reduction in cervical cancer due to potential cross-protection.

Quadrivalent vaccine was associated with total discounted cost savings ranging from EUR 544–1,020 million vs. EUR 177–538 million with the bivalent vaccination (100-y time horizon). Genital warts prevention thanks to quadrivalent HPV vaccination accounted for EUR 306–380 million savings (37–56% of costs saved). In contrast, the maximal assumed cross-protection against cervical cancer resulted in EUR 13–33 million savings (4%). Prevention of vulvar, vaginal and anal cancers accounted for additional EUR 71–89 million savings (13%).

In France, the quadrivalent HPV vaccination would result in significant incremental epidemiological and economic benefits vs. the bivalent vaccination, driven primarily by prevention of genital warts. The present analysis is the first in the French setting to consider the impact of HPV vaccination on all HPV diseases and non-vaccine types.

Introduction

The human papillomavirus (HPV), primarily the high risk HPV types 16 and 18, is a necessary cause of cervical cancer and is associated with other anogenital cancers in significant proportions as well as a subset of head and neck cancers.[1] Additionally, the low risk HPV types 6 and 11 are the leading cause of anogenital warts[2] and recurrent respiratory papillomatosis (RRP).[3-5] Currently, two vaccines are available: a bivalent vaccine targeting HPV types 16 and 18 and a quadrivalent vaccine targeting HPV types 6, 11, 16 and 18. Both vaccines are approved for the prevention of cervical cancer and precancerous lesions.[6-13] The quadrivalent vaccine is also indicated for the prevention of vulvar and vaginal precancerous lesions as well as genital warts.[14,15] Moreover, clinical efficacy in terms of anal cancer precursors has been demonstrated with the quadrivalent vaccine and recently acknowledged by the EMA as a new pharmacologic property.[16] Both vaccines are assumed to provide lifelong protection against HPV vaccine strains; however, the duration of vaccine protection can only be determined with extensive follow up of vaccinees over a period of decades. The findings of recent studies provide evidence for sustained protection for at least 10 y against vaccine types, which is expected to persist over time.[17,18] Additionally, both vaccines have been shown to provide a degree of cross-protection against cervical lesions caused by non-vaccine types (driven by HPV 31 for the quadrivalent vaccine and HPV 31, 33 and 45 for the bivalent vaccine),[16,19,20] although the clinical relevance of such an effect is still unknown and its duration seems to be short-lived.[17,21]

The epidemiological and economic burden associated with HPV-related cancers and other diseases is substantial. In France in 2007, the total cost of HPV-related cancers was estimated at EUR 240 million, of which EUR 156 million (65%) were due to non-cervical cancers.[22] 85% of HPV-related cancer costs (EUR 204 million) were attributable to HPV 16/18.[22] Additionally, a separate study in France estimated that the treatment of genital warts in females was associated with total annual direct medical costs between EUR 13–24 million from a third party payer perspective and between EUR 19–34 million from a societal perspective.[23] HPV also causes RRP; although data relating to the economic burden of RRP in the French setting are lacking, in the UK total hospital costs due to RRP have been estimated at GBP 4 million per year.[24]

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Both HPV vaccines are available in France, with vaccination targeted at girls aged 14 y, with a catch up program introduced alongside each vaccine and targeted at girls and young women aged 15–23 y. Fagot et al. reported vaccine uptake rates in France shortly after the introduction of HPV vaccination (2007 for quadrivalent and 2008 for bivalent vaccine, respectively). By the end of 2009, just under 30% of the target population (females aged 14 y in 2007–2009) had completed the three dose course of vaccination.[25] Notably, females aged 14 y in 2007–2009 constituted only one third of vaccinated people aged 14–23 y over this time period, with females in the "catch-up" populations representing two thirds of vaccine recipients over this time period.

In addition to HPV vaccination, the French National Authority for Health (HAS) recommends screening for cervical cancer every 3 y in women aged 25–65 y. Approximately 55% of women in France undergo regular cytological testing, and approximately 70% of new cervical cancer cases occur in non-screened women.[25] The overall cost (from a healthcare payer perspective) associated with pap screening for cervical cancer in France, which includes both screening, diagnosis and the management of abnormal findings was EUR 197 million.[26] In contrast to cervical cancer, there are no effective preventive strategies against extra-genital, head and neck or anal disease available (no systematic screening). Consequently, there may be an unmet medical and public health need with regard to these cancer types.[16]

The public health impact and cost-effectiveness of HPV vaccination in terms of the prevention of precancerous lesions and cervical cancer has been widely studied in a number of settings, although a small proportion of studies have also captured the benefits of vaccination (with the quadrivalent vaccine) in terms of the reduction in the incidence of genital warts.[27-30] The focus of previous analyses on cervical cancer only may lead to an underestimation of the true public health and economic benefits of HPV vaccination. Emerging evidence with regard to the effects of each vaccine (efficacy in non-cervical diseases, cross-protection, long lasting effect), and epidemiological and economic burden associated with a wider range of HPV diseases should be considered in future analyses. Previous analyses comparing the quadrivalent vaccine (or bivalent vaccine) vs. screening alone have been performed in the French setting,[31-33] but analyses simultaneously comparing the quadrivalent vs. the bivalent vaccine in the French setting are lacking. The objective of the current analysis was to compare the epidemiological and economic impact of vaccination either with bivalent or quadrivalent HPV vaccine, accounting for differences in licensed outcomes, protection against non-vaccine HPV types and prevention of HPV 6/11-related diseases, and uncertainty around potential class effects as well as duration of protection against vaccine and non-vaccine HPV types in the French setting. However, it should be noted that the direct comparison of vaccine efficacy for both vaccines was not deemed possible owing to heterogeneity between clinical trials in terms of study population, distribution of HPV types and methods of analysis used.

