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Perspective

HPV vaccination: Are we overlooking additional opportunities to control HPV infection and transmission?

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ABSTRACT

Human papillomavirus virus-like particles (HPV VLPs) have distinctive immunogenic properties that generate a durable antibody response, producing high-quality neutralizing antibodies. By vaccination, i.e., intramuscular injection of these HPV VLPs, the viral survival strategy of avoiding exposure to the systemic immune system is completely overruled, and large amounts of vaccine-induced systemic antibodies are generated. These systemic circulating antibodies are easily transuded to the genital mucosa and are detectable in female genital secretions. It is well accepted that these antibodies interact with the virions presented by an infected partner and inhibit infection. However, much less attention has been paid to the role of anti-HPV vaccine-induced antibodies in an HPV-infected individual where infectious virions are encountered by neutralizing antibodies in mucosal secretions. There is a clear need to further investigate and document this role. Indeed, if HPV vaccination of HPV-infected women has an effect on HPV transmission, auto-inoculation, and relapse after treatment, this may influence how we model, assess, and implement HPV vaccination programmes.

Introduction

The impact of human papillomavirus (HPV) vaccination, provided sufficient vaccination coverage is reached, has been overwhelming. Important decreases in the prevalence of detectable HPV DNA and genital warts have been reported in vaccinees, as well as in unvaccinated individuals, regardless of sex, through herd protection (Cameron et al., 2016; Drolet et al., 2015). A rapid and significant decline in genital warts over time has also occurred in boys and men younger than 30 years of age in population programmes of female-only vaccination (quadrivalent vaccine) reaching vaccination coverage over 50% (Drolet et al., 2015).

To better understand the potential impact of HPV vaccination, it is important to recognize that HPV and its mode of infection have particular characteristics that shape the host immune response and permit vaccine-induced antibodies to counter the infection.

A unique combination of potent antigens and a susceptible immune ignored virus

First, HPV viral-like particles (VLPs) have distinctive antigenic properties. In fact, B-cell receptors interact with the dense, optimally spaced, and repetitive protein arrays on the surface of the VLPs, which promote the induction of an exceptionally potent antibody response. Indeed, the oligomerization of B-cell receptor/VLP signalling complexes leads to robust activation and proliferation signals, high levels of antibodies with high avidity, and long-lived plasma cells that continuously produce antibodies for many years after vaccination (Gomes et al., 2017). Interestingly, this potent antibody response underpins the ongoing randomized trials of single-dose schedules (Kreimer et al., 2018).

Second, HPVs have evolved to maintain immune ignorance rather than develop mechanisms to actively counter the mucosal and systemic immune system (Schwarz and Leo, 2008; Roden and Stern, 2018). Fortunately, injection of the parental VLPs, as is done when vaccinating, overcomes this immune system evasion strategy. In fact, HPV vaccination generates 10- to 100-fold higher levels of L1-specific serum neutralizing antibodies than a natural infection (Stanley, 2010).

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Finally, anti-HPV antibodies play a unique and decisive role in the protection against HPV infection. This has been elegantly shown in animal models. Passive immunization, injecting sera from 4vHPV immunized mice interperitoneally, conferred neutralizing protection in mice genitally challenged with pseudovirions (PsVs) (Longet et al., 2011). It is important to mention that anti-HPV IgG antibodies were also detected at the mucosal level, demonstrating the transudation of IgG.

