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Modelling multi-site transmission of the human papillomavirus and its impact on vaccination effectiveness

P. Lemieux-Mellouki[a,b,*], M. Drolet[a], M. Jit[c,d], G. Gingras[a,b], M. Brisson[a,b,e]

[a] CHU de Québec Research Center – Université Laval
[b] Department of Social and Preventive Medicine, Laval University, Québec, Canada
[c] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom
[d] Modelling and Economics Unit, Public Health England, London, United Kingdom
[e] Department of Infectious Disease Epidemiology, Imperial College, London, United Kingdom

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ABSTRACT

Objective: Previous HPV models have only included genital transmission, when evidence suggests that transmission between several anatomical sites occurs. We compared model predictions of population-level HPV vaccination effectiveness against genital HPV16 infection in women, using a 1) uni-site (genital site), and a 2) multi-site model (genital and one extragenital site).

Methods: We developed a uni-site and a multi-site deterministic HPV transmission model, assuming natural immunity was either site-specific or systemic. Both models were calibrated to genital HPV16 prevalence (5%–7.5%), whilst the multi-site model was calibrated to HPV16 prevalence representative of oral (0%–1%) and anal (1%–7.5%) sites. For each model, we identified 2500 parameter sets that fit endemic genital and extragenital prevalences within pre-specified target ranges. In the Base-case analysis, vaccination was girls-only with 40% coverage. Vaccine efficacy was 100% for all sites with lifetime protection. The outcome was the relative reduction in genital HPV16 prevalence among women at post-vaccination equilibrium (RRprev). RRprev was stratified by extragenital prevalence pre-vaccination.

Results: Under assumptions of site-specific immunity, RRprev with the multi-site model was generally greater than with the uni-site model. Differences between the uni-site and multi-site models were greater when transmission from the extragenital site to the genital site was high. Under assumptions of systemic immunity, the multi-site and uni-site models yielded similar RRprev in the scenario without immunity after extragenital infection. In the scenario with systemic immunity after extragenital infection, the multi-site model yielded lower predictions of RRprev than the uni-site model.

Conclusions: Modelling genital-site only transmission may overestimate vaccination impact if extragenital infections contribute to systemic natural immunity or underestimate vaccination impact if a high proportion of genital infections originate from extragenital infections. Under current understanding of heterosexual HPV transmission and immunity, a substantial bias from using uni-site models in predicting vaccination effectiveness against genital HPV infection is unlikely to occur.

1. Introduction

Human papillomavirus (HPV) is a sexually transmitted infection (STI), able to infect the basal epithelial layer of the cervix, oral cavity, the anus and the genitals. The main focus of HPV related research and prevention has historically been cervical cancer, for which HPV is the necessary cause. This is mainly because cervical cancers account for an estimated 87% of all HPV-attributable cancers worldwide (Forman et al., 2012). However, research on non-cervical HPV infections and disease has dramatically increased since 2005. Two main reasons explain this intensified focus on non-cervical HPV: 1) a steep increase in the incidence of oropharyngeal and anal cancers in the US and other high income countries (Forman et al., 2012; Gillison et al., 2012a) and 2) recent results showing that HPV vaccines are highly effective at preventing persistent HPV infection and pre-cancerous lesions in sites other than the cervix (Munoz et al., 2010; Goldstone et al., 2013; Herrero et al., 2013; Gillison et al., 2014).

Despite the recent focus on non-cervical HPV research, there remain significant gaps in knowledge, particularly around HPV transmission to and immunity between cervical and non-cervical sites. The few

* Corresponding author at: Centre de recherche du CHU de Québec, Axe Santé des populations et pratiques optimales en santé, 1050 Chemin Sainte-Foy, Québec, G1S 4L8, Canada.
E-mail address: philippe.lemieux-mellouki.1@ulaval.ca (P. Lemieux-Mellouki).

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epidemiological studies on multi-site HPV infection/transmission suggest that autoinoculation within one host, or inter-site transmission between individuals may occur (Heijne et al., 2017; Hernandez et al., 2008; Vogt et al., 2013). Plausible modes of inter-site transmission include oral sex, anal sex, or indirect transmission through contact with hands. Autoinoculation between the genital and oral or anal sites could occur through intermediate contact with the hands (Cook, Thompson El Fau - Kelso et al.; Simpson, Blomfield et al.) or through virus shedding in the anogenital region (Goodman, Shvetsov Yb Fau - McDuffie et al.). Therefore, HPV infection at one site is likely dependent on transmission from other sites. As for natural immunity, studies suggest that production of antibodies is much more frequent following cervical infections than non-cervical infections (Carter et al., 2000; Giuliano et al., 2015). However, it is unclear whether antibody response is synonymous with systemic protection against subsequent infections at other sites. Furthermore, the role of local immunity, either humoral or cell-mediated, in protecting against subsequent infections is not well understood. Hence, there could be site-specific differences in immune response and vulnerability to subsequent infections.

