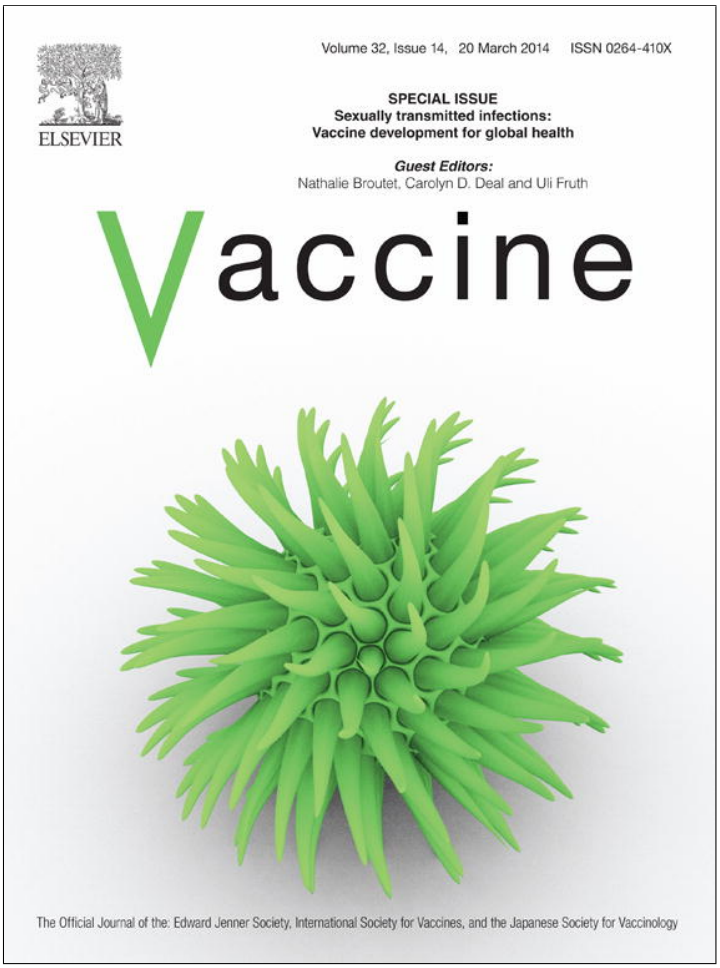

Vaccine 32 (2014) 1595–1601

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

HPV vaccines to prevent cervical cancer and genital warts: an update

Carine Dochez [a,*], Johannes J. Bogers [b,c], Rita Verhelst [a,c], Helen Rees [d]

[a] Network for Education and Support in Immunisation, Department of Epidemiology and Social Medicine, University of Antwerp, Campus Drie Eiken, Universiteitsplein 1, 2610 Antwerp, Belgium
[b] Laboratory of Cell Biology and Histology, University of Antwerp, Middelheimcampus, Groenenborgerlaan 171, 2020 Antwerp, Belgium
[c] International Centre for Reproductive Health, Department of Obstetrics and Gynaecology, Ghent University, De Pintelaan 185, 9000 Ghent, Belgium
[d] Reproductive Health and HIV Institute, University of the Witwatersrand, Corner Esselen and Klein Streets, Hillbrow, 2038 Johannesburg, South Africa

ARTICLE INFO

Article history:
Received 19 July 2013
Received in revised form 24 October 2013
Accepted 24 October 2013

Keywords:
Cervical cancer
Genital warts
HPV vaccines
New developments

ABSTRACT

Cervical cancer is an important public health problem worldwide, and especially in developing countries. The link between cervical cancer and oncogenic human papillomavirus (HPV) infection has been clearly established. Furthermore, non-oncogenic HPV are responsible for the majority of genital warts. Two prophylactic HPV vaccines are available, which have the potential of considerably reducing HPV-related morbidity and mortality. Both vaccines are based on virus-like particles of the L1 capsid protein, and are highly efficacious and immunogenic if given before exposure to HPV, i.e. to adolescent girls between 9 and 13 years of age in a three-dose schedule. This review describes the immunology of natural HPV infections and the immune response evoked through vaccination. The current duration of protection is 8.4 years with the bivalent vaccine (HPV16/18) and 5 years with the quadrivalent vaccine (HPV6/11/16/18). Research is on-going to evaluate the efficacy of the current vaccines in a two-dose schedule, as compared to the recommended three-dose schedule. To increase the protection, the development and testing of a nine-valent prophylactic HPV vaccine (HPV6/11/16/18/31/33/45/52/58) is being undertaken. Research is also directed towards therapeutic vaccines and the development of a prophylactic L2 vaccine.

1. Introduction

Cervical cancer is an important public health issue. In 2008, worldwide around 530,000 new cases of cervical cancer were reported, and 275,000 deaths [1]. In 2004, 16,000 women still died in the European Union from this disease even with a screening programme in most countries [2]. In other parts of the world the incidence and mortality are much higher with cervical cancer ranking in the top five of causes of death in women [1].

HPV was recognized as the cause of cervical cancer in 1992 [3] and it was later confirmed that virtually all cervical cancers contain oncogenic human papillomavirus (HPV) DNA [4]. This led to the conclusion that HPV is a necessary factor in the initiation of cervical cancer with the highest worldwide attributable fraction ever identified for a specific cause of a major human cancer [5].

The main histological types of cervical cancer are squamous cell carcinoma (SCC) and adenocarcinoma, of which the first accounts for 90–95% of invasive cancer cases. The development of SCC is a multistage disease beginning with pre-invasive lesions, which may regress, persist or progress towards invasive cancer.

Genital warts (condyloma acuminata) are attributed to non-oncogenic HPV types [6–8]. Although generally regarded as benign, condylomata caused by HPV can be difficult to treat and recurrence occurs frequently. Self-reported incidences of clinically diagnosed genital warts confirm that these are common in both women and men. Ever having had clinically diagnosed genital warts was reported by 10.6% of almost 70,000 Nordic women aged 18 to 45 years in 2005 and by 7.9% of almost 23,000 Danish men in the same age category in 2007 [9,10]. In 2000, in the UK, 4.1% of women and 3.6% of men aged 16–44 years reported ever being diagnosed with genital warts [11]. In the United States (1999–2004, age category 18–59) and Australia (2001–2002, age category 16–59), the cumulative incidence was 7.2% and 4.4% among women, respectively, and 4.0% among men [12,13].

