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Publication Date

2017-12-01

DOI

10.1016/j.pvr.2017.06.002

Peer reviewed



HPV vaccination of immunocompromised hosts



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ARTICLE INFO

Keywords:

Human papillomavirus (HPV)
Vaccination
Immunocompromised hosts
HPV related cancers
HPV Guidelines

ABSTRACT

It is well-established that immunocompromised people are at increased risk of HPV-related disease compared with those who are immunocompetent. Prophylactic HPV sub-unit vaccines are safe and immunogenic in immunocompromised people and it is strongly recommended that vaccination occur according to national guidelines. When delivered to immunocompromised populations, HPV vaccines should be given as a 3-dose regimen.

1. Introduction

For the immunocompetent host, there are clear guidelines on the use of prophylactic human papillomavirus [HPV] vaccines (bivalent [2vHPV], quadrivalent [4vHPV] and nonavalent [9vHPV]) available from various international public health authorities, regulatory agencies and societies. These include the World Health Organisation (WHO) [1,2], European Medicines Agency (EMA) [3,4], as well as numerous national advisory committees worldwide, such as the Food and Drug Administration (FDA), US Advisory Committee on Immunisation Practices (ACIP) [5–10] American Society of Clinical Oncology [ASCO], Australian Therapeutic Goods Administration (TGA), Australian Technical Advisory Group on Immunisation [11], National Advisory Committee on Immunisation (NACI) in Canada [12], and International Papillomavirus Society (IPVS) [13]. The

currently licensed vaccines are viral-like-particles, which are subunit, non-replicating, and do not contain any infectious component. There is good evidence that HPV 16 and 18 contribute globally to 70% of cervical cancers [14], 78% of HPV related vulvar cancer [15], 65% of vaginal [16] and 90% of anal cancers in both sexes [17], as well as a geographically variable proportion of oropharyngeal cancers. Hence, the expected reduction in disease is substantial for those vaccinated with the 2vHPV or 4vHPV vaccine when given prior to HPV infection. Moreover, with the new 9vHPV vaccine, the proportion of the cancer burden that is potentially preventable in women rises an incremental amount to approximately 90% [18,19], 92% [15], 86% [16] and 95% [17], respectively, for cervical, vulvar, vaginal and vulvar cancer. These guidelines generally focus attention on vaccination of female preadolescents (target age is country-specific and dependent upon delivery strategy) from 9 to 14 years of age and prior to sexual debut, although

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<http://dx.doi.org/10.1016/j.pvr.2017.06.002>

Received 28 April 2017; Received in revised form 2 June 2017; Accepted 2 June 2017

Available online 03 June 2017

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some have included a catch-up period up to 26 years of age. In some countries, there is a gender-neutral approach including boys. Based on immunogenicity data, and following endorsement from the WHO in 2014, a two-dose regimen is now recommended in many countries for immunocompetent individuals aged under 15 years at receipt of the first vaccine dose, with a dose interval of at least 6 months. Those who are 15 years or older at first dose, or those who are immunocompromised, require the standard three-dose vaccination schedule [1].

Guidelines for HPV vaccination of the immunocompromised host are provided in some countries by specialist immunisation advisory groups or societies [20–24]. In many countries immunisation for these groups is recommended, regardless of age, but not nationally funded. In this position statement, we outline the rationale for ensuring that clinicians, patients and policy makers explicitly consider the potential role of HPV vaccination in immunocompromised individuals.

2. Immunocompromised hosts

Immunocompromised hosts include those with infections affecting immune competency such as human immunodeficiency virus (HIV), and those on immunosuppressive and/or immunomodulatory treatment for autoimmune conditions (e.g. multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus (SLE)), or for prevention of graft rejection among those who are post-transplantation.

It has been well documented that HIV-positive women, have an overall higher prevalence of HPV DNA two or threefold higher than HIV negative women [25] (60–70%), have a higher prevalence of high-risk-HPV DNA (20–35%) [26], types that are known to cause cancer, more likely to have multiple HPV types present (35–50%) [25], higher HPV viral loads (45–60%) [25] and persistent HR-HPV infections (45% vs 15%) [25–29]. Notably a lower CD4 count in female patients is strongly associated with cervical and anal high grade squamous intraepithelial lesions (HSIL). There is also a greater risk of vulvar HSIL [30], a 10-fold greater risk of anal cancer [31] and a three to five fold higher risk for cervical SIL, with invasive cervical cancer being an AIDS-defining illness [32–36]. In addition for males and females who are HIV-positive there is a higher risk of HR-HPV anal infection, anal HSIL and anal cancer [37,38]. Although this association is presumably due to impaired ability to clear HPV and increased reactivation of latent infection [39–45], other mechanisms may be involved that result in cellular immune dysfunction [46,47].

Those who are immunocompromised for reasons other than HIV infection are also at increased risk of HPV infection, HSIL and cancer compared with immunocompetent individuals [25–36,39,40,43,45, 48–54]. For example, prior to prophylactic vaccines being available, bone marrow transplantation patients had a higher rate of cervical HSIL than in the age-adjusted general population [48]. Moreover, it was recognised that allogeneic transplant recipients had a higher rate of cervical abnormalities than did patients receiving autologous transplants [48,54]. Higher rates of cervical abnormalities have also been found in studies of women with SLE, rheumatoid arthritis and inflammatory bowel disease when on immunosuppressant medications [43,45].