None of the 19 HPV transmission-dynamic models developed over the past 10 years to assess HPV vaccination effectiveness (Brisson et al., 2015) have incorporated multi-site infections/transmission, which may have biased their predictions. Indeed, all previous models were "uni-site" models, where infection is only acquired and transmitted at one site in women (implicitly the cervico-vaginal region) and men (implicitly the penis). Furthermore, the bulk of previous models were only fit to age-specific HPV infection data at the cervico-vaginal site (Canfell et al., 2012). By ignoring other potential markers of infection and sources of transmission from extragenital infections, these uni-site models may be biased in their predictions of long term post HPV vaccination dynamics (e.g., herd effects and population-level effectiveness).

Given that the predictions of previous HPV models, based on a uni-site transmission paradigm, were highly influential in HPV vaccination policy decisions worldwide (Jit and Brisson, 2011), it is important to assess the robustness of the predictions to assumptions about multi-site transmission and natural immunity. The objectives of this study are to: 1) compare predictions of HPV16 vaccination effectiveness and herd effects between multi-site and uni-site transmission-dynamic models, under various assumptions of HPV16 transmission and natural immunity, and 2) understand the effect of the key factors of transmission responsible for difference in predictions of HPV16 vaccination effectiveness between multi-site and uni-site models.

2. Material and methods

We developed two multi-site models and one uni-site model to address our objectives.

2.1. Comparing predictions of HPV16 vaccination effectiveness between multi-site and uni-site transmission-dynamic models

2.1.1. Model structure

To address objective 1, predictions of HPV16 vaccination effectiveness are compared between a uni-site and a multi-site model. We developed a uni-site and a multi-site deterministic HPV16 transmission model based on the Susceptible-Infectious-Recovered paradigm (see the Supplementary material for the flow diagrams and the model equations). For both models, the population is 1) heterosexual, 2) open and stable (deaths balance births), and 3) stratified according to gender and two levels of sexual activity. Mixing between levels of sexual activity was assumed to be random. For simplicity, we did not stratify the models by age. On average, individuals spend 15 years in the modelled population, representing the peak years of sexual activity (15–30 years).

The only structural differences between the uni-site and multi-site models are in HPV16 transmission and natural immunity. The uni-site model represents transmission between the cervico-vaginal site and penis, and the probability of natural immunity following clearance is allowed to vary between 0 and 100% in both women and men. On the other hand, the multi-site model represents the following four transmission pathways: 1) extragenital → extragenital, 2) extragenital → genital, 3) genital → genital and 4) genital → extragenital. In the multi-site model, the extragenital site can either be the oral or anal site. Each pathway has its own probability of transmission, which is modeled per sexual partnership (i.e., we did not model duration of sexual partnerships, the specific number of different acts within a partnership or use transmission probabilities per act).

Scenarios with and without autoinoculation between the two sites were investigated. With autoinoculation, individuals infected at one site can get infected at the other site without sexual exposure, according to two time-homogeneous rates corresponding to the two possibilities (genital → extragenital and extragenital → genital). Given uncertainty in the literature about natural immunity and the possible impact of natural immunity assumptions on predictions, we modelled 4 scenarios. In scenario 1, individuals can only acquire immunity upon clearing genital infection and immunity protects against subsequent genital infections, but not against extragenital infections (*Local immunity after genital infection only)*. In scenario 2, individuals can acquire local immunity upon clearing genital and extragenital infections (*Local immunity after genital and extragenital infections)*. In scenario 3, individuals can only acquire immunity upon clearing genital infection and immunity protects against subsequent infection at any site (*Systemic immunity after genital infection only*). Finally, in scenario 4, individuals can acquire systemic immunity upon clearing genital or extragenital infection (*Systemic immunity after genital and extragenital infection)*.

2.1.2. Parameterization and fitting procedure

To compare vaccination effectiveness predictions between the uni-site and multi-site models, the models were calibrated to the same pre-vaccination HPV16 prevalence at the cervico-vaginal site (prevalence = 5.0–7.5%). The lower and upper bounds of HPV16 prevalence were based on estimates from two studies among US women between 14 and 30 years old (around 5.0% (Hariri et al., 2011) and 7.5% (Wheeler et al., 2013)). In addition, the multi-site model was calibrated to HPV16 prevalence representing either the oral (prevalence = 0.0–1.0% (Kreimer 2011; Gillison et al., 2012b)) or the anal site (prevalence = 1.0–7.5% (Goodman et al., 2008; Nyitray et al., 2011, 2015)) (see Table 1). We chose wide ranges for HPV16 prevalence at the extragenital sites to enable greater generalizability of results. The models were calibrated to HPV16 prevalence by varying HPV16 transmission probabilities from females to males and from males to females. A maximum relative difference of ± 15% was allowed between male-to-female and female-to-male probabilities of transmission. In scenarios with autoinoculation, the two rates of autoinoculation (genital → extragenital and extragenital → genital) were also varied and assumed to be the same for males and females. All other parameters were also identical between males and females and were fixed based on available data in the literature (Insinga et al., 2007, 2015) and prior modelling work (Brisson et al., 2013) (see Table 1). To select the parameters that produced the best fit to the HPV16 prevalence data, we used a 4 step procedure: 1) each parameter was given a uniform prior (probability of transmission between 0 and 100%), 2) parameter sets were drawn from the prior distributions using Latin Hypercube Sampling (McKay et al., 1979; Van de Velde et al., 2012), 3) parameter sets were selected if they produced HPV16 prevalence estimates within the prespecified target intervals (see Table 1), and 4) the calibration procedure was stopped once about 2500 parameter sets were selected. The uni-site model was calibrated a single time while the multi-site model was calibrated eight times for each of the four different scenarios of natural immunity and the two scenarios of autoinoculation (with or without).