2. Papillomavirus

Human papillomaviruses are small non-enveloped DNA viruses that belong to the Papovaviridae family. The viral capsid is composed of two proteins: the major L1 and minor L2 proteins. There are 170 different HPV types identified, 40 of which infect the genital tract [14]. These mucosal HPV types are classified as low-risk (LR) and high-risk (HR) types based on the prevalence ratio in cervical cancer and its precursors. LR-HPV types, such as 6 and 11, induce

* Corresponding author. Tel.: +32 3 265 2891; fax: +32 3 265 2875.
E-mail address: carine.dochez@uantwerpen.be (C. Dochez).

0264-410X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2013.10.081

benign lesions with minimal risk of progression to malignancy, HR-HPV have higher oncogenic potential. Approximately 99% of cervical cancers contain HPV DNA of HR-HPV types, with type HPV16 being the most prevalent, followed by types 18, 31, 33, and 45 [15].

Most HPV infections are transient and are spontaneously cleared or suppressed by the host immune response. It is unclear whether these infections resolve by complete viral clearance or by maintenance of a latent phase in the basal cells of the epithelium, in which the virus replicates at extreme low levels without full viral expression [16].

Infections that are not cleared at an early stage progress towards premalignant squamous intraepithelial lesions (SIL), histopathologically referred to as cervical intraepithelial neoplasia (CIN). Low-grade lesions, LSIL (cytological classification) or CIN1 (histological classification), represent a chronic HPV infection in which HPV DNA is episomal and intact virion production and shedding occurs (both by high-risk HPV as well as low-risk HPV, e.g. HPV11). Lesions are frequently cleared by the immune system, however, some lesions do not spontaneously regress and can persist for a long period. Viral persistence within the host cells is an uncommon event that is necessary for progression to malignancy. Clonal progression of the persistently infected epithelium can lead to high-grade lesions (HSIL or CIN2-3), which in turn can progress towards invasive disease [16]. The progression towards high-grade disease (HSIL/CIN3) is often with a different strain of HPV and not necessarily a progression of low-grade disease.

HIV infected women have a higher prevalence of HPV infection and are often infected with multiple HPV types. They are at an increased risk for persistent HPV infection and progression to HSIL/CIN3 compared to HIV-uninfected women [17].

3. Immunology of natural HPV infections

HPV infections with mucosal types are very common, especially in young women. Most natural HPV infections are cleared through an immune response in which two pathways can be differentiated.

Firstly, the humoral response leads to the production of neutralizing antibodies, which will prevent the virus to enter the epithelial cell. This immune response takes approximately 6 to 18 months to mount and serological levels are low, with approximately 70% of individuals raising detectable levels of antibodies against a type-specific L1 epitope [18]. These antibodies, although useful in the prevention of primary infection of basal keratinocytes, are insufficient to prevent new infections.

Secondly, the HPV enters the cell through contact with the basal membrane and through the interaction with alpha-6 integrin, which is a natural component of the hemidesmosal complex that binds the epithelial cell to the basal membrane [19]. More specifically, the L1 part of the virus binds to laminin-5. Thereafter, the virus is transferred to alpha-6 integrin and internalized. The internalization process is still not completely understood [20].

After internalization, the epithelial cell sheds the capsid, losing L1 and L2, explaining the difficulty for the type-specific anti-L1 antibodies to react. The cellular clearance of HPV is therefore dependent on cytotoxic T cells that react with infected cells through the recognition of expressed viral proteins (like E6 and E7) [19]. Genital HPV infection is therefore associated with a defective Th1 profile and an increase of the permissive Th2 profile of cytokine production [21]. Indeed, both experimentally as well as clinically, cellular clearance of HPV infection is linked to a Th1 cytokine response and cytotoxic T lymphocytes, raised against HPV epitopes can eradicate HPV-related tumours. Finally, this mechanism forms the basis of therapeutic vaccines as discussed later in this paper.

4. Immune response after vaccination

The commercially available vaccines are constructed using virus-like particles (VLPs) that consist of L1. It is widely accepted, but clinically only proven in animal experiments, that these vaccines protect by invoking an antibody response [18]. This serological response is much stronger (1–4 logs higher) than the response towards a natural infection, which is likely due to the use of specific adjuvants, the strong immunogenicity of the VLPs themselves, as well as the route of administration. In vaccinated individuals, an adaptive immune response is induced after intramuscular injection.

Most research is done looking at IgG antibodies, specifically raised against type-specific L1 proteins. As the capsule of the natural HPV virion also expresses the L2 protein, using L2 VLPs is currently being investigated and promising but technically more challenging (see later).

The L1 IgG is expressed in the cervical mucus, suggesting a role for immediate neutralizing of the virus. This also explains the importance of vaccination before the sexarche, as the efficacy of L1 vaccines against internalized virus remains unclear.

The vaccine protection persists even with very low antibody levels [18]. This suggests that an initial high titer serological response from the current bivalent and quadrivalent vaccines may provide prolonged protection, even after waning of antibody levels.

5. *Current vaccines*

Current HPV vaccines are produced using recombinant technology, by inserting the L1 gene into a host (e.g. yeast or baculovirus), which then produces L1 proteins in abundance. These L1 proteins self-assemble into empty shells or virus like particles (VLPs). VLPs are similar in shape and size to the HPV virion, but do not contain viral DNA, and are therefore non-infectious and non-oncogenic [22,23].

Currently there are two HPV vaccines on the market: the bivalent vaccine Cervarix™, containing VLP antigens for HPV types 16 (20 μg) and 18 (20 μg); and the quadrivalent vaccine Gardasil™, containing VLP antigens for HPV types 16 (40 μg) and 18 (20 μg), as well as non-oncogenic HPV types 6 (20 μg) and 11 (40 μg). The VLPs are combined with an adjuvant to enhance the immune response. The bivalent vaccine is formulated with a unique adjuvant, AS04, including 3-*O*-desacyl-4′monophosphoryl lipid A and aluminium salt. The quadrivalent vaccine uses a classical adjuvant, amorphous aluminium hydroxyl-phosphate sulphate [22–24].

Both vaccines are given in a three-dose schedule as intramuscular injection: 0, 1 and 6 months for the bivalent vaccine and 0, 2 and 6 months for the quadrivalent vaccine [22].

