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HPV vaccination and cancer prevention

A. Athanasiou, MBBS [a, b], S. Bowden, MBBS [a, b], M. Paraskevaidi, BSc, PhD [a], C. Fotopoulou, PhD [a, b], P. Martin-Hirsch, MBBS, BSc, MD, FRCOG [e], E. Paraskevaidis, PhD [c, d], M. Kyrgiou, MSc, PhD, MRCOG [a, b, *]

[a] *Department of Metabolism, Digestion and Reproduction, Department of Surgery and Cancer, IRDB, Imperial College London, London, UK*
[b] *West London Gynaecological Cancer Centre, Hammersmith Hospital, Imperial Healthcare NHS Trust, London, UK*
[c] *University Hospital of Ioannina, Ioannina, Greece*
[d] *St Mary's Hospital, Imperial Healthcare NHS Trust, London, UK*
[e] *Central Lancashire Teaching Hospitals, Preston, UK*

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A B S T R A C T

Prophylactic vaccines have been found to be highly effective in preventing infection and pre-invasive and invasive cervical, vulvovaginal and anal disease caused by the vaccine types. HPV vaccines contain virus-like particles that lack the viral genome and produce high titres of neutralising antibodies. Although the vaccines are highly effective in preventing infections, they do not enhance clearance of existing infections. Vaccination programmes target prepubertal girls and boys prior to sexual debut as efficacy is highest in HPV naïve individuals. School-based programmes achieve higher coverage, although implementation is country specific. Vaccination of older women may offer some protection and acceleration of impact, although this may not be cost-effective. HPV-based screening will continue for vaccinated cohorts, although intervals may increase.

* Corresponding author. Room 3006, 3rd Floor, Institute of Reproductive and Developmental Biology, Department of Metabolism, Digestion and Reproduction – Department of Surgery and Cancer, Imperial College London Du Cane Road, W12 0NN, London, UK.
E-mail address: m.kyrgiou@imperial.ac.uk (M. Kyrgiou).

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Background

The awareness that human papillomavirus (HPV) is causally associated with virtually all (99.7%) cases of cervical cancer cases has revolutionised cervical cancer prevention and led to the development of prophylactic HPV vaccines [1]. In 1976, zur Hausen made the assumption that the very same virus that caused genital warts may be responsible for cervical, penile, anal and vulvar cancer [2] and subsequently pioneered ground-breaking research which isolated HPV from cervical and other anogenital cancer biopsies [3]. It is now hoped that the combination of prophylactic HPV vaccination (primary prevention) and enhanced detection through HPV-based testing (secondary prevention) will eliminate cervical cancers in countries with established screening and an HPV national immunisation programme (NIP) [4].

Epidemiology of HPV-related disease

Over 200 HPV subtypes have been identified, 40 of which are known to infect the anogenital area. Of these, 13 can initiate a neoplastic process and are commonly known as high-risk HPV (hrHPV). According to the International Agency of Research on Cancer (IARC), hrHPV types are: HPV16/18/31/33/35/39/45/51/52/56/58/59; HPV68 is probably carcinogenic, while HPV66 is no longer in the high-risk list [5].

HPV is thought to cause 5% of all cancers in men and 10% in women [6]. Before introduction of HPV vaccination, over 50,000 new cases of HPV-related cancers were diagnosed annually in Europe (2003–2007) (Fig. 1a and b) [7]. Persistent infection with hrHPV infection is responsible for approximately 100% of cervical cancers, 70% of vaginal cancers, 40% of vulvar cancers, 29% of penile cancers, 87% of anal cancers and 20% of oropharyngeal cancers in Europe (Fig. 2) [7]. Of the above-mentioned HPV-associated cancers, two hrHPV types (HPV16/18) are the causative factor in the majority (73–94%), while HPV16/18 along with five other hrHPV types (HPV31/33/45/52/58) are responsible for up to 98% of cases (Fig. 2) [7]. In cervical cancer, HPV16 is responsible for two-thirds of cases, HPV16/18 genotypes cause over 70% of cases and HPV31/33/45/52/58 account for the remaining 20% (Fig. 2) [7]. These 7 subtypes also cause 80% of pre-invasive cervical disease. The burden of genital warts is high; before the introduction of HPV vaccination approximately 700–900,000 new cases were diagnosed in Europe each year [7]. It has been estimated that the lifetime risk of developing warts is over 10% [8]. Genital warts are caused by low-risk HPV (lrHPV) types (which do not cause cancer); HPV6/11 are responsible for 85% of genital warts [9].

HPV infection is also common in men with a prevalence of 23% for penile HPV infection in the USA. In a study from the Netherlands, 62% of MSM (men who have sex with men) were seropositive for at least one hrHPV, and 41% had detectable DNA by polymerase-chain reaction (PCR) at the anus, penis or oral cavity. HPV infection rates were 20% higher in HIV-positive than HIV-negative MSM [10].

Organised population-based screening programmes have substantially reduced the incidence and mortality from cervical cancer [11]. In the UK, the introduction of a call and recall system in 1988 had resulted in large decreases in both incidence (from 15.0 to 9.8 per 100,000 women) and mortality from cervical cancer (from 5.8 to 2.2 per 100,000 women) by 2007 [12]. Although cervical cancer is no longer one of the ten most common cancers in developed countries such as the UK [13], it remains the most common cancer in lesser-developed countries and the fourth most common globally [14]. Population-based screening with high coverage requires infrastructure, organised health services and substantial resources unavailable in many countries. HPV prophylactic vaccination therefore represents the primary most feasible option for prevention in these settings.

Pathophysiology of HPV infection and natural history

Infection by HPV is very common and often happens soon after sexual debut, whilst invasive cancer is a relatively rare outcome of HPV infection. It is estimated that more than 80% of women will have been infected with HPV at least once by the age of 50, with the highest incidence rates being observed in young sexually-active women under 25 years of age [15].

