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ORIGINAL ARTICLE

Public health impact of human papillomavirus vaccination on prevention of cervical cancer in France

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Abstract
Objective To evaluate the cervical cancer (CC) reduction at individual and population level following different prevention strategies (age-specific vaccination and/or screening) in France.
Methods A lifetime Markov model was constructed with 11 health states covering the progression from human papillomavirus (HPV) infection to the development of precancerous lesions, CC and death. A screening module took into account the effects of detection and early treatment. Cohorts of girls were entered into the model at age 11 years; the model was run for 95 years using one-year cycles.
Results Vaccination combined with screening substantially reduced the incidence of precancerous lesions and CC compared with screening alone. Vaccination was beneficial regardless of age at vaccination, but the greatest benefit was obtained with an early vaccination. The clinical results were the best for vaccination at 11–13 years when lifetime horizon was considered, and for vaccination at 15–17 years for shorter observation period.
Conclusion The model results indicate that HPV vaccination offers additional protection against CC when combined with screening. The optimum starting age for vaccination varies depending on the observation period duration.

Keywords Vaccination · Human papillomavirus · Cervical cancer · Public health

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Introduction

Infection with oncogenic human papillomavirus (HPV) is a necessary condition for developing cervical cancer, though it is not the only cause (Walboomers et al. 1999). Cervical cancer affects around 3,400 women [95% confidence interval (CI) 2,874–3,900] per year across the French population (Remontet et al. 2003) and the 5-year survival rate remains low (67.8%) (Sant et al. 2003).

It has been shown that screening using the cervical smear test (Papanicolaou test, also called the Pap test or Pap smear) is successful in reducing the incidence of mortality from cervical cancer, particularly in organised screening programmes (Peto et al. 2004;Raffle et al. 2003). Public health policies aiming to implement generalised screening in women have led to a high coverage rate in some countries. In France, where the screening strategy is essentially opportunistic, coverage in 2006–2008 was estimated at 57% (defined as the percentage of women who had a cervix examination in the previous 3 years) (s.n. 2010).

Recently, a promising additional public health tool has become available on the market: vaccination against certain HPV types that demonstrated to be highly effective against HPV-types 16 and 18 infections and precancerous

lesions in large phase III randomised clinical trials (Munoz et al. 2010; Paavonen et al. 2009). Oncogenic HPV-types, HPV-16 and HPV-18 represent the two most frequent types representing around 70% of all the causes of cervical cancer worldwide (WHO/ICO 2009). Vaccination of young women in the age range of 15–25 years provided a high protection level of over 90% against incident HPV infection and up to 100% against persistent HPV infection caused by the two HPV-types (Paavonen et al. 2009; Garland et al. 2007). Protection beyond these two types has also been reported from the recent clinical trial resulting in a broader coverage of HPV types (Paavonen et al. 2009). In older women, aged 25–55 years, trials have shown that vaccination induces a robust and persistent immune response (Schwarz et al. 2009) even though the immunogenicity results were lower in women aged above 25 ((Schwarz et al. 2009; Munoz et al. 2009). In France, the target group are the 14-year-old female. Despite the reported efficacy of the vaccine, the current vaccine coverage remains low with 24% having received the three doses in 2008 (Fagot et al. 2011).

Given that, the data are available for only a relatively short follow-up period (7.3 years (De Carvalho et al. 2010) compared with the very long time-course for developing the cancer (several decades), the clinical data cannot show the global impact of vaccination on morbidity and mortality from cervical cancer. Therefore, modelling techniques are needed to provide first estimates of the long-term potential benefits of vaccination. Models also allow comparison of estimated effectiveness and cost-effectiveness between different vaccination strategies (Dasbach et al. 2006), and several studies in this area have already been published (Barnabas and Garnett 2004; Goldie et al. 2004; Hughes et al. 2002; Kulasingam and Myers 2003; Sanders and Taira 2003).