Both vaccines have been found to be safe and well tolerated. Local reactions like pain, swelling and redness can occur, but are usually of short duration. Systemic adverse reactions could include fever, nausea, dizziness, fatigue, headache and myalgia. The vaccines can be safely administered with other paediatric and adolescent vaccines [22]; they can also be safely administered to boys [25,26].

5.1. *Efficacy of bivalent and quadrivalent vaccine*

The quadrivalent vaccine has been evaluated in two phase III studies, FUTURE I and FUTURE II [27]. The bivalent vaccine has been evaluated in two phase III studies, PATRICIA and the Costa Rica HPV vaccine trial [28,29]. Clinical efficacy against infection and cervical lesions associated with HPV16 and HPV18 has been demonstrated up to 8.4 years with the bivalent vaccine, and up to 5 years with the quadrivalent vaccine [24,30–32].

High efficacy was obtained with the quadrivalent vaccine in the FUTURE I and II trials (Table 1), associated with HPV16/18. The

Table 1
Protection of young women against incident cervical disease by the quadrivalent vaccine in FUTURE I and FUTURE II trials, related to HPV16 and 18.

	% Efficacy (95% CI)
ATP	
CIN2	100 (94.7–100)
CIN3	96.8 (88.1–99.6)
AIS	100 (30.9–100)
ITT-naïve	
CIN2	100 (91.9–100)
CIN3	100 (90.5–100)
AIS	100 (<0–100)
ITT	
CIN2	54.8 (40.8–65.7)
CIN3	45.1 (29.8–57.3)
AIS	60.0 (<0–87.3)

AIS: Adenocarcinoma in situ; ATP: According to Protocol; CI: Confidence interval; CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; ITT: Intention-to-treat. Data from [30].

lower efficacy observed in the Intention To Treat (ITT) analysis, as compared to the IIT-naïve analysis, is explained by the inclusion of women with prevalent infection at entry. Irrespective of HPV type, the efficacy was 43.0% (95% CI: 13.0–63.2) against CIN3 in the ITT-naïve and 16.4% in the ITT analysis [30].

High efficacy was obtained with the bivalent vaccine in the PATRICIA trial (Table 2) associated with HPV16/18. Also high efficacy was observed in the Total Vaccinated Cohort (TVC)-naïve, irrespective of HPV type, of 93.2% (95% CI: 78.9–98.7) against CIN3+. In the TVC analysis, the efficacy was 45.6% (95% CI: 28.8–58.7) against CIN3+ irrespective of HPV type [30].

In the Costa Rica HPV vaccine trial, efficacy was 90.9% (95% CI: 82.0–95.9) against one year persistent HPV16/18 infection in the ATP cohort and 49.0% (95% CI: 38.1–58.1) in the ITT [30].

5.2. Quadrivalent vaccine and genital warts

Vaccine efficacy studies found that among HPV-naive women the quadrivalent HPV vaccine has nearly 100% protection against genital warts associated with HPV6 and 11, and an efficacy of about 83% for all genital warts [27,33,34]. In intention-to-treat analyses, in which young women were vaccinated regardless of their prior HPV exposure but with a maximum of four lifetime sexual partners and no history of abnormal cervical smears, an efficacy against all genital warts of 62% was reported [27].

In Australia, Sweden, Denmark and the United States substantial decreases in genital warts cases have been observed following the initiation of a national vaccination programme. In April 2007, Australia began vaccinating women aged 12–27 years. In the following year the proportion of women under 28 years with warts diagnosed decreased by 25.1% (95% CI: 30.5–19.3%) per quarter. Also, a modest decline in wart cases among heterosexual men but no change in number of wart cases among homosexual men was observed [35]. Furthermore, 5 years later, the absence of genital warts in vaccinated women, as well as the near disappearance of genital warts in women and men under 21 years of age was reported, suggesting that the basic reproductive rate of the virus had fallen below one and that heterosexual men are protected by a strong herd immunity [36,37]. Most likely due to higher coverage, the Australian data show a larger decline in genital wart cases in both women and men than seen in studies in Sweden, Denmark and the USA [38–41].

Since genital warts have a short incubation time of approximately 3 months after incident HPV infection, measuring the incidence of genital warts allows for early evaluations of the effectiveness of the quadrivalent HPV vaccine. In an effectiveness study covering the entire Swedish population, HPV vaccine effectiveness against genital warts was the highest (93%) for younger age cohorts (aged <14 years) and vaccine effectiveness decreased with increasing age, resulting in no clear effectiveness for women vaccinated when older than 22 years [39,40]. Although the effectiveness for other HPV-associated clinical outcomes might be different from that of genital warts, these data suggest that targeting girls that have not been exposed to HPV may be most cost effective in reducing HPV associated complications.

Table 2
Protection of young women against incident cervical disease by the bivalent vaccine in the PATRICIA trial, related to HPV16 and 18.

	% Efficacy (95% CI)
ATP	
CIN2+	94.9 (87.7–98.4)
CIN3+	91.7 (66.6–99.1)
AIS	100 (−8.6–100)
TVC-naive	
CIN2+	99.0 (94.2–100)
CIN3+	100 (85.5–100)
AIS	100 (15.5–100)
TVC	
CIN2+	60.7 (49.6–69.5)
CIN3+	45.7 (22.9–62.2)
AIS	70.0 (−16.6–94.7)

AIS: Adenocarcinoma in situ; ATP: According to protocol; CI: Confidence interval; CIN: Cervical intraepithelial neoplasia; HPV: Human papillomavirus; TVC: Total vaccine cohort. Data from [30].

5.3. Immunogenicity and duration of protection

Both vaccines are highly immunogenic with the highest immune responses being observed in young girls aged 9–15 years [25]. HPV16 antibody titres produced are several fold higher than after natural infection: these titres remain high for at least 8.4 years for the bivalent vaccine with 100% seropositivity maintained and at least 5 years for the quadrivalent vaccine with 98.8% seropositivity maintained [24]. The bivalent vaccine induces sustained antibody titres for HPV18 several fold higher than after natural infection, 8.4 years after initial vaccination with 100% seropositivity maintained. However, for the quadrivalent vaccine, 18 months after first vaccination, the induced antibody titres for HPV18 return to the level of natural infection, with a reduction in seropositivity over time [42]. A correlate for protection has not yet been established and further studies will determine whether these decreasing antibody levels are linked to reduced effectiveness.