Results

Based on licensed disease endpoints, assuming lifetime protection against vaccine HPV types-related diseases and 20 y protection against non-vaccine HPV types-related cervical cancer (Scenario A), the quadrivalent HPV vaccination would result in 45% additional HPV-related cancer cases avoided annually (corresponding to 831 cases of vulvar, vaginal and anal cancers per year) compared with the bivalent vaccine (in a steady-state situation, at 100 y). The bivalent vaccine would prevent 17 additional cases of cervical cancer due to its extended cross-protection effect in comparison with quadrivalent vaccine (**Fig. 1**). The quadrivalent HPV vaccination would also lead to the prevention of 72,026 cases of genital warts on an annual basis (among both genders).

Scenarios B and D explored pessimistic and optimistic estimates of cross-protection, based on 95% CIs and scenario C assumed a 32-y duration of protection against vaccine HPV types. In scenarios B to D, according to licensed disease endpoints, the quadrivalent vaccine would prevent annually between 638 and 831 additional cases of vulvar, vaginal and anal cancers (at steady-state) compared with the bivalent vaccine, when varying duration of protection toward vaccine types (lifetime vs. 32 y), whereas the bivalent vaccine would avoid between 2 and 110 additional cervical cancer cases, compared with the quadrivalent vaccine, depending on cross-protection mean efficacy and duration of protection assumed (**Fig. 1**).

In more conservative scenarios (Scenarios E to H), all cancers associated with HPV 16 and 18 were also assumed to be prevented by bivalent vaccine. Scenarios E to H effectively compared the incremental health and economic benefits of the additional number of cervical cancer cases prevented by the bivalent vaccine due to cross-protection, vs. the benefits associated with the prevention of genital warts (between 53,041 and 72,026 cases per year) due to the quadrivalent vaccine.

Regardless of the scenario tested, the quadrivalent HPV vaccination was projected to lead to substantial incremental economic benefits over bivalent vaccination (**Figs. 2 and 3**). Over the study time period (i.e., 2012–2112), in scenarios A, B, C and D the quadrivalent HPV vaccination was associated with additional costs savings over bivalent vaccination ranging from EUR 306–380 million due to the prevention of genital warts (54% of total cost saved), vs. EUR 13–33 million additional savings over quadrivalent vaccination when assuming a maximal cross-protective effect with the bivalent vaccine (4% of total disease cost saved). Moreover, EUR 71–89 million would be saved due to prevention of non-cervical (vulvar, vaginal, anal) cancer cases for quadrivalent vs. bivalent vaccination. The incremental costs savings over quadrivalent vaccination associated with a potential higher cross-protective effect of the bivalent vaccine were minor (4% of total savings) in comparison with the savings due to the prevention of genital warts due to the quadrivalent vaccine (54% of total costs saved). Economic benefits of the quadrivalent HPV vaccination are also expected over short-term time horizons due to the early impact of the reduction of the incidence of genital warts (4 y post vaccine introduction).[34,35] In the first 15 y following

the introduction of vaccination, the model predicted that 93.8% of costs avoided would be linked to the prevention of genital warts; in comparison, over the same period only 0.7% of total savings would be associated to potential cross-protective effect on cervical cancers (**Fig. 2**).

Absolute cost-savings due to HPV vaccination were greatest in Scenarios E (lifetime protection for vaccine HPV types and 20 y protection for non-vaccine HPV types) and H (lifetime protection for vaccine and non-vaccine HPV types, efficacy against non-vaccine HPV types at 59.4% for the bivalent vaccine and 36.4% for the quadrivalent vaccine). In these two scenarios, the bivalent and quadrivalent vaccines were assumed to protect against all HPV 16/18 related cancers (cervical, vulvar, vaginal, anal and head and neck and penile cancer) and the quadrivalent vaccine was also assumed to confer protection against genital warts and RRP. In scenarios E and H, absolute discounted cost-savings were approximately EUR 1,000 million for the quadrivalent vaccine and approximately EUR 530 million for the bivalent vaccine (+89% disease cost savings with quadrivalent vs. bivalent vaccination) (**Fig. 3**).

Sensitivity analyses showed that the results were most sensitive to changes in discount rate. After discounting, the next most important parameter influencing results was change in the costs of treatment (**Fig. 4**). Additionally, although the results of the sensitivity analyses around cost per episode of RRP and the burden of RRP are not key drivers of results, it should be noted that the incidence of RRP in comparison with other HPV-related diseases is relatively low, so proportionally; the impact of changes in assumptions around RRP is higher than suggested in **Figure 3**.