Most studies have restricted their evaluation to vaccinating single cohorts of girls prior to starting sexual activity. This approach is valuable, but provides limited information on vaccination at a population level. The present paper addresses this information gap by evaluating the impact of HPV vaccination with the bivalent vaccine from a public health perspective using a multi-cohort modelling exercise. The study simulates the epidemiological consequences of different vaccination strategies across different age cohorts in France using a succinct model, based on an existing model (Goldie et al. 2004) and close to the one developed by Kulasingam and Myers 2003 that allows transparent estimation of the cost-effectiveness of HPV vaccination using a data set that is easily accessible for most countries. Its objectives were to evaluate the optimum starting age for vaccination from a public health perspective, model the cervical cancer risk reduction achieved by vaccination or screening alone or in combination, and compare the public health impact of different vaccination strategies.

Methods

A succinct cohort model based on a Markov process was developed in Microsoft Excel to simulate the short- and long-term consequences of HPV vaccination against cervical cancer (Debicki et al. 2008). This succinct model uses an input data set that is easily accessible for most countries. It has shown similar robustness and accuracy than a detailed model in replicating cervical cancer-related disease (Debicki et al. 2008). The model structure is summarised in Fig. 1. The model takes into account the direct causal relationship between oncogenic HPV infection and the subsequent long-term development of cervical cancer through a series of intermediate pathological stages that can be identified and treated. The model also includes a screening module that allows detected pre-cancerous lesions to be treated and thus reduces disease progression. The screening therefore alters the natural history of the oncogenic processes (Peto et al. 2004). It was assumed that all cervical cancers would be detected and therefore treated. Finally, the model evaluates the impact of vaccination against certain HPV-types by reducing the incidence of HPV infection, therefore reducing the risk of dysplasia and ultimately of cervical cancer. The model therefore assumes vaccine efficacy against new infections only; existing lesions or infections at the time of vaccination will follow the natural disease history.

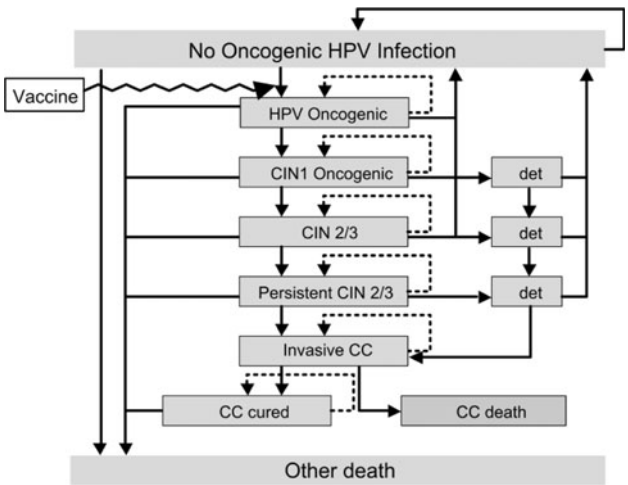

Fig. 1 Overview of the model showing the 11 health states and the transitions between health states with assigned transition probabilities. *det* precancerous lesions detected by the screening, same pathways but with different probabilities, *CC* cervical cancer, *CIN* cervical intraepithelial neoplasia, *HPV* human papillomavirus

