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Different Challenges in Eliminating HPV16 Compared to Other Types: A Modeling Study

Iacopo Baussano,[1] Fulvio Lazzarato,[1,2] Guglielmo Ronco,[3] Matti Lehtinen,[4,5] Joakim Dillner,[5] and Silvia Franceschi[1]

[1]International Agency for Research on Cancer, Lyon, France; [2]Unit of Cancer Epidemiology, AOU Città della Salute e della Scienza, Hospital of Turin, and [3]Department of Cancer Screening, Centre for Epidemiology and Prevention in Oncology, Turin, Italy; [4]University of Tampere, Finland; and [5]Department of Laboratory Medicine, Karolinska Institute, Huddinge, Sweden

Background. Human papillomavirus (HPV) vaccination is still not reaching many high-risk populations. HPV16/18 vaccines offer cross-protection against other types, for example, HPV45. Both direct vaccine efficacy and indirect herd protection contribute to vaccination effectiveness.

Methods. We used a dynamic transmission model, calibrated to cervical screening data from Italy, to estimate vaccination effectiveness against HPV16 and HPV45 infection, assuming for HPV45 either 95% or lower cross-protection.

Results. Basic reproductive number was smaller (2.1 vs 4.0) and hence vaccine effectiveness and herd protection stronger for HPV45 than for HPV16. The largest difference in the reduction of infection prevalence in women <35 years old was found at 70% coverage in girls-only vaccination programs (99% vs 83% for total protection for HPV45 and HPV16, respectively, mainly owing to stronger herd protection, ie, 37% vs 16%). In gender-neutral vaccination, the largest difference was at 40% coverage (herd protection, 54% vs 28% for HPV16 and HPV45, respectively). With ≥80% coverage, even 50% cross-protection would reduce HPV45 by ≥94%.

Conclusions. The characteristics of individual high-risk HPV types strongly influence herd protection and determine the level of coverage and cross-protection required to reduce or eliminate the infection through HPV vaccination. HPV16 infection and related cancers are the most difficult to eliminate.

Keywords. herd effect; HPV vaccination; cross-protection; cervical cancer control.

Currently licensed viruslike particle vaccines against human papillomavirus (HPV) are nearly 100% efficacious in the prevention of infection from vaccine targeted HPV types [1]. Both the bivalent (2V) and quadrivalent (4V) vaccines target the high-risk (HR) types HPV16 and HPV18, which account for approximately 70% of all cervical cancers worldwide [2], whereas the newer 9-valent vaccine also targets HR HPV31/33/45/52/58 [3], raising the proportion of preventable cervical cancers to approximately 90% [2]. However, findings from randomized controlled trials [4–6] and population-based surveys conducted after the implementation of HPV vaccination programs [7–10] showed that the 2V vaccine and, to a lesser extent, the 4V vaccine also offer some cross-protection against other HR types that are phylogenetically related to HPV16 or HPV18, such as HPV31, HPV33, and HPV45.

Adequate vaccination coverage in adolescent girls (or in girls and boys, ie, gender-neutral vaccination) is a key condition for the favorable impact of vaccination. Minimal coverage thresholds for HPV control or elimination depend on the efficacy of the vaccine in vaccinated individuals (direct protection) and the strength of herd protection, that is, the indirect protection against the infection among unvaccinated individuals [11]. In a sexually transmitted infection, such as HPV infection, herd protection is governed by the probability of infection transmission, the duration of the infection, and sexual activity pattern, which varies in different populations [11]. As a result, the overall effectiveness of HPV vaccination at a population level, that is, the sum of vaccine efficacy and herd protection, is population specific and, within the same population, type specific.

Empirical data have provided early evidence of substantial herd protection in the few years after the start of HPV vaccination programs [1, 7–10]. In the present report, we used the International Agency for Research on Cancer's deterministic transmission dynamic model [12, 13] to estimate long-term effectiveness and herd protection by coverage, separately for girls-only and gender-neutral vaccination programs. The focus is on HPV16, the most prevalent [14] and most carcinogenic [15] type, which is the most apt to persist [5, 16], and HPV45, as an example of another relatively common carcinogenic type targeted by one but not all available HPV vaccines.