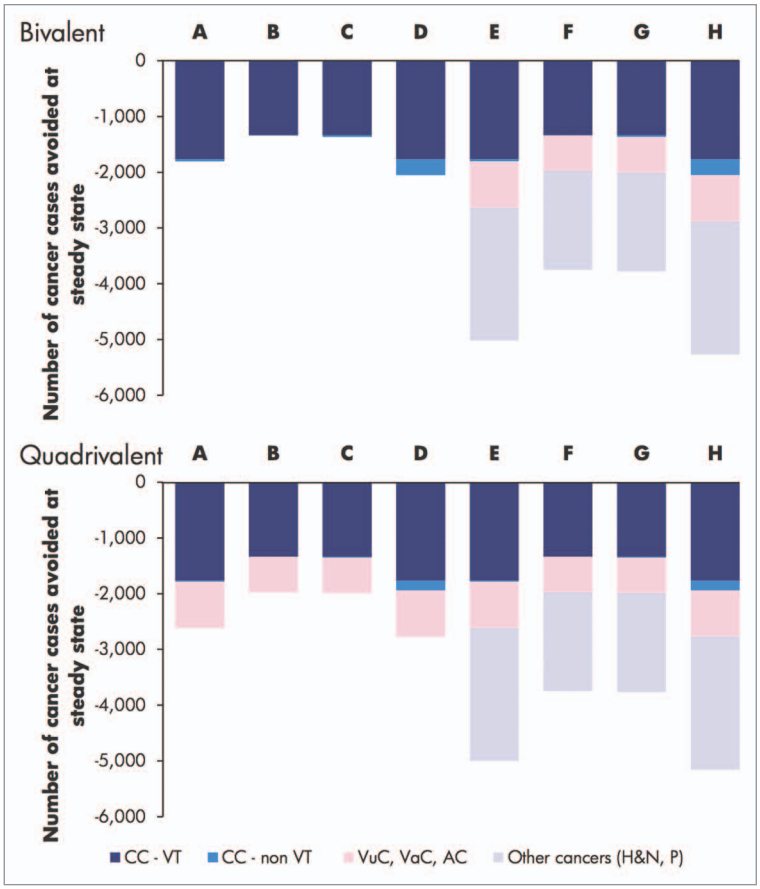

Figure 1. Comparison of annual number of cancer cases avoided at steady-state (100 y) depending on vaccination strategy. AC, anal cancer; CC, cervical cancer, H and N, head and neck cancers; P, penile cancer; VaC, vaginal cancers; VT, vaccine-types; VuC, vulvar cancers. Twelve Non-vaccine HPV types for bivalent vaccine (HPV 31, 33, 45 driven) and 10 non vaccine types for quadrivalent vaccine (HPV 31-driven).

Discussion

The analysis presented here is the first to compare the epidemiological and economic benefits associated with quadrivalent HPV 6/11/16/18 vaccination vs. the bivalent HPV 16/18 vaccination in addition to cervical cancer screening in the French setting. Addition of the bivalent or quadrivalent vaccines to screening was associated with both clinical and economic benefits over screening alone. Overall, the results suggest that quadrivalent HPV vaccination is associated with substantial incremental epidemiological and economic benefits in comparison with the bivalent vaccination, driven in the short term by a reduction in the incidence of genital warts in females and males due to herd immunity, and in the long-term by an incremental benefit in terms of reduction in the incidence of vulvar and vaginal cancers in females and anal cancer in both genders, with prevention of anal cancers in males attributable to indirect effects (herd immunity). Although the bivalent vaccine was projected to prevent more cases of cervical cancer due to a potentially higher cross-protective effect, the magnitude of this incremental benefit was small (accounting for up to 5% of cases avoided in scenario analysis), regardless of the scenario investigated. It should also be noted that a degree of uncertainty remains with regard to the clinical relevance and duration of cross-protection, which is likely to be short-lived.[17,21] Scenario analysis was conducted to assess variability around uncertain parameters, with both clinical and economic results robust to variation. Finally, this benefit was outweighed by the greater incremental benefits associated with the prevention of genital warts afforded by the quadrivalent vaccine and the reduction in non-cervical HPV-related cancers. Although it was assumed in scenarios E to H that benefits against HPV 16 and 18 related non-cervical cancers were provided by both vaccines, efficacy against vulvar, vaginal and anal precancerous lesions has only been demonstrated and acknowledged by health authorities for the quadrivalent vaccine.[16]

A point of note is that the model did not account for differences in duration of protection between the two vaccines; indeed, the duration of protection of HPV vaccines can only be determined with extensive follow up of vaccinees over a period of decades. However, along with scientific knowledge on HPV immunology, the clinical efficacy data, the demonstration of an immune memory, epidemiological follow-up studies and mathematical modeling can be used as indicators of long-term