Model description

The model runs in annual cycles over a period of 95 years from a starting age of 11 years. It is therefore expected that everyone in the starting age cohort followed over a lifetime will have died by the time all cycles have been run. The model tracks the starting age cohort through 11 health states. In the base-case, girls are enrolled in an age cohort that is not infected with oncogenic HPV types. Transition to the next health state corresponds to an infection with oncogenic HPV. Infection with low-risk HPV is not directly included in the model, although CIN stage 1 (CIN1) cases expected to result from low-risk HPV infection are added to CIN1 calculated by the model. After infection with oncogenic HPV, three subsequent pre-cancerous states are defined: CIN1, CIN stage 2/3 (CIN2/3) and CIN2/3 persistent. Lesions progress along these three health states, although regression can occur to the "no oncogenic HPV" state either spontaneously following normal viral clearance (50% for CIN1 and 27.5% for CIN2/3 (Debicki et al. 2008), or following detection through screening and subsequent treatment. The model assumes that all CIN2/3 lesions are attributable to oncogenic HPV infections only. The evolution of these lesions to cancer is dependent on whether the infection becomes persistent. We therefore introduced into the model the health state of a persistent CIN2/3 lesion. When people reach that state, they no longer spontaneously regress but they can only progress to cancer if not detected through screening and successfully treated. The transition probability from "persistent CIN2/3" to "cancer" is generated through model calibration using French epidemiological data on cervical cancer as no data were available elsewhere. The end-states in the model are specific death due to cervical cancer and death due to other causes.

Data input

For each CIN health states a corresponding "CIN detected" health state is added to the model. This allows for a specific evaluation of the impact of screening between the age of 25 and 65 years, using French data. When screening occurs, existing CIN can be detected proportionally to the screening sensitivity and thereafter treated and eventually cured. In the model, we assumed that 57% of the women undergo a regular 3-year cytological screening between the ages of 25 and 65 years (s.n. 2010).

Vaccine efficacy was modelled by reducing the probability of acquiring new HPV infection, taking into account the expected reduction of cancer cases, the ultimate vaccine target. The data used for the efficacy of the vaccine against each type of lesion are reported in Table 1, and assume an additional impact of the vaccine on other oncogenic HPV-type infections and cancer, also called 'cross-protection' (Skinner et al. 2009; Tjalma et al. 2009; Szarewski 2010) observed with the bivalent vaccine. The model uses the same vaccination scheme as in the clinical trials (three doses) and provides lifetime protection against targeted oncogenic HPV. The lifetime protection was assumed based on the latest modelling of seropositivity showing protection duration of at least 25 years (David et al. 2009).

Vaccine efficacy was different for females in pre- (HPV naïve) versus post-HPV exposure condition [Total Vaccinated Cohort DNA negative irrespective of HPV serostatus data (TVC DNA−)]. Pre- and post-exposures were differentiated based on the French distribution of age at sexual debut (Darroch et al. 2001). A linear regression truncated at 0 and 100% was derived in excel to estimate at each age the proportion of women pre- or post-sexual debut.

All transition probabilities are derived from French national statistics and literature review. Some, as HPV incidence, was age-dependent whereas others are fixed across age. HPV incidence was derived from published available data in France on HPV prevalence using a sub-model described elsewhere (Demarteau et al. 2011). A full list of the probabilities has previously been published (Demarteau et al. 2011). The model was calibrated to the cancer incidence rates reported in the French national registry, and the mortality rates predicted by the model matched well with registry data (s.n. 2011). The model results closely match the incidence and mortality data for invasive cervical cancer reported by the French national cancer registry (s.n. 2011) for women aged 60–65 years or less, and tend to underestimate cancer incidence and mortality in older ages.

Outcomes

The model estimates over a lifetime include the incident number of CIN lesions, the number of cervical cancer cases, number of deaths due to cervical cancer, number of deaths due to cervical cancer before 60 years of age and the total life expectancy of the cohort under study. These outcome measures can be compared between vaccinated and unvaccinated age cohorts. All outcomes reported are lifetime incident cases occurring at vaccination age.