The immunogenicity of the bivalent and quadrivalent vaccine was compared in a head-to-head trial. Neutralising antibodies (nAbs) against HPV16 and HPV18 were 3.7 and 7.3-fold higher, respectively for the bivalent vaccine compared to the quadrivalent vaccine in women of age 18–26 years old at month 7 after receiving the first dose [43]. These differences remained similar in older age groups. After 24 months of follow-up, the GMTs of nAbs were 2.4–5.8-fold higher for HPV16 and 7.7–9.4-fold higher for HPV-18 with the bivalent versus the quadrivalent vaccine [24,44]. This observation remained similar up to 48 months of follow-up: GMTs of nAbs were consistently higher in those receiving the bivalent vaccine across all age strata: 2.0–5.2-fold higher for HPV16 and 8.6–12.8-fold higher for HPV18 [45].

The use of different adjuvants in the vaccines might explain these differences in immunogenicity [46]. The difference in immune response observed at month 7 between the two vaccines was sustained up to month 48. However, the long-term clinical implications of these observed differences in antibody response need to be determined. An anamnestic response was observed after the administration of a fourth dose after 5 years for the quadrivalent vaccine [47] and after 7 years for the bivalent vaccine [48].

In a phase I/II study in South Africa, the bivalent HPV vaccine was shown to be immunogenic and well tolerated in HIV-infected women up to 12 months after vaccination. All subjects, both

HIV-positive and HIV-negative were seropositive at month 2, 7 and 12, although antibody titers were lower in HIV-positive children [49]. Similar results were observed with the quadrivalent vaccine [50]. Several studies are currently on-going in HIV-positive adolescent girls and young women to evaluate the safety and immunogenicity of HPV vaccines [17].

5.4. Cross-protection

Both HPV vaccines have some cross-protection against types that are not included in the vaccines, possibly explained by phylogenetic similarities between L1 genes from vaccine and non-vaccine types: HPV16 is phylogenetically related to HPV types 31, 33, 52 and 58 (A9 species); and HPV18 is related to HPV45 (A7 species). In a meta-analysis, cross-protection was shown with the quadrivalent vaccine against HPV31; while the bivalent vaccine showed cross-protection against HPV types 31, 33 and 45. There was little evidence of cross-protection against HPV types 52 and 58 [51,52].

Efficacy of the bivalent vaccine against incident infection with HPV31 up to 6.4 years was 59.8% (95% CI: 20.5–80.7); and 77.7% (39.3–93.4) against HPV45. Vaccine efficacy was also observed after 3.3 years of follow-up against CIN2+ associated with HPV31. No cases associated with HPV45 were observed in the vaccine group, while few cases were observed in the placebo group (PATRICIA trial). End-of-study results found vaccine efficacy of 100% (95% CI: 41.7–100) against CIN2+ associated with HPV45 in the TVC-naïve. As HPV45 is common in adenocarcinoma, this might add to the overall protection of the vaccine [24,53,54].

5.5. Strain–replacement

Vaccination with HPV vaccines is expected to reduce the prevalence of the HPV vaccine types. There might, however, be concern how this would affect the distribution of other oncogenic HPV types. Human papillomaviruses are genetically very stable DNA viruses. Escape mutants or new HPV types are therefore unlikely to develop [55,56]. HPV type replacement after vaccination depends whether there is natural competition between HPV types, and if this competition is stronger than the cross-protection afforded by the vaccine [55,56]. As vaccine-induced cross-protection against HPV31, 33 and 45 is much higher than that induced after natural infection, it is unlikely that type replacement will take place for these types [56]. But even if type replacement would occur, it remains to be seen if it would have implications on public health. The risk of developing cancer due to HPV16 or 18 is much higher than the risk of developing cancer by other HPV types [56].

A study conducted in the US showed that 4 years after vaccination with the quadrivalent vaccine, the HPV vaccine types decreased in vaccinated (31.8%), as well as non-vaccinated (30.2%) individuals. The prevalence of non-vaccine type HPV increased 14% for all participants [57]; however, it was not mentioned which types did increase.

5.6. Three-dose versus two-dose schedule

Reducing the number of doses of the HPV vaccine could have important public health implications, as adherence to the schedule and thus coverage might increase with reduced number of vaccine doses.

In the Costa Rica Vaccine Trial, in which many women missed one or more of the three doses of a randomly assigned bivalent HPV vaccine or control (hepatitis A) vaccine, the efficacy of fewer than three doses was evaluated up to 4.2 years after vaccination. Vaccine efficacy against 12-month persistent HPV16/18 infection was 80.9% (95%CI = 71.1–87.7%) for three doses of the HPV vaccine, and 84.1% (95%CI = 50.2–96.3%) for two doses. No cross-protection against HPV31, HPV33 and HPV45 was observed after administering two doses [58].

The immunogenicity of the bivalent HPV vaccine when administered in different formulations (20 μg versus 40 μg of each antigen) and different two-dose schedules (2 months apart versus 6 months apart) to healthy females stratified by age (9–14; 15–19; 20–25 years) was compared to its licensed vaccination schedule (three-dose, 20 μg of each antigen) [59]. Overall, a higher antibody response was observed in the age group 9–14 years, as compared to the age group 15–25 [59]. At one month after the last dose, all two-dose schedules in the primary target population (girls aged 9–14 years) were immunological non-inferior to the three-dose schedule in the age group in which efficacy has been demonstrated (15–25 years) [59]. At month 24, this non-inferiority was maintained for administrations 6 months apart but lost for administrations 2 months apart [59]. These antibody responses to a two-dose schedule in girls 9–14 years of age at month 0, 6 remained comparable to the licensed three-dose schedule in women 15–25 years of age up to 3 years after first vaccination [60].

Girls of 9–13 years of age received either three doses of the quadrivalent vaccine at 0, 2 and 6 months or two doses at 0 and 6 months. Young women of 16–26 year of age received three doses at 0, 2 and 6 months. One month after receiving the last dose of the quadrivalent vaccine, non-inferiority of the vaccine was observed between two or three doses. However, loss of non-inferiority was observed in the two-dose schedule for HPV18 at month 24 and for HPV6 at month 36 [61].

Quebec and Mexico are currently implementing an HPV vaccination programme using an extended interval between doses (vaccination at 0, 6 and 60 months) and short-term effectiveness of less than three doses can be monitored [58]. The issue of cross-protection and duration of protection with less than three doses need to be further studied before any recommendation can be made.