Table 1
Uni-site and multi-site model calibration.

	Multi-site model	Uni-site model
Calibration target: HPV16 prevalence (females)	Genital [5%-7.5%] (Hariri et al., 2011; Wheeler et al., 2013) Extragenital [0%-7.5%] (Goodman et al., 2008; Kreimer et al., 2011; Nyitray et al., 2011; Gillison et al., 2012, 2015)	Genital [5%-7.5%] (Hariri et al., 2011; Wheeler et al., 2013)
Scenarios of natural immunity	• Local immunity after genital infection, • Local immunity after genital and extragenital infection, • Systemic immunity after genital infection, • Systemic immunity after genital and extragenital infection	• Immunity after genital infection
Varying parameters	Probabilities of transmission[a]: • Genital → Genital, • Genital → Extragenital, • Extragenital → Extragenital, • Extragenital → Genital Rates of autoinoculation: • Genital → Extragenital, • Extragenital → Genital	Probabilities of transmission[a]: • Genital → Genital
Fixed parameters	Average duration of infection: • 1.5 years (based on cervical HPV (Insinga, Dasbach et al., 2007)) Effective average rate of new partner acquisition per year (2015): • Low level of activity (95%): 1.4 • High level of activity (5%): 5.7 Probability of developing natural immunity after infection (Brisson, Laprise et al., 2013): • 45%	Same values of fixed parameters as in the multi-site model

[a] Male-to-female and female-to-male probabilities of transmission were allowed to be different (maximum relative difference allowed = ± 15%). All other parameters were equal between men and women.

2.1.3. Analysis design and outcome

To investigate the effect of multi-site transmission on estimates of vaccination effectiveness, we modelled a girls-only vaccination scenario, assuming 100% vaccine efficacy against infection (at all modelled sites) and lifelong duration of protection.

For comparisons between the uni-site and multi-site model predictions of vaccination effectiveness, we used the relative reduction in genital HPV16 prevalence at the post-vaccination equilibrium compared to no vaccination. Results are presented using the median, the minimum and maximum, the 25th and 75th percentiles of simulation results using the 2500 parameter sets identified through calibration.

We assumed vaccination coverage was 40% in the base case, but varied coverage between 0% and 100% in sensitivity analyses.

2.2. Understanding the effect of the key factors of transmission responsible for difference in predictions of HPV16 vaccination effectiveness between multi-site and uni-site models

To address objective 2, we proceeded in two steps:

2.3. Step 1: analysis with a simplified multi-site model

First, a simplified homogeneous multi-site model was used for general tractability and theoretical insights. We identified three key factors responsible for differences in HPV vaccination effectiveness predictions between the multi-site and uni-site models (see Supplementary materials): 1) the proportion of all incident genital infections that are due to extragenital → genital transmission at pre-vaccination equilibrium (Factor 1: proportion of genital infections caused by extragenital infections); this proportion is obtained by dividing the incidence of genital infections caused by the transmission of an extragenital infection to the genital site by the total incidence of genital infections, 2) proportion of extragenital infections caused by genital infections at pre-vaccination equilibrium (Factor 2), 3) proportion of susceptibles to extragenital infections at pre-vaccination equilibrium (Factor 3).

2.3.1. Model structure

The simplified multi-site model follows the same Susceptible-Infected-Recovered structure as the model described in Section 2.1.1 (see Supplementary material for the model equations) with the four transmission pathways modelled as probabilities per instantaneous partnership. However, in contrast, the model includes one level of sexual activity, one gender, no autoinoculation, and transmission from individuals infected at the genital and extragenital sites occur independently (i.e., two independent modes of transmission).

2.3.2. Parameterization and fitting procedure

We used the same values of duration of infection and probability of natural immunity as for the model developed for objective 1 (see Table 1). For simplicity, natural immunity was assumed to be local after genital infections (which corresponds to scenario 1 in objective 1).

We aimed to assess the effect of genital → extragenital and extragenital → genital transmission probabilities on predicted vaccination effectiveness. To do this, we calibrated the four transmission probabilities to targets of 7% for endemic genital prevalence and 3% for endemic extragenital prevalence. These targets were based on HPV16 prevalence targets for objective 1. The four transmission probabilities were calibrated by solving algebraically the model equations to obtain 10 000 parameter sets.