Vaccination impact as a function of age

The impact of age at vaccination was estimated at the population level and at the individual level. For each

Table 1 Vaccine efficacy

Disease stages	Efficacy against HPV 16–18 infection			Cross-protection[a]			Global efficacy (EV + PC) (%)
	Efficacy (E)	Prevalence HPV 16–18 among all HR-HPV infections (P) (WHO/ICO 2009) (%)	Effectiveness against HPV 16–18 infections (EV = $E \times P$) (%)	Efficacy (E')	Prevalence cross protection types (P') (WHO/ICO 2009) (%)	Cross-protection effect (PC = $E' \times P'$) (%)	
Pre-HPV exposure							
CIN1	98% (Paavonen et al. 2009; Harper 2008)	25	24	48% (Tjalma et al. 2009)	75	36	61
CIN2/3	98% (Paavonen et al. 2009; Harper 2008)	52	51	68% (Skinner et al. 2009)	48	33	84
Cancers	98% (Paavonen et al. 2009; Harper 2008)	70	69	68% (Skinner et al. 2009)	30	20	89
Post-HPV exposure							
CIN1	89% (Wheeler and HPV Patricia Study Group 2010)	25	24	33% (Wheeler and HPV Patricia Study Group 2010)	75	25	47
CIN2/3	89% (Wheeler and HPV Patricia Study Group 2010)	52	51	47% (Skinner et al. 2009)	48	23	69
Cancers	89% (Wheeler and HPV Patricia Study Group 2010)	70	69	47% (Wheeler and HPV Patricia Study Group 2010)	30	14	76

CIN cervical intraepithelial neoplastic lesion, *HPV* human papillomavirus

[a] Cross-protection based on HPV-31/33/35/39/45/51/52/56/58/59

assessment, the age at vaccination ranges from 11 to 55 years.

At the population level, the vaccine effect was assessed on a single cohort of 100,000 11-year-old girls followed over a lifetime. The cohort was assumed to be vaccinated at 100% to assess the maximum effect of the vaccine. The outcomes reported correspond to the lifetime number of incident cancer, and CIN cases prevented with the vaccine combined with existing screening pattern and coverage compared with screening only, presented both as absolute risk (number of cancer cases prevented per 100,000 women) and relative risk reduction (% reduction in cancer cases).

At the individual level, the vaccine effect was assessed by estimating the remaining lifetime risk of developing cervical cancer at the age of vaccination, per woman. The absolute lifetime risk of developing cervical cancer by age is calculated for a woman under six different scenarios: (1) neither screening nor vaccination, (2) screening every 3 years up to 65 years of age with no vaccination, (3) screening every 10 years up to 65 years of age with no vaccination, (4) vaccination with no screening, (5) vaccination with screening every 3 years up to 65 years of age, and (6) vaccination with screening every 10 years up to 65 years of age. It was assumed that a woman following the screening programme would have a Pap smear every 3 years (or as specified in the scenario) between the age of 25 and 65 years.

Vaccination strategies

The effect of vaccination at different ages was evaluated with age cohorts of 370,000 girls each, the average size of birth cohorts of adolescent girls in France. Three vaccination strategies were compared, vaccination of cohorts of girls aged 11–13, 14–16 or 15–17 years. The simulation assumes that the entire age cohort is vaccinated over the first year as well as each new subsequent cohort entering the selected age over a period of 20 years. The outcomes are assessed for all the cohorts together over 20, 30, 60 and 90 years following the implementation of the vaccination program.

A sensitivity analysis at the individual level was conducted assuming no cross-protection to assess the effect of reduced vaccine efficacy.

Results

Vaccination impact as a function of age

The model results indicated that vaccination with 100% vaccine coverage combined with screening would significantly reduce the number of cervical cancer cases compared with screening alone (from 78% for a vaccination at 11 years of age to 35% for a vaccination at 55 years of age). Figure 2 shows the influence of age at vaccination on the number of cervical cancer cases avoided. The number of cases prevented increases with earlier age at vaccination, but vaccination as late as age 55 years would still prevent a substantial percentage of cases. Similarly, the number of CIN2/3 cases would be reduced by 77% for vaccination at age 11 years, and by 47% for vaccination at age 55 years, compared with screening alone.