METHODS

Study Population and Assumptions About Sexual Behavior and Vaccination

We simulated a population with a sex-equal and assortative sexual behavior characteristic of many high-income countries,

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Correspondence: I. Baussano, MD, MSc, PhD, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69372 Lyon Cedex 08, France (baussanoi@iarc.fr).

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that is, with relatively similar sexual behavior in women and men, including similar age between partners [13]. In particular, we simulated the sexual behavior of the Italian population as reported in a nationwide population-based survey [17]. The observed and modeled age-specific prevalence of HPV16 and HPV45 in the prevaccination era is shown in Figure 1A. The simulated population was open stable and stratified by age (range, 10–70 years) and 3 classes of sexual activity (high, intermediate, and low), characterized by an age-specific number of new sexual partners per year (Supplementary Table S1). Sexual mixing is measured on a scale from 0 (fully assortative, ie, like with like) to 1 (random mixing). In the present study, we set the assortative mixing for sexually activity classes or age groups to either 0.30 (high) or 0.75 (low) as shown in Table 1. We also assumed that sexual activity did not start before age 14 years and that all women and men were initially susceptible to HPV16 and HPV45.

Vaccine efficacy against HPV16 and HPV45, when targeted by the vaccine, was set to be 95% [5]. The strength of cross-protection against HPV45 in randomized controlled trials [4–6] and population-based surveys [7, 9, 10, 19] is lower and less consistently reported, and we therefore investigated 3 possible levels: 70%, 50%, and 30%. Finally, we assumed that immunity for HPV16 and HPV45 (targeted and cross-protection) from 3 or 2 doses (at 6-month intervals) was the same and lifelong in both sexes [6, 20], and that vaccine coverage in gender-neutral vaccination programs was the same in boys and girls.

Model Parameterization and Calibration

In a previous article [12] we reported the calibration and validation process of our model for 13 HR HPV types. Briefly, 100 000 sets of parameter values were generated by independently sampling, for each parameter, a uniform distribution within a prespecified range of values, using a Latin hypercube algorithm. Each set of values was used to generate a model-based age-specific curve of prevalence for each HPV type. Finally, each model's output was compared with the observed age-specific prevalence of each HR HPV type, by calculating binomial log likelihood. We fitted our model to HPV16 and HPV45 age-specific prevalence curves in Italian women [12, 18, 21] by calibrating the average persistence (determined by the rate of clearance) of HPV16 and HPV45 infections [5]. Figure 1B shows the per capita annual clearance rates of incident HPV16 and HPV45 infection, as estimated by calibrating the base-case model to type and age-specific prevalence curves from Italy. Early HPV45 clearance rate was higher (2.7 per person-year on average, or 22% per month) than HPV16 clearance rate (1.5 per

