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Projected impact of *Cervarix*™ vaccination on oncogenic human papillomavirus infection and cervical cancer in the United Kingdom

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Abbreviations: CC, Cervical cancer; CIN2+, High-grade cervical intraepithelial neoplasia; HPV, Human papillomavirus; UMV, Universal mass vaccination

We developed a dynamic compartmental model to assess the impact of HPV Universal Mass Vaccination (UMV) with *Cervarix*™, which offers protection against HPV16/18 and cross-protection against other cancer-causing types, using up-to-date efficacy data. Analyses were performed in the UK because of the large amount of high quality epidemiological data available. For each HPV type/group of types considered, the model was calibrated to 14 epidemiological datasets (prevalence of HPV infection, cervical intraepithelial neoplasia (CIN): CIN1, CIN2, CIN3 pre-screening and cervical cancer (CC) incidence over 10 y post-screening). Impacts of cross-protection, female catch-up vaccination, and additional male vaccination on oncogenic infections, high-grade CIN (CIN2+) and CC were evaluated. Our results show that female UMV with 80% coverage and cross-protection against high-risk types resulted in 81% CIN2+ and 88% CC reductions vs. 57% and 75%, respectively, without cross-protection. Vaccinating 40% of males and 80% of females was equivalent to 90% female-only coverage regarding CIN2+ (87% and 87%, respectively) and CC (93% and 94%, respectively) reductions. Female-only coverage of 80% substantially reduced male HPV16 and 18 infection due to herd protection (74% and 89%, respectively). Increasing female coverage to 90% reduced HPV16 and HPV18 infections in males relatively similarly to 80% female combined with 40% male coverage. Model outcomes strengthen previous conclusions about the significant added value of *Cervarix*™ cross-protection for CC prevention, the primary HPV vaccination public health priority. Regarding female CC prevention and male HPV16/18 infection, small increases in female coverage induce similar benefits to those achieved by additionally vaccinating men with 40% coverage.

Introduction

Human papillomavirus (HPV) is a necessary cause of cervical cancer (CC),[1] the second most common cancer among women worldwide. More than 500,000 cases and 250,000 deaths occur annually,[2] with HPV16/18 accounting for >70% of CC.[3]

HPV vaccines, *Cervarix*™ and *Gardasil*™, provide 99% protection against HPV16/18-associated high-grade cervical intraepithelial neoplasia (CIN2+).[4-6] *Cervarix*™ provides significant cross-protection against CIN2+ associated with HPV31 (89.4%), HPV33 (82.3%) and HPV45 (100%),[7] the next most common cancer-causing types.[3] The United Kingdom (UK) introduced school-based universal mass vaccination (UMV) with *Cervarix*™ in 2008, achieving 84% coverage (complete 3-dose schedule) in 12–13 y-old girls and 47% coverage in catch-up cohorts of 17–18 y-old girls.[8] Starting in September 2012, UMV of 12–13 y-old girls was implemented using *Gardasil*™.

Mathematical models are important tools to assess the population-level impact of vaccination on disease.[9] To account for infection dynamics and evaluate herd protection, a dynamic modeling approach is necessary. Few HPV models with vaccination published thus far are dynamic.[9] The 2 dynamic models projecting long-term population-level impact of UMV[10,11] and possible benefits of male HPV vaccination in the UK[10] either accounted for cross-protection using pooled estimates for efficacy against all non-16/18 oncogenic types (although not as base-case)[10] or did not account for cross protection.[11] We present a calibrated dynamic transmission model assessing the

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potential population-level impact of UMV with *Cervarix*™ on incidence of oncogenic HPV infections in men and women, CIN2+ and CC in the UK, accounting for cross-protective effects of vaccination using individual efficacy estimates for HPV31/33/45 and the 9 other oncogenic (35/39/51/52/56/58/59/66/68) types pooled.

Results

Model calibration

Figure 1 shows the best model fit vs. age-specific prevalence data[12,13] for HPV16. **Figure 2** shows the best model fit vs. data for HPV16 for age-specific incidence of CC from 1997–2006.[13,14] Values of the sets of best fit HPV type-specific parameters indicate higher transmissibility for HPV16 than HPV18 and faster clearance of infections caused by HPV18 than HPV16 (**Table S1**).

Vaccine scenarios

Under the base-case scenario of 80% female vaccination coverage, the model predicted 81% (range 70–87% using 95% lower and upper confidence limits for vaccine efficacy against HPV16/18/31/33/45 and the 9 oncogenic types pooled) reduction in CIN2+ incidence and 88% (range 80–92%) reduction in CC incidence due to all oncogenic HPV types considered by the time steady state was reached (**Fig. 3**, **Table 1**). Cross-protection