For an unvaccinated and unscreened woman the lifetime absolute risk for developing cervical cancer is stable up to the age of 25 years (age of first incidence of cervical cancer). Thereafter, as some cancers have already occurred, the risk falls progressively with age (Fig. 3). Figure 3 shows the lifetime risk of a woman, as of a given age, undergoing different screening patterns, vaccination at that given age or a combination of both. Vaccination at age 11 years reduces the lifetime risk of cervical cancer to a level similar to that for screening every 5 years. The combination of screening every 3 years and vaccination

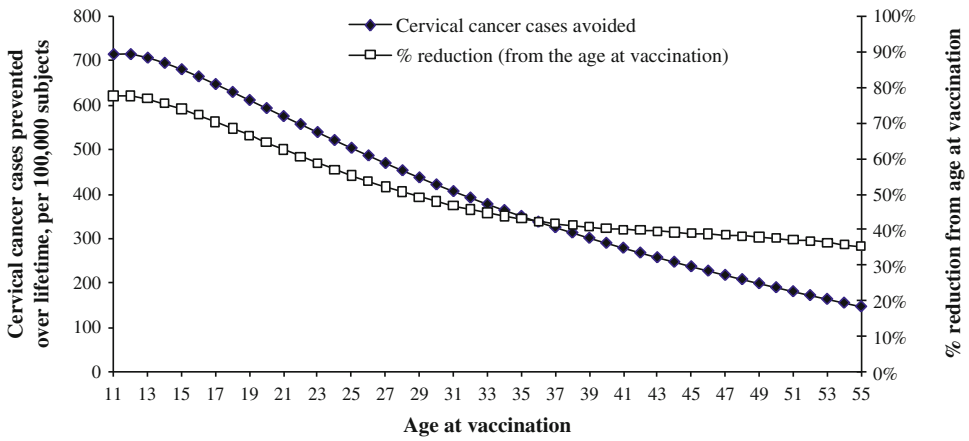

Fig. 2 Reduction in cervical cancer cases as a function of age of vaccination, compared with a cohort undergoing screening only