6. New developments

6.1. Nine-valent vaccine

The currently registered vaccines cover only HPV6, HPV11, HPV16 and HPV18. It is estimated that this would protect against 70% of all squamous cell cancers. To increase the protection, studies are on-going to increase the number of HPV types to nine by adding HPV31/33/45/52 and 58 to the quadrivalent vaccine [62]. This vaccine, codenamed V503, is tested in 8 trials registered at clinicaltrials.gov [63]. Three trials completed testing in 11–26 year old females, alone or in combination with Menactra™ (meningococcal vaccine), Adacel™ (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine) or Repevax™ (diphtheria, tetanus, pertussis and polio vaccine). Five active trials are testing 16–26 year old females in the US and in Japan and measuring vaccine efficacy based on viral (presence or absence of HPV virus) or clinical outcome (prevention of warts). The results of the trials are still unpublished. From mathematical modelling it was calculated however that this vaccine could raise the protection to 90% of all SCC cases worldwide [62].

6.2. Prophylactic L2 vaccines

A major problem, especially when seen from a worldwide public health aspect, is the type-specificity of the current L1 vaccines. Although the addition of types is being tested (see nine-valent vaccines), a pan-HPV vaccine that could be easily and cheaply produced (one antigen instead of nine or more) would limit the need for further cervical cancer screening interventions. Indeed, these have to remain in place with the current vaccine strategy as a significant fraction (approximately 30%) is caused by high-risk HPV types, which are not covered in the current formulation [64]. This

double-barrel strategy becomes a heavy burden on public health spending and is difficult to implement in low-income countries.

Human papillomaviruses are small non-enveloped DNA viruses of which the capsid contains mainly the L1 protein but also smaller amounts of L2. The L1 is abundantly present in a multivalent format in which the epitopes are present as a dense, highly repetitive array, which strongly stimulates B cells [18]. In contrast, in the natural infection the L2 protein is barely visible for the immune system. However, the L2 protein becomes more exposed after the virus binds to the basement membrane due to conformational changes. This short and transient exposure however fails to elicit any anti-L2 neutralizing antibody response.

This could partly explain the conservation of the L2 epitope. Indeed, a small proportion of the L2 protein, especially between amino acid 20 and 38, is highly preserved between various high-risk HPV types [64]. In addition, different antibodies against this region show neutralizing activity against a wide range of papillomaviruses.

The main problem up to now with L2-based vaccines is poor immunogenicity, as the titers of neutralizing antibodies are much lower [64].

Recently, more success has been obtained in mice by the use of bacteriophage VLPs [65] and orally administered *Lactobacillus casei* expressing L2 on their surface [66]. The latter induced a significant vaginal mucosal immunity with production of broadly protective IgA, which could be effective in early phases of the viral infection, suggesting that this type of oral immunisation may be a promising strategy for prophylactic vaccination of humans.

In addition to the use of bacteriophages, combinations of (cocktails of) adjuvantia, multimerisation and epitope display techniques have been tested leading to antibody responses which were only slightly lower than the responses elicited by L1.

Potentially due to the physiological role of L2 in the viral entry and intracellular trafficking it has been shown that L2 vaccination can be therapeutic against papillomas, even without eliciting a neutralizing antibody response [67]. In the latter case, a heavy T cell infiltrate mounted a cellular response, killing infected cells and inducing rapid clearance of virus and lesion. The L2 vaccines are therefore promising for the future but further clinical testing in human patients needs to be done before further conclusions can be drawn.

6.3. Therapeutic vaccines

There has been a long history of trials to develop therapeutic vaccines against HPV. Most vaccines aim to increase the T-cell immune response using viral vectors, recombinant DNA or other. Nine unsuccessful studies are summarized by Stern et al. [68]. Limited success was recently shown using synthetic or recombinant HPV16E6 related peptides. Clinicaltrial.gov lists 3 active, on-going trials on therapeutic HPV vaccines. Safety issues and issues of administration of the vaccine limit the potential use of 4 non-clinicaltrial.gov-listed compounds currently in phase I or II (personal communication, Genticel, France). Recently a phase I trial using recombinant HPV16E7 and HPV18E7 concluded that the product was safe to use and a phase II trial has been planned (personal communication, Genticel, France).

7. Public health issues

The currently available vaccines, Cervarix™ and Gardasil™, are recommended for prophylactic use. They will not clear an existing infection or disease. To obtain optimal benefit of the vaccine, it must be given before exposure to HPV, which is before sexual debut [22,69]. The vaccines can be administered to persons 9 years old and above. Although specific target age groups may differ among countries, many countries start the vaccination for girls at age 11–12 years [70]. In the United Kingdom, catch-up vaccination is considered cost-effective for females aged 13–18 years [71].

Currently, vaccination for males is not recommended [22], though some countries, like Australia and USA, do vaccinate males as well [37,41]. Adding males in a HPV vaccination programme might have direct benefits in protecting against HPV-related cancers in men and anogenital warts [72]. However, mathematical models revealed that increasing vaccine uptake among adolescent girls is more effective in reducing HPV infection rather than including boys in existing vaccination programmes [72,73]. Vaccinating the sex with the highest prevalence will reduce the population prevalence most effectively [73]. The cost-effectiveness of including males depend on the predicted herd immunity in heterosexual males derived from vaccinating females, and the proportion of all male HPV-related disease in homosexual men [72]. However, the HPV-related burden of disease is lower in males than in females [72], and the incremental benefits of adding boys are dependent on the coverage in girls [74]. If coverage in girls is higher than 50%, including boys in the vaccination programme is likely not cost-effective [72].

The introduction of HPV vaccine in industrialised countries (e.g. United Kingdom, Australia, Belgium) is achieving good coverage through school-based vaccination programmes. These countries aim to vaccinate all girls around the age of 12 years, and also include catch-up vaccination of slightly older adolescents during the first years of introduction. Vaccination coverage of above 70% has been observed in both Australia and the United Kingdom [75,76]. In Belgium, 83.2% vaccination coverage was observed for the third dose [77]. In contrast, in the United States, the coverage of the three-dose series of HPV vaccine was only 34.8% in 2011 and 33.4% in 2012 among 13 to 17 year old girls vaccinated by primary care physicians [78]. A higher coverage is being achieved through school-based vaccination programmes, rather than through primary care-based programmes. However, school-based programmes need to make increased efforts to reach out-of-school children, especially in low-resource countries [70].