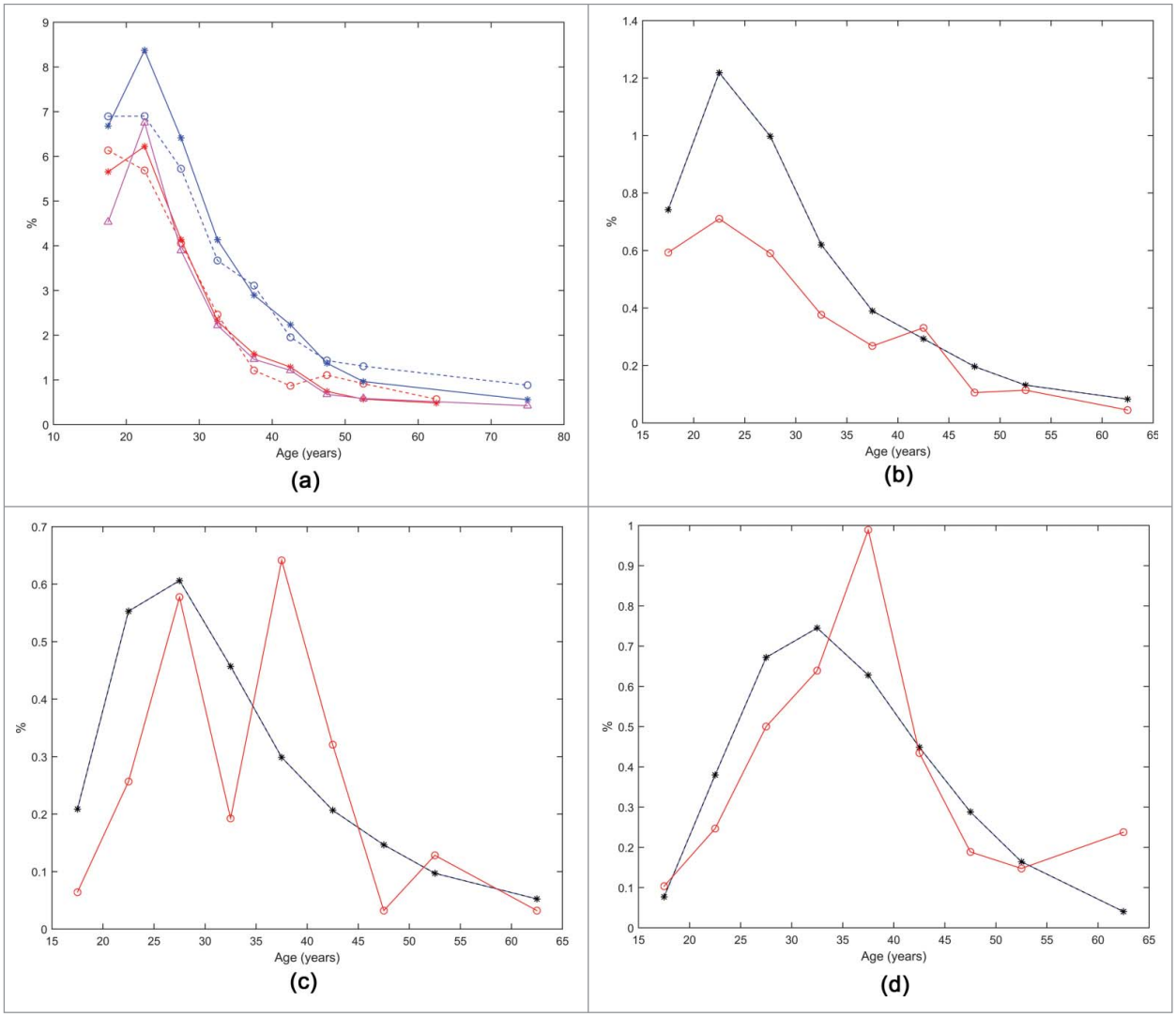

Figure 1. Calibration – model projections vs. observed for HPV16 – prevalence at steady state prior to screening. (**A**) Prevalence of HPV infection. Red circles: HPV infection normal in females observed; Red stars: HPV infection normal in females model; Blue circles: all HPV infection in females observed; Blue stars: all HPV infection in females model (i.e., both with normal and with abnormal cytology; Magenta triangles: all HPV infection in males model). (**B**) Prevalence of CIN1 (Red: observed; Black: model-projected). (**C**) Prevalence of CIN2 (Red: observed; Black: model-projected). (**D**) Prevalence of CIN3 (Red: observed; Black: model-projected). The age values for the points on all **Figure 1** plots correspond to the midpoint of the corresponding age intervals, with the exception of the last point which corresponds to the age group of 55 y and older. Those age intervals here are: 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, and 55+ y.

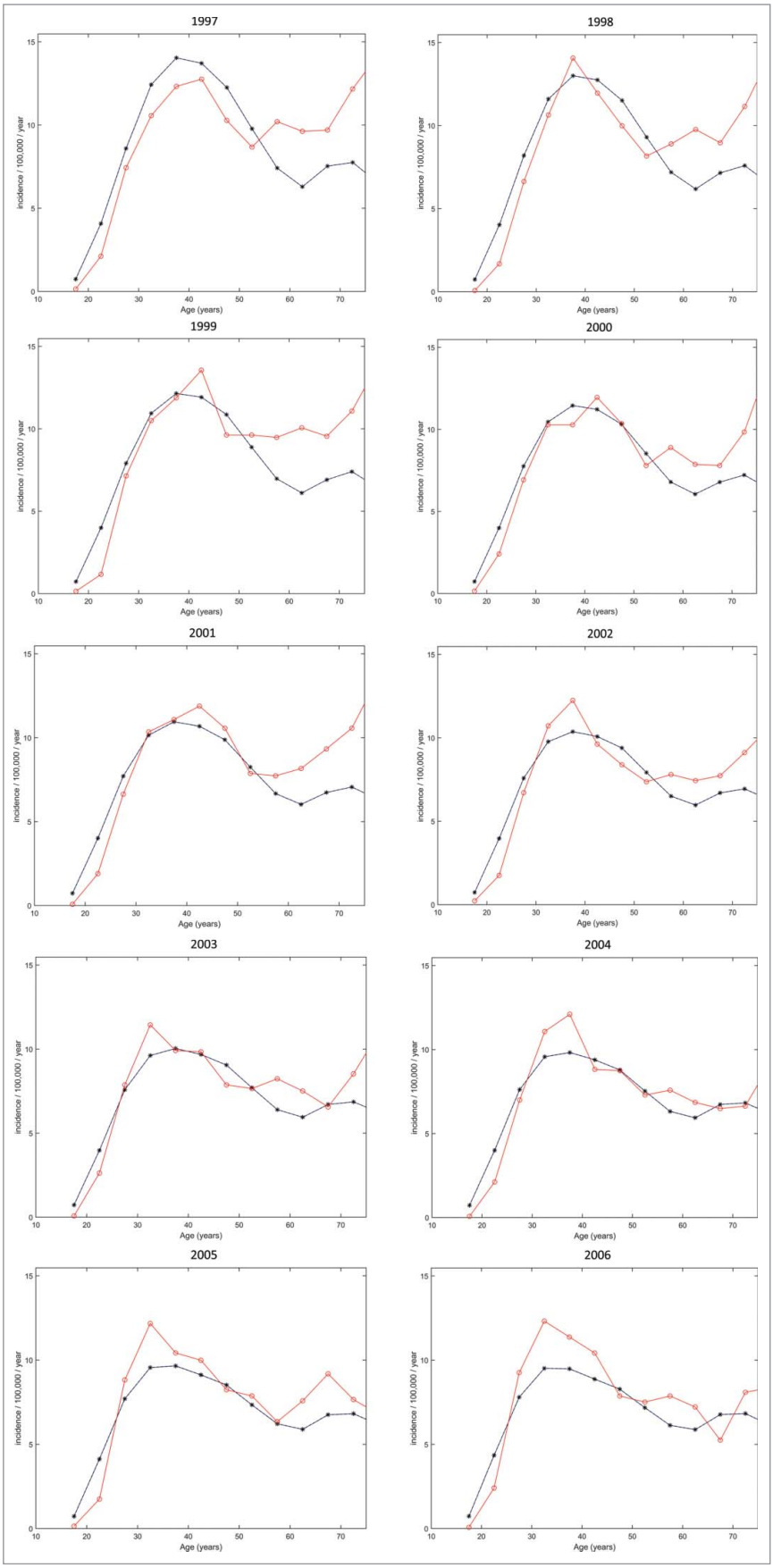

Figure 2. Calibration – model projections vs. observed for CC incidence associated with HPV16 over time, with screening. Red: observed; Black: model-projected. The age values for the points on all **Figure 2** plots correspond to the midpoint of the corresponding age intervals. Those age intervals here are: 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70–74 y.

contributed to a significant proportion of the HPV vaccination impact such that if vaccine effects were limited to HPV16/18, the reduction in CIN2+ and CC incidence was estimated at 57% (range 54–58% using 95% lower and upper confidence limits for vaccine efficacy against HPV16/18) and 75% (range 71–77%), respectively. The contribution of cross-protection remained substantial when assumed duration of cross-protection was reduced from lifelong to 20 y for non-16/18 types (overall impact 72–77% for CIN2+ and 83–84% for CC, depending on how waning of vaccine protection was modeled) (**Table S2**). An evaluation of vaccine-induced herd protection was made by comparing the 90% (respectively 96%) reduction in HPV16 (respectively HPV18) CIN2+ incidence at post-vaccination steady-state (**Table 1**) projected by the dynamic model for the base-case vs. an estimated 79.2% reduction accounting for direct effects only. The 79.2% reduction based on direct effects only was simply derived from the assumed base-case coverage (80%) and the 99% efficacy against CIN2+ for HPV16 and HPV18 (**Table 2**): 80% × 99% = 79.2%. The differences in reductions whether one accounts for the indirect effects of vaccination or not therefore indicated an additional relative 14% for HPV16, and 21% for HPV18, respectively reduction induced by herd protection.