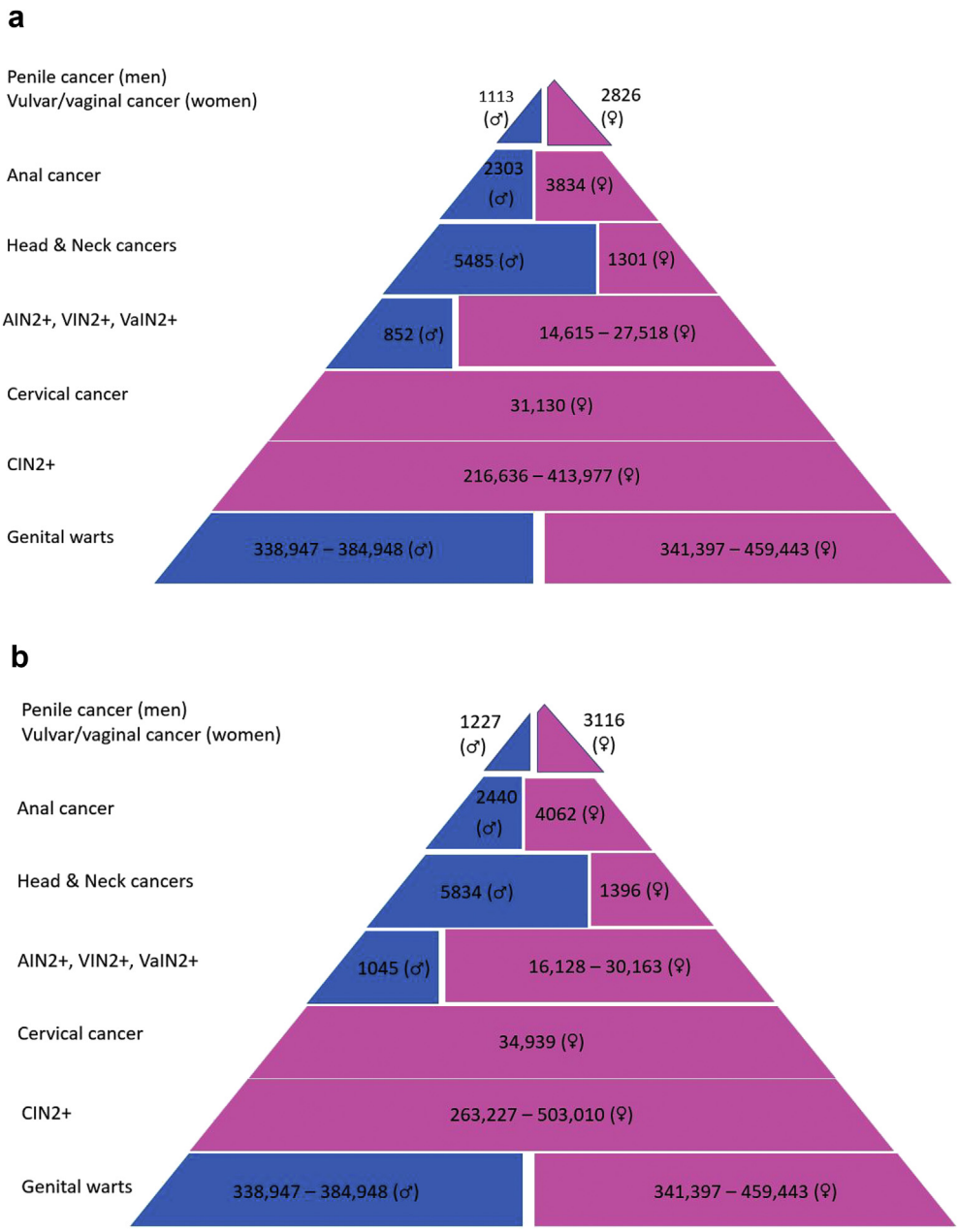

Fig. 1. Incidence of HPV6/11/16/18/31/33/45/52/58-related pre-invasive and invasive disease in Europe per annum during 2003–2007.**b**: Incidence of all HPV-related pre-invasive and invasive disease in Europe per annum during 2003–2007.

HPV infects epithelial basal cells where micro-trauma exposes the basement membrane. Initially, HPV replicates along with host basal cells, maintaining a steady number of HPV DNA copies, while expression of early (E) HPV genes (responsible mostly for viral replication and transcription; Fig. 3) is limited. As host keratinocytes make their way towards the upper layer of the epithelium (where they stop dividing and start differentiating), the expression of early HPV genes increases and HPV DNA

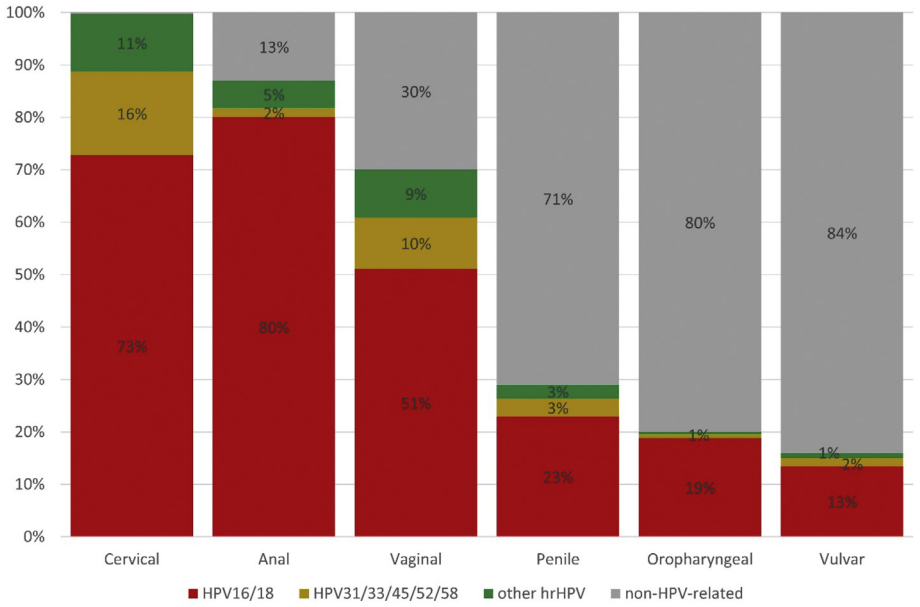

Fig. 2. Cancers caused by HPV.