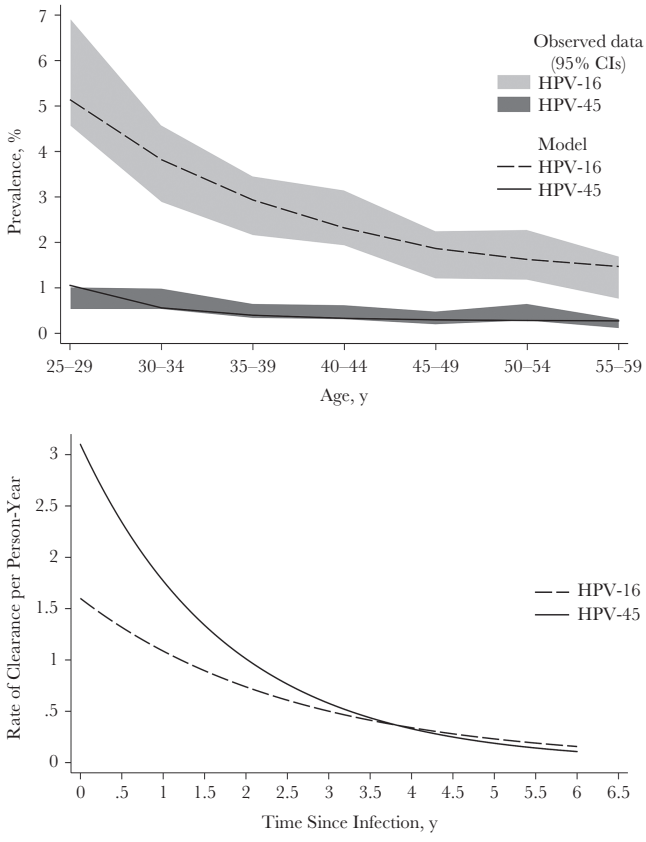

Figure 1. Age-specific prevalence of human papillomavirus (HPV)16 and HPV45 in the prevaccination era, including observed data [18] and model outputs [12] (*A*) and rates of clearance according to model outputs (*B*). CIs, confidence intervals.

Table 1. Model Parameters Related to Sexual Behavior, Vaccine Performance, and Infection for HPV16 and HPV45

	HPV16			HPV45				
					Sensitivity Analysis by			
		Sensitivity Analysis by Sexual Assortative Mixing					Sexual Assortative Mixing	
Parameter	Base Case	High	Low	Base Case[a]	Infection Duration[b]	Immunity After Clearance[c]	High	Low
New sexual partners per year, mean, No.	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Mixing between sexual activity classes[d]	0.75	0.3	0.75	0.75	0.75	0.75	0.3	0.75
Mixing between age groups[d]	0.3	0.3	0.75	0.3	0.3	0.3	0.3	0.75
Vaccine efficacy, %	95	95	95	95 or less	95 or less	95 or less	95 or less	95 or less
Duration of vaccine protection	Lifelong	Lifelong	Lifelong	Lifelong	Lifelong	Lifelong	Lifelong	Lifelong
Assumed or calibrated								
Infection duration, mean, mo	11[e]	11[f]	11[f]	5[e]	11[f]	3[e]	5[f]	5[f]
Transmission probability per sexual partnership, %	70[f]	70[f]	70[f]	70[f]	25[e]	70[f]	70[f]	70[f]
Immunity after infection clearance in women, %[f]	30	30	30	30	30	0	30	30
Calculated								
Basic reproductive number ($R0$)	4.1	5.6	2.9	2	1.5	1.3	2.7	1.4
Gender-neutral vaccination coverage sufficient for elimination, %	75	81	67	49	38	21	62	30

Abbreviation: HPV, human papillomavirus.

[a]Same type-specific transmission probability as HPV16.

[b]Same type-specific infection duration as HPV16.

[c]Absence of immunity after HPV45 clearance.

[d]This is a measure of the tendency for individuals with similar sexual activity to form sexual partnerships. It is measured on a scale where fully and randomly assortative (ie, like-with-like) mixing corresponds to values of 0 and 1, respectively.

[e]Parameters that have been calibrated.

[f]Parameters that have been assumed.

person-year or 12% per month). Clearance rates of both types decrease over time and converge at approximately 0.14 per person-year after 6 years since infection (Supplementary Table S2), in accordance with empirical evidence [22, 23].

Different parameter values were either assumed or calibrated according to a base-case scenario and various sensitivity analyses (Table 1). In the base-case scenario, we set (1) the average duration of infection to be 11 and 5 months for HPV16 and HPV45, respectively; (2) the probability of transmission per sexual partnership of both HPV16 and HPV45 to be 70% in both sexes [12, 24, 25]; and (3) the probability of developing type-specific immunity after infection clearance, for both types, to be 30% in women and 0% in men [26]. For both HPV16 and HPV45, we also assessed the sensitivity of model outputs to alternative sexual mixing patterns forcing assortative mixing by sexually activity class and by age to be alternatively high (ie, 0.3) or low (ie, 0.75). A larger number of different scenarios were considered for HPV45 to assess the impact of different levels of cross-protection from vaccines that do not target HPV45 and the robustness of model outputs to the uncertainty of type-specific natural history, that is, duration of infection and immunity after clearance [26] (Table 1). For each sensitivity analysis, we used the single best-fitting set of parameters corresponding to the prespecified assumptions. Details about the model structure and calibrating process are reported in the Supplementary Data.