2.3.3. Analysis design and outcome

For objective 2, we used the minimum vaccination coverage needed to eliminate the infection in the population as our main outcome (the elimination threshold, q_c). We estimated the elimination threshold from the basic reproductive number (R_0). For the simple multi-site model, the elimination threshold is given by $\left(1 - \frac{1}{R_0}\right)$. We computed R_0 as the leading eigenvalue of the Next-Generation-Matrix (Driessche and

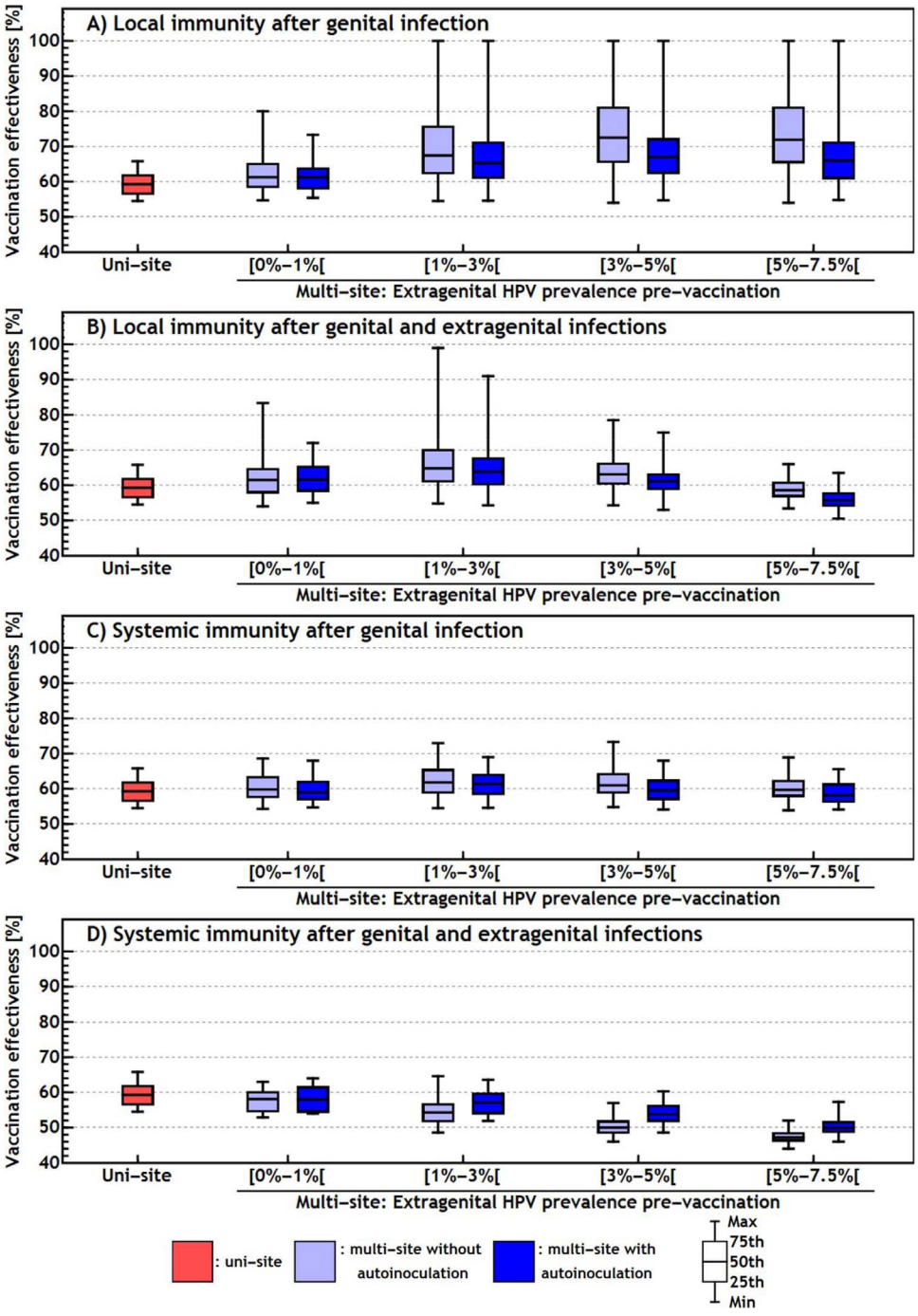

Fig. 1. Population-level vaccination effectiveness of HPV16 vaccination with a multi-site and uni-site models: comparison by prevalence of extragenital HPV16. Vaccination program is girls-only with 40% coverage and vaccine is assumed to have 100% efficacy and lifelong duration for the two sites of infection. Vaccination effectiveness = relative reduction in genital HPV16 prevalence at the post-vaccination equilibrium compared to no vaccination.

Watmough 2008).

2.4. Step 2: analysis with the heterogeneous multi-site model

In step 2, we assessed the effect of Factors 1, 2 and 3 on predicted HPV16 vaccination effectiveness using the heterogeneous multi-site model described in Section 2.1.1. To achieve this, we calculated, before vaccination, from all the parameter sets identified during the calibration process in objective 1: the proportion of genital infections caused by extragenital infections (Factor 1), the proportions of extragenital infections caused by genital infections (Factor 2), and the proportion of susceptibles to extragenital infections (Factor 3). We then examined the relationships between these outcomes and HPV16 vaccination effectiveness.