replicates rapidly and reaches thousand copies per cell. In differentiated host cells in the uppermost layers, expression of late (L) HPV genes (forming the viral capsid proteins L1 and L2; Fig. 3) occurs and HPV virions assemble and are released. The whole viral life-cycle lasts at least 3 weeks and is completely intraepithelial. HPV does not cause cytolysis or cell death and is released only from fully differentiated keratinocytes that would anyway desquamate and die. In addition, HPV inhibits the synthesis and release of cytokines from infected cells. As a result, HPV effectively evades the activation of inflammatory cascades including Langerhan's and dendritic cells' activation for a prolonged period. The fact that HPV is released only from the surface of the epithelium where there is sparse lymph or blood drainage also explains the delay of the initiation of the immune response and the lack of viraemia [16].

In the majority, the host immune system will eventually activate and clear the infection: 80% of cases clear within 24 months and 90% of cases within 48 months. Median time to clearance is higher for hrHPV types than lrHPV types (lrHPV: 8 months; hrHPV: 11–17 months) [17]. The clearance of the virus is largely attributed to a cell-mediated immune response after antigen-presenting cells (APCs) present HPV proteins (mostly E2 and E6) to T-helper cells, which subsequently activate cytotoxic T-cells; to a more limited degree, the humoral immune response to L1 protein is also important. However, the actual antibody response in a natural HPV infection is rather poor: antibody production is slow (for example, median time to seroconversion is 8 months for HPV16), antibody titre levels are low and some women never seroconvert, especially if the infection is transient [16]. Only 50–70% of women with incident HPV infection seroconvert and this offers limited to no protection against new infections from the same subtype [18]. In a cohort of university students with at least 12 months of follow-up, 91% with a persistent HPV16 infection (more than 6 months) seroconverted in contrast to 29% with a transient HPV16 infection (less than 6 months) [19].

A persistent HPV infection might progress to cervical intra-epithelial neoplasia (CIN) and if left untreated, subsequently to cancer; this carcinogenic process has traditionally been thought to approximate 10–15 years but in some cases the span might be shorter [15]. Integration of HPV DNA to host genome is a crucial part in the carcinogenesis process in most cases. While HPV DNA is largely episomal in uncomplicated HPV infections and most low-grade lesions (CIN1), integration into host DNA in high-grade lesions (CIN2/3) and cancer is increasingly common. This integration disrupts the regulation of the expression of the HPV oncoproteins E6 and E7, which are then produced in large amounts [20].

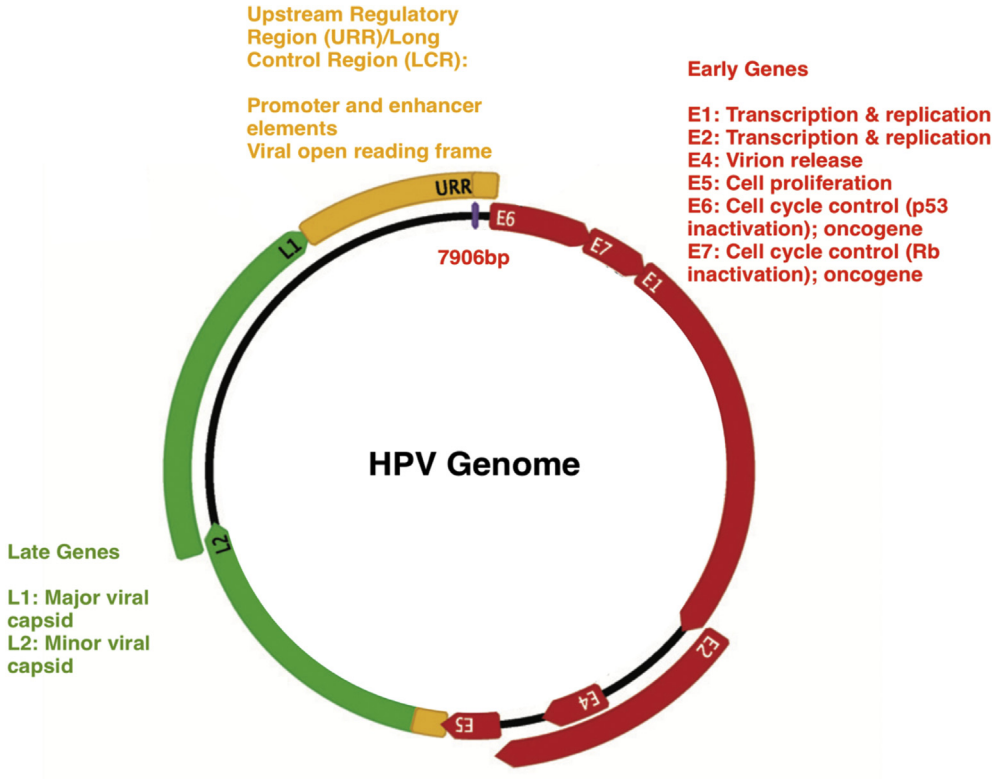

Fig. 3. HPV genome structure.