When considering female vaccination coverage ranging from 70–100%, the overall impact of vaccination once estimated at steady-state ranged from 74–91% for CIN2+ and 80–97% for CC, respectively (**Fig. 4**; **Table S2**). Impact of vaccination on CIN2+ and CC was stronger on HPV18 than HPV16 (e.g., 96% vs. 90% reduction for CIN2+ and 96% vs. 90% for CC at 80% coverage), except at 100% coverage where both HPV types were projected to be virtually eliminated (**Table S2**).

Catch-up vaccination scenarios were also considered, assuming 50% coverage for 2 consecutive years in 16–18, 16–25, and 16–35 y-

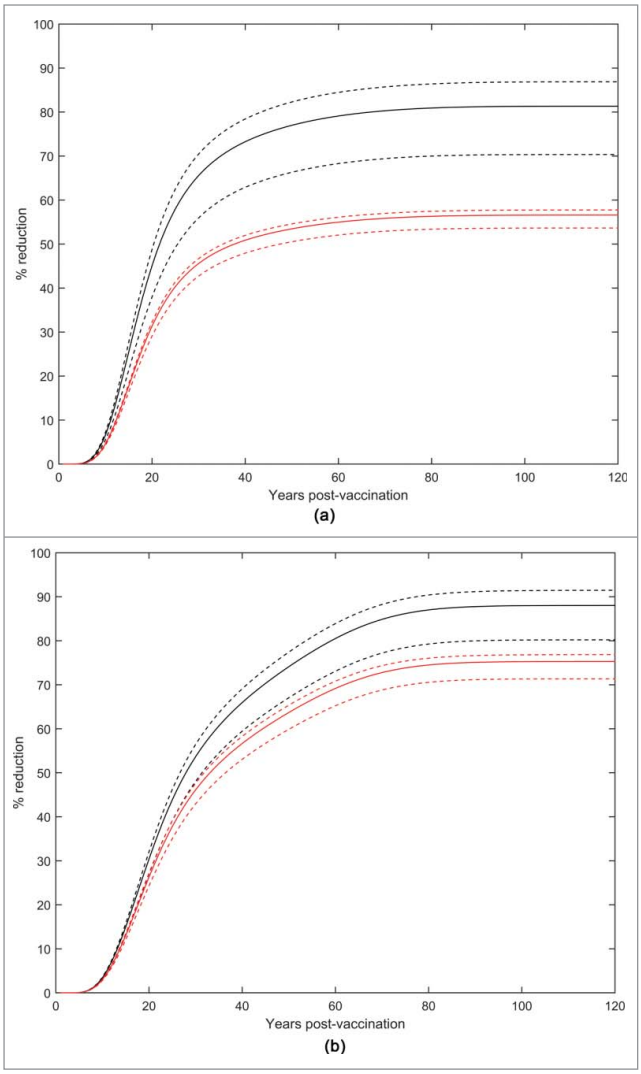

Figure 3. Impact of vaccination with cross-protection observed for *Cervarix*™ vs. no cross-protection. Black: *Cervarix*™ with observed cross-protection for HPV31/33/45 and further 9 oncogenic types pooled (--- using 95% lower limit (LL) and upper limit (UL) estimates for the efficacy of *Cervarix*™, respectively); Red: without cross-protection for HPV31/33/45 and further 9 oncogenic types pooled (--- using 95% LL and UL for the efficacy of *Cervarix*™ for HPV16 and HPV18, **Table 2**). The plot shows the pooled outcome across all the oncogenic HPV types considered in the model. (**A**) Percent reduction in CIN2+ incidence. (**B**) Percent reduction in CC incidence.

olds (**Fig. 5**). The time-period until a substantial population-level reduction in the outcomes was reached was reduced for catch-up programs targeting wider age ranges. As an illustration, the model predicted 50% population-level reductions in CIN2+ could be achieved after 20, 17 and 16 y, respectively, vs. after 22 y without catch-up; 50% population-level reduction in CC could be achieved after 27, 23 and 20 y, respectively, vs. after 28 y without catch-up.

Among women, provided that 80% vaccine coverage was maintained, the addition of male vaccination resulted in reductions in CIN2+ increasing from 81% to 84% with 20% male coverage and to 91% with 80% male coverage; reduction in CC increasing from 88% to 91% with 20% male coverage and to 97% with 80% male coverage (**Fig. 6**; **Table S2**). Reductions achieved through addition of male vaccination at 40% coverage (87% for CIN2+ and 93% for CC) were approximately equivalent to increasing female-only vaccination coverage from 80% to 90% (87% for CIN2+ and 94% for CC). If male coverage was increased to 40% but female coverage decreased to 70%, the overall reductions achieved were about the same as those for 80% female-only coverage (82% for CIN2+ and 89% for CC).

HPV16/HPV18 infections in males were predicted to decrease by 74% and 89%, respectively, at 80% female-only coverage, increasing to 87% and 100%, respectively, at 90% female coverage (**Fig. 7A, C**). Vaccinating 20–80% of males while maintaining 80% female coverage was predicted to result in decreases in male HPV16/HPV18 infection of 83% to 100% and 97% to 100%, respectively (**Table S2**). Thus, compared with 90% female-only coverage, 80% female coverage plus 40% male coverage resulted in about a 4% further absolute decrease in male HPV16 infection (91%) and no difference in male HPV18 infection (100%) (**Fig. 7B, D**). If female vaccination coverage decreased to 70%, then male vaccination would have to achieve between 40% and 60% coverage to obtain the same population-level impact on HPV16 and HPV18 infections in men as 90% female-only coverage (**Table S2**).

Discussion

Using assumptions based on published data, we developed a dynamic model to evaluate the population-level impact of vaccination with *Cervarix*™ based on the most recent efficacy data available for this vaccine, including against cross-protective HPV types.[6,7] The model was based on UK data because the large amount of high quality epidemiological data available in the UK allowed for the simultaneous calibration of the model to 14 different (age-stratified) data sets in order to estimate the type-specific model parameters in a more robust way.

Our model reproduced well the observed epidemiological HPV data in the UK[12-14] and allowed us to further assess the population-level impact of various vaccination strategies, including UMV scenarios, vaccination of both men and women, and use of an HPV vaccine with significant cross-protection against high-risk types.