Individuals who are HIV positive remain at risk for acquiring new HPV infections which likely can be prevented by HPV vaccination. This includes prevention of HR infections that can progress to HSIL. It is to be noted that highly active antiretroviral therapy (HAART) has modest effect or no effect on HPV carriage, clearance or persistence [28] although recent reports suggest a decline in cervical HSIL [55]. Recent studies show that management guidelines for women on HAART with HIV viral suppression, can parallel guidelines for healthy women [56]. Moreover, immunosuppressed patients are also at a higher risk of HSIL due to low risk HPV types [57–59]. In those who are HIV-positive, as all immunosuppressed peoples, there is also greater risk of genital warts being recalcitrant to treatment [30].

2.1. A growing evidence base: HPV vaccine studies in immunocompromised people

The increased risk of HPV infection and associated diseases in immunocompromised men and women warrants a strong emphasis on vaccinating these individuals according to the relevant national guidelines. Individuals who meet these guidelines may be vaccinated while immunocompromised or ideally, prior to the development of immunocompromised status.

The 4vHPV vaccine has been administered to HIV-positive children 7–12 years of age with seroconversion rates greater than 96% [60]. Antibody titres for HPV 6/11/16/18, were 30–50% lower compared with historical age-matched controls, but higher than natural infections and in the range where clinical efficacy is seen in adults [60]. Studies in vertically-acquired HIV-positive adolescents adult men and women show high rates of seroconversion (95–100%), with no adverse effects on CD4 or plasma HIV RNA levels [61–68]. We currently await efficacy data, although 4vHPV vaccine will likely benefit immunocompromised men and women when vaccinated in the recommended age range, despite the lower titres seen in this population.

For the 2vHPV vaccine, similar studies in HIV-positive women demonstrated high seroconversion rates, and sustained positivity for anti-HPV 16 and 18 over 12 months. Although lower antibody titres were seen than in HIV-negative controls, the titres remained well above levels seen following natural infection [69]. As with the 4vHPV vaccine, the 2vHPV vaccine showed no adverse effect on CD4 count over time, nor effect on HIV viral load over time: however these studies have been performed in largely HIV positive subjects enrolled with reasonably high CD4 counts.

Vaccination in other immunocompromised groups, including patients with solid organ transplants and autoimmune disorders have demonstrated lower titres of antibodies in these patients compared with controls. These included patients with juvenile idiopathic arthritis, SLE, juvenile dermatomyositis, and kidney and lung transplant [70–73]. One study noted that titres appeared to differ by type of immunosuppressive drug treatment, with patients on mycophenolate producing lower HPV antibody titres than patients on other drugs [73]. Another study indicated that lung transplant patients had much lower antibodies than other solid organ transplant recipients [70]. However, these studies all showed that the vaccines were safe and consistently found that HPV vaccination was not associated with significant adverse effects and importantly, the clinical course of these diseases were also not affected [73–75].

Given that the recommendation for two dose schedules of HPV vaccines is currently based upon bridging data, showing equivalent immunogenicity in immunocompetent young adolescents as three doses in older persons in whom efficacy has been assessed, there is no current evidence to support equivalence in immunocompromised individuals. Consequently, the recommendations for those who are immunosuppressed or HIV-positive should be for 3 doses, within the recommended age guidelines and as early as possible prior to the onset of immunocompromise. Continued research in this group of vaccine recipients is necessary.

3. Screening remains important

Currently screening remains a critical component of cervical cancer prevention for all women, regardless of HPV vaccination status. Because of their increased risk of cervical HSIL and cervical cancer, risk of disease due to non-vaccine HPV types and the lack of efficacy studies post-vaccination, secondary prevention through screening remains critical for immunocompromised women, regardless of HPV vaccination status. Most countries recommend more frequent screening for these women than for the general population on the basis of their higher risk [76–79]. Studies are in progress to determine whether screening for, and treatment of, anal HSIL is of value in preventing anal cancer in at-risk populations [80–82].

4. Key points

IPVS statement on HPV vaccination and immunocompromised hosts

- Immunocompromised people are at increased risk of HPV-related disease, compared with immunocompetent people.
HPV vaccination is safe in immunocompromised people (e.g., HIV-positive [+] individuals, transplant recipients).
- Current vaccines are simple, non-replicating subunit vaccines and hence, not infectious.
- Given current knowledge, HPV vaccines will likely benefit immunocompromised men and women, especially when vaccinated in the recommended age range.
- It is ideal to vaccinate everyone according to national guidelines, before people become immunocompromised.
- For those who are immunocompromised at the time of vaccination, 3 doses are currently recommended.
- Antibody titres in response to vaccination are often lower than those in immunocompetent people, but the clinical relevance of this is yet unknown. Efficacy data following vaccination in immunocompromised people are very limited to date.
- Vaccines that have broad coverage or cross-coverage should be encouraged for HIV (+) men and women given growing evidence that the distribution of HPV types in cancers may be broader than that seen in the immunocompetent population.
- Cervical cancer screening remains an important public health complement to HPV vaccination for the prevention of cervical cancer.

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