The high price of the current HPV vaccines has been a hurdle in the introduction of the vaccines, especially in developing countries [79]. Industrialised countries pay a price as high as 120 USD per dose [79]. Around 40 countries had introduced HPV vaccine into their national immunization programme by the beginning of 2012 [70].

Since May 2013, the GAVI Alliance, through UNICEF, can purchase the quadrivalent vaccine at a reduced price of US$ 4.50 per dose, and the bivalent vaccine for US$ 4.60 per dose [80]. With this commitment, more countries will be able to introduce this life-saving vaccine. The first countries benefitting from GAVI support through HPV demonstration projects include Kenya, Ghana, Lao PDR, Madagascar, Malawi, Niger, Sierra Leone and Tanzania [80].

However, middle-income countries have limited or no access to external funding for the introduction of new vaccines. As a consequence, these countries might lag behind in the introduction of new vaccines [81]. Members of the Pan American Health Organization (PAHO) can buy the HPV vaccine at a reduced cost: the PAHO Revolving Fund offers the vaccines at around US$ 13 per dose [82]. Some other middle-income countries have received support for HPV vaccine introduction from external sources like donations from manufacturers and supported programme-assisted funding [81]. As of September 2012, 10 middle-income countries have introduced HPV vaccine and another 12 countries are conducting pilot studies [81].

8. Conclusion

The two available prophylactic HPV vaccines have the potential of considerably reducing HPV-related morbidity and mortality.

Both vaccines are based on VLPs of the L1 capsid protein, and are highly immunogenic and efficacious if given before exposure to HPV, i.e. to adolescent girls between 9 and 13 years old in a three-dose schedule. However, some challenges, such as the cost of the vaccines and the logistics and delivery of a vaccine to adolescent girls, prevent high global coverage of the HPV vaccine.

With the recent price reduction offered to the GAVI Alliance, more low-income countries will be able to introduce the HPV vaccine, although challenges for co-payments and a sustainable delivery platform remain. Innovative financing mechanisms will be needed to address this, as well as the needs of middle-income countries.

Reducing the number of doses of the HPV vaccine could have important public health implications, as adherence to the schedule and thus coverage might increase, while the costs related to the delivery of the vaccine will reduce.

Furthermore, the current HPV vaccines protect against 70% of cervical cancers, i.e. those caused by HPV type 16 and 18, and provide some additional cross-protection against types not included in the vaccine. The development of a nine-valent or a universal HPV vaccine will increase the protection and further reduce the need for HPV screening programmes.

Disclaimer

The authors alone are responsible for the views expressed in this article and do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Conflict of interest

None declared.

References

[1] Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L, et al. Global burden of human papillomavirus and related diseases. Vaccine 2012;30 Suppl 5:F12–23.

[2] Arbyn M, Raifu AO, Weiderpass E, Bray F, Anttila A. Trends of cervical cancer mortality in the member states of the European Union. Eur J Cancer 2009;45:2640–8.

[3] Munoz N, Bosch FX. HPV and cervical neoplasia: review of case-control and cohort studies. In: Munoz N, Bosch FX, Shah KV, Meheus A, editors. The epidemiology of human papillomavirus and cervical cancer. Lyon, France: IARC Scientific Publications No. 119; 1992. p. 251–61.

[4] Walboomers JM, Meijer CJ. Do HPV-negative cervical carcinomas exist. J Pathol 1997;181:253–4.

[5] Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L, et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine 2008;26 Suppl 10:K1–16.

[6] Gissmann L, Wolnik L, Ikenberg H, Koldovsky U, Schnürch HG. zur Hausen H Human papillomavirus types 6 and 11 DNA sequences in genital and laryngeal papillomas and in some cervical cancers. PNAS 1983;80(2):560–3.

[7] Aubin F, Prétet JL, Jacquard AC, Saunier M, Carcopino X, Jaroud F, et al. Human papillomavirus genotype distribution in external acuminata condylomata: a large French National Study (EDiTH IV). Clin Infect Dis 2008;47(5):610–5.

[8] Garland SM, Steben M, Sings HL, James M, Lu S, Railkar R, Barr E, Haupt RM, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. J Infect Dis 2009;199(6):805–14.

[9] Kjaer SK, Tran TN, Sparen P, Tryggvadottir L, Munk C, Dasbach E, et al. The burden of genital warts: a study of nearly 70,000 women from the general female population in the 4 Nordic countries. J Infect Dis 2007;196(10):1447–54.

[10] Munk C, Nielsen A, Liaw KL, Kjaer SK. Genital warts in men: a large population-based cross-sectional survey of Danish men. Sex Transm Infect 2012;88(8):640–4.

[11] Fenton KA, Korovessis C, Johnson AM, McCadden A, McManus S, Wellings K, et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital Chlamydia trachomatis infection. Lancet 2001;358(9296):1851–4.

[12] Dinh TH, Sternberg M, Dunne EF, Markowitz LE. Genital warts among 18- to 59-year-olds in the United States: national health and nutrition examination survey, 1999–2004. Sex Transm Dis 2008;35(4):357–60.

[13] Grulich AE, de Visser RO, Smith AM, Rissel CE, Richters J. Sex in Australia: knowledge about sexually transmissible infections and blood-borne viruses in a representative sample of adults. Aust NZ J Public Health 2003;27(2):230–3.

[14] de Villiers E-M. Cross-roads in the classification of papillomaviruses. Virology 2013;445:2–10.

[15] Clifford GM, Gallus S, Herrero R, Munoz N, Snijders PJF, Vaccarella S, et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. Lancet 2005;366:991–8.

[16] Schiffman M. Integration of human papillomavirus vaccination, cytology, and human papillomavirus testing. Cancer 2007;111:145–53.

[17] Denny LA, Franceschi S, de Sanjosé S, Heard I, Moscicki AB, Palefsky J. Human papillomavirus, human immunodeficienty virus and immunosuppression. Vaccine 2012;30S:F168–74.

[18] Stanley M, Pinto LA, Trimble C. Human papillomavirus vaccines—immune responses. Vaccine 2012;30 Suppl 5:F83–7.

[19] Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30 Suppl 5:F55–70.

[20] Horvath CAJ, Boulet GAV, Renoux VM, Delvenne PO, Bogers J-PJ. Mechanisms of cell entry by human papillomaviruses: an overview. Virol J 2010;7:11.