Model projections indicated that female UMV with 80% vaccination coverage with cross-protection against high risk HPV31/33/45 and the 9 other oncogenic types pooled can result in notably higher reductions in HPV-related cervical disease, vs. no cross-protection: 81% vs. 57% for CIN2+ and 88% vs. 75% for CC. The model also projected that catch-up programs can increase the speed at which disease reductions can be achieved. For both CC and precancerous lesions, the greatest impact of catch-up vaccination on reducing incidence during the first decades post-vaccination (see **Fig. 5**) was with catch-up vaccination among women aged 16–35 y, illustrating potential effects of catch-up programs with wider age groups. The impact of the

Table 1. Percentage reduction in the incidence of HPV-associated disease outcomes based on model projections for the base-case of 80% UMV coverage in females, no vaccination in males and no catch-up vaccination

		Percentage reduction in incidence			
HPV Type	**Time post-vaccination (years)**	**HPV infection in women**	**HPV infection in men**	**CIN2+**	**CC**
16	25	72.7	52.9	63.9	44.3
18	25	78.1	62.7	70.6	52.7
All*	25	35.7	28.6	58.0	43.9
16	50	84.3	67.4	85.4	76.0
18	50	89.8	79.5	90.1	83.0
All*	50	41.5	35.9	77.0	74.1
16	120	88.2	73.9	90.3	90.4
18	120	95.0	89.4	96.1	95.9
All*	120	43.8	39.5	81.3	88.0

Note: assuming point estimates for vaccine efficacies and lifelong vaccine protection.
All*: all oncogenic HPV types considered in the model.

catch-up program is most apparent in the first 40 y post-vaccination.

The projections for vaccination programs among males and females vs. females only are particularly noteworthy. For CC reduction, increasing female coverage from 80% to 90% is approximately equivalent to 80% female plus 40% male coverage. The model projects that 80% female UMV coverage induces reductions of HPV16 and HPV18 infections in men by 74% and 89% respectively, by herd protection. Since anal and penile cancers in men are primarily caused by HPV16/18,[15,16] this suggests that female UMV with high coverage can confer substantial benefits to men, although our model is somewhat limited by only taking into account heterosexual contacts. A relatively low coverage in males coupled with reduced coverage in females (for example 60% in females and 20% in males, see **Table S2**) may potentially lead to higher risk of CC. Greater impact of herd protection on CIN2+ for HPV18 vs. HPV16 in our model is likely due to higher HPV16 transmissibility and faster HPV18 clearance (as estimated by model calibration). The fact that the mean duration of infection estimated from the model is shorter for HPV18 than for HPV16 is consistent with estimates of those durations noted by Trottier et al.[17]

A major strength of this analysis is that for each HPV type or group of types considered, the model was simultaneously calibrated to 14 (age-stratified) epidemiological datasets using a complex optimization scheme. This is a novelty of the current model as compared to prior dynamic models of HPV in the UK that either used estimates from the literature for the model parameters[11] or selected those sets of parameters for which the outcomes were the closest to the data observed among a great amount of scenarios covering different combinations of assumptions.[10] The model reproduces data well, providing a good basis for further projections. Divergence after age 70 likely reflects more uncertainty in older age groups, for example, the model assumes constant sexual behavior over time, which may be less accurate for older age groups. Another novelty of the model is the use of the most recent type-specific efficacy data available for *Cervarix*™ against infection and against CIN2+, while prior models either didn't account for cross-protection[11] or only used an estimate for all cross-protective types pooled.[10]

Our model has limitations. As data accounting simultaneously for age and HPV type are sparse, we assumed the same HPV age distributions for each type. Due to uncertainty about progression and regression rates, point-values for these parameters need to be estimated by calibration. For evaluation of catch-up vaccination, we assumed the same vaccine efficacy in older women, however, it might be lower than in younger women due to past HPV

Table 2. *Cervarix*™ vaccine efficacy values used in the model[6,7]

	Efficacy against HPV infection**			Efficacy against CIN2+		
	Point estimate	**Lower limit*** **	**Upper limit*** **	**Point Estimate**	**Lower limit*** **	**Upper limit*** **
HPV16	94.7%	91.8%	96.7%	99.0%	94.2%	100%
HPV18	92.3%	86.5%	96%	99%	94.2%	100%
HPV31	77.1%	67.2%	84.4%	89.4%	65.5%	97.9%
HPV33	43.1%	19.3%	60.2%	82.3%	53.4%	94.7%
HPV45	79.0%	61.3%	89.4%	100%	41.7%	100%
9 HPV types pooled*	12.8%	4.4%	20.6%	51.6%	27.8%	68.1%

All efficacy values from analyses in the total vaccinated HPV-naive cohort; *HPV35/39/51/52/56/58/59/66/68 pooled: previously unpublished efficacy data originates from the PATRICIA study in the total vaccinated HPV-naive cohort; **6 months persistent infection; ***95% lower and upper confidence limits.

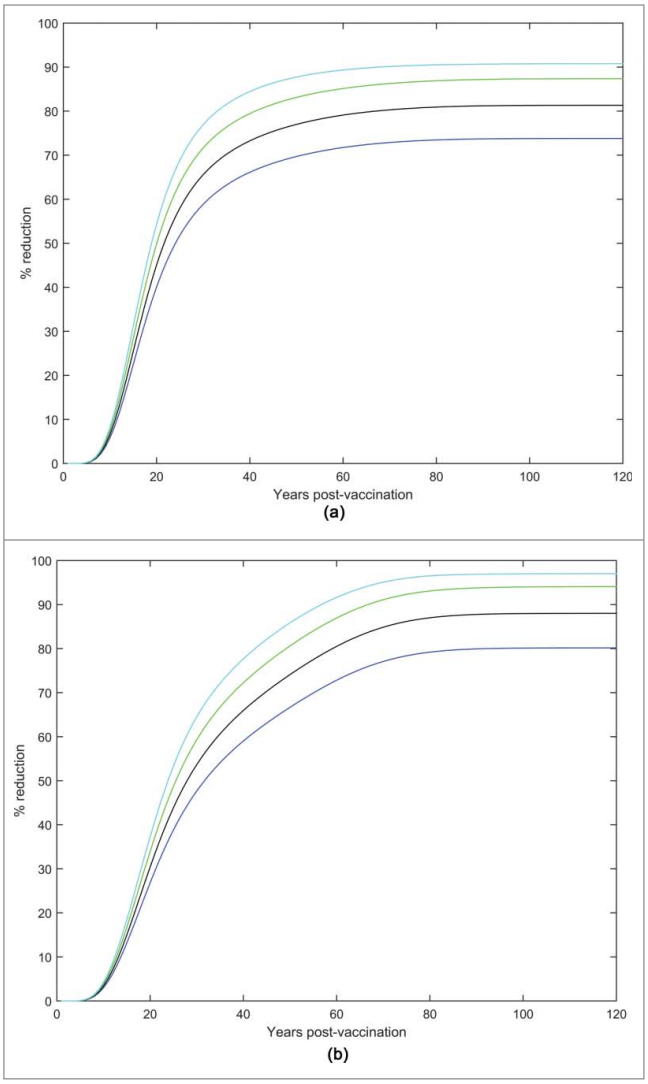

Figure 4. Impact of vaccination with varying UMV coverage. Blue: 70%; Black: 80% (base-case); Green: 90%; Cyan: 100%. The plot shows the pooled outcome across all the oncogenic HPV types considered in the model. (**A**) Percent reduction in CIN2+ incidence. (**B**) Percent reduction in CC incidence.