Model-Based Analyses

For each scenario, we calculated the basic reproductive number (R_0, ie, the average number of secondary infections resulting from 1 case of either HPV16 or HPV45 infection in a totally

susceptible population), using the next-generation matrix method [27]. For model predictions, outcomes were measured as the percentage prevalence reduction (%PR) in HPV16 and HPV45 compared with no vaccination in women aged 15–34 years at postvaccination equilibrium (ie, approximately 50 years after the introduction of vaccination).

The primary outcome was overall vaccine effectiveness. Herd protection was the difference between overall effectiveness, estimated by the model, and direct vaccine efficacy, estimated by multiplying vaccination coverage by 95% efficacy or by the level of cross-protection against HPV45, as reported. Girls-only and gender-neutral vaccination programs were separately assessed.

RESULTS

In the base-case scenario, R_0 estimate is substantially larger for HPV16 than for HPV45 (4.1 and 2.0, respectively) (Table 1), and this difference has a large influence on the effectiveness of vaccination. Figure 2A and 2B show the type-specific %PR by coverage from a vaccine targeting both types in either a girls-only or a gender-neutral vaccination program, respectively. The area between the curve of overall effectiveness against HPV45 and HPV16 and the straight curve of 95% vaccine efficacy (common to the 2 types) represents herd protection. In a girls-only vaccination program, the largest difference in overall effectiveness between HPV16 and HPV45 steadily increases up to approximately 70% coverage (%PR, 99% for HPV45 vs 83% for HPV16). The difference between types is entirely accounted for by the larger contribution of herd protection for HPV45 than HPV16 (33% vs 16% of the %PR, respectively) (Figure 2A). In a gender-neutral vaccination program, the largest difference in %PR is already reached at approximately 40% coverage (92% for HPV45 vs 66% for HPV16), with herd protection accounting for more than half of the total %PR of HPV45 (Figure 2B). Coverage of 75% and 49%, respectively, therefore seems sufficient in gender-neutral vaccination for the elimination HPV16 and HPV45 among women aged 15–34 years.

Figure 3 shows the effectiveness of a vaccine that offered only 50% cross-protection against HPV45 by coverage level. At 70% coverage in girls-only vaccination, the %PR is 59% and herd protection accounts for 24% of this effect. If boys were also vaccinated, the %PR from cross-protection would increase to 86%, of which 51% is from herd protection.

Sensitivity analyses, for example, assuming no difference in duration of infection between HPV16 and HPV45 or no immunity after clearance for HPV45, had little impact on the greater difficulty in eliminating HPV16 compared with HPV45 shown by the base-case scenario (Table 1). Likewise, an increase and a decrease in assortative mixing between sexual classes or age groups increased and decreased, respectively, the coverage level necessary to eliminate both HPV16 and HPV45 (Table 1).

Table 2 shows the overall effectiveness and herd protection against HPV16 and HPV45 according to coverage level,