Licensed HPV prophylactic vaccines

Three HPV vaccines are currently licenced (Table 1). The first HPV vaccine to be licenced in Europe was the quadrivalent Gardasil against HPV6/11/16/18 in September 2006, followed by the bivalent Gardasil against HPV 16 and 18 in September 2007. In June 2015, license was granted for the nonavalent Gardasil9, which provides protection against five additional HPV types (31/33/45/52/58) compared to its predecessor. The availability of vaccines varies amongst countries. For example, only Gardasil9 is available in the USA, while Cervarix has been withdrawn in the UK.

How HPV vaccines work

All licensed vaccines are virus-like particles (VLPs) which bear resemblance to HPV but lack the viral DNA and are non-infectious. For the development of vaccines, the HPV L1 capsid protein is expressed in yeast (Gardasil and Gardasil9) or insect (Cervarix) cells and then self-assembles to form the VLPs. VLPs evoke a stronger humoral immune response against L1 than a natural HPV infection, with seroconversion rates against the vaccine-specific HPV types at almost 100% within 1 month after completion of vaccination scheme [21–23]. Antibody titre is also higher. Antibody titre peaks 1 month after the last dose (i.e. at 7 months) and reduces thereafter and reaches a plateau at 18–24 months, which is over 10-fold higher compared to a natural HPV infection [22]. Adjuvants contained in the vaccine can explain this enhanced antibody production and they also promote the generation of B memory cells [24]. Antibody titre is age-dependent and is higher for children and adolescents less than 15 years of age compared to older people even when fewer doses are administered to the younger individuals [25,26].

Table 1
Vaccine types.

Multivalency (Trade Name, Manufacturer)	Bivalent (Cervarix®, GlaxoSmithKline)	Quadrivalent (Gardasil®, Merck)	Nonavalent (Gardasil9®, Merck)
Coverage	HPV16/18	HPV6/11/16/18	HPV6/11/16/18/31/33/45/52/58
Adjuvant	Adjuvant System 04 (AS04): aluminium hydroxide and monophosphoryl lipid A (MPL)	Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)	Amorphous Aluminium Hydroxyphosphate Sulfate (AAHS)
Age range & gender (as approved by FDA)	9-25 y (females)	9-26 y (females-males)	FDA: 9-45 y (females-males)
Age range & gender (as approved by EMA)	From 9 y without upper limit (females-males)	From 9 y without upper limit (females-males)	From 9 y without upper limit (females-males)
Vaccination course (as approved by FDA)	All ages: 0, 1, 6 m	All ages: 0, 2, 6 m	≥15 y: 0, 2, 6 m <15 y: 0, 6–12 m
Vaccination course (as approved by EMA)	≥15 y: 0, 1, 6 m <15 y: 0, 5–13 m	≥14 y: 0, 2, 6 m <14 y: 0, 6–12 m	≥15 y: 0, 2, 6 m <15 y: 0, 6–12 m
Route	Intramuscular	Intramuscular	Intramuscular
Contraindications	Severe allergic reaction to previous dose; hypersensitivity to latex	Severe allergic reaction to previous dose; hypersensitivity to yeast	Severe allergic reaction to previous dose; hypersensitivity to yeast

HPV enters the basal cells through a micro-abrasion in the epithelium. The wound exudate contains, amongst others, a high titre of anti-L1 IgG antibodies that have been produced after the vaccination. These leaked antibodies then attach to L1 protein and prevent virus entry into cell [16] (Fig. 4).

Anti-L1 antibodies are specific to the HPV type/VLP that triggered their production with multivalent vaccines containing different VLP for each HPV type [27]. Studies have shown that HPV vaccines also afford some protection (referred to as cross-protection) against similar HPV types not contained in the vaccine [21].

Recommended HPV vaccination schemes

HPV vaccination is recommended at the age of 9–14, with most NIPs targeting girls (and in some countries also boys) aged 11–13 years. Vaccination at a young age is optimal, because vaccines are less effective after onset of sexual intercourse and exposure to HPV [28]. In addition, the immunogenic response to vaccines is enhanced in younger individuals [25,26].

The current recommendations of the typical Gardasil9 [29] course are:

- Women <15years (min age: 9): two-dose schedule at 0 and 6–12 months. The second dose should not be given less than 5 months after the first. If this occurs, a third dose should be given at least 4 months after the second. If interrupted, the course should be resumed and not repeated. A delayed second dose at 3–5 years ('1 + 1' schedule) might be considered in countries dealing with a current or looming supply shortage, as long as compliance with the second dose can be ensured [30].
- Women ≥15 years of age: three-dose schedule is at 0, 2 and 6 months. The second dose should not be given in less than 1 month after the first, and the third not in less than 3 months after the second dose and 5 months after the first. If a dose was administered at a shorter interval, it should be repeated after another minimum interval elapses. All three doses should be ideally given within a 12-month period. If the course is interrupted, it should be resumed (and not repeated) and should allow appropriate intervals between the remaining doses.

Currently, there is no recommendation for a booster. Population-based data from Nordic countries suggest protection for over 12 years [31], whilst statistical models have projected high antibody levels for at least 20 years; protection may well be lifelong. The vaccines should not routinely be interchanged and ideally, one type of vaccine should be used for the entire regime. 'Repeat vaccination' with