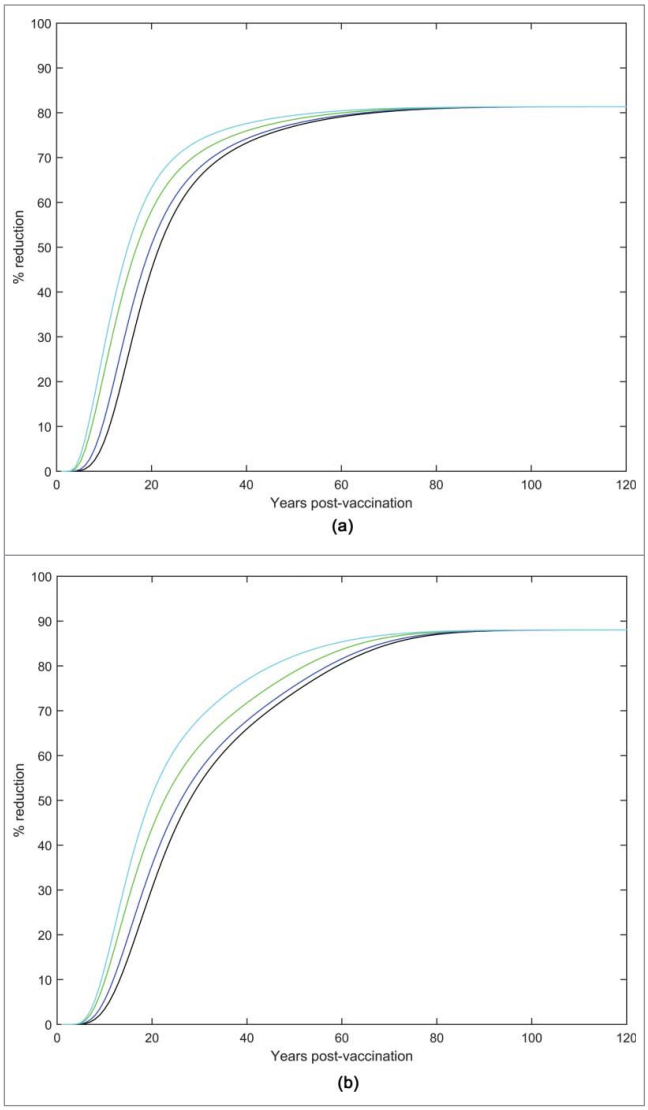

Figure 5. Impact of catch-up vaccination. Black: UMV 80% coverage and no catch-up (base-case); Blue: UMV 80% coverage and catch-up 50% coverage in 16–18 y-old; Green: UMV 80% coverage and catch-up 50% coverage in 16–25 y-old; Cyan: UMV 80% coverage and catch-up 50% 16–35 y-old. The plot shows the pooled outcome across all the oncogenic HPV types considered in the model. (**A**) Percent reduction in CIN2+ incidence. (**B**) Percent reduction in CC incidence.

exposure. In the absence of *Cervarix*™ efficacy data in males, we assumed similar vaccine efficacies as in females. The model considers only heterosexual contacts, and may therefore to some extent over-estimate the magnitude of the herd protection in men induced by female vaccination by not accounting for HPV transmission between men who only have sex with men. Another limitation is uncertainty about efficacy for HPV31/33/45 and the 9 other oncogenic types pooled, addressed through sensitivity analyses. We assessed outcome sensitivity to duration of vaccine protection for HPV31/33/45 and the 9 other oncogenic types pooled, while assuming lifelong protection for HPV16/18, as supported by sustained efficacy for 6.4 y[18] and high HPV16/18 antibody titers for 9.4 y without signs of waning.[19] Modeling of antibody titer data, using the modified power-law and piece-wise models, predicts that HPV16 and HPV18 antibody titers will be sustained well above natural infection levels for at least 20 y post-vaccination.[19,20] Assuming 20-y rather than lifelong protection for the cross-protective types had little impact on the model projection. Finally, this model focused specifically on vaccination impact on CC and pre-cancerous lesions and oncogenic HPV infections, and did not evaluate non-cervical HPV-related cancers.

Most evaluations of HPV vaccination impact have used static approaches.[9,21] More complex and data-demanding dynamic models are needed to account for the full vaccination impact, including herd protection, and to quantify gender-specific

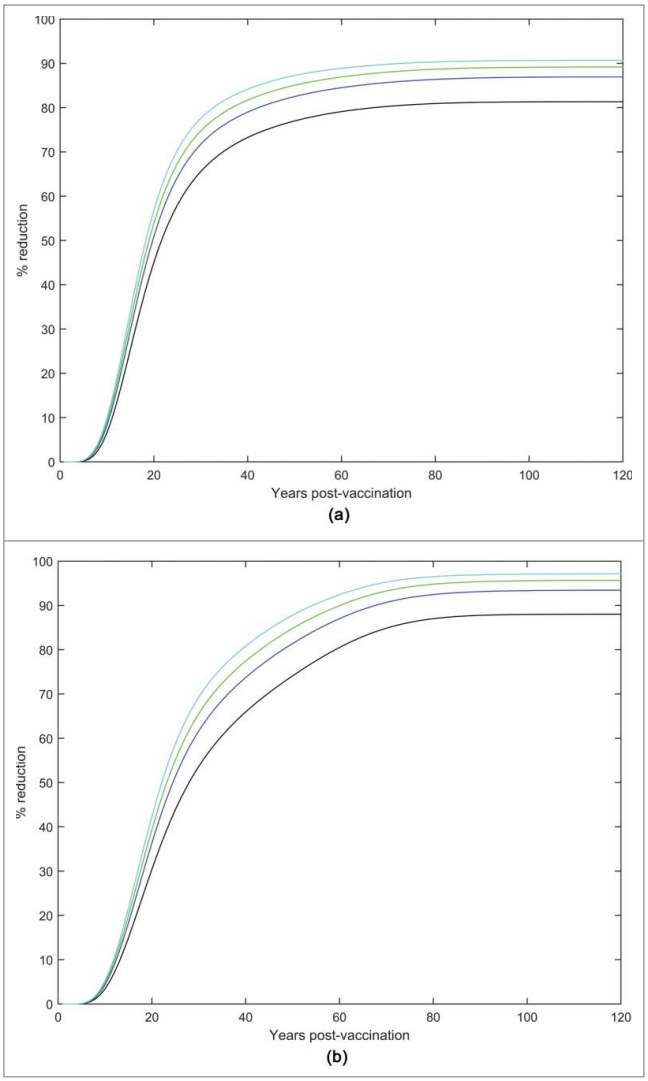

Figure 6. Impact of vaccinating males and females on CIN2+ and CC. Female vaccination with 80% coverage and varying levels of male vaccination coverage. Black: base-case (no male vaccination); Blue: 40% coverage in males; Green: 60% coverage in males; Cyan: 80% coverage in males. The plot shows the pooled outcome across all the oncogenic HPV types considered in the model. (**A**) Percent reduction in CIN2+ incidence. (**B**) Percent reduction in CC incidence.