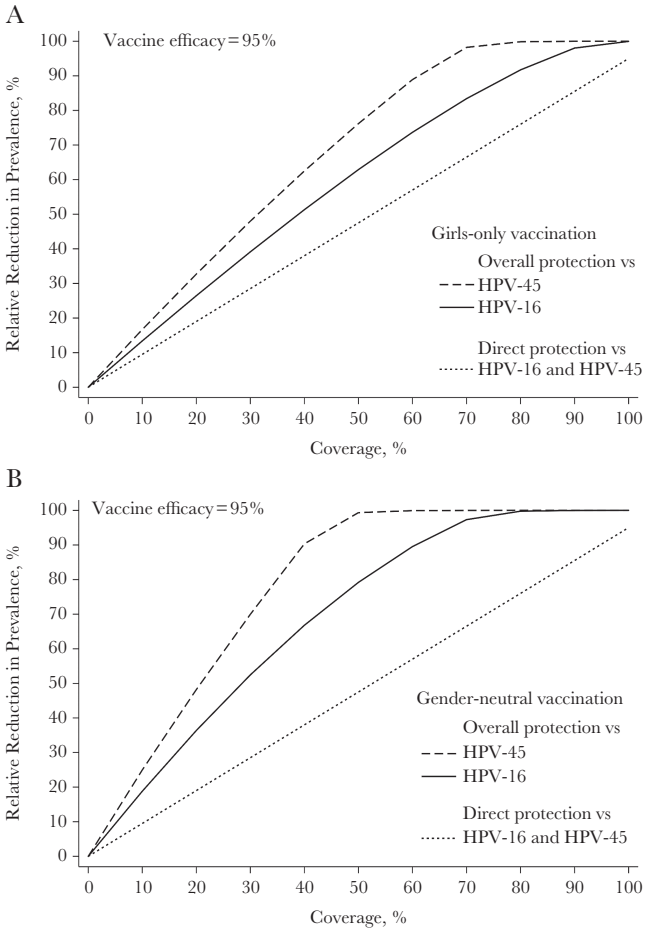

Figure 2. Relative reduction in prevalence of human papillomavirus (HPV)16 and HPV45, among all women aged 15–34 years after vaccination of 11-year-old girls (*A*) or girls and boys (*B*), by coverage and type of protection.

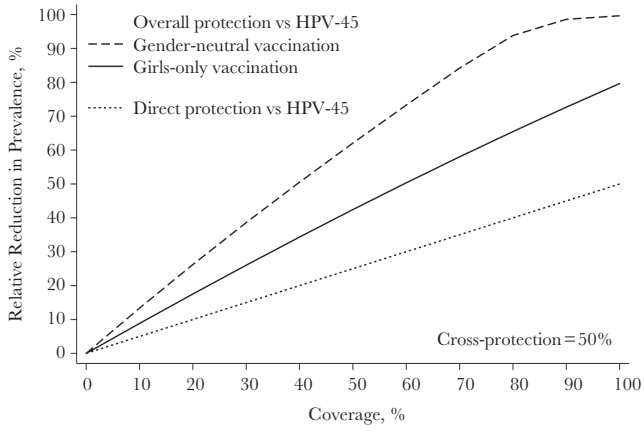

Figure 3. Relative reduction of prevalence of human papillomavirus (HPV)45 from 50% cross-protection among all women aged 15–34 years after vaccination of 11-year-old girls only and gender-neutral vaccination, by coverage and type of protection.

Table 2. Percentage Reduction in HPV16 and HPV45 Prevalence Among Women Aged 15–34 Years After Girls-Only or Gender-Neutral Vaccination Compared With No Vaccination by Vaccine Efficacy, Coverage, and Biological Scenarios

		Reduction in Prevalence, % (Herd Protection, %)							
		Girls-Only Vaccination				Gender-Neutral Vaccination			
		Base Case		Sensitivity Analysis (HPV45) by		Base Case		Sensitivity Analysis (HPV45) by	
Vaccine Efficacy, %	Coverage, %	HPV16	HPV45[a]	Infection Duration[b]	Immunity After Clearance[c]	HPV16	HPV45[a]	Infection Duration[b]	Immunity After Clearance[c]
95	40	51 (13)	63 (25)	93 (55)	100 (62)	67 (29)	90 (52)	99 (61)	100 (62)
	60	74 (17)	89 (32)	99 (42)	100 (43)	90 (33)	100 (43)	100 (43)	100 (43)
	80	92 (16)	100 (24)	100 (24)	100 (24)	100 (24)	100 (24)	100 (24)	100 (24)
70[d]	40	…	47 (19)	80 (52)	84 (56)	…	69 (41)	97 (69)	100 (72)
	60	…	68 (26)	95 (53)	100 (58)	…	96 (54)	100 (58)	100 (58)
	80	…	88 (32)	99 (43)	100 (44)	…	100 (44)	100 (44)	100 (44)
50[d]	40	…	34 (14)	63 (43)	63 (43)	…	51 (31)	51 (31)	99 (79)
	60	…	50 (20)	84 (54)	89 (59)	…	73 (43)	73 (43)	100 (70)
	80	…	65 (25)	94 (54)	100 (60)	…	94 (54)	94 (54)	100 (60)
30[d]	40	…	21 (9)	40 (28)	40 (28)	…	31 (19)	66 (54)	68 (56)
	60	…	31 (13)	58 (40)	58 (40)	…	46 (28)	85 (67)	94 (76)
	80	…	41 (17)	72 (48)	74 (50)	…	60 (36)	94 (70)	100 (76)