[21] Sahebali S, Van den Eynden G, Murta EF, Michelin MA, Cusumano P, Petignat P, et al. Stromal issues in cervical cancer: a review of the role and function of basement membrane, stroma, immune response and angiogenesis in cervical cancer development. Eur J Cancer Prev 2010;19:204–15.

[22] World Health Organization. Human papillomavirus vaccines. WHO position paper. Weekly epidemiological record 2009, vol. 84 (15); 2009. p. 118–31.

[23] World Health Organization. The immunological basis for immunization series. Module 19: human papillomavirus infection. WHO, Department of Immunization, Vaccines and Biologicals; 2011.

[24] Romanowski B. Long-term protection against cervical cancer infection with the human papillomavirus. Hum Vaccines 2011;7(2):161–9.

[25] Block SL, Nolan T, Sattler C, Barr E, Giacoletti KE, Marchant CD, et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6: 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics 2006;118(5):2135–45.

[26] Petaja T, Keranen H, Karppa T, Kawa A, Lantela S, Siitari-Mattila M, et al. Immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in healthy boys aged 10–18 years. J Adolesc Health 2009;44(1):33–40.

[27] Dillner J, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, Hernandez-Avila M, et al. On behalf of FUTURE I/II Study Group. Four years efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomized controlled trial. BMJ 2010;341:c3493.

[28] Paavonen J, Naud P, Salmeron J, Wheeler CM, Chow SN, Apter D, et al. Efficacy of human papillomavirus (HPV)-16/18 ASO4-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomized study in young women. Lancet 2009;374(9686):301–14.

[29] Herrero R, Wacholder S, Rodrigeuz AC, Solomon D, Gonzalez P, Kreimer AR, et al. Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: a community-based randomised clinical trial in Guanacaste, Costa Rica. Cancer Discovery 2011;1(5):408–19.

[30] Schiller JT, Castellsagué X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;30S:F123–38.

[31] Villa LL, Costa LRL, Petta CA, Andrade RP, Paavonen J, Iversen O-E. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer 2006;95:1459–66.

[32] Roteli-Martins CM, Naud P, De Borba P, Teixeira JC, De Carvalho NS, Zahaf T, et al. Sustained immunogenicity and efficacy of the HPV-16/18 ASO4-adjuvanted vaccine. Hum Vaccines Immunother 2012;8(3):390–7.

[33] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356(19):1928–43.

[34] Muñoz N, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. Impact of human papillomavirus (HPV)-6/11/16/18 vaccine on all HPV-associated genital diseases in young women. J Nat Cancer Inst 2010;102(5):325–39.

[35] Fairley CK, Hocking JS, Gurrin LC, Chen MY, Donovan B, Bradshaw CS. Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination programme for young women. Sex Transm Infect 2009;85(7):499–502.

[36] Read TR, Hocking JS, Chen MY, Donovan B, Bradshaw CS, Fairley CK. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. Sex Transm Infect 2011;87(7):544–7.

[37] Ali H, Donovan B, Wand H, Read TR, Regan DG, Grulich AE, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. BMJ 2013;346:f2032.

[38] Baandrup L, Blomberg M, Dehlendorff C, Sand C, Andersen KK, Kjaer SK. Significant decrease in the incidence of genital warts in young Danish women after implementation of a national human papillomavirus vaccination program. Sex Transm Dis 2013;40(2):130–5.

[39] Leval A, Herweijer E, Arnheim-Dahlström L, Walum H, Frans E, Sparén P, et al. Incidence of genital warts in Sweden before and after quadrivalent