reductions in outcomes. Two dynamic compartmental deterministic models have projected the HPV vaccination impact in the UK in addition to screening.[10,11] The models differ in HPV types considered and type groupings. Only ours models individually both vaccine- and non-vaccine oncogenic types (HPV16/18/31/33/45 and 9 further oncogenic types pooled), allowing the model to account for the most recent type-specific *Cervarix*™ efficacy data. The models also differ in how disease progression, clearance and natural immunity parameters were estimated. Dasbach et al.[11] and Elbasha et al.[22] modeled these parameters based on values from the literature; Choi et al. considered numerous parameter combinations and retained only those for which model-projected age-dependent HPV prevalence and CC incidence were close to the data.[10] We projected vaccination impact using the parameters for which the model outcomes simultaneously best fit various age- and type-specific epidemiological data. Type-specific parameters were estimated by solving a complex optimization problem with parameters constrained by natural history data.[23,24]

Our model estimated a relatively short mean duration of natural immunity (0.9 y) following HPV16/18 infection while Dasbach et al. estimated 10 y to lifelong.[11] Choi et al. evaluated different values from no to full natural immunity and obtained better model fits when assuming <3 y duration.[10] Approximately 50–70% of women develop antibodies after natural infection with HPV16 or HPV18.[25-27] However, what level of naturally-acquired antibody provides protection remains uncertain, with studies so far producing unclear and conflicting results.[28-32] It is not implausible that naturally-acquired antibodies may offer only short-term protection as estimated in our model. Given the uncertainty about natural immunity, we have modeled it in a simple way, assuming that all individuals have a temporary immunity against type-specific infection after clearing an HPV infection without having progressed (flowing in the model from the state "HPV infection (normal)" to the state "Immune temporary"). The mean duration of natural immunity estimated in the model should therefore be interpreted as a mean across all individuals, although some individuals may experience longer duration of natural immunity than others.

CC model projections for UMV 60 y after introduction of vaccination and considering CIN2/3 excluding CC at steady state were produced for comparison with published projections. Our model projects an extra 16% reduction in CC by cross-protection 60 y post-vaccination, using *Cervarix*™ efficacy data for HPV31/33/45 and the 9 other oncogenic types pooled, which is higher than the 5–10% projected by Choi et al.[10] assuming 27% efficacy for all oncogenic non-vaccine types pooled. This high level of cross-protection for CC is reflected in *Cervarix*™ clinical trial data showing 93% efficacy against CIN3+ irrespective of HPV type.[6] Our model projects reductions of 91% for HPV16/18 (pooled) CIN2/3 and 91% for CC incidence at steady-state, relatively close to the 85% and 86% reductions, respectively, projected by Dasbach et al.[11] We also illustrate the additional benefit induced by herd protection in males, by vaccinating only females.

In conclusion, this dynamic compartmental model provides important insight into potential effects of HPV vaccination programs on burden of oncogenic HPV infection and CC in the UK. By accounting for individual protective effects of *Cervarix*™ against HPV16/18, the 3 next most common cancer-causing types (HPV31/33/45) and 9 other oncogenic types pooled, the model projections substantially strengthen conclusions from previous models about the important added value of cross-protection for CC prevention. Regarding prevention of CC and HPV16/18 infection in males, increasing female coverage from 80% to 90% results in similar benefits to those achieved by 40% coverage in men, without risking decreased female vaccination coverage, which could potentially threaten CC prevention, which remains the public health priority of HPV vaccination

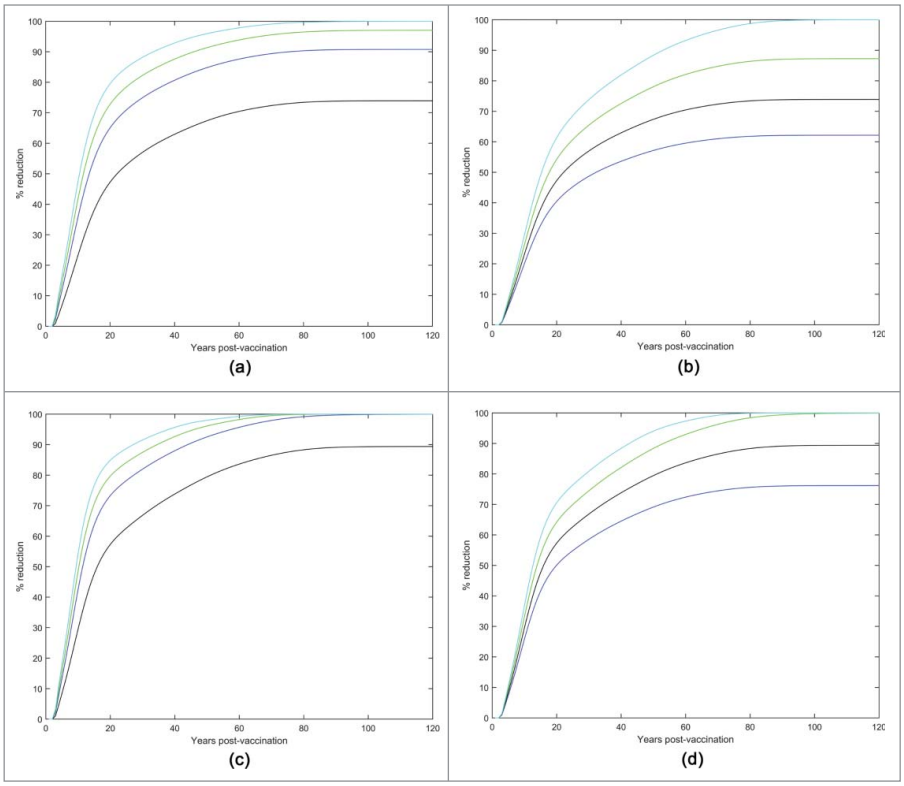

Figure 7. Impact of vaccinating males and females vs. higher UMV coverage in females on HPV16 and HPV18 infection in males. (**A**) and (**C**) Higher coverage in females, no male vaccination: Coverage in females: Blue: 70%; Black: 80% (base-case); Green: 90%; Cyan: 100%. (**B**) and (**D**) Female and male vaccination: Coverage 80% female UMV and Black: 0% in males (base-case); Blue: 40% in males; Green: 60% in males; Cyan: 80% in males. (**A**) and (**B**) Percent reduction in HPV16 infection in males; (**C**) and (**D**) Percent reduction in HPV18 infection in males.

programs. The model was employed here in the UK setting based on epidemiological data availability. However, this framework could be used to evaluate the impact of *Cervarix*™ in other countries where appropriate epidemiological data for HPV is available.