3. Results

3.1. Comparing predictions of HPV16 vaccination effectiveness between multi-site and uni-site transmission-dynamic models

3.1.1. Effect of multi-site transmission on vaccination impact assuming local immunity only after genital infection (scenario 1) or local immunity after genital infection and extragenital infection (scenario 2)

Under the assumption of local immunity after genital infection, the impact of vaccination on the population-level prevalence of genital HPV16 infection predicted by the multi-site model is similar to the uni-site model when extragenital prevalence is low, but the multi-site model predicts substantially greater vaccination effectiveness when extragenital prevalence is high (Fig. 1A and Table 2). The difference is

Table 2
Predicted effectiveness of vaccination against genital HPV16 infection for the multi-site and uni-site models by scenario and extragenital prevalence.

	Multi-site				Uni-site
	Extragenital prevalence				
	[0%–1%]	[1%–3%]	[3%–5%]	[5%–7.5%]	
Scenario 1					
with Autoinoculation	61%(58–64)	65%(62–71)	67%(63–72)	66%(61–71)	59%(57–62)
without Autoinoculation	61%(58–65)	67%(62–76)	73%(66–81)	72%(66–81)	
Scenario 2					
with Autoinoculation	62%(58–65)	64%(60–68)	61%(59–63)	56%(54–58)	59%(57–62)
without Autoinoculation	62%(58–65)	65%(61–70)	63%(60–66)	57%(59–61)	
Scenario 3					
with Autoinoculation	59%(57–62)	61%(59–64)	60%(57–62)	58%(56–61)	59%(57–62)
without Autoinoculation	61%(58–64)	62%(59–65)	61%(59–64)	60%(58–62)	
Scenario 4					
with Autoinoculation	58%(56–62)	57%(54–60)	54%(52–56)	50%(49–52)	59%(57–62)
without Autoinoculation	58%(55–61)	54%(52–56)	50%(49–51)	47%(47–48)	

In the base-case, vaccination program is girls-only with 40% coverage and vaccine is assumed to have 100% efficacy and lifelong duration for the two sites of infection. Models predictions are presented as the median and intervals denote the 25th-75th percentiles of predictions.

even greater when comparing the 75th quantiles or the maximum predicted effectiveness (Fig. 1A and Table 2). Finally, the inclusion of autoinoculation caused a decrease in predicted effectiveness by around 6 percentage points, assuming an extragenital prevalence between 3.0% and 7.5%.

Under the assumption of local immunity after genital and extragenital infection, predicted effectiveness with the multi-site model is slightly greater than with the uni-site model when extragenital prevalence is low, and slightly lower when extragenital prevalence is high (Fig. 1B and Table 2). As in scenario 1, the distribution of predicted effectiveness with the multi-site model is much more skewed toward higher values (see Fig. 1B and Table 2). Overall, the difference in predictions between the two models is lower in scenario 2 than in scenario 1. Autoinoculation had little impact on predicted effectiveness.

3.1.2. Effect of multi-site transmission, assuming systemic immunity after genital infection only (scenario 3) or systemic immunity after genital and extragenital infection (scenario 4)

Under the assumption of systemic immunity after genital infection, predictions with both models are almost identical with or without autoinoculation (Fig. 1C and Table 2). Under the assumption of systemic immunity after genital and extragenital infections, predicted effectiveness with the multi-site model is lower than with the uni-site model (Fig. 1D and Table 2). The difference between the uni-site and multi-site models increases with higher extragenital prevalence. Autoinoculation caused an increase in predicted effectiveness up to 5 percentage points, assuming an extragenital prevalence of 3.0%-7.5%.

3.1.3. Sensitivity analyses

The qualitative differences between the uni-site and multi-site model predictions are not affected by vaccination coverage as long as coverage is below the elimination threshold (see Fig. S6 in Supplementary materials). For example, under the assumption of local immunity after genital infection (scenario 1), differences between the uni-site and multi-site models start diminishing as coverage exceeds 50% (when the upper range of the multi-site model's predictions reach the elimination threshold) and disappear if coverage exceeds 75% (elimination of HPV16 with both the uni-site and multi-site models).

3.2. Understanding the effect of the key factors of transmission responsible for difference in predictions of HPV16 vaccination effectiveness between multi-site and uni-site models

3.2.1. Effect of inter-site transmission on the elimination threshold with the simple homogeneous multi-site model

Fig. 2 shows that the elimination threshold decreases with increasing extragenital → genital transmission (Factor 1) and/or decreasing genital → extragenital transmission (Factor 2). It can also be extrapolated from Fig. 2 that the minimum elimination threshold decreases as the proportion of susceptibles to extragenital infection increases (Factor 3). This result is stated in full and demonstrated in Section 2.3 of the Supplementary materials. Briefly, the minimum value of the elimination threshold for the multi-site model (3% in Fig. 2) is equal to 1-proportion of susceptibles to extragenital infections. Thus, if the proportion of susceptibles to extragenital infections increases, 1-