Abbreviation: HPV, human papillomavirus.

[a]Same type-specific transmission probability as HPV16.

[b]Same type-specific infection duration as HPV16.

[c]Absence of immunity after HPV45 clearance.

[d]Level of cross-protection.

inclusion of boys, and, for HPV45, different assumptions about vaccine efficacy and type-specific natural history (see Table 1). Compared with the base-case model, sensitivity analyses produced higher %PR for nearly all different combinations of factors, mainly owing to stronger herd protection. The data in Table 2 therefore confirm the general finding that HPV45 is easier to eliminate than HPV16 and that the higher the coverage, the lower the contribution of vaccinating boys in addition to girls.

Figure 4A and 4B show the %PR of HPV45 from gender-neutral vaccination by coverage in 2 hypothetical populations with sexual mixing patterns different from that in the base-case scenario. In a population with high assortative mixing (Figure 4A), the curves for HPV45 and HPV16 become closer, and the difference in herd protection diminishes. Conversely, the difference in %PR between the 2 HPV types in a population with low assortative mixing (Figure 4B) is even larger than in the base-case scenario (Figure 2B), and herd immunity increases. This difference reaches a maximum at 30% coverage (already sufficient to eliminate HPV45).

Figure 5 presents a comparison of the %PR of HPV45 that can be achieved by a vaccine's 50% cross-protection by coverage and sexual mixing. The impact of such a vaccine is much stronger in a population with low assortative mixing; in such a population, HPV45 elimination is seen at 60% coverage whereas the same coverage approximately halves HPV45 prevalence in a population with high assortative mixing. Supplementary Table S3 shows detailed estimates of %PR and herd protection for girls-only vaccination and several levels of cross-protection.

Changes in R_0 estimate underlie the findings of sensitivity analyses. The assumption of the same infection duration for HPV16 and HPV45, and of no acquired immunity after HPV45 clearance, slightly decreases the HPV45 R_0 (from 1.5 to 1.3) (Table 1). Changes in the assortativeness of sexual mixing produce opposite effects (Table 1). In a highly assortative population, the R_0 increases for HPV16 (from 4.1 in the base-case model to 5.6) and HPV45 (from 2.0 to 2.7). Conversely, in a population with low assortative mixing, the R_0 decreases to 2.9 for HPV16 and 1.4 for HPV45, thus explaining the vast predominance of the herd effect in Figure 4B.

DISCUSSION

Our present report highlights the important role of herd protection in the elimination of HPV infection, especially of HPV types less prone to long-term persistence than HPV16. It also shows that for any level of population coverage, and also in the presence of less than 95% vaccine efficacy, the success of a vaccination program is larger the lower the prevaccination prevalence of an individual HPV type. At ≥60% coverage in gender-neutral programs, for instance, even 50% cross-protection could eliminate HPV45. This phenomenon is mainly due to larger herd protection for HR types such as HPV45 that are less able than HPV16 to induce long- term persistence [5, 16]. In fact, for any infection, the magnitude of herd protection

