

What determines the type-specific prevalence of high-risk human papillomavirus (HPV) infection? – implications for the impact of vaccination against types 16 and 18

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A new paradigm for cervical cancer prevention

Throughout the twentieth century, vaccines have repeatedly proven successful in bringing some equity in health care to the different regions of the world. Since cervical cancer has become recognized as an infectious disease, namely one resulting from a genital papillomavirus infection, the prospect of vaccination offers new hope for global cervical cancer control.

Cervical cancer is the second most common cancer among women worldwide, with an annual incidence of approximately half a million cases. Over 80% of these occur in developing countries, where case-fatality rates (number that die from cervical cancer divided by the number of cervical cancer cases) are disproportionately higher than in developed regions (1). Global access to human papillomavirus (HPV) vaccination is only possible if manufacturers are willing to lower their prices for developing countries. If they do, not only the vaccinees might benefit but also the non-vaccinees, as vaccination brings about a reduction in the transmission of oncogenic papillomavirus throughout the population.

Here some thought is given to those factors that determine the pre-vaccine prevalence of oncogenic papillomavirus infection and consider their role in determining the impact of vaccination.

Papillomavirus infection and cancer

Papillomaviruses form a diverse group of non-enveloped double-stranded DNA viruses that replicate exclusively in the body surface tissues of mammals, birds, and a small number of reptiles. They were first identified when it was shown that skin warts, or papillomas, could be transmitted between individuals by a filterable infectious agent (2). Nowadays, several hundreds of distinct species – traditionally referred to as ‘types’ – have been determined that are highly adapted to replication in a single host species’ tissue. Although not a typical outcome of infection, some papillomaviruses can cause cancer in the epithelial tissues they inhabit. The development of papillomavirus-induced cancers typically occurs over the course of many years (3).

About 30 of the HPV types are associated with infection of the ano-genital region, 14 of which have been classified as oncogenic. It is firmly established that persistent infection with one of these so-called high-risk HPV (hrHPV) types is a prerequisite for the development of cervical cancer. High-risk types are also associated with cancer of the penis, vulva, vagina, and oropharyngeal tract (1). The identification of HPV as a causative agent of cancer paved the way for the development of prophylactic vaccines against hrHPV infections, primarily intended to act as a vaccine against cervical cancer. Two vaccines have currently been licensed for use in young women and pre-adolescent girls (Gardasil®, Cervarix®). Both vaccines target oncogenic HPV types 16 and 18 and one of them (Gardasil®) also targets HPV types 6 and 11, primarily associated with genital warts. HPV16 and 18 stand out as both the most prevalent and the most oncogenic among the hrHPV types and are associated with 70 to 76% of the cervical cancers worldwide (4).

Prevalence of oncogenic papillomavirus types

Estimating the impact of HPV vaccination on the reduction in the rate of cervical cancer requires an understanding of the determinants that govern the prevalence of the various hrHPV types prior to vaccination. Epidemiological studies have provided ample evidence that sexual partners are the source of practically all incident genital HPV infections. The fact that hrHPV is sexually transmitted partly explains the age-specific patterns in hrHPV prevalence data and the geographic variation in hrHPV infection risk (5). However, it is unclear why some high-risk types are more widespread than others. One can think of various theoretical explanations that broadly fall in two categories.

The first category relates to differences in the course of hrHPV infection, due to variations in the virus life cycle and in the type-specific immune responses induced during infection (6, 7). Specifically, there are significant differences in clearance rate between hrHPV types (8), with an apparent relation to oncogenicity (9). Differential clearance offers one clue in explaining why some types are more widespread than others, especially if

a reduced clearance rate amounts to a prolonged opportunity for transmission. In this sense, the universally high prevalence of HPV16 could be a reflection of the comparatively long duration of infection and likewise of a prolonged period over which sexual partners are exposed to infection.

The second category of determinants relates to the likelihood of transmission of HPV infection. Imagine two virus types that are characterized by a similar course of infection, but have a different likelihood of transmission given a contact between an infected and an uninfected person. Of the two types, the one with the highest likelihood of transmission is expected to spread more easily and attain the highest population prevalence (10). Note that the cause for an increased likelihood of transmission may be ascribed to the infected person (who could have increased infectiousness due to e.g. a higher viral load), to the uninfected person (who could have increased susceptibility due to e.g. a relatively poor immune response), or to basic viral characteristics, e.g. a more efficient attachment to the epithelial cell surface or a relatively fast internalisation of bound virions (6). Either way, the universally high prevalence of HPV16 could be a reflection of the relative ease by which it is passed on from one person to another.