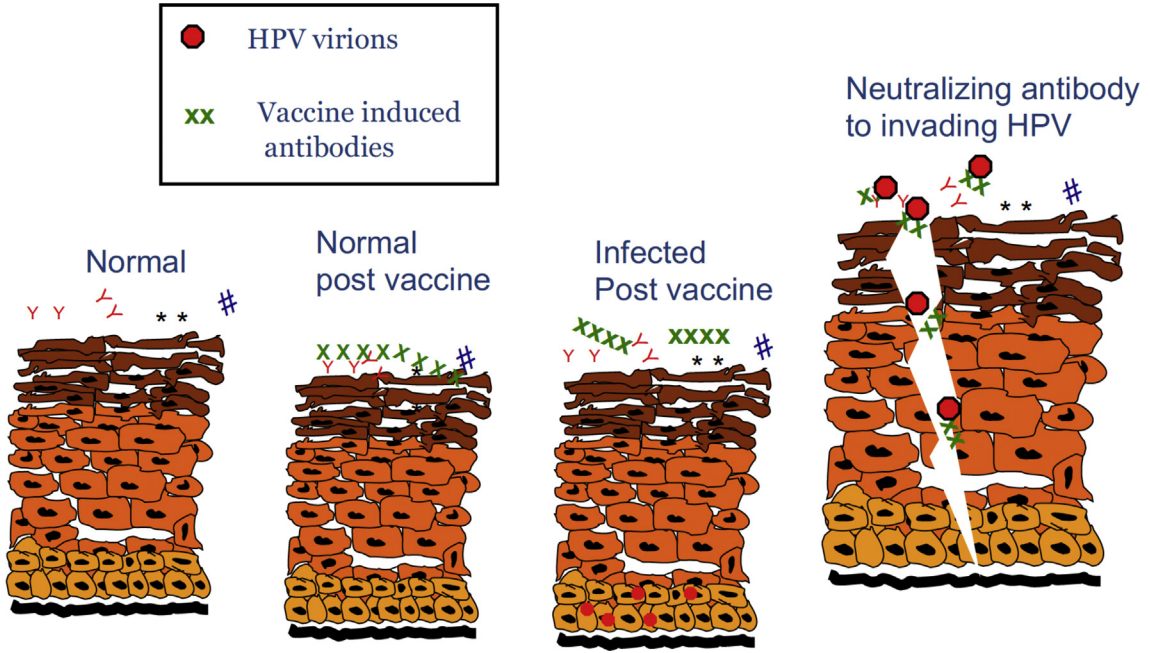

Fig. 4. HPV vaccination induces the production of neutralizing antibodies against HPV. The exudate after a micro-trauma of cervical epithelium contains vaccine-induced antibodies, which bind to HPV particles and prevent them from reaching and entering basal cells. Vaccines are not effective against a pre-existing infection.

Gardasil9 is possible for those previously vaccinated with Gardasil or Cervarix on an individual basis but has not been shown to be cost-effective.

One-dose schemes are investigated. A post-hoc analysis of CVT and PATRICIA trial participants (aged 15–26 years) found that vaccine efficacy was similar regardless of number of doses [32]. Population-based studies from Australia [33] and the USA [34] have also reached the same conclusion for women aged 15 or less [33] or 15–19 years [34], which could not be explained by herd protection [33]. Despite these promising results, one-dose schemes for children (or two-dose courses for older women) are not yet recommended.

Efficacy of HPV vaccines from clinical trials

The efficacy of HPV vaccines has been thoroughly investigated in several large randomised clinical trials (RCTs) with over 70,000 participants. The largest trials performed are PATRICIA [35] for the bivalent (versus control) and FUTURE I/II [36] for the quadrivalent (versus control) vaccine (Table 2). Other trials include the CVT [37], Chinese [38], Japanese (2v) [39] and GSK [22] for the bivalent (versus control), Japanese (4v) [40] for the quadrivalent (versus control), and Broad Spectrum HPV Vaccine Study [21] for the nonavalent (vs quadrivalent) vaccine. Efficacy against cervical or vulvovaginal disease caused by vaccine-specific HPV types was estimated to be greater than 95% in HPV-naïve women.

Anogenital warts

The protection of quadri- and nonavalent vaccine against HPV6/11-related genital warts is up to 97% in HPV-naïve women [36] and approximately 89% in HPV-naïve men [41]. The bivalent vaccine is not effective against warts.

Cervical HPV infection

The efficacy of bivalent and quadrivalent vaccines against an incident HPV16/18 infection is up to 87% in HPV-naïve women, while the efficacy against a persistent HPV16/18 infection (>6 months) rises to 94% [42]. There is also some additional protection against subtypes not included in the vaccine, referred to as 'cross-protection'. For the bivalent vaccine, this was 77% against HPV31, 43% against HPV33, and 79% against HPV45 [43]. For the quadrivalent vaccine, the corresponding protection was 46%, 29% and 8%, respectively [43]. The risk reduction of persistent infections by the additional 5 HPV genotypes in nonavalent vaccines, when compared to the quadrivalent vaccine, was consistently over 95% for all genotypes [21].

Table 2
Efficacy for HPV-related disease based on trial data (PATRICIA [35] for Cervarix, FUTURE I/II [36] for Gardasil) for HPV-negative women at baseline aged 15–26.

Outcome	Risk in reference group (per 10,000 women)	Risk with Cervarix (per 10,000 women)	VE	Risk in reference group (per 10,000 women)	Risk with Gardasil (per 10,000 women)	VE
Persistent HPV16/18 infection (6 m)	698	45	94%	336	24	93%
CIN 2+, HPV16/18	178	2	99%	190	0	99%
CIN 3+, HPV16/18	50	0	98%	94	0	99%
CIN 2+, any HPV	312	112	65%	291	167	43%
CIN 3+, any HPV	81	5	93%	143	78	46%
Genital warts, HPV6/11	NA	NA	NA	291	9	97%
VIN/VaIN 2+, HPV16/18	NA	NA	NA	42	2	95%
VIN/VaIN 2+, any HPV	NA	NA	NA	65	15	77%

VE: vaccine efficacy; NA, not available; NS: not significant.

