Abstract

Human papilloma virus (HPV) imposes an immune chemical burden on the world's population. HPV vaccine offers us the hope of eventually eradicating HPV-related diseases. Various studies have been conducted and reported a reliable data for safety, immunogenicity and effectiveness of HPV vaccines. In spite of the excellent safety, immunogenicity and efficacy profile of HPV vaccines, acceptance and coverage rates are still far from desirable in the majority of communities that introduced routine active immunization programs. Healthcare providers’ HPV vaccine recommendation practices could reflect the patients and their parents recognition of and desire to reduce the disparities. Developing provider interventions to increase vaccine recommendation is a viable way to improve catch-up vaccination rates among both the sexes. As HPV vaccines are reported to be generally safe and well-tolerated, high vaccine coverage rates are necessary to achieve in order to yield a better impact of vaccination. Otherwise the vaccination effort will fall short of reaching its maximum public health benefit.

Introduction

HPV infections are considered to be the most commonly sexually transmitted infections (STIs) worldwide. HPV's are small, non-enveloped, double-stranded DNA viruses, and more than 40 genotypes have been associated with infection of the female genital tract [1]. Non-cancerous cutaneous manifestations of HPV are the com-
mon warts, plantar warts, plane warts, anogenital warts and epidermodysplasia verruciformis. Mucosal manifestations of HPV are oral warts, condylomata, focal epithelial hyperplasia (Heek’s disease), nasal and conjunctival papillomas, laryngeal papillomas and cervical lesions [2]. A casual link has been found between HPV and cervical, penile, vulvar, vaginal, anal and oropharyngeal carcinoma [3]. Specifically, HPV causes 530,000 cervical cancer cases worldwide yearly as well as 90% of anal cancers and approximately 50% of oropharyngeal, penile, vaginal and vulval cancers [4]. Altogether HPV is estimated to be the casual agent in 5% of all human cancers with HPV 16 by far and away the major player [5]. More than any other cancer, cervical cancer reflects striking global health inequity. Although the majority of infections cause no symptoms and are self-limited, persistent genital HPV infection can cause cervical cancer in women and other types of anogenital cancers and genital warts in both men and women [6]. HPV infection varies with age in women with the peak prevalence in the late teens and twenties declining steadily throughout the subsequent decades, in contrast men acquire infection in the late teens and the prevalence remains constant throughout the subsequent decades [5].

HPV vaccination provides effective protection against HPV and its associated adverse health outcomes. Two safe and highly efficacious HPV prophylactic vaccines are currently unavailable, a bivalent (Cervarix*) and a quadrivalent Gardasil*), being the most effective intervention to control for HPV and cervical cancer, particularly in lower resource countries. Both vaccines prevent infection by HPVs 16/18, responsible for about 70% invasive cervical cases, and Gardasil also includes HPVs 6/11, which cause approximately 90% of external genital warts. The quadrivalent vaccine is also recommended for boys and men aged 11-12 years, and for men aged 22-26 years who have sex with men or who are immuno-compromised. These vaccines are close to 100% effective, against the vaccine types, when administered in a 3 dose course, and thus, over 100 countries have licensed the vaccine, and some have already included them in their national immunization programs, especially developed countries [7]. In several countries (Australia, Great Britain, and the United states) with a national HPV vaccination program, there has been observed a decrease in HPV prevalence in the vaccinated population [8,9,10]. The Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) recommend routine HPV vaccination for females and, also since 2011, for males at 11 or 12 years of age, as well as “catch-up” vaccination of up to the age of 26 years (females) and 21 years (males) [11].
HPV vaccination is complicated because strong endorsement of its value by both parents and providers is accompanied by popular concerns about general vaccine safety and the proprietary of administering a vaccine for sexually transmitted disease (STD)[12,13]. Provider recommendation is considered the most important factor in HPV vaccine uptake.

The risk of HPV infection persists throughout a woman’s sexual life. Therefore, the duration of protection provided by HPV vaccination is critical to overall vaccine effectiveness. Moreover, concerns about vaccine safety and related adverse events have been identified as an important barrier to vaccination and one of the reasons for low HPV vaccination coverage in some settings [14]. It is important to establish systems for continued monitoring of vaccine immunogenicity, efficacy and safety over time.

Safety, Immunogenicity and Efficacy

HPV infections trigger both humoral and cellular response in the host immune system. The humoral immune response to HPV infection involves producing neutralizing antibody against the specific HPV type, specifically the specific L1 major capsid protein. This process is typically somewhat slow and weak, and only about 60% of women with a new HPV infection develop antibodies to it [15,16]. The cell-mediated immune response to early HPV onco-proteins may help eliminate established HPV infection [17]. In contrast to antibodies, the T-cell response to HPV has not been shown to be specific to the HPV type [18]. Clinically cervical HPV infection is common, but most lesions go into remission or resolve as a result of the cell-mediated immune response [17,18].

Availability of the prophylactic HPV vaccine is seen as a key strategy in reducing the burden of cervical cancer in low and middle income countries (LMICS) where this has so far been unachievable [19,20]. World Health Organization (WHO) recognizes the global importance of preventing cervical cancer and HPV-related diseases, constitutes a public health problem [19]. Currently, two HPV vaccines are available: a quadrivalent vaccine against types 6, 11, 16 and 18 (Gardasil; Merck) and a bivalent vaccine against types 16 and 18 (Cervarix; GlaxoSmithKline). The quadrivalent vaccine was approved by the US Food and Drug Administration (FDA) in 2006, and the bivalent vaccine was approved in 2009 [21,22]. The antigens for both the vaccines are virus like particles (VLPs) derived from the L1 surface protein of the respective types of the virus. The VLPs are non-pathogenic and cannot infect cells, since they do not have viral genome. The vaccines induce high titer of serum immunoglobulin G antibody against respective HPV types, which is secreted in the cervico-vaginal secretion and is also exuded from the micro-abrasions in the epithelium. Presence of the antibodies at
the point of viral entry ensures the neutralization of the virus before it gets an opportunity to bind to infect the basal keratinocytes [23].