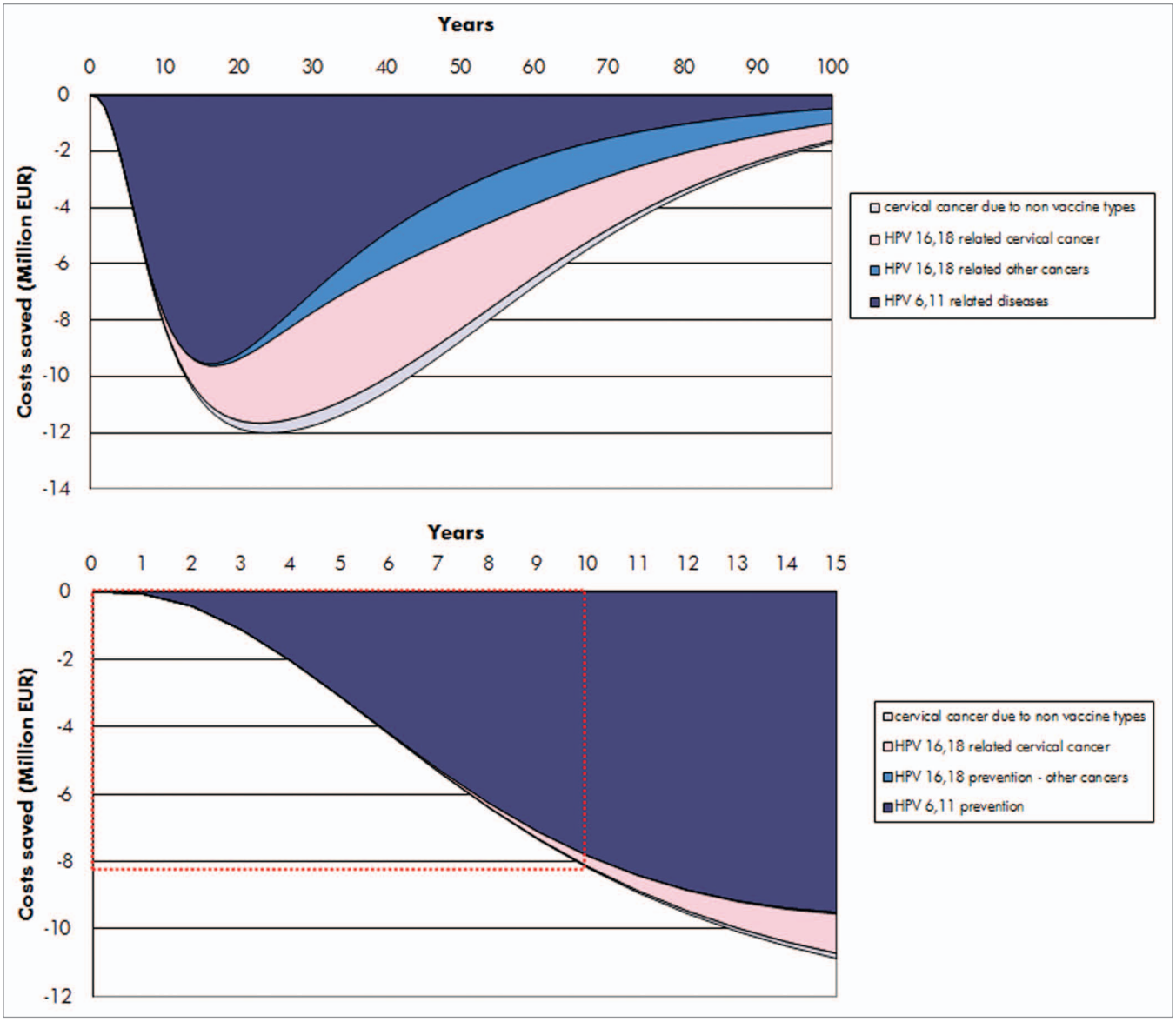

Figure 2. Discounted healthcare cost savings over 100 (2012–2112) years and early benefit analysis over first 15 y. A, anal cancer; CC, cervical cancer; GW, genital warts; Va, vaginal cancer; Vu, vulvar cancer; VT, vaccine types; non VT, non-vaccine types. Health cost savings breakdown attributable per type of HPV-related disease: vaccine type HPV-related diseases (HPV16/18/6/11 for the quadrivalent vaccine and HPV 16/18 for the bivalent vaccine) vs. non vaccine type HPV-related diseases. Lifetime duration of protection for HPV-vaccine types and 20-y duration of protection for non-vaccine HPV types were assumed, 4% discount rate (costs). Vaccine efficacy based on scenario E.

protection. In the absence of an immune correlate for HPV virus-like particle vaccine induced immunity,[36] and together with the emerging evidence that very low levels of antibody (at the limits of current assay detection), are protective, measured antibody concentrations cannot be employed as predictors of clinical efficacy and long-term protection of HPV vaccines.

The results of the present analysis largely concur with those of previously published studies by independent teams from other settings including, Canada, Ireland and the UK.[27,29,37] These three studies reported that the bivalent vaccine price should be lower than that of quadrivalent vaccine in order to be equivalently cost-effective, despite differences in modeling and country specific data. In the Canadian setting, Brisson et al. suggested that the bivalent vaccine needs to be 26% cheaper than the quadrivalent for equivalent cost effectiveness. In Ireland, Dee et al. showed that bivalent vaccine would need to be 22% cheaper than the quadrivalent vaccine. In the UK, Jit el al., found that the price difference between the two vaccines required for equivalent cost-effectiveness ranges from 19 to 35 GBP (EUR 23–42) depending on the scenario investigated. Such findings were acknowledged by ECDC in its updated guidance published in 2012.[38]

The latest study from the UK showed that the bivalent vaccine had a small advantage vs. the quadrivalent vaccine in terms of reduced incidence of cervical intraepithelial neoplasia and cervical cancer, when assuming a better cross-protection profile, but that the quadrivalent vaccine was associated with significant

incremental economic benefits even in the most conservative scenarios considering that both vaccines protect against non-cervical cancers. Jit et al. concluded in their UK-based study that the prevention of genital warts provided by the quadrivalent vaccine was the main contributor to the reduction in healthcare costs and QALYs lost and to the better cost-effectiveness vs. the bivalent vaccine.[27] More specifically, of total costs saved with the quadrivalent vaccine GBP 160–240 million were due to the prevention of genital warts.

The findings of this study in combination with the aforementioned ones contrast with another published study which concluded that additional level of cross protection of the bivalent vaccine would result in a substantial reduction in cervical cancer burden offsetting costs avoided due to the prevention of genital warts due to the HPV 6/11.[28] Several methodological differences in modeling, with some potentially limiting may account for differences in findings. First, herd immunity could not be taken into account as the model used was a static Markov model, resulting in an underestimation of the reduction in genital wart burden. Furthermore, the genital wart related burden of disease existing prior to HPV vaccination was deemed to be under-estimated in terms of absolute incident cases and related treatment costs. In addition, lifelong duration of protection was assumed in base case for cross-protection against CIN2/3 and CC lesions. The findings of previous analyses and new scientific evidence that has recently emerged have been reflected in recent policy decisions. In particular, in the UK, the Department of Health has stipulated that from September 2012, the quadrivalent vaccine will be administered in preference to the bivalent vaccine. This decision was taken on the basis that the quadrivalent vaccine provided better value for money in comparison with the bivalent vaccine.[39] One of the key drivers behind the UK decision is the additional benefit in terms of the prevention of genital warts. As shown here and in a previous Europe-wide analysis,[40] the use of the quadrivalent vaccine results in a substantial reduction in the incidence of genital warts in both genders. Moreover, the impact of the quadrivalent vaccine in terms of the reduced incidence of genital warts becomes manifest over a relatively short time period and has been directly observed at the population level in routine clinical practice. Read et al. showed that in a 4-y period following the inception of a vaccination program with high coverage rates the incidence of genital warts declined by approximately 90% in heterosexual individuals aged < 21 y.[34] Genital warts represent a substantial proportion of the overall burden of disease related to HPV. In a recent review Raymakers et al.[41] report that genital warts were responsible for 9–10% of all visits to sexual health clinics and consequently that any decision regarding HPV vaccination should incorporate the impact of vaccination on the burden of genital warts since this burden is considerable.[35,42]