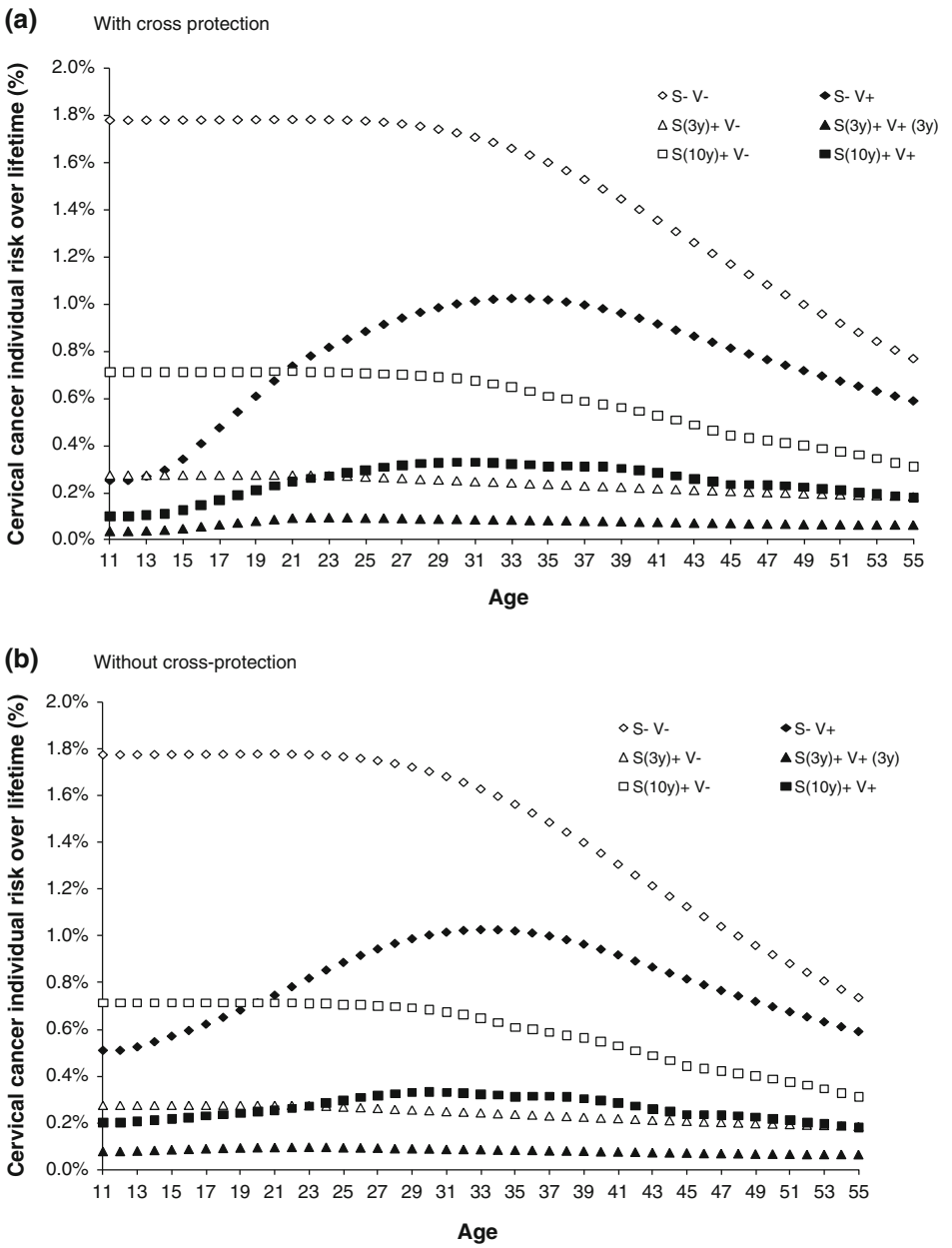

Fig. 3 Lifetime risk of developing cervical cancer at different ages for a woman under six scenarios. **a** With cross-protection. **b** Without cross-protection. (S−V−), no screening nor vaccination; (S(3*y*)+V−), screening every 3 years up to 65 years of age with no vaccination; (S(10*y*)+V−), screening every 10 years up to 65 years of age with no vaccination; (S−V+),vaccination with no screening; (S(3*y*)+V+), vaccination with screening every 3 years up to 65 years of age; (S(10*y*)+V+), vaccination with screening every 10 years up to 65 years of age

achieves a greater reduction than either alone, with a 48-fold risk reduction compared with a woman undergoing neither vaccination nor screening. When compared to a woman screened every 3 years a sevenfold risk reduction is reached.

The risk curves for vaccination and screening have a different profile over time because the two prevention techniques act differently. Vaccination is a single event and acts by preventing the HPV infections that can lead to cancer. With vaccination at later ages, some cancer cases will already have developed before vaccination. In contrast, screening is considered to be continuous between the ages of 25 and 65 years and can thus detect more cases.

Vaccination strategies

The outcomes resulting from vaccination, with 100% coverage, of cohorts aged 11–13, 14–16 or 15–17 years over a 20-year campaign are presented in Table 2. When considering a lifetime (90 years) horizon, vaccination of the youngest age cohort (11–13 years) prevented a greater number of CIN cases, cancer cases and deaths than vaccination at older ages. However, when shorter time horizons of 20 or 30 years were considered, vaccination of the oldest cohort (age 15–17 years) prevented more CIN cases, cancer cases and deaths than vaccination of the younger cohorts as an intervention in older cohorts will result in earlier positive outcomes (Table 2).