Neutralizing antibodies play a crucial role

The current understanding of antibody-mediated protection is built on the major role of neutralizing antibodies, and different potentially complementary mechanisms have been postulated (Stanley, 2010). For virions to access the basal mucosal cells, epithelial microlesions are required. It has been proposed that virions are neutralized by systemic neutralizing antibodies that exude from these microlesions and scavenge the mucosal membrane. As internalization is a relatively slow process that requires a series of conformational changes, there is sufficient time for vaccine-induced antibodies to interact with the virions and disrupt this process. However, vaccine-induced antibodies present at the mucosal level, which are also transudated, most likely via interaction with the neonatal Fc receptor, may play a major role (Schwarz, 2009; Einstein et al., 2011; Stanley et al., 2006; Li et al., 2011). Previous studies have shown that the genital mucosa of vaccinated girls also harbours detectable vaccine-induced transuded IgG, and moderate to high correlation coefficients between serum and cervical IgG titres have been reported (Schwarz et al., 2009). Scherpenisse et al. reported transudated anti-HPV IgG antibody concentrations in cervicovaginal samples of up to 2% of the concentration detected in serum (Scherpenisse et al., 2013). This finding indicates that we may have, solely by transudation, anti-HPV antibodies at 'neutralizing' concentrations. Indeed, Longet et al. reported in their animal model that serum antibody levels >100-fold lower than those detectable by in vitro PsV neutralization assays are sufficient to confer protection against an HPV PsV genital infection (Longet et al., 2011). The neutralizing capacity of cervicovaginal lavage samples from immunized non-human primates has also been demonstrated in an HPV-11 athymic mouse xenograft neutralization assay (Lowe et al., 1997). It is important to add that levels of detectable vaccine-induced cervicovaginal antibodies vary across the menstrual cycle (Nardelli-Haefliger et al., 2003). The potential impact of this variation on protection and prevention of transmission should be taken into account in future research.

HPV vaccination of HPV-infected women is equally immunogenic and completely safe

It has been shown that HPV vaccination of previously HPV-infected women is safe and generates a high-level immune response (Arbyn et al., 2018; Group FIS, 2007; Haupt et al., 2011; Meites et al., 2019). Therefore, even in women with a productive infection, vaccination will lead to a potentially neutralizing amount of transudated anti-HPV antibodies in their cervicovaginal secretions. Furthermore, protection against non-prevalent HPV types included in the vaccine is activated as in HPV-naïve women.

First, this concept suggests that vaccination may prevent infectious virions from a productive infection spreading from sites with low potential for malignant progression to the cervical transformation zone with higher potential for progression (Schiller and Davies, 2004). Second, vaccination may also decrease the likelihood that women with a productive infection transmit the infection to their sexual partner, as already postulated by Schiller et al. in 2004 (Schiller and Davies, 2004). Indeed, in HPV-vaccinated women, newly produced viral particles are shed in a milieu with highly potent anti-HPV antibodies that are able to interact with and neutralize the viral particles. This finding may imply that HPV-infected HPV-vaccinated women will no longer (or to a lesser extent) be able to re-infect themselves or transmit their infection(s). A special discussion of transmission interruption could be initiated in relation to the high-risk groups for transmission, e.g. commercial sex workers, currently outside of any special vaccination programmes (Schim van der Loeff et al., 2019).

Paradoxically, during follow-up of women with an existing infection in randomized controlled vaccine trials (RCTs), no impact of vaccination on the rate of progression was shown. However, it should be noted that these trials were not designed to demonstrate the potential impact of vaccination on auto-inoculation. In most RCTs, cervical sampling occurred prior to vaccination, which as we discuss below, may impact the risk of acquisition and perhaps the natural course of the infection. In addition, HPV DNA assays with a defined clinical cut-off will predominantly identify women who already have a clinical lesion that is not affected by vaccination.

Although it remains difficult to investigate experimentally or epidemiologically whether vaccination does block transmission, further efforts are needed. For instance, including self-collected none invasive cervicovaginal secretion sampling and using sensitive analytical assays in the design of future vaccine trials may help to further investigate what is happening at the level of the genital mucosa.

The potential impact of vaccination on HPV transmission will likely be more prominent in women than in men; viral particles are less likely to come into contact with mucosal transduced antibodies in men.