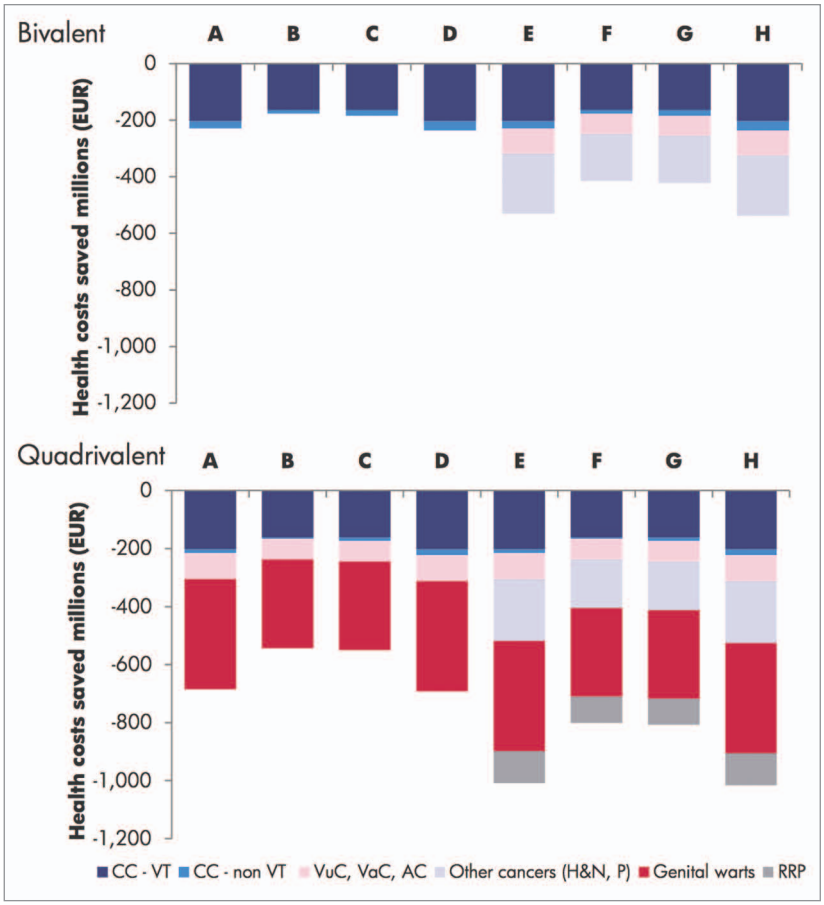

Figure 3. Scenario analysis summary: discounted direct medical costs avoided over 100 y, including costs associated with genital warts, cervical cancer (vaccine and non-vaccine types) and other HPV 6/11/16/18 conditions. AC, anal cancer; CC, cervical cancer; H and N, head and neck cancers; P, penile cancer; VaC, vaginal cancers; VT, vaccine-types; VuC, vulvar cancers 12 Non vaccine HPV types for bivalent vaccine = HPV 31, 33 and 45-driven; 10 non vaccine HPV types for quadrivalent vaccine = HPV 31-driven, for cervical cancer.

As with all modeling studies, the present analysis is associated with both strengths and limitations. One of the key strengths of the present analysis is its comprehensive nature in terms of capturing potential benefits of vaccination in terms of HPV-16/18 related cancers other than cervical cancer and RRP, which although rare is associated with relatively high treatment costs. The potential cross-protection effect against non-vaccine HPV types was not simulated directly in the dynamic transmission model as per HPV 16/18 infections and related cervical cancer. The natural history of the disease (transmission, progression to disease, screening programs and treatment) was assumed to be applicable to non-vaccine HPV strains. The cross-protection effect was therefore inferred indirectly via the analysis of the outputs of the dynamic model for vaccine types 16/18. Even though this approach may not be as accurate as direct analysis through the dynamic transmission model, such an analysis may help to assess the extent of the incremental benefits driven by cross-protection

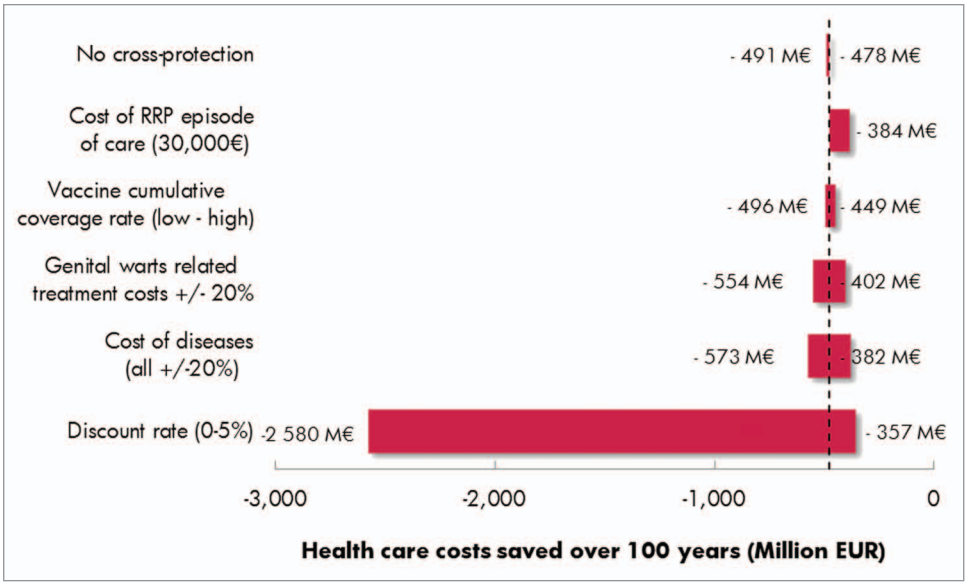

Figure 4. Tornado diagram showing total incremental savings due to quadrivalent vs. bivalent vaccination over the period 2012–2112 (Scenario E). Sensitivity analyses were conducted with the effect on the cost saving calculated. The dotted line represents the baseline cost saving (EUR 478 million). Bars extending to the left of the chart represent scenarios were cost savings were increased, while bars extending to the right represent reduced cost savings. Results were most sensitive to changes in the discount rate. Quadrivalent vaccination was found to be cost saving over bivalent vaccination in all analyses RRP, recurrent respiratory papillomatosis.

toward cervical cancers. The annual proportional reductions in HPV-related disease incidence due to vaccination were also proportionally adjusted due to the difference in efficacy and duration of protection assumed against non-vaccine-HPV types vs. vaccine HPV types 16 and 18.

