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

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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

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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).