Materials and Methods

A deterministic compartmental model of HPV transmission in females and males was developed. The model is mechanistic, accounting for HPV natural history, transmission within the population, and type-specific characteristics. It is also dynamic, with risk of infection in susceptible individuals, i.e., the *force of infection* (specific to HPV type, gender, age and sexual activity), changing over time with prevalence.

Two dynamic models of HPV in the UK have already been developed in the past.[10,11] However, those models either had a rather complex structure (number of compartments and flows) and used estimates from the literature for the model parameters,[11,22] or involved a very large amount of computations to estimate those combinations of parameters that best fit the epidemiological data, using a large number of scenarios.[10] Our approach aimed at achieving a good balance between realism and complexity, with a model whose structure captures the key aspects of HPV natural history and the impact of screening and vaccination, while at the same time keeping enough tractability to estimate the parameters for each single HPV type or group of types modeled. This approach allowed us to calibrate the model for each single type or group of types modeled to multiple (14) epidemiological data sets. The model was calibrated not only to prevalence data prior to screening, but also simultaneously to incidence rates of cervical cancer with screening year-by-year over a period of 10 consecutive years, which has not been done in the UK thus far. The model also used type-specific efficacies against HPV infection and against CIN2+ from the most recent *Cervarix*™ clinical studies, while Dasbach et al.[11] did not assume any cross-protection and Choi et al.[10] used a pooled estimate of efficacy for cross-protective types (although not for the base-case).

Our model also explicitly models 2 types of efficacies, against infection and against CIN2+ if infected based on *Cervarix*™ type-specific efficacies against those 2 outcomes. While the model by Dasbach et al.[11] assumed 2 different efficacies against infection and against CIN2+, the model by Choi et al.[10] assumed 100% efficacy against vaccine-type HPV infection.

The model is stratified by gender, age and sexual activity. There are 80 one-year demographic groups and 8 larger age groups for sexual contacts (15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–64 and 65–94 y). Regarding demography, we assumed a steady-state age pyramid. The steady-state age distribution was obtained using age-specific death rates in the UK,[33] and model-derived growth rate of 0.28%.[34]

Sexual activity is stratified by mean number of new sexual partnerships annually (0, 1, 2, 3–4 and 5+).[35] In the model, the mean number of new sexual partners per year is both gender- and age-specific,[35] and the model stratifies the population both by age group and by mean number of new sexual partners according to the gender- and age-group specific distribution of the mean number of new sexual partners from the NATSAL study.[35] For sexual contacts, mixing is assumed to be a linear combination of assortative and random mixing for age and sexual activity of partners, with a proportion ε_{age} (respectively ε_{sexact}) of contacts with proportionate mixing with respect to age (respectively sexual activity) and the remaining proportion with assortative mixing.

The model was calibrated for HPV-16 for different combinations of values of ε_{age} and ε_{sexact} in a plausible range supported by the available literature. We further selected the one giving the best fit across all data sets, with $\varepsilon_{age} = 0.5$ and $\varepsilon_{sexact} = 0.5$ (as evaluated with the sum of squares), for the calibration of all HPV types/groups of types and the projection of the outcomes. The populations of each gender, age group and sexual activity group are subdivided into mutually exclusive disease states: Susceptible, HPV-infected (normal), Temporarily protected against new HPV infection by the same HPV type, CIN1, CIN2, CIN3, CC or CC-cured, and Vaccination status. Individuals flow through states according to the *force of infection* and estimated clearance rates, waning of natural immunity, and cervical disease progression/regression. In the model, individuals who are in given infection/disease state remain in the same sexual activity class as long as they remain in the same sexual activity age group (e.g., one of the 8 age groups related to mixing). However, every time individuals flow (by aging) from one of those 8 mixing age groups to the next mixing age group, they are redistributed to the compartments of the different sexual activity sub-groups of the same disease/infection state according to distribution of those sub-groups in this new mixing age group.

The model compartments for non-vaccinated females and the flows between those compartments are represented in **Figure 8**. In males, there are only 3 of those compartments in the model (Susceptible, HPV Infection (normal), and Immune (temporary)), with their related flows. There are similar specific compartments and flows for vaccinated individuals in the model. Regarding clearance from CIN states, we assume that 50% who clear a CIN go back to the HPV Infection state while the remaining 50% go back to the Susceptible state.

In the absence of evidence of interactions between infections with different types, each of the 5 following HPV types were modeled individually (16/18/31/33/45) as they are the most common cancer-causing types in the UK. Nine other oncogenic types (35/39/51/52/56/58/59/66/68) for which *Cervarix*™ has shown some cross-protection as well were modeled pooled and estimates of the pooled *Cervarix*™ efficacies against HPV infection and CIN2+ were used for those 9 types. In order to model the 9 other oncogenic types (35/39/51/52/56/58/59/66/68) pooled without artificially having a pooled type, we calibrated the model with a single set of natural history parameters vs. the mean observed data across all 9 types. The pooled efficacy for the 9 types pooled (**Table 2**) was used to project the impact of vaccination, then the 9 corresponding outcomes were summed up in the outcomes shown. Overall, all the HPV types considered in the model account for 100% of cervical cancer in the UK prior to vaccination.[13] All the other oncogenic types were not considered in the model.

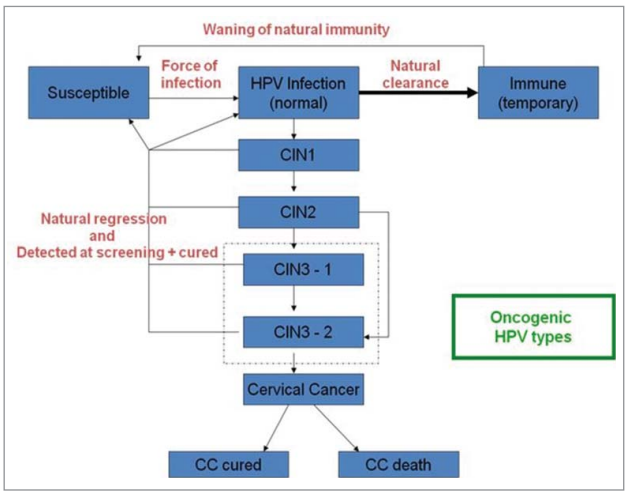

Figure 8. Disease states and flows (HPV type specific) in females for the different oncogenic types considered in the model, either individually or pooled.