The study assessed outcomes over a 100-y time horizon. Assessing the cumulative direct medical cost savings over a long time horizon has been commonly reported in several economic evaluations addressing HPV vaccination, even if time horizons may have differed between studies (from 50 to 100 y depending on the modeling assumptions).[27,29-31] This approach is required given the time delay of development of the HPV-related disease following persistent infection. Moreover, to take into account indirect benefits, and the possibility of sexual activity among different age/gender groups, a population dynamic model is a relevant way of modeling. In comparison with other vaccination programs, HPV vaccination differs because of the important delay between protection and expected clinical benefits.

Scenario analyses were performed to handle uncertainty around duration of vaccine protection, cross-protective effects and a potential class effect on non cervical cancers. In the most conservative scenario (Scenario H) where for the bivalent vaccine a higher and longer-lasting cross-protective effect was assumed (although clinical relevance remains unknown and cross-protection is likely to be short lived) in addition to protection against all non-cervical HPV 16 and 18 related cancers, the quadrivalent vaccination has shown a superior economic profile due to HPV 6/11 disease prevention. Univariate sensitivity analyses were also performed around key input data and assumptions to assess the robustness of the conclusions. Overall, changes in discount rates of future costs were the most influential parameter.

A potential caveat of the present analysis is the availability of model input data. In particular, robust epidemiological and cost data relating to RRP in the French setting are lacking, consequently surrogate data from Denmark and the United States were used for the incidence and cost of RRP, respectively. As the results of sensitivity analyses showed, although the incidence of RRP is low, changes around assumptions in terms of treatment costs had a substantial impact on results. As such, incorporation of data specific to the French setting would be required to improve the value of the estimates provided here. There are also inherent limitations associated with modeling long-term outcomes from short-term clinical trial data. In particular, although data are available for cervical cancers, the development of HPV-related carcinomas (vulvar, vaginal and anal cancers) may develop years after the initial infection event, and as such events cannot reasonably be captured within the time frame of a clinical trial. Consequently, high grade precancerous lesions were used as a surrogate marker. Of note, cervical cancer screening was assumed to remain unchanged after the implementation of HPV vaccination. This assumption would not impact on incremental results, since it is likely that potential reduced uptake of screening services would impact equally on both HPV vaccines.

Further analyses accounting for vaccination costs as well as the utilities related to the different HPV-related disease, are worthy of further investigation. Including costs of vaccination, such as vaccine costs, staff costs and advertising, would allow incremental cost-effectiveness (as expressed in cost per case avoided) or cost-utility (as expressed in cost per QALY gained) of HPV vaccines to be calculated, which was beyond the scope of this study. Future incremental cost-effectiveness analyses would further inform decision makers on HPV vaccine's value for money. Despite not fulfilling all the criteria of a full economic evaluation, the present analysis remains one of the most comprehensive analyses of the impact of HPV vaccination to date and illustrates the public health impact of the bivalent and quadrivalent vaccine, taking into account cross-protection against cervical cancer caused by non-vaccine HPV types and also the incidence of broader diseases: vaginal, vulvar, anal, penile and head and neck carcinoma, RRP and genital warts.

Materials and Methods

Epidemiological model structure. Our analysis is based on the findings of a previously published dynamic transmission model (Dasbach).[43] In summary, Elbasha et al. constructed a population dynamic model to account for both the direct and indirect effects of vaccination (herd immunity) in the US settings. The model incorporated 23 age groups, ranging from birth to 85 y or older. The division of the population, based on age and gender, allows for the patterns of HPV transmission among sexually active groups to be modeled accurately. This includes age and gender specific patterns of HPV transmission among sexually active groups, cervical and vaginal cancer screening patterns, risk of disease, and vaccination strategies. The model estimated long-term clinical outcomes in terms of the incidence of HPV-associated disease. Herd immunity for males against a range of HPV-related diseases was taken into accounted: anogenital warts and RRP for HPV 6/11, and penile, anal and head, and neck cancers for HPV 16/18. The model incorporated US-specific data related to sexual mixing patterns, HPV transmission, screening and HPV-related curative treatments for diagnosed cases. For the present analysis, this US-based model was partially adapted through incorporation of vaccine coverage rates and compliance rates specific to the French setting.

The analysis consisted of indirectly comparing the outcomes of HPV vaccination, in addition to screening, vs. screening alone in the French setting. Girls were assumed to be vaccinated either with the quadrivalent vaccine or the bivalent vaccine.

Epidemiological model outcomes. A two-stage indirect approach was undertaken to compare the addition of either quadrivalent or bivalent vaccination to screening. Reduction of epidemiological burden as well as direct medical costs savings were assessed separately for each vaccine vs. the common baseline comparator (screening). As a first stage, the partially adapted dynamic transmission model of Elbasha and Dasbach was run for the two vaccination strategies separately (bivalent or quadrivalent vaccine plus screening vs. screening only), with their respective inputs according to a scenario analysis and the screening only scenario (detailed below).[43] The dynamic transmission model was used to calculate the absolute incidence of HPV-related disease cases per year over a 100-y time horizon, for each of the two vaccination strategies in addition to screening only. The outputs of the dynamic transmission model were annual HPV-related disease incidence (by gender and by age class). These incidences were adjusted per 100,000 persons per year according to the age distribution of the US population. These incidences were calculated for HPV-related disease cases attributable to vaccine-types (HPV 16/18 for bivalent vaccine and HPV 16/18/6/11 for quadrivalent vaccine).

As a second stage, these standardized absolute incidence rates were used to compute, within Microsoft Excel 2003, the annual proportional reductions in disease incidence due to a given vaccination strategy vs. baseline scenario (screening only) for each HPV-related disease. These proportional reductions were then applied to French incidence data reflecting incidence prior to the implementation of HPV vaccination (screening only) at the national level. The incident cases avoided reported in the analysis are therefore related to the whole French population (2008 census). This approach permitted the calculation of the number of HPV-related disease cases avoided due to the protection against vaccine HPV types in addition to cervical cancer screening.