Model-based estimation from HPV prevalence data

Several of the viral and immunologic features that determine the pre-vaccine prevalence of hrHPV types become apparent in the age-specific profile of infection. For instance, all studies find that the prevalence of hrHPV infection is highest in young adults (5). Given that most individuals initiate sexual activity between 15 and 20 years of age, one might infer that hrHPV types should be transmitted relatively easily. Moreover, the prevalence of hrHPV infection declines with age, although both the starting age and the strength of this decline vary across studies and geographic regions. To a degree, this pattern represents reduced sexual activity at older age, but in addition, it is maybe shaped by the build-up of resistance to re-infection following repeated exposure to a particular HPV type. The strength of the decline in prevalence with age likewise depends on the duration of infection, as a gradual decline may be indicative of a relatively slow viral clearance.

Various features of the course and transmission of hrHPV infection can be disentangled by fitting a model to cross-sectional prevalence data. In doing so, one must assume that the prevalence of infection in the pre-vaccine era reflects a dynamic equilibrium of virus transmission in a single host population. Note that in all but the simplest of models, the function that describes the age-specific prevalence of infection is not explicitly known and has to be found by numerical approximation. We developed an elaborate model to describe hrHPV prevalence in the Netherlands, considering the importance of variation in sexual activity and of age-specific

preferences in sexual contacts in determining the endemic steady state in the general population (11). Two large-scale surveys on sexual behaviour were used to build a sexual contact network underlying the hrHPV transmission model. Next, this model was fitted to the prevalence of hrHPV DNA in cervical smears collected in the baseline round of a prospective population-based cervical cancer screening trial. This trial was aimed at the implementation of hrHPV testing in cervical screening in the Netherlands and included close to 45,000 women (8, 9). Longitudinal observations from the same trial were added to the estimation framework to inform those parameters related to the course of hrHPV infection.

The study confirmed that hrHPV is transmitted very easily. Per-partnership transmission probability (if either partner is infectious and the other is susceptible) was consistently estimated above 0.40 for each type, with an average of 0.79 for all of the 14 hrHPV type-specific estimates combined (11). Additionally, it was found that the decrease in hrHPV prevalence with age could not be explained by decreasing sexual activity and cervical screening only, but that it also required the presence of significant type-specific immunity derived from natural infection. The model nonetheless allowed a considerable variation in the duration of resistance to re-infection between individual hosts. It would be interesting to assess whether a less gradual decline in hrHPV prevalence with age, as is observed in some geographic regions (5), might be due to a less long-lived immune response.

To address the question why some high-risk types are more widespread than others, we also performed regression analyses of the type-specific prevalence on the type-specific model parameters (11). It turned out that the strongest determinant of hrHPV prevalence was the proportion of incident genital HPV infections that developed into a persistent infection. Differences in estimated transmission probabilities explained only a minor proportion of the differences in prevalence among the hrHPV types. Thus, it seems that the high prevalence of HPV16 is predominantly a reflection of the comparatively long duration of infection rather than the ease by which HPV16 spreads.

Implications for the impact of HPV16/18 vaccination

Wide-scale HPV vaccination is expected to reduce the transmission risk in the sexually active population, which conjures a benefit for non-vaccinees. The extent of this indirect effect of vaccination (commonly referred to as herd immunity) depends on the basic reproduction number, a measure for the transmission potential of an infection: the higher the basic reproduction number, the less the benefit through reduced transmission (10). The basic reproduction number increases both with the duration of infection (prolonged infection affords an increased opportunity for transmission) and with the

transmission probability in an infectious-susceptible partnership. According to our estimates, the prime targets of vaccination (HPV16/18) provide the greatest opportunity for transmission among the 14 hrHPV types. Combined with the generally high transmission probability of hrHPV infection, one might therefore expect only a moderate role of herd immunity in determining the impact of HPV vaccination. Thus, for types 16 and 18, extensive vaccination coverage and high vaccine efficacy will be required to substantially reduce the rate of cervical cancer. On the other hand, HPV16/18 vaccination induces significant cross-protection to other hrHPV types (notably types 31, 33, 45, and 58) that are characterized by a lower transmission potential. The reduction in transmission risk may be more pronounced for these types, especially as the efficacy of cross-protection appears to be high (12).

Finally, the transmission potential of a sexually transmitted infection critically depends on the sexual contact network. In populations with a high pre-vaccine prevalence of hrHPV infection, the network might be such that HPV spreads easily due to high contact rates between infectious and susceptible individuals. Theory then predicts a relatively low population impact of HPV vaccination, compared to populations with a low prevalence prior to vaccination. If, however, the high pre-vaccine prevalence of hrHPV infection in some geographic regions is caused by poor immunologic features (resulting from poor nutrition or co-infection with e.g. HIV), then the extent of herd immunity that follows from HPV vaccination may be comparable to that in low-risk regions.

Future research should further uncover the epidemiologic determinants of hrHPV infection, with special regard to the differences in prevalence between geographic regions. This knowledge, in turn, will facilitate a better country-specific assessment of the potential benefit of HPV vaccination.

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