CIN

A Cochrane Review [42] demonstrated that in women aged 15–26 who were hrHPV naive when vaccinated and received at least one dose of the bivalent or quadrivalent vaccine, risk of HPV16/18-associated CIN2+ was reduced by 99%, CIN3+ by 99%, and AIS by 90%. The risk of any CIN2+ or CIN3+ (i.e. irrespective of the HPV type causing the lesion) was reduced by 63% and 79%, respectively. When women were included regardless of baseline HPV status, receiving at least one dose of the bivalent or quadrivalent vaccine reduced the risk of CIN2+ or CIN3+ associated with HPV16/18 by 48% and 45% respectively, and the risk of any CIN2+ or CIN3+ irrespective of HPV type by 21% and 33%, respectively. If a woman is sero- or PCR positive for some HPV vaccine types, efficacy against CIN2+ related to remaining vaccine-specific HPV types is not compromised [28]. A non-inferiority trial of the non-avalent vaccine has shown equal efficacy to the quadrivalent vaccine against persistent infection or high-grade cervical, vulvar or vaginal disease caused by HPV16/18 and additional protection against HPV31/33/45/52/58 - it was found to reduce high-grade lesions caused by HPV31/33/45/52/58 by over 96% amongst women HPV negative at the time of vaccination [21].

Cervical cancer

A cancer-registry follow-up of two phase III trial of the bi- or quadrivalent vaccine-trial cohorts was published from Finland with more than 10 years of follow-up and over 3000 vaccinated women and 190,000 follow-up years [44]. There were no cases of cervical cancer or other HPV-related cancers (vulva, vagina, anal or oropharyngeal cancers) amongst the vaccinated, whilst there was a reported incidence of 6.4/100,000 woman-years for cervical and 8.0/100,000 for all HPV-associated cancers amongst the unvaccinated.

Non-cervical HPV-related disease

The efficacy of bivalent vaccine against high-grade HPV16/18-related vulvar intraepithelial neoplasia (VIN2+) or vaginal intraepithelial neoplasia (VaIN2+) is 95% in HPV-naïve population and 77% against any VIN2+ or VaIN2+ [36]. In women regardless of baseline HPV status, efficacy against VIN/VaIN 2+ associated with HPV16/18 was 76% and against any VIN/VaIN 2+ 51% [36]. The nonavalent vaccine is as effective as the quadrivalent for the prevention of HPV16/18-related VIN2+ or VaIN2+, but has the additional risk reduction of HPV31/33/45/52/58-related VIN2+ or VaIN2+ by up to 100% [21].

The data on the efficacy of the vaccination against anal intraepithelial neoplasia (AIN), anal cancer and oropharyngeal cancer in females is limited. In a nested analysis of a Costa Rica vaccination trial, it was found that the bivalent vaccine reduces the risk of anal HPV16/18 infection by 84% in HPV-naïve population, which was comparable to the reduction of the risk of cervical HPV16/18 infection [45]. The Costa Rica vaccination trial also showed that bivalent vaccination decreases the risk of oral HPV16/18 by 93% regardless of HPV status at baseline, a percentage that was higher than the respective risk reduction for cervical HPV16/18 infection (72%) [46].

Vaccination in men reduced the rate of persisting HPV16/18 infections by 88% in oral cavity, but only by approximately 50% in the anogenital area (regardless of HPV status). However, in HPV-negative men, persisting anogenital infections were reduced by over 80% [47]. The vaccine had some efficacy in reducing AIN 2 or 3 (62% and 47%, respectively). Evidence on penile intraepithelial neoplasia (PeIN) 2 or 3, anal cancer, penile cancer or head-and-neck squamous cell cancer is still limited [47] In HPV-naïve men, quadrivalent vaccine has been shown to reduce the risk of a persistent anal HPV16/18 infection by 96% [48], of AIN2+ by 75% [48] and of high-grade penile intraepithelial neoplasia (PIN2+) by up to 100% [41].

Efficacy of HPV vaccines from 'real-life' data on population-level impact

There is an accumulation of 'real-life' data on the high impact of HPV vaccination on the prevalence of HPV-related disease in both vaccinated and unvaccinated individuals that support previously published robust evidence from trials.

Genital warts

In Australia, nationwide vaccination with the quadrivalent vaccine showed a rapid drop in anogenital warts in females aged 21–30 and less than 21 by 73% and 93%, respectively, within only 5 years after the onset of vaccination, and in males less than 30 as well through herd protection [81]. A recent meta-analysis [49] of studies from 14 high-income countries reported that the incidence of genital warts was reduced within 5–8 years by 67% in girls (15–19 years) and by 48% in boys (15–19 years). A statistically significant reduction in older age groups was also observed (women 20–24 years: 54%; women 25–29 years: 31%; men 20–24 years: 32%).

Cervical HPV infection

In Scotland, the bivalent HPV vaccine was implemented in girls aged 12/13. The prevalence of vaccine-specific types (HPV16/18) and others through cross-protection (HPV31/33/45), was reduced by over 85% when these girls reached the first screening round 7 years post-vaccination [50]. In the UK, HPV16/18 prevalence was reduced by 82%, with a 49% reduction in the non-vaccine HPV types 31/33/45 [51]. Overall, in high-income countries, HPV16/18 prevalence was reduced within 5–8 years by 83% in girls (15–19 years), by 56% in women aged 20–24 years and by 37% in women aged 25–29 years. A reduction of HPV31/33/45 prevalence by 54% has been also observed in girls [49].

CIN

In Scotland, in the 1995-96 birth cohort (vaccination at the age of 12/13 with coverage at 90%), diagnoses of CIN3+ were reduced by 89%, of CIN2+ by 88% and of CIN1+ by 79% in the first round of screening at the age of 20. When stratified by immunisation status, in the unvaccinated 1995/1996 birth cohort diagnoses of CIN3+ were reduced by 100%, of CIN2+ by 67% and of CIN1+ by 63%, which is highly suggestive of herd immunity [52]. In Australia that first implemented gender-neutral vaccination in 2007, low-grade and high-grade CIN decreased by 34% and 47% respectively, with a greater reduction in younger women (<20 years old) [53]. Overall, in high-income countries, diagnoses of CIN2+ were reduced within 5–9 years by 51% in girls (15–19 years) and by 31% in women aged 20–24 years [49].

