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Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage

Julia M.L. Brotherton [a, b, *], Paul N. Bloem [c]

[a] National HPV Vaccination Program Register, VCS, East Melbourne, Victoria, Australia
[b] School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia
[c] Expanded Programme of Immunization, World Health Organization, Avenue Appia 20, 1211, Geneva, Switzerland

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A B S T R A C T

Persistent oncogenic human papillomavirus (HPV) is the cause of cervical cancer, as well as cancers of the anus, penis, vulva, vagina and oropharynx. There is good evidence that prophylactic HPV vaccines are immunogenic and effective against targeted-type HPV infections and type-specific genital lesions, including high-grade cervical intraepithelial neoplasia (CIN), when administered prior to HPV infection. There is good evidence that HPV vaccines are safe in population usage, with the most frequent adverse event being injection-site reactions. There is evidence to support some cross-protection against non-targeted types occurring following the administration of HPV vaccines. There is limited evidence suggesting that HPV vaccines may be beneficial in preventing future disease in women treated for high-grade CIN. This chapter focuses on the accumulated evidence regarding the global use of the three licensed HPV vaccines including safety, immunogenicity, duration of protection, effectiveness, coverage to date and barriers to higher coverage.

* Corresponding author. PO Box 310, East Melbourne, 8002, Victoria, Australia.
E-mail addresses: jbrother@vcs.org.au (J.M.L. Brotherton), bloemp@who.int (P.N. Bloem).

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In 2017, it is 11 years since the first prophylactic virus-like particle (VLP)-based human papillomavirus (HPV) vaccine was registered for use following extensive randomised trials demonstrating high efficacy. These vaccines can no longer be considered 'new' vaccines and are amongst the most studied vaccines ever. Enormous progress has been made since then in demonstrating the safety of the vaccines, their high efficacy against HPV infection and a range of HPV-related diseases in both sexes, and in how best to deliver population-based HPV vaccination programmes. This year, the WHO released an updated position paper on the use of HPV vaccines, recommending that all countries now proceed with national implementation of HPV vaccine, implement a catch-up for 9–14-year-olds (and if feasible and affordable up to 18 years of age) and noting that all the three licensed HPV vaccines have excellent safety, efficacy and effectiveness [1]. The challenge now is in achieving high global coverage by addressing barriers to vaccine access, addressing vaccine hesitancy, and developing accurate and comparable methods for monitoring coverage over time. In this review, we update previous reviews of the global situation in relation to HPV vaccines [2,3] and provide clinicians with an up-to-date understanding of the vaccines so that they can best support their use in routine practice.

Vaccine efficacy and immunogenicity

The initial HPV vaccine trials, of both the quadrivalent HPV vaccine (4vHPV) and the bivalent HPV vaccine (2vHPV), provided convincing evidence of very high efficacy (90–100%) of the vaccines against type-specific genital HPV infection and related disease (cervical and, for 4vHPV, vulval and vaginal intraepithelial neoplasia) when administered to young females naïve to the targeted vaccine types [4,5]. The 2vHPV vaccine contains VLPs for HPV types 16 and 18, the most oncogenic HPV types responsible for about 71% of cervical cancers [6]. The 4vHPV vaccine also contains HPV16 and 18 VLPs, with the addition of VLPs of types 6 and 11, which are responsible for about 90% of genital warts [7]. These trials were followed by trials evaluating immunogenicity in preadolescents, demonstrating equivalence [8,9], and in older women up to age 55 (2vHPV) and age 45 (4vHPV) (demonstrating immunogenicity and efficacy) [10,11]. In addition, trials were conducted for 4vHPV vaccine to determine efficacy in males against genital warts and both penile and anal intraepithelial neoplasia [12,13]. The 2vHPV also has demonstrated efficacy against targeted-type oral, vulval and anal HPV infections [14].

It was not anticipated that the vaccines would necessarily provide any important cross-protection against HPV types closely related to those included in the vaccines. However, significant cross-protection, albeit at lower levels of absolute efficacy than for targeted HPV types, has been clearly established for the 2vHPV. The 4vHPV has more limited cross-protection, best demonstrated against type 31 [15,16]. The 2vHPV has established substantive cross-protection against types 31/33/45-related cervical intraepithelial neoplasia (CIN) [14]. Recent data from Scotland have validated the high degree of cross-protection against types 31/33/45 from the 2vHPV vaccine trials by finding a similar high degree of protection in population usage [17]. The 2vHPV has a very effective adjuvant, ASO4, which results in significantly higher antibody titres than 4vHPV (as demonstrated in a head-to-head trial) [18], and it is likely that this is the mechanism that induces the superior degree of cross-protective efficacy. No waning of vaccine-derived protection against HPV has yet been seen in long-term follow-up studies of trial participants with either vaccine [19,20], with duration of efficacy thus confirmed to be at least 10 years and as yet no established antibody titre threshold for protection. Titres appear stable in the cohorts, with 16/18 plateau level titres maintained at a higher level for 2vHPV than 4vHPV recipients [18]. At present, there is no indication that a booster will be required for cohorts vaccinated with the three-dose schedule.

In fact, the high immunogenicity of the VLP-based vaccines, and the higher titres observed when the vaccine is given to younger adolescents [21], led to trials evaluating the immunogenicity of two-dose schedules (a prime–boost schedule with dose two 6–12 months after dose one rather than the initial prime–prime–boost schedule of 0, 1–2 and 6 months) [22]. Based on the finding of equivalence of immunogenicity to the three-dose schedule in older women, in 2014, the WHO approved the use of HPV vaccines in a two-dose schedule for immunocompetent females aged 14 years and under at the time of the first dose [23]. By 2016, 65% countries with HPV on their national programme

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