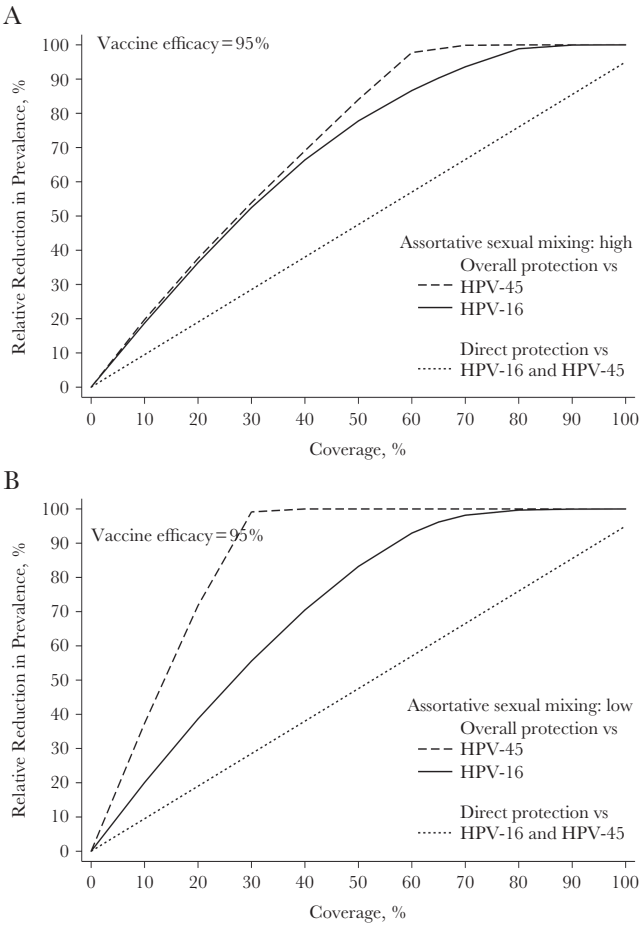

Figure 4. Relative reduction of prevalence of human papillomavirus (HPV)16 and HPV45, among all women aged 15–34 years after vaccination of 11-year-old girls and boys in a population with high (*A*) or low (*B*) assortative sexual mixing, by coverage and type of protection.

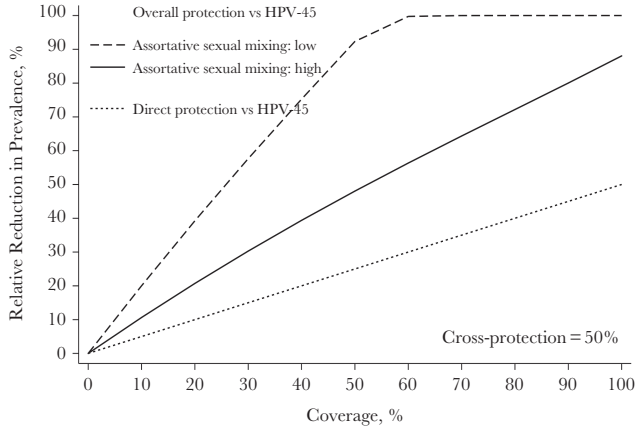

Figure 5. Relative reduction of prevalence of human papillomavirus (HPV) 45 from 50% cross-protection among all women aged 15–34 years after vaccination of 11-year-old girls and boys in populations with high or low assortative sexual mixing, by coverage and type of protection.

against an individual HPV type is governed by its transmission potential (R_0), which depends on the duration of the infectious period [11, 28]. Our estimate of R_0 for HPV16 (4.1) was larger than that for HPV45 (2.0) in our base-case scenario that assumes the same transmission probability and immunity after clearance and found an approximately 2-fold longer duration of HPV16 than of HPV45 infection. Alternative hypotheses that assumed no difference in infection duration between the 2 types and no natural immunity for HPV45 showed, an even greater difference between the 2 types.

Another enhancer of herd protection is vaccinating boys in addition to girls. The benefit of gender-neutral vaccination is therefore most important if either coverage or vaccine efficacy are suboptimal, for example, with coverage <60% for the elimination of HPV16 using an HPV16 targeting vaccine or with partial cross-protection only against HPV45. We also projected the effects of different vaccination scenarios on the eventual decline of cervical cancer due to HPV16 and HPV45 in a country such as Italy (Supplementary Table S3). As for the corresponding infections, the elimination of HPV16-related cervical cancer requires the highest level of vaccine efficacy and coverage, whereas partial cross-protection may be sufficient to eliminate cervical cancer associated with HPV45 and possibly other HR HPV types that may share with HPV45 a shorter infection duration and less ability to produce cancer than HPV16 and HPV18.