Cervical cancer

It is estimated to take many years to see the full impact of vaccination. However, some countries have already reported a decrease in the incidence rates of cervical cancer, with the USA reporting a reduction by 29% in women aged 15–24 years during 2011–2014 compared to 2003–2006 (pre-vaccination era) [54]. In Australia, it is projected through mathematical models that cervical cancer will be eradicated within 20 years [55].

Safety

The Global Advisory Committee on Vaccine Safety (GACVS), which cooperates with World Health Organisation(WHO), regularly reviews safety data on HPV vaccines. In its last review on July 20, 17 [56], when more than 270 million doses had been administered, it concluded that HPV vaccines are 'very safe' and that there is no good evidence for an association with any major side effects or significant medical conditions including but not limited to, Guillain-Barré syndrome (GBS), complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency, primary ovarian failure, venous thromboembolism (VTE), autoimmune diseases, death or any other medically significant condition or new onset of any chronic disease. According to GACVS, the risk of anaphylactic shock is extremely low (1.7 cases per million doses). SAGE (Strategic Advisory Group of Experts on immunisation), another advisory group to WHO, also highlighted the 'excellent safety' of HPV vaccines during its latest meeting in June 2019 [30]. However, HPV vaccines should not be administered to people with known hypersensitivity to any

HPV vaccine component, or a severe allergic reaction to a previous dose. For example, Gardasil or Gardasil9 should not be administered to people with hypersensitivity to yeast, and Cervarix to people with hypersensitivity to latex [57]. Syncope, another oft-cited side effect, is probably psychogenic [56]; albeit uncommon, it is advised that patients remain seated or in the supine position for 15 min post vaccination [57]. Most common side effects are injection site reactions (pain, redness and swelling). Other mild and transient side effects include fever, headache, fatigue, nausea and muscle or joint pain. According to the Advisory Committee on Immunisation Practices (ACIP), which cooperates with CDC, people with mild acute disease can receive the vaccine, but people with moderate or severe acute disease are advised to recover first. In pregnant women who inadvertently received the HPV vaccine, no adverse outcomes in mother or foetus have been reported so far. Such women should be reassured, but the next dose should be administered after pregnancy. Similarly, in women with known pregnancy, HPV vaccination should be delayed after delivery. HPV vaccines are safe for breastfeeding mothers [57].

Vaccination in special groups

Vaccination in men

Non-cervical HPV-related malignancies are prevalent in both women and men. Immunogenicity in males is non-inferior to that observed in females. During the first implementation, many countries targeted only females, although more recently gender-neutral NIPs are increasingly being introduced (Australia, US, Canada and in Europe Austria, Denmark, Norway, Switzerland, Croatia, UK and Germany). Gender-neutral vaccination of men addresses concerns on gender inequality. It protects men that have sex with men (MSM) that would be otherwise unprotected. Many countries with female only NIPs already offer the vaccine to MSM as HPV infection is common. Although heterosexual men have a lower risk of HPV-related cancers, vaccinating men offers both individual protection and will faster achieve 'herd immunity' through decreasing the overall HPV reservoir (particularly when coverage in women is below 80%). Nonetheless, should there be vaccine supply shortage, vaccination of boys should be delayed to prioritise vaccination of girls [30].

Older women and previous or current HPV infection

Antibodies from clearance of a natural HPV infection are not protective against reinfection. Although the rate of new infections does decrease with age, reinfections do occur. Data from RCTs have shown prevention of new HPV infections and disease up to the age of 45 [58] and older women are still likely to benefit. There is data from 3 clinical studies and 2617 women to suggest that the quadrivalent vaccine still offers some protection in women that are HPV DNA negative despite being seropositive (no women versus 7 cervical diseases and 8 external genitalia cases related to the vaccine type in the placebo group) [59]. The vaccines are not effective against HPV types for which women are DNA positive, although there are no safety concerns. Routine HPV DNA and/or serology is not recommended before vaccination. Catch-up vaccination programmes up to age 26 in Australia or 16–18 in the UK have accelerated the effect of immunisation programs at the onset, but cost-effectiveness rapidly declines after 25. Although vaccination is possible on an individual basis, the cost-effectiveness does not currently permit population-wide recommendation for HPV vaccination at least in developed countries. In times of supply shortage, vaccination of older women should be avoided in order to facilitate vaccination of prepubertal girls [30].

Vaccination in women after local treatment for CIN

HPV vaccines are prophylactic and do not treat already acquired infections. After local treatment for CIN, the risk of recurrence of pre-invasive disease is up to 8%. These women rapidly get re-infected and remain at higher risk of recurrence and invasive cancer. Secondary indirect data from vaccine trials

have shown that the risk of recurrent CIN2+ after local treatment for CIN is lower in vaccinated women than women who have never been vaccinated by 65%–88% [60,61], and the risk of new HPV16/18 or HPV31/33/45 is also reduced by 58% and 37% respectively [62]. In non-randomised studies of vaccinated women post-treatment, a 65–81% reduction in recurrent CIN2+ was observed when compared to unvaccinated women [63,64]. Randomised studies and cost-effectiveness analyses are needed before recommendation of routine HPV vaccination after local treatment.