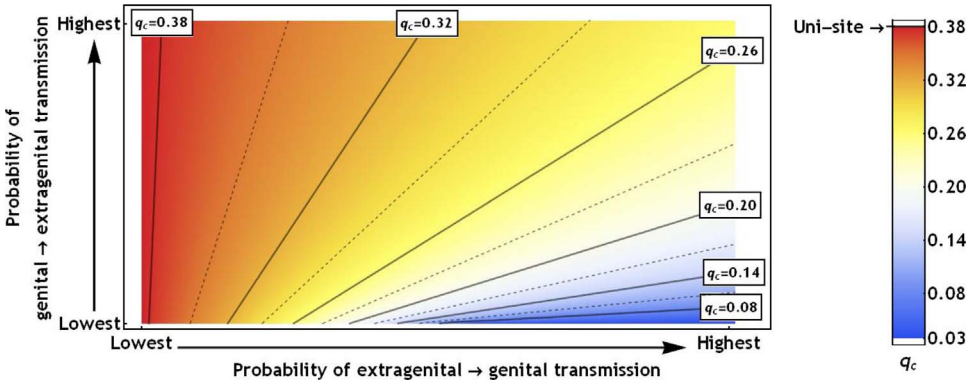

Fig. 2. Effect of transmission parameters on the elimination threshold (q_c) of the multi-site model. The model was calibrated to a genital prevalence of 7% and an extragenital prevalence of 3%. The x-axis represents probability that a male with an extragenital infection infects the genital site of his partner during a partnership, and the y-axis represents the probability that a male with a genital infection infects the extragenital site of his partner during a partnership. q_c = elimination threshold, minimum vaccination coverage needed to achieve elimination assuming a vaccine with 100% efficacy and lifelong duration. Elimination threshold for the uni-site model is given by the black line on the scale for the elimination threshold.