The present analysis also took into account cross-protection against cervical cancers caused by non-vaccine HPV types based on the findings of clinical studies.[19,20] Specifically, the model assumed vaccine efficacy (95% CI) of 46.8% (30.7–59.4%) against 12 non-vaccine HPV types (HPV 31, 33 and 45-driven) for the bivalent vaccine and 23.4% (7.8–36.4%) against 10 non-vaccine HPV types (HPV 31 driven) for the quadrivalent vaccine (**Table 2**).[19,20] Similarly, as with the vaccine HPV types, annual proportional reductions were applied to the cervical cancer incident cases (attributable to non-vaccine HPV types) in order to estimate the number of additional cervical cancer cases avoided due to cross-protective effects against non-vaccine HPV types. As non-vaccine types were not incorporated within the dynamic transmission model at the time of the present analysis,[43] we assumed that these annual proportional reductions in the incidence of cervical cancer attributable to non-vaccine HPV types followed the same pattern over time as cases attributable to vaccine HPV types (16/18). Moreover, these annual proportional reductions were adjusted (i.e., proportionally diminished) to take into account the fact that vaccine efficacy was assumed to be lower against non-vaccine types (as discussed above). Additionally, current evidence suggests that the duration of cross-protection is short-lived.[17,21] As such, a shortened duration of protection against non-vaccine HPV types was assumed (10 y, 20 y) in comparison with the lifetime (or 32 y, depending on scenario; **Table 2**) duration of protection assumed for vaccine HPV types. Consequently, only the avoided cases attributable to non-vaccine types over this shortened time period were taken into account in the analysis.

The analysis was performed over a 100-y time horizon from 2012–2112. Results are presented at steady-state (100 y) and over the entire 100-y time horizon to account for maximum benefit of both vaccine strategies.

Screening and HPV vaccination strategies. The target population for vaccination was females aged 14–23 y with either the bivalent HPV 16/18 vaccine or the quadrivalent HPV 16/18/6/11 vaccine (**Table 2**). The model considered the impact on the total male and female French population (see Modeled population section below). Vaccine coverage rates and compliance were derived from French published literature for the years 2009 and 2010 and extrapolated to provide estimates for coverage rates in 2012, i.e., 66% cumulative vaccine coverage rate for 14 y old and catch-up cohorts in 2012.[25] HPV vaccination consists of a course of three injections and not all patients complete the full vaccination course. Consequently, a compliance of 2.7 doses was assumed, with lower vaccine efficacy assumed in females who did not receive the full course (**Table 3**).

Cervical cancer screening program is assumed to remain unchanged following the implementation of vaccination. Previously published US based parameters (annual rates of screening by age class)[43] were used in this analysis. In addition, 5% of females were assumed to never have been screened. Further details were published elsewhere.[43]

Table 1. Prevalence, incidence and costs of HPV-related disease in France

Endpoint	Incidence (ref)	Prevalence (ref)			
		HPV 16/18	HPV 6/11	Total annual cost	Cost per incident case[a]
Genital warts, females	53,507[23]	-	90%[45]	-	370[23]
Genital warts, males	60,338[23,46b]	-	90%[45]	-	278[23]
RRP, females	25[47c]	-	90%[48]	-	190,748
RRP, males	25[47c]	-	90%[48]	-	190,748
Cervical cancers	2,810[49]	76%[1]	-	43,862,125[50]	17,482
Vulvar cancers	609[51]	36.6%[51]	-	8,506,755[52]	14,807
Vaginal cancers	192[51]	61.3%[51]	-	5,990,638[52]	33,073
Anal cancers, females	641[51]	78.6%[51]	-	22,200,000[53]	36,711
Anal cancers, males	241[51]	78.6%[51]	-	10,000,000[53]	43,983
Head and neck cancers, females[d]	3,616[49]	24%[54,55e]	-	66,600,000[56]	19,155
Head and neck cancers, males[d]	10,347[49]	24%[54,55e]	-	334,900,000[56]	33,662
Penile cancers	361[57]	34.3%[58]	-	4,912,191[59]	14,424

RRP, recurrent respiratory papillomatosis. All costs are presented in 2010 EUR. [a]Cost per incident case is taken directly from source or calculated as total annual cost divided by number of incident cases. [b]Number extrapolated based on UK figures due to lack of data specific to the French setting (53% of cases of genital warts were found in males).[46c] No French epidemiological data were available for RRP; non-gender specific data from the Danish setting were used as a proxy where 0.35–0.38 incident cases per 100,000 person years were reported, leading to 51 annual cases using 2008 population data. This figure was rounded to 50 and then divided by 2 to provide gender-specific data. [d]Includes tongue (including base of the tongue, other parts of the tongue), mouth (including gum, floor of the mouth, palate), tonsil, oropharynx, piriform sinus, hypopharynx and larynx. [e]Mean weighted value for head and neck cancers.

Prevalence and incidence data for HPV associated diseases were derived from French published literature and IARC database (**Table 1**). Incidence rates retrieved from IARC database were applied to the French female population (2006 census), giving total annual incident cases per HPV-related diseases.

Modeled population. The population modeled is not only the cohort of screened (and vaccinated) girls aged from 14 to 23 y but the whole female and male population. This allows the analysis to take into account sexual mixing patterns and their role in HPV infection transmission. In addition, the model incorporates a new cohort of girls eligible to receive the vaccination each year over the entire horizon of the analysis. Therefore, there are as many cohorts of vaccinated girls (for a given age) as the time horizon.