Table 2 Long-term outcomes of three vaccination strategies in cases averted and % reduction compared to the current situation

	Strategy A 11–13 years only (N = 8,510,000)	Strategy B 14–16 years only (N = 8,510,000)	Strategy C 15–17 years only (N = 8,510,000)
CIN2/3			
20 years horizon	63,479 (77%)	74,501 (66%)	73,401 (60%)
30 years horizon	147,135 (77%)	157,931 (71%)	154,266 (66%)
60 years horizon	327,448 (77%)	325,024 (74%)	314,933 (71%)
90 years horizon	380,367 (77%)	366,323 (74%)	352,182 (71%)
Cervical cancer			
20 years horizon	1,323 (85%)	2,053 (71%)	2,197 (63%)
30 years horizon	7,460 (86%)	9,540 (77%)	9,812 (71%)
60 years horizon	45,438 (86%)	46,595 (82%)	45,783 (79%)
90 years horizon	66,701 (86%)	64,979 (83%)	63,019 (81%)
Cervical cancer death			
20 years horizon	174 (85%)	292 (67%)	316 (59%)
30 years horizon	1,340 (86%)	1,797 (76%)	1,869 (70%)
60 years horizon	12,020 (86%)	12,489 (82%)	12,315 (79%)
90 years horizon	20,994 (86%)	20,758 (84%)	20,242 (81%)
Cervical cancer deaths before 60 years			
20 years horizon	174 (85%)	292 (67%)	316 (59%)
30 years horizon	1,340 (86%)	1,797 (76%)	1,869 (70%)
60 years horizon	10,703 (86%)	10,550 (81%)	10,169 (78%)
90 years horizon	11,445 (86%)	10,885 (82%)	10,403 (78%)

CIN cervical intraepithelial neoplastic lesion

Sensitivity analysis

The results of the individual impact analysis after setting cross-protection data to zero are presented in Fig. 3. The exclusion of cross-protection reduces the overall benefit of vaccination. The lifetime CC risk reduction between a combination of vaccination at 11-year old and an every 3-year screening compared to no prevention strategy is reduced to a 23-fold risk reduction or fourfold compared to a woman screened every 3 years without vaccination.

Discussion

The results presented here indicate that early vaccination of girls against cervical cancer with the bivalent HPV vaccine combined with the current French screening programme would substantially reduce the number of CIN and cervical cancer cases compared with screening alone, consistent with the previous published modelling studies (Dasbach et al. 2006).

The individual lifetime risk of cervical cancer was reduced by a factor of 48 (23 when no cross-protection is assumed) when vaccination at age 11 years was combined with screening every 3 years, compared with no screening or vaccination. When compared to a woman screened every 3 years, only adding vaccination at 11 years of age reduces the lifetime risk by a factor of seven (four without cross-protection). Vaccination was beneficial regardless of the age at vaccination and with or without screening, but the greatest benefit was obtained with early vaccination and screening combined. Thus, it would be important to maintain screening even with a routine vaccination programme. These findings are consistent with previously reported cohort-based modelling studies indicating that the greatest benefit is obtained by combining early vaccination (before girls become sexually active) with subsequent organised screening (Goldie et al. 2006; Kulasingam and Myers 2003). Early vaccination (age 11 years) alone reduced the individual lifetime risk of cervical cancer as much as regular screening every at 5 years. This may be especially important in developing countries, where regular screening programmes may be difficult to implement due to resource constraints.

Three vaccination strategies were compared from a public health perspective, vaccination at age 11–13, 14–16 or 15–17 years. When a lifetime horizon (90 years) was considered, the clinical results were best for vaccination at age 11–13 years. However, if shorter and fixed observation periods were considered, such as 20 or 30 years post-vaccination time horizon, the model showed that vaccination age at 15–17 years would prevent more cancer cases and deaths than vaccination at younger ages. This is because the risk of disease is closer for girls vaccinated at the later

age. Some will assume that with lifelong protection provided by the vaccine, a lifelong time horizon should be considered when evaluating its value. Others would prefer to consider the effect of vaccination of different age-groups at fixed points in time. A trade-off must be made between overall maximum risk reduction in the long term, and benefits measured in the short- or medium-term.