human papillomavirus vaccine availability. J Infect Dis 2012;206(6):860–6.
[40] Leval A, Herweijer E, Ploner A, Eloranta S, Fridman Simard J, Dillner J, et al. Quadrivalent human papillomavirus vaccine effectiveness: a Swedish national cohort study. J Nat Cancer Inst 2013;105(7):469–74.
[41] Bauer HM, Wright G, Chow J. Evidence of human papillomavirus vaccine effectiveness in reducing genital warts: an analysis of California public family planning administrative claims data, 2007–2010. Am J Public Health 2012;102(5):833–5.
[42] Harper DM, Williams KB. Prophylactic HPV vaccines: current knowledge of impact on gynecologic premalignancies. Discovery Med 2010;10(50):7–17.
[43] Einstein MH, Baron M, Levin MJ, Chatterjee A, Edwards RP, Zepp F, et al. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. Hum Vaccines 2009;5(10):705–19.
[44] Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 vaccine and HPV-6/11/16/18 vaccine: follow-up from months 12–24 in a phase III randomised study of healthy women aged 18–45 years. Hum Vaccines 2011;7(12):1343–58.
[45] Einstein M. On behalf of the HPV-010 Study Group. Comparison of immunogenicity of two prophylactic human papillomavirus (HPV) vaccines as month 48. Int J Gynecol Obstetrics 2012;119S3:S334.
[46] Giannini SL, Hanon E, Moris P, Van Mechelen M, Morel S, Dessy F, et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VPL vaccine formulated with the MPL/aluminium salt combination (ASO4) compared to aluminium salt only. Vaccine 2006;24:5937–49.
[47] Olsson SE, Villa LL, Costa RL, Petta CA, Andrade RP, Malm C, et al. Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine 2007;25(26):4931–9.
[48] McKeage K, Romanowski B. AS04-adjuvanted human papillomavirus (HPV) types 16 and 18 vaccine (Cervarix(R)): a review of its use in the prevention of premalignant cervical lesions and cervical cancer causally related to certain oncogenic HPV types. Drugs 2011;71(4):465–88.
[49] Denny L, Hendricks B, Gordon C, Hervé C, Thomas F, Hezareh M, et al. Safety and immunogenicity of the HPV-16/18 ASO4-adjuvanted vaccine in HIV-positive women in South Africa up to 12 months after vaccination. Int J Gynecol Obstetrics 2012;119(Supp 3):S323–4.
[50] Levin MJ, Moscicki A, Song L, Fenton T, Meyer WA, Read JS. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6: 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. J Acquir Immun Defic Syndr 2010;55(2):197–204.
[51] Kemp TJ, Hildesheim A, Safaeian M, Dauner JG, Pan Y, Porras C, et al. HPV16/18 L1 VLP vaccine induces cross-neutralising antibodies that may mediate cross-protection. Vaccine 2011;29(11):2011–4.
[52] Malagon T, Drolet M, Boily M-C, Franco EL, Jit M, Brisson J, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:781–9.
[53] Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S, et al. Comparison of the immunogenicty of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18-45 years. Hum Vaccines 2011;7(12):1359–73.
[54] Wheeler CM, Castellsague X, Garland SM, Szarewski A, Paavonen J, Naud P, et al. Cross-protective efficacy of HPV16/18 ASO4 adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomized, double blind PATRICIA trial. Lancet Oncol 2012;13(1):100–10.
[55] Dillner J, Arbyn M, Unger E, Dillner L. Monitoring of human papillomavirus vaccination. Clin Exp Immunol 2010;163:17–25.
[56] Tota JE, Ramanakumar AV, Jiang M, Dillner J, Walter SD, Kaufman JS, et al. Epidemiologic approaches to evaluating the potential for human papillomavirus type replacement postvaccination. Am J Epidemiol 2013, http://dx.doi.org/10.1093/aje/kwt018.
[57] Kahn JA, Brown DR, Ding L, Widdice LE, Shew ML, Glynn S, et al. Vaccine-type human papillomavirus and evidence of herd protection after vaccine introduction. Pediatrics 2012, http://dx.doi.org/10.1542/peds. 2011-3587.
[58] Kreimer AR, Rodriguez AC, Hildesheim A, Herrero R, Porras C, Schiffman M<ET-AL. Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. J Nat Cancer Inst 2011;103:1–8.
[59] Romanowski B, Schwarz TF, Ferguson LM, Peters K, Dionne M, Schulze K, et al. Immunogenicity and safety of the HPV-16/18 ASO4-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule. Results from a randomized study. Hum Vaccines 2011;7(12):1374–86.
[60] Schwarz T, Romanowski B, Peters K, Dionne M, Schulze K, Ramjattan B, et al. Immune response to the HPV-16/18 ASO4-adjuvanted vaccine administered as a 2-dose or 3-dose schedule up to 3 years after vaccination. Int J Gynecol Obstetrics 2012;119S3:S476.
[61] Dobson SRM, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs. 3 doses in young women. JAMA 2013;309(17):1793–802.
[62] Serrano B, Alemany L, Tous S, Bruni L, Clifford GM, Weiss T, et al. Potential impact of a nine-valent vaccine in human papillomavirus related cervical disease. Infect Agent Cancer 2012;7:38.
[63] V503, ClinicalTrials search result.
[64] Karanam B, Jagu S, Huh WK, Roden RBS. Developing vaccines against minor capsid antigen L2 to prevent papillomavirus infection. Immunol Cell Biol 2009;87:287–99.
[65] Tumban E, Peabody J, Peabody DS, Chackerian B. A universal virus-like particle-based vaccine for human papillomavirus: longevity of protection and role of endogenous and exogenous adjuvants. Vaccine 2013;31:4647–54.
[66] Yoon S-W, Lee T-Y, Kim S-J, Lee I-H, Sung M-H, Park J-S, et al. Oral administration of HPV-16 L2 displayed on *Lactobacillus casei* induces systematic and mucosal cross-neutralizing effects in Balb/c mice. Vaccine 2012;30:3286–94.
[67] Tumban E, Peabody J, Peabody DS, Chackerian B. A pan-HPV vaccine based on bacteriophage PP7 VLPs displaying broadly cross-neutralizing epitopes from the HPV minor capsid protein, L2. PLoS One 2011;6:e23310.
[68] Stern PL, van der Burg SH, Hampson IN, Broker TR, Fiander A, Lacey CJ, et al. Therapy of human papillomavirus-related disease. Vaccine 2012;30:F71–82. Suppl 5.
[69] Botha MH, Dochez C. Introducing human papillomavirus vaccines into the health system in South Africa. Vaccine 2012;30S:C28–34.
[70] Markowitz LE, Tsu V, Deeks SL, Cubie H, Wang SA, Vicari AS, et al. Human papillomavirus vaccine introduction—the first five years. Vaccine 2012;30S:F139–48.
[71] Jit M, Choi YH, Edmunds WJ. Economic evaluation of human papillomavirus vaccination in the United Kingdom. BMJ 2008;337:a769.
[72] Canfell K, Chesson H, Kulasingam SL, Berkhof J, Diaz M, Kim JJ. Modeling preventative strategies against human papillomvirus-related disease in developed countries. Vaccine 2012;30S:F157–67.
[73] Bogaards JA, Kretzschmar M, Xiridou M, Meijer CJLM, Berkhof J, Wallinga J. Sex-specific immunization for sexually transmitted infections such as human papillomavirus: insights from mathematical models. PLoS Med 8(12):e1001147. http://dx.doi.org/10.1371/journal.pmed.1001147
[74] Marty R, Roze S, Bresse X, Largeron N, Smith-Palmer J. Estimating the clinical benefits of vaccinating boys and girls against HPV-related diseases in Europe. BMC Cancer 2013;13:10.
[75] Australian Government. Department of health and aging. ⟨http://www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-hpv⟩ [cited 11 June 2013].
[76] Department of Health. Annual HPV vaccine coverage in England in 2009/2010. ⟨https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147510/dh_123826.pdf⟩ [cited 11 June 2013].
[77] Top G, Paeps A. HPV vaccinatie in Vlaanderen – resultaten van het eerste vaccinatiejaar 2010–2011. Infectieziektebulletin http://www.infectieziektebulletin.be/defaultSubsite.aspx?id=31494# [cited 12 June 2013].
[78] Centers for Disease Control and Prevention. Human papillomavirus vaccination coverage among adolescent girls, 2007–2012, and postlicensure vaccine safety monitoring, 2006–2013—United States. MMRW 2013;62(29):591–5 http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6229a4.htm [cited 2 September 2013].
[79] Editorial. Financing HPV vaccination in developing countries. Lancet 2011;377(9777):1544.
[80] GAVI Alliance. http://www.gavialliance.org/library/news/press-releases/2013/hpv-price-announcement/ [cited 11 June 2013].
[81] Kaddar M, Schmitt S, Makinen M, Milstien J. Global support for new vaccine implementation in middle-income countries. Vaccine 2013;31S:B81–96.
[82] PAHO Revolving Fund. Vaccine prices; 2013 http://www.paho.org/hq/index.php?option=com_content&view=article&id=1864&Itemid=2234&lang=en [cited 12 June 2013].