Costs. Direct medical costs were sourced from published literature and where necessary converted to 2010 EUR using purchasing power parity conversion rates (**Table 1**). Costs are presented as cost per incident case with an episode of care defined as all direct inpatient and outpatient costs incurred from diagnosis to resolution of the case (with the exception of cervical cancer where only inpatient costs were available). Costs were sourced from published literature and the mean cost per incident case calculated by dividing total annual cost by the number of incident cases. Where possible, costs were derived from French data sources, with surrogate data from other settings used when French data were not available. Future costs and clinical outcomes were discounted at a rate of 4% per annum in line with current guidelines for the French setting.[44]

Scenario and sensitivity analyses. Two distinct series of scenarios were considered in the analysis: in the first series (scenarios A, B, C and D) it was assumed that the quadrivalent vaccine provided protection against cervical, vulvar, vaginal, and anal cancers, and that the bivalent vaccine protected against cervical cancers onlyas per current indications and pharmacologic properties. In the second and more conservative series of scenarios (scenarios E, F, G and H), efficacy against HPV 16/18-related vulvar, vaginal and anal cancer was assumed to be equivalent for both vaccines, although only the quadrivalent vaccine has demonstrated efficacy against precursors of these cancers (**Table 2**). In addition, equivalent vaccine efficacy was assumed against penile and a subset of head and neck cancers associated with HPV 16 and 18 for both vaccines. In all scenarios, only the quadrivalent vaccine provided protection against HPV 6/11-related diseases (genital warts and RRP) (**Table 3**).[43]

Scenario analyses also accounted for uncertainty around the duration of protection for vaccine and non-vaccine HPV types and efficacy against non-vaccine HPV types (**Table 2**). Univariate sensitivity analyses were also performed to explore uncertainty around parameters including vaccine coverage rates and treatment costs. Specifically, sensitivity analyses in which vaccine coverage rates (cumulative coverage rates for females aged 14–23 y) were set to a low of 50% and a high of 90% were performed. Analyses were also performed in which the treatment costs of genital warts only and the treatment costs of all HPV-related diseases were decreased and increased by 20% relative to the base case to assess the impact of uncertainty around treatment costs. Uncertainty around the burden of RRP and the cost of an episode of care for RRP were also examined. Sensitivity analysis was also performed around the discount rate (costs) in which it was set to 0% and 5% per annum.

Conclusion

The present economic model findings concur with the findings of previous analyses by academic teams in a number of other

Table 2. Scenario and sensitivity analysis

Scenario	Bivalent vaccine				Quadrivalent vaccine			
	HPV vaccine types		Non HPV vaccine types (cervical cancers)		HPV vaccine types		Non HPV vaccine types (cervical cancers)	
	Duration of protection (years)	Clinical endpoints	Mean efficacy (%)	Duration of protection (years)	Duration of protection (years)	Clinical endpoints	Mean efficacy (%)	Duration of protection (years)
A	Lifetime	Cervical cancers	46.8	20	Lifetime	Cervical, vulvar, vaginal, anal cancers and genital warts	23.4	20
B	32 y		30.7	10	32 y		7.8	10
C	32 y		46.8	20	32 y		23.4	20
D	Lifetime		59.4	Lifetime	Lifetime		36.4	Lifetime
E	Lifetime	All cancers[a]	46.8	20	Lifetime	All cancers[a] plus genital warts and RRP	23.4	20
F	32 y		30.7	10	32 y		7.8	10
G	32 y		46.8	20	32 y		23.4	20
H	Lifetime		59.4	Lifetime	Lifetime		36.4	Lifetime

HPV, human papillomavirus, RRP, recurrent respiratory papillomatosis. [a]Refers to cervical, vulvar, vaginal, anal, head and neck and penile cancers. Vaccine efficacy parameters against non-vaccine types were derived from Brown et al. 2009[21] and Wheeler et al. 2012[20] for the quadrivalent and bivalent vaccine respectively. Efficacy of quadrivalent vaccine against vaccine HPV types was derived from Elbasha and Dasbach 2010[43] and was applied as well to bivalent vaccine (see **Table 3**).

settings including the UK, Canada and Ireland.[27,29,37] The results showed that vaccination with the quadrivalent HPV 6/11/16/18 vaccine is associated with greater economic benefits in comparison with the bivalent HPV 16/18 vaccine in the French setting.

The incremental economic benefits associated with quadrivalent vaccination were driven by the prevention of genital warts (with EUR 306–380 million savings corresponding to 37–56% of total healthcare costs saved over 100 y) whereas the potential cross-protective effect against cervical cancer accounted for marginal incremental costs savings (EUR 13–33 millions, corresponding to approximately 4% of total healthcare costs saved). Moreover, based on licensed endpoints, quadrivalent vaccination was estimated to lead to incremental savings of EUR 71–89 million due to the prevention of vulvar, vaginal and anal cancers.

New evidence from epidemiological, clinical and economic studies should be considered in further analyses evaluating the public health impact and cost-effectiveness of HPV vaccination, as well as remaining uncertainty (e.g., epidemiologic trends for HPV disease incidence, vaccine coverage, duration of protection, efficacy against non-vaccine types), in order to better inform policy makers. In particular, overall vaccine benefits in terms of all HPV-related conditions should be assessed based on country-specific data and local context.

Disclosure of Potential Conflicts of Interest

X.B., M.A. and N.L. are employees of SPMSD. S.R. and R.M. are employees of HEVA, which has received consulting fees from SPMSD. Editorial assistance was provided by J.SP and W.V. from Ossian Health Economics and Communications. This study was supported by funding from SPMSD.

Table 3. Vaccine efficacy parameters and assumptions[a]

Efficacy parameter	HPV genotype			
	6	11	16	18
Against transient infection[†,‡]				
Cervical, vaginal and vulvar diseases	-	-	76.0%	96.3%
Genital warts and HPV 6, 11	76.1%	76.1%	-	-
Against persistent infection				
Anal disease	-	-	98.8%	98.4%
Cervical, vaginal and vulvar diseases	-	-	98.8%	98.4%
Against individual diseases				
Genital warts	98.9%	100.0%	-	-

Unit: percentage. Values were derived from reference 33. [†]Efficacy against genital infection in females is assumed to prevent transmission of genital infection to males, and vice versa. [‡]Efficacy for 1 and 2 doses assumed to be 23% and 45% of efficacy of the full 3 doses, respectively.[43] *Efficacy against anal, head and neck and recurrent respiratory papillomatosis diseases is conferred through protection against infection only. [a]Only the quadrivalent vaccine has demonstrated efficacy beyond cervical cancer prevention and protects against HPV6/11 related diseases.

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