Table S3 shows the HPV prevalence in women with normal cytology, low-grade lesions, high-grade lesions and cervical cancer by type[13] that are either modeled individually (HPV16/18/31/33/45) or modeled pooled (9 types pooled) or not modeled (all low-risk types). Only those types for which samples were tested and data reported in the 2007 WHO report[13] are included, as specified in the table footnotes. HPV6/11 were detected in 7.3% of low grade-lesions and 0.4% of high-grade lesions. Based on testing of only 94 high-grade lesions, other low-risk types were detected in 11.7% of high-grade lesions due primarily to HPV73 (prevalence 10.6%). More recent data based on testing of 2,132 high-grade lesions showed 2.2% HPV73 prevalence among high-grade lesions.[36]

The HPV type distributions across all age groups are used,[13] and the same age-specific distributions are used for each type or group of types considered. CC screening and treatment are accounted for by adjusting natural regression rates from the 3 CIN states accordingly, based on time-varying age-specific screening coverage rates from the cytology-based screening program in the UK, screening sensitivity and percentage successfully treated. The sensitivity of the test to CIN1, CIN2 and CIN3, the percentage of detected CINs who are treated and the percentage of successful treatments are given in **Supplemental Table 4**. We accounted in the model for the changes in screening rates and targeted age groups over time.[37]

The model considers 2 types of vaccination effects based on HPV type-specific *Cervarix*™ efficacy. The efficacy against HPV infection ($E_{infection}$) is modeled as a reduction in the rate at which susceptible individuals are infected and the residual efficacy against CIN2+ if nevertheless infected ($E_{residual}$) is modeled as a reduction in the rate of progressing from the CIN1 state to CIN2 state. The efficacy values used for $E_{infection}$ represent vaccine efficacy against infection, and were based on observed efficacy against persistent infection as these were the closest available data. The efficacy values used for $E_{residual}$ represent residual efficacy against CIN2+ if nevertheless infected (assumed to decrease CIN1 to CIN2 progression rate in the model), and were derived from the efficacy against persistent infection and the efficacy against CIN2+ as follows, assuming the 2 types of effects are multiplicative: $E_{residual} = 1 - ((1 - E_{CIN2+})/(1 - E_{infection}))$. For example, for HPV33, the point estimates of the efficacy of *Cervarix*™ are 43.1% against infection and 82.3% against

CIN2+ (**Table 2**),[6,7] i.e., $E_{infection} = 0.431$ and $E_{CIN2+} = 0.823$ for HPV33. Hence the risk ratios in females who are vaccinated vs. those who are not are $RR_{infection} = 1 - 0.431 = 0.569$ and $RR_{CIN2+} = 1 - 0.823 = 0.177$ against infection and CIN2+ respectively. The formula above simply assumes that the risk ratio for CIN2+ is the product of risk ratios against infection and against CIN2+ conditional on being infected $RR_{residual}$, i.e., $RR_{CIN2+} = RR_{infection} \times RR_{residual}$, hence $RR_{residual} = RR_{CIN2+} / RR_{infection} = (1 - 0.823) / (1 - 0.431) = 0.311$. Hence, the residual efficacy estimate is $E_{residual} = 1 - RR_{residual} = 1 - 0.311 = 0.689 = 68.9\%$.

Vaccination efficacies against infection and CIN2+ are based on up-to-date *Cervarix*™ data (**Table 2**).[6,7] Previously unpublished efficacy for the 9 other oncogenic HPV types pooled originates from the PATRICIA study in the total vaccinated HPV-naive cohort (using conditional exact method) (**Table 2**). Those type-specific efficacies (individually or pooled for the 9 other types) were not used in prior HPV dynamic models in the UK.

Model calibration to epidemiological data prior to vaccination

For each HPV type or group of types considered in the model, 18 parameters were estimated from calibration (**Table S1**). Model outcomes were simultaneously calibrated to 14 (age-stratified) data sets representing: age and type-specific prevalence of HPV infection, CIN1, CIN2 and CIN3, all pre-screening (**Fig. 1**)[12] age and type-specific incidence of cervical cancer yearly in England from 1997–2006 (**Fig. 2**).[14] As the prevalences of infection, CIN1, CIN2 and CIN3 from[12] and the incidences of cervical cancer from[14] were reported pooled across all HPV types, those prevalences and incidences were split for calibration purposes between the different oncogenic HPV types (or group of types) considered in the model based on the type-specific prevalences in the UK prior to vaccination for the different kinds of outcomes.[13] As an illustration, **Figure 1** presents the derived age-specific prevalences for HPV16 for all HPV infections (**Fig. 1A**, curve with blue circles), normal-cytology HPV infections (**Fig. 1A**, curve with red circles), CIN1 (**Fig. 1B**, red curve), CIN2 (**Fig. 1C**, red curve), CIN3 (**Fig. 1D**, red curve). **Figure 2** presents the derived age-specific incidence of cervical cancer for HPV16, year by year over a 10-y period between 1997 and 2006 (**Fig. 2**, red curves). Note that the data observed for cervical cancer in 1997–2006 already account for the successful impact of the screening program on cervical cancer. More precisely, for each HPV type or group of types considered in the model, the model parameters were estimated by optimization, by minimizing simultaneously the weighted sum of squares of the differences between the outcomes projected by the model and the outcomes observed, across the 14 datasets and age groups. Weights were used to carry out a normalization of the data sets, using ratios of medians of the different data sets (across age groups). Due to variability of published male HPV prevalence estimates, model outcomes for male HPV prevalence were not calibrated to age-specific data, however, the ratio males:females for overall HPV prevalence was constrained for calibration to be between 0.4 and 1.6, based on evidence that prevalence is quite similar between genders.[38-41]

For each HPV type or group of types considered, the best fit model parameters were used to evaluate population-level impact of the following vaccination scenarios:

- UMV of females only at age 15 y (first year for which sexual contact data are available) at 60–100% coverage, with 80% coverage used as base-case
- UMV of females only with catch-up at 50% coverage over 2 consecutive years for ages up to 18, 25, and 35 y
- UMV of females at 60–80% coverage and males at 20–80% coverage.

The contribution of cross-protection against HPV31/33/45 and the 9 other oncogenic types pooled to prevention of CIN2+ and CC was assessed for the base-case (80% UMV in females only). We evaluated the additional benefit induced by herd protection for CIN2+ by comparing model-projected reduction in CIN2+ incidence for HPV16/18 at post-vaccination steady-state with the reduction by direct effect only, computed as the product of vaccine efficacy against CIN2+ by vaccination coverage.

We assessed the sensitivity of outcomes to mean duration of vaccine protection by assuming instead of lifelong vaccine protection for all oncogenic types (base-case), a lifelong vaccine protection for HPV16/18 and shorter mean duration of vaccine protection for HPV31/33/45 and the 9 other oncogenic types pooled. Sensitivity analysis was conducted using mean duration of vaccine protection (d) of 20, 30 or 50 y for HPV31/33/45 and the 9 pooled oncogenic types, and by modeling waning of vaccine protection either using age-specific efficacies ($E_{infection}$ and $E_{residual}$) for HPV31/33/45 and the other 9 oncogenic types pooled that drop to zero after d years (i.e., when individuals enter the age group 15 + d), or assuming for HPV31/33/45 and the other 9 oncogenic types pooled that individuals flow back from the vaccinated states to their corresponding non-vaccinated state at a constant rate of 1/d. Computations were performed in *Matlab* (version 2013a).

Disclosure of Potential Conflicts of Interest

TP Van Effelterre, SM Taylor and C Hogea are all employees of the GSK group of companies and hold shares in GSK Vaccines as part of their employee remuneration.

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Trademark

Cervarix is a trademark of the GSK group of companies. *Gardasil* is a trademark of subsidiary of Merck & Co., Inc.

Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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