We think that the assumptions used in the base-case scenario best reflected the findings of studies on HPV natural history, for example, lack of substantial heterogeneity between carcinogenic HPV types in transmission rates [12, 24, 25, 29] and in the probability of developing type-specific immunity after infection clearance [26]. In contrast, the duration of carcinogenic HPV infection has been shown to be heterogeneous by type [5, 16], with HPV16 the type the most apt to persist, thus its greater ability to induce long-term persistence and malignant transformation than other HR types [14, 30]. Indeed, the estimate of the difference in the average duration of HPV16 and HPV45 (11 and 5 months, respectively) calibrated by the base-case scenario was even larger than in previous work, for example, 12 and 8 months, according to the largest published meta-analysis [16]. In fact, the average duration of HPV16 infection was generally evaluated over relatively short follow-up periods and predominantly among cytologically normal women [16], or was truncated by detection and treatment of HPV16-associated lesions.

Nevertheless, we performed several sensitivity analyses based on assumptions about the natural history of HPV45 or sexual mixing that differed from those used in the base-case scenario. They confirmed the greater difficulty of eliminating HPV16 compared with HPV45. Only high assortativeness in sexual mixing between sexual classes and age groups raised the HPV45 R_0 sufficiently to attenuate the difference in type-specific herd immunity.

The differences between HPV16 and HPV45 herein reported agree with the findings of Brisson et al [31, 32], who showed stronger vaccine effectiveness against HPV11/6 types than against HPV16/18 owing to differences in duration of infectiousness and, hence, in R_0. Indeed, these relationships between HPV types may be generalizable, because the R_0 range calculated by our model (2.1–4.0 in the baseline scenario) plausibly reflects those of the most important carcinogenic HPV types. Our estimates fall within the range of other sexually transmitted infections, such as human immunodeficiency virus [33], syphilis [34], gonorrhea, and chlamydia [35]. Conversely, R_0 values for sexually transmitted infections are substantially lower than those for childhood epidemic infections (eg, measles, whooping cough, rubella, and poliomyelitis), which require >90% coverage to be controlled [36].

The strengths of the present study include the use of a validated transmission model to represent changes in HPV prevalence. Transmission models can capture the dynamics of infection circulation [11] in a population and have the distinct advantage of including the effect of herd immunity attributable to vaccination [37]. We could also derive estimates of the parameters governing the natural history of HPV16 and HPV45 infections from the calibration to a large clinical trial conducted in Italy [18], whereby we were able to predict accurately the incidence of HPV infection in HPV negative women. This allowed us to provide a range of uncertainty for each parameter estimate [12].

The limitations of the present study mainly derive from the uncertainties that remain in some of the model assumptions. Cross-protection against HPV45 in clinical trials, for instance, ranged between 8% and 79% and was consistently higher for 2V than for 4V vaccine [5, 6]. Population-based studies from postvaccination surveys also showed a partial efficacy against HPV31/33/45 as a combined end point of approximately 40% for 4V [9] and 50% for 2V [7, 10] vaccine. Preliminary data also suggest that cross-protection against HPV31/33/45 is comparable for 2 or 3 doses [6, 7, 9, 10] and may be of long duration [6, 20], and that precancerous lesions deriving from nonvaccine HPV types are also substantially reduced by 2V vaccination [38]. Obviously, the sexual behavior of women and men is population-specific, and its description is always an oversimplification because accurate information on sexual networks (eg, sequential or concurrent sexual partnerships) are very difficult to obtain.

In conclusion, the characteristics of individual HR HPV types strongly influence herd immunity and determine the level of coverage and type-specific vaccine efficacy (including cross-protection) that are required to reduce or eliminate the infection through HPV vaccination. HPV16 is harder to eliminate than HPV45 and, probably, any other type. Our findings are particularly relevant to low- and middle-income countries that are especially challenged by programmatic difficulties [39] and increases in the cost of vaccines according to the number of targeted types [40].

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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