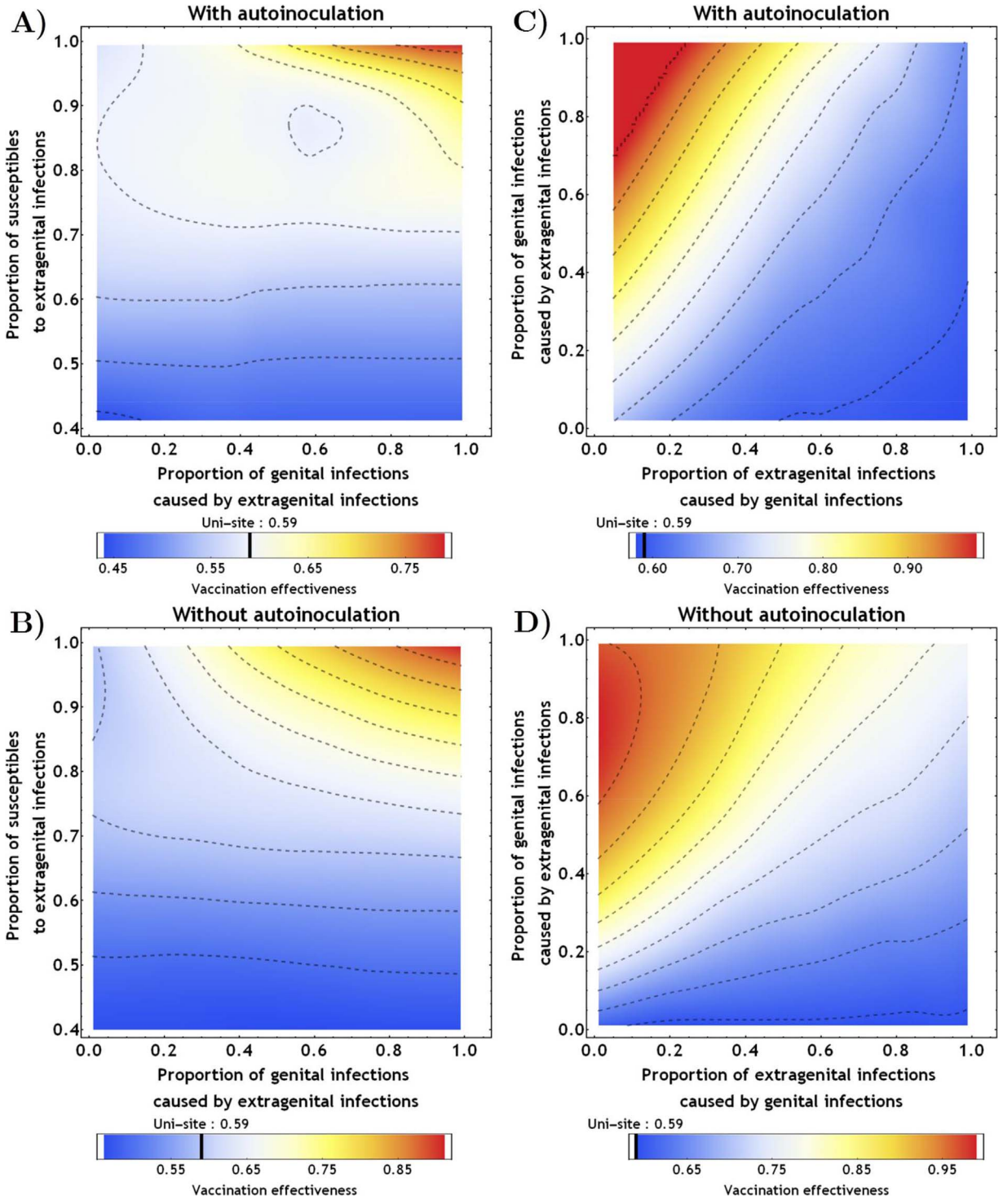

Fig. 3. Effect of inter-site transmission and proportion of susceptibles to extragenital infection on average predicted effectiveness with the multi-site model. A) Vaccination effectiveness as function of the proportion of susceptibles to extragenital infections and of the proportion of genital infections caused by extragenital infections (with autoinoculation), B) (without autoinoculation), C) Vaccination effectiveness as function of the proportion of genital infections caused by extragenital infections and of the proportions of extragenital infections caused by genital infections (with autoinoculation), D) (without autoinoculation). IMPORTANTLY: In C) and D) we show the results for simulations where the proportion of susceptibles to extragenital infections is higher than 90% (below this value there was no variability in vaccination effectiveness). Vaccination effectiveness = relative reduction in genital HPV16 prevalence at the post-vaccination equilibrium compared to no vaccination. Proportion of genital infections caused by extragenital infections = (Incidence of genital infections caused by extragenital infections)/(Total incidence of genital infections). Incidence = (contact rate) x (probability of transmission) x (prevalence of infected) x (prevalence of susceptibles to genital infections). OF NOTE: The median prediction of vaccination effectiveness from the uni-site model is given by the black line on the vaccination effectiveness scales. The relation between variables was smoothed through local polynomial regression.

proportion of susceptibles to extragenital infections decreases and so does the minimum elimination threshold. The maximum value of the elimination threshold (38% in Fig. 2) is equal to 1-proportion of susceptibles to genital infections. Hence, the maximal value of the elimination threshold for the multi-site model corresponds to the elimination threshold of a uni-site model of the genital site, and the minimal value to the elimination threshold of a uni-site model of the extragenital site. In particular, if the proportions of susceptibles to

genital and extragenital infections are the same, the elimination threshold of the multi-site model will be the same as the elimination threshold of the uni-site model.

In the Supplementary materials, we show analytically the results presented above and that they are not dependent on specific parameter values or assumptions of natural immunity.

3.2.2. Effect of inter-site transmission and proportion of susceptibles to extragenital infection on predictions of HPV16 vaccination effectiveness

Fig. 3 shows HPV16 vaccination effectiveness predictions of the heterogeneous multi-site model as a function of the three key factors, measured at pre-vaccination equilibrium: 1) the proportion of genital infections that were caused by an extragenital infection, 2) the proportion of extragenital infections that were caused by a genital infection, and 3) the proportion of susceptibles to extragenital infections. The relationships are all monotonic with predicted vaccination effectiveness increasing when the proportion of susceptibles to extragenital infections increases, when the proportion of genital infections caused by extragenital infections increases, and when the proportion of extragenital infections caused by genital infections decreases. These results were the same when including autoinoculation or not.

4. Discussion

In this paper, we examined whether the predictions of traditional uni-site models that were used to inform decisions about vaccination are biased because they do not take into account transmission between different sites. Our results suggest that the difference between the predictions of the uni-site and multi-site models are a function of natural immunity assumptions and prevalence at the extragenital site. Under the assumption of local immunity (scenario 1 and 2), vaccination effectiveness predictions with the multi-site model are either equal or greater than with the uni-site model. This difference increases when assuming that a greater proportion of HPV16 genital infections was produced by extragenital infections. Under the assumption that natural immunity confers systemic protection against infection at all sites (scenario 3 and 4), the multi-site model predictions of vaccination effectiveness were either the same or lower than the uni-site model predictions.

The effects of natural immunity assumptions are essentially due to differences in the proportions of susceptibles to genital infections and to extragenital infections (Factor 3). The proportion of susceptibles to extragenital infection is the highest under scenario 1 of local immunity after genital infection, because there is no natural immunity to extragenital infections. Predicted effectiveness is consequently highest under scenario 1. The proportion of susceptibles to extragenital infection is lower in scenario 3 (systemic immunity after genital infection) than scenario 2 (local immunity after genital and extragenital infections) and is the lowest in scenario 4 (systemic immunity after genital and extragenital infections). In scenario 3, the proportion of susceptibles to extragenital infection is roughly the same as the proportion of susceptibles to genital infection, which explains why the multi-site and uni-site models predict similar effectiveness. Under scenario 4, the proportion of susceptibles to genital infection is exceptionally lower than for the uni-site model: natural immunity post-extragenital infection hinders the transmission to genital sites.