Vaccination in immunocompromised patients

Immunosuppressed patients are at higher risk of HPV-related disease than immunocompetent and it is highly recommended that they receive a three-dose vaccination course; immunobridging studies to compare antibody titres between immunocompromised children vaccinated with two doses and immunocompromised adults vaccinated with three doses have not been performed yet [65]. A study [66] of HIV-positive children with CD4% more than 15 has found that the quadrivalent vaccine is safe, does not affect CD4 count or HIV viral load, and achieves seroconversion rates over 96% for all vaccine-specific HPV types. A study [67] of HIV-positive adults has found that seroconversion rates after the quadrivalent vaccine depend on CD4 count (85–100% if CD4 count more than 200/μL and 75–93% if less than 200/μL). Because HIV might change the relative carcinogenicity and the distribution of HPV types in HPV-related cancers [68,69], multivalent vaccines or vaccines with strong cross-protection should be preferred in HIV-positive patients [65]. HPV vaccination is also recommended for transplant recipients and patients with autoimmune disorders, since it does not change the course of the disease [65]. Antibody titres are lower than in immunocompetent age-matched individuals and might be affected by the type of immunosuppressant [65]. Clinical efficacy data are limited for immunocompromised patients [66,69,70].

Herd immunity, coverage & cost-effectiveness

The implementation strategy ultimately depends on local resources, infrastructure and varies for different health systems. Less than 30% of low- and lower middle-income countries have introduced HPV NIPs, in contrast with 55% of upper middle- and 80% of high-income countries [70]. In countries with HPV NIPs, coverage rate is highest for school-based programmes (over 90% in Rwanda [71], over 80% in the UK and Australia [72]), compared to just 66% in the USA and approximately 20% in Austria. Therefore, school-based NIPs are preferred because they can increase coverage in the optimum age [73].

Unvaccinated individuals benefit from indirect HPV protection through a reduction in circulating HPV in the community - known as herd immunity. Increases in coverage exponentially decrease HPV prevalence; a coverage rate as low as 20% in females can give rise to herd immunity, reducing HPV16 prevalence by 27% in females and 17% in males within 70 years. Further increases in coverage enhance herd immunity and at 80% can reduce HPV16 prevalence by 93% in females and 83% in males within 70 years. It has been projected that at least 80% coverage in girls-only vaccination and 60% in gender-neutral vaccination is necessary to achieve a reduction in HPV16 prevalence over 90% in females and 80% in males within 70 years – consequently, this has been set as the minimum coverage target by many countries. Elimination of HPV16 within 70 years requires either girls-only coverage close to 100% or girls-and-boys coverage at 80% [74].

HPV vaccination prior to sexual debut is highly cost-effective. In a modelling study of 179 countries, it was found that HPV vaccination of 12-year old girls is cost-effective in all but 6 countries (where incidence of cervical cancer is low), and very cost effective in 156 countries [75]. Cost-effectiveness of male vaccination mostly depends on the coverage rates in females and is country-specific. Coverage in most European countries varies between 19 and 86% [76]. Studies from Germany and the Netherlands have demonstrated that based on the low coverage in some countries and low cost of the vaccine, vaccination of boys is cost-effective and gender-neutral vaccination will optimise benefits from herd immunity until coverage is further improved. An economic analysis in Sweden, a country where coverage rate in females is over 80%, concluded that male vaccination would still be cost-effective [77].

HPV vaccination in older women is controversial and the upper recommended age is country specific. Economic analysis of 17 studies in 26 countries reports great variations across countries, with low resource settings, and countries with lack of organised screening and significant disease burden benefiting the most from NIPs [75]. In the Netherlands, HPV vaccination was estimated to be most cost-effective for ages 12–16 but also remains cost-effective up to the age of 25 [78]. In the USA, HPV vaccination of women older than 30 years attending HPV-based screening, was found to offer only a marginal benefit [79]. Although it is an individual choice for older women, universal vaccination cannot currently be recommended due to cost-effectiveness.

Cervical screening and vaccination

Cervical screening and vaccination will be complementary synergistic strategies for cervical cancer prevention for several decades although major changes in screening are anticipated. Future screening will include a mixture of unvaccinated, vaccinated and partially vaccinated women. Discrimination of screening based on vaccination status of each individual woman will be impractical in most settings. Future protocols may include prolonged intervals of 5–7 years for hrHPV-based screening or even later age of initiation around the age of 30. The maximum age for HPV vaccination, as well as the intervals and number of HPV tests that vaccinated women should undergo per lifetime, is an important research topic [80]. The optimal screening model is being investigated in numerous studies.

Summary

HPV vaccines are highly effective in preventing anogenital warts and cervical, anal, vulvar, vaginal, oropharyngeal and penile pre-malignant and malignant disease caused by vaccine-specific HPV types. The efficacy of HPV vaccines has been demonstrated not only in multiple high-quality clinical trials but also in population-based studies which have shown an overall reduction of HPV-related diseases through herd immunity. HPV vaccination should be directed at prepubescent children before coitarche, because immunogenicity is higher under the age of 15 and the efficacy of vaccination decreases after prior exposure to HPV. Male vaccination is the most cost-effective in countries with low female coverage (<80%), but gender-neutral vaccination policies have many additional benefits, and are being adopted in many countries with high female coverage. Vaccination of older individuals is generally not considered cost-effective and it should be evaluated on an individual basis. In the era of HPV-based screening, with future potential for reduced screening intervals in vaccinated women, HPV vaccination may become a sensible policy for older females as well.

Declaration of Competing Interest

None.

Practice points

- The target group of HPV vaccination programmes should be prepubertal girls and boys prior to coitarche, and the programmes should have a catch-up vaccination for adolescents and young adults.
- Older women can be vaccinated, but the efficacy of vaccines is lower and the cost-effectiveness is questionable.
- A two-dose vaccination course is recommended for ages 9–14 years (0 m, 6–12 m), while the standard three-dose course is recommended for older ages (0 m, 2 m, 6 m).
- Vaccination programmes should aim for a coverage rate of at least 80% if only girls are vaccinated, and 60% if both genders are vaccinated.
- Vaccination also offers herd immunity to unvaccinated men and women.

Research agenda

- Screening strategies and screening intervals in vaccinated cohorts.
- Cost-effectiveness of vaccination in older women.
- Efficacy of HPV vaccination after local treatment for cervical pre-invasive disease.
- Single dose vaccine efficacy.

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