Potential benefit of HPV vaccination when screening HPV-positive women

Cervical screening is a major tool contributing to the early detection and subsequent removal of precancerous lesions. However, the collection of cervical cells from women with a productive genital HPV infection could also create new infection sites for circulating infectious virions in the genital tract. Indeed, the principle of a cytobrush is to remove epithelial cells and consequently create microlesions, which in turn provide passage for HPV to infect mucosal basal cells. Of note, in the animal model mentioned above, cytobrushes were also used to create effective entry sites for pseudovirions (Roberts et al., 2007). The more direct and compelling study of Roberts et al. in macaques confirms the hypothesis that cytology screening in women might lead to a transient enhancement of susceptibility to HPV infection (Roberts et al., 2011). Currently, the impact of screening on auto-inoculation is unknown, so further research on this topic is merited. In this context, vaccination of young women prior to cervical cancer screening may be beneficial in addition to the well-established advantage of vaccinating prior to sexual debut.

It is recognized that these biologically plausible hypotheses warrant further proof. However, if confirmed, these may have a substantial impact on how we model, assess, and implement HPV vaccination programmes more effectively.

Most vaccine impact models disregard vaccinating adult women because type-specific HPV exposure is likely to have occurred and the benefits to the individual are seen as marginal. However, if the hypothesis above is true, vaccination of HPV-infected women will not only reduce auto-inoculation but also offer additional protection to the group (herd protection) by neutralizing the infectious virions being shed. Asymptomatic individuals with productive lesions shedding infectious viral particles are the main source for spreading the infection in the

population. Therefore, strategies that potentially reduce this transmission must be explored to accelerate the reduction in infection. The change to primary HPV DNA screening will identify HPV DNA-positive women who have no or only low-grade lesions (approximately 5–10%), for whom current treatment is not recommended.

Clearly, from this perspective, the indication for vaccination would benefit from expanding the target population, including HPV-positive women identified at screening (in addition to the conventional high-risk groups) and eventually include a broader age range in primary vaccination campaigns (Bosch et al., 2016). A temporal drawback in this proposal reflects that in the current global context of ongoing vaccine shortage, and the big disparity between high income and low and middle income countries, other strategies instead of extending the target group for vaccination may provide a much bigger global public health benefit. However, the better we understand the potential of HPV vaccination, the better we can make informed decisions.

Vaccination reduces the risk of clinical disease relapse after treatment

The first evidence that HPV vaccination also reduces post-treatment relapse is becoming available. As well as the previous clinical observations of Kang et al., Ghelardi et al. showed that post-treatment vaccination of women resulted in an 81.2% (95% confidence interval 34.3–95.7%) risk reduction of clinical disease relapse (Ghelardi et al., 2018; Kang et al., 2013). These observations are an additional argument for vaccination of HPV-positive women, as they show an additional individual benefit in the case of disease progression.

Conclusions

Based on the discussion above, we would like to call for further investigation and documentation of the potential public health benefits of vaccination of HPV-positive women. For modellers, these data would provide an additional effect that should be considered when designing HPV vaccination impact models exploring and quantifying the herd protection observed in population programmes. Finally, these additional modes of protection may also reduce the existing reluctance to vaccinate (young) women post-sexual debut or known high-risk groups such as sex workers.

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Ethical approval

Ethical approval was not required.

Conflict of interest

AV University of Antwerp obtained unrestricted educational grants from GSK, Merck, and Sanofi Pasteur; speakers fees from Merck were paid directly to an educational fund held by the University of Antwerp. AV is co-founder of Novosanis, a spin-off company of the University of Antwerp. FXB received research funding via his institution from GSK, Merck, Qiagen, Roche, and SPMSD, and reimbursement of travel expenses for attending symposia, meetings and/or speaking at conferences from GSK, Merck, Qiagen, Roche, and SPMSD. PVD acts as principal investigator for HPV vaccine trials conducted on behalf of the University of Antwerp, for which the University obtained research grants from vaccine manufacturers; speaker's fees for presentations were paid directly to an educational fund held by the University of Antwerp. PVD is co-founder of Novosanis, a spin-off company of the University of Antwerp.

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