Current evidence from the literature seems to lend more support to the assumption of systemic immunity following clearance of genital infection (scenario 3) (Carter et al., 2000; Brouwer et al., 2015a; Giuliano et al., 2015). To our knowledge, there is no direct evidence and no literature about the possibility of local immunity against HPV infections (scenario 1 & 2). Yet, both the acquired humoral and cell-mediated immune system could theoretically have site-specific differences, which could result in greater natural immunity at the site of a previous infection. For example, Tissue-Resident Memory T-cells could be responsible for differential local immunity (Gebhardt and Mackay, 2012). On the other hand, vaccination should induce systemic HPV immunity, which is supported by recent studies (Beachler et al., 2016). Whether systemic immunity also extends to naturally acquired antibodies remains unknown. If this was the case, systemic immunity would be more likely following cervical HPV infection than infection at any other sites, because the rate of seroconversion is the highest following cervical infection and is very low for other sites of infection (Carter et al., 2000; Brouwer et al., 2015a; Giuliano et al., 2015). Thus, the higher rate of seroconversion in women should result in greater protection of women against extragenital HPV infections, and this has been proposed as an explanation for the gender-difference in oral HPV prevalence (Gillison, Broutian et al., 2012). However, a protective effect of antibodies on acquisition of extragenital infections has not yet been demonstrated (Beachler et al., 2015; Pierce Campbell et al., 2016). Furthermore, prevalence of anal HPV is not lower in women compared to men, but this could be due to a strong correlation in the timing of anal and genital HPV acquisition in women (hence women may acquire anal HPV before acquiring natural immunity).

Our study is the first to calibrate a multi-site model to HPV prevalence to assess differences in predicted effectiveness with traditional uni-site models. To our knowledge, two multi-site models have been published (Heijne et al., 2017; Brouwer et al., 2015b; Hui et al., 2015), and none of which has examined the impact of vaccination. In particular, Brouwer et al. (Brouwer et al., 2015b) have shown that a substantial bias can occur by calibrating a model without autoinoculation if the true model generating the data has autoinoculation. Our results show that models with autoinoculation predict lower effectiveness than models without autoinoculation in some specific contexts (e.g., when the proportion of individuals susceptible to genital infections is similar to the proportion of those susceptible to extragenital infections). However, the effect of autoinoculation was much lower than in the theoretical example presented in Bouwer et al. This may be because Bouwer et al., did not include natural immunity in their models and did not calibrate their model to endemic prevalence of HPV. Hui et al. (Hui et al., 2015) have shown that pharyngeal and anal infections by gonorrhea can explain the substained transmission to the urethral site in a Men-who-have-Sex-with-Men population in which transmission occurs through oral⇔genital, oral⇔anal, and anal⇔genital contacts. They are able to show that transmission of gonorrhea can be disrupted by preventing only oral⇔genital transmission. Unlike the work of Hui et al. (Hui et al., 2015), we cannot determine from the calibration we performed whether a specific HPV transmission pathway (e.g., genital → oral autoinoculation) is essential or important for sustained transmission of HPV infections. This would require further knowledge on the relevant modes of HPV transmissions which could include non-penetrative acts such as kissing or sexual touching.

This study has three main limitations. First, for simplicity, we calibrated our modeIs using probabilities of HPV transmission, while other parameters remained fixed at values extracted from the literature. We examined different assumptions (and values) of natural immunity. Varying the probability of natural immunity affects the proportion of susceptibles to infection at the different sites. We observed that increasing the probability of natural immunity to extragenital infections from 0% (scenario 1) to 45% (scenario 2) decreased the proportion of susceptibles to extragenital infections and thus decreased predicted effectiveness with the multi-site model. Varying clearance rates also affects the proportion of susceptibles: for a given prevalence of infection, increasing clearance rates increases the proportion of immune individuals and decreases the proportion of susceptibles. Second, we assumed near-symmetrical transmission parameters between women and men. We show in the Supplementary materials that there may be additional dynamics to consider when the prevalences are highly asymmetrical between women and men, but the bounds on the elimination threshold we observed in Fig. 2 would not change. Finally, we did not include specific sexual acts (e.g., oral sex) in our model, which implies that there is no within-individual correlation in sexual

practices.

HPV may be able to infect other sites than the anal, genital and oral canals. For instance, nails are known to harbor HPV DNA and subungual cancers have been attributed to HPV16 (Moy et al., 1989). The inclusion of these other sites of infection in HPV models could affect predictions of vaccination effectiveness against genital infection only if infections at these sites can be transmitted to the genital site (even indirectly) or if they contribute to natural immunity to genital infections. Some of the results presented here can be generalized to any number of sites. Thus, if the simple multi-site HPV model was to include three or more sites of infection (e.g., genital, oral and anal), predicted effectiveness would be in-between effectiveness predicted with two uni-site models of the two sites with the highest and lowest proportions of susceptibles. However, for the heterogeneous multi-site model of objective 1, the minimum predicted effectiveness with the multi-site model can theoretically be lower than the effectiveness predicted with a uni-site model fitted to genital HPV (the site with the lowest proportion of susceptibles) as shown in Fig. 1B. This phenomenon can be amplified with additional sites (see Supplementary materials).

5. Conclusions

In conclusion, for the assessment of vaccination effectiveness against genital infections and diseases, multi-site transmission of HPV is important to model if: 1) a significant proportion of genital infections originates from an extragenital site, or 2) extragenital infection contributes significantly to the natural immunity against genital infection. Currently, there is no strong evidence that extragenital infections are a reservoir for genital infections in heterosexual transmission of HPV or that natural immunity following extragenital infections would protect against future genital infections. Hence, the possibility of a strong bias from using a uni-site model to assess vaccination effectiveness against genital HPV16 in women is unlikely given our current understanding of the natural history of HPV infection.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.epidem.2017.08.001.

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