The optimal vaccination strategy is likely to vary between countries and public health policies. This study helps to identify the variables that need to be taken into account when analysing alternative vaccination strategies, such as the coverage rate and type of cervical cancer screening or age at vaccination. In addition, the budget impact should also be considered. As information becomes available on long-term vaccine effectiveness and safety beyond the 7.3 years for which the clinical data are currently available (s.n. 2010; De Carvalho et al. 2010), the total management programme for cervical cancer is likely to evolve. Modelling exercises such as the current study will be valuable in defining the combination of vaccination and screening that offers the most efficient overall disease management strategy.

Recent data from the clinical trials suggest that vaccination against cervical cancer continues to be beneficial in inducing serological antibody responses against oncogenic HPV-16 and HPV-18 and thus potentially reducing the risk for cervical cancer even above the age of 25 years (Schwarz et al. 2007). Vaccination strategies focussing on these women could also be considered in the near future. Additional research is needed to confirm those findings and to identify subgroups which may benefit most.

The National French Technical Committee for Vaccination has provided guidelines on vaccination against cervical cancer. Such guidelines recommend vaccination of all girls at the age of 14 years with catch-up to the age of 23 years for girls and women who had no sexual activity or, later, in the year following the beginning of their sexual life. This decision was based on the closeness to risk of infection as discussed above, and on the potential benefit/risk ratio of vaccinating sexually active girls in the context of a recommended medical contact for teenagers at the beginning of their sexual lives. However, other countries have adopted a different starting age of vaccination, most of them selecting a younger age (Crosbie and Kitchener 2007; Markowitz et al. 2007; s.n. 2007; Saslow et al. 2007), which will lead to the largest reduction in disease burden over the long term. In addition to the expected disease burden reduction, practical or logistical reasons such as the presence of school-based information programmes on sexually transmissible diseases and contraception may also influence the decision on vaccination age.

The present model was designed to be as succinct as possible and to use information easily accessible in France or in many other countries without needing additional studies or specific data research. Compared with some other more parameter-rich models already published on the subject, the model is simple and straightforward. This makes it ideal for countries that have no access to detailed data or that are limited in the amount of specific data available on screening and HPV testing. This model can therefore evaluate the possible impact of vaccination even in countries with limited input data available. However, it is possible that the lack of detail may underestimate the true benefit of vaccination. For example, the model does not include dynamic HPV transmission and therefore underestimates the benefit of herd protection expected provided by vaccination (Dasbach et al. 2006). On the other hand, potential effect on viral ecology is also not taken into account. The model also cannot assign cases to specific HPV types or assess the effect of HPV DNA testing as a screening method. On the other hand, the model assumes a lifetime protection of vaccination. This can be obtained with a vaccine with a real lifetime protection, or with the administration of a booster if needed. Data are, however, still lacking for the long-term vaccine efficacy. The analysis does not apply if a booster dose is needed and only a proportion of the vaccines received the booster. In this case, the public health effect would be reduced. We also assume 100% vaccine coverage of the cohort. A lower coverage rate could be expected in all age groups, but even more in older ones which would also result in a lower reduction in the HPV burden than estimated. A coverage lower than 100% would result in a proportional reduction in cancer cases prevented. Nevertheless, the results show some interesting baseline features on which the future assessments can be built for evaluating vaccination strategies in France. Similar results can be expected in countries with HPV epidemiology, screening and disease management similar to that observed in France.

In conclusion, this modelling study evaluating the public health benefit of vaccination against cervical cancer illustrates the benefit of adding vaccination to screening. The results suggest that the optimum starting age for vaccination may vary depending on the time perspective chosen, with a lifetime horizon favouring early vaccination and a shorter horizon (20 or 30 years) favouring later vaccination.

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Conflict of interest Nadia Demarteau, Denis Granados, Abdelkader El Hasnaoui and Baudouin Standaert are employees of

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