Both bivalent and the quadrivalent vaccines have been rigorously evaluated through phase III randomized placebo controlled trials (RCTs). Two phase III RCTs have evaluated the bivalent vaccine and three phase III RCTs have evaluated the quadrivalent vaccine [24]. In the phase III trials there were subjects without any evidence of HPV infection or cytological abnormality and also subjects with active or past HPV infection and even cytological abnormalities. To compensate for the expected difference in outcomes in these two major subgroups, the trials analyzed the vaccine efficacy in two different efficacy cohorts—per-protocol population and the intention-to-treat population. The per-protocol population included those who neither had positive serology (indicative of past infection) nor DNA in cervix (indicates active infection) for the target HPV types and received three doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year. This population in real life represents young sexually naïve subjects receiving full doses of the vaccines within one year.

For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25]. For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25]. For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25]. For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25]. For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25]. For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25]. For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25]. For any new vaccine there are concerns about vaccine-induced medical conditions, especially systemic autoimmune disorders and neurological disorders. The long term follow up of the subjects participating in the RCTs did not have higher incidence of these conditions compared with the control group [25].

WHO, United Nations Populations Fund (UNFPA), International Union Against Cancer (UICC), International federation of Gynecologists and Obstetricians (FIGO) and other organizations that influence public health policies globally have unanimously endorsed HPV vaccines as an effective cancer prevention option [28]. The Strategic Advisory Group of Experts (SAGE) on immunization, which reports to the Director-General of WHO on issues ranging from vaccine research and development to immunization delivery, probably that the introduction of vaccines is likely to bring great benefits worldwide, particularly to those developing countries where cervical cancer is a major cause of death, and screening programs are limited or absent [28].

Therapeutic DNA vaccines against HPV have been tested in several clinical trials. These vaccines target the E6 and E7 viral peptides, which are fundamental proteins for tumorigenesis and tumor maintenance and tumor main-
tenance within infected epithelial cell; immune responses against the viral peptides have been shown to control cervical intraepithelial neoplasia (CIN) and other HPV-related diseases [29]. Whereas Gardasil and Cervarix induce prophylactic immunity via the production of antibodies, therapeutic HPV vaccines trigger antigen-specific action by cytotoxic T lymphocytes (CTLs). These CTLs recognize and attack epithelial cells infected by HPV as well as tumor cells. Additionally, DNA vectors themselves have been demonstrated to trigger innate inflammatory responses due to an immune-stimulatory effect [30]. Compared to peptide and subunit vaccines, DNA vaccines are more stable at wider temperature ranges, which inherently lowers production and distribution costs. These attributes have made E6/E7 DNA vaccines attractive investigational options for treating existing HPV infections [4].

Vaccine Research Center (VRC) independently evaluated innate and adaptive immune responses in healthy young women following vaccination with the 2 FDA licensed HPV vaccines [14]. The VRC, USA trial was conducted to comprehensively evaluate and compare humoral and cellular responses induced by Cervarix and Gardasil recipients [14]. The study reported a comprehensive immune comparison between Cervarix and Gardasil, with novel data on T cell responses, avidity, and an extensive time course of circulating plasma cytokine profiles following vaccination [31]. It has been observed in the study that both vaccines induced strong antibody responses with differences in magnitude of titers achieved. Levels of HPV-16 and HPV-18 antibodies after 3 doses of vaccine were significantly higher for Cervarix than levels induced in Gardasil recipients, and peak antibody titers were achieved after only two doses of Gardasil, whereas peak titers were observed after 3 doses of Cervarix—indicating more prominent booster effect from the third dose of Cervarix. There were evaluated levels of phylogenetically related, non-vaccine neutralizing antibodies and observed neutralizing HPV-31 antibodies were induced at statistically higher levels in Cervarix recipients than Gardasil recipients following 3 doses of vaccine [31]. That was the very first study that evaluated and compared circulating cytokines most notable difference observed is an increased chemokine and cytokine (IL-12p40, IL-8, IP-10, MCP-1 and MIP-1β) response in Gardasil recipients following first vaccination which peaks at day 5 and extends through day 14. With the exception of IL-12p40, a T cell stimulating factor, Gardasil recipients showed elevated circulating pro-inflammatory markers (IL-6, IL-1α, IL-1β) following first (3-7 hours) and third vaccination (7 hours through month 7) when compared to Gardasil. This data suggested that the TLR4 ligand adjuvant may have a stimulatory effect on pro-inflammatory cytokines. The data showed that for the HPV vaccine types antibody titers are achieved in Gardasil after the second dose of vaccine, whereas with Cervarix the titers are further boosted after the third dose.
of vaccine. The two vaccines additionally showed differences in circulating cytokine profiles, which may be attributed to the differences in adjuvant formulation [31].

There are several aspects of the immune response to HPV vaccines that must be taken into account in order to understand the available information and the problems to be faced in the collection of data on long-term protection. The immunogenicity of the two vaccines is expected to be different, due to the effect of the adjuvants. In fact, while quadrivalent HPV vaccine uses aluminium hydroxyphosphate sulfate (AS04), bivalent HPV vaccine uses aluminium hydroxide and monophosphoryl Lipid A (MLP) as adjuvant [14,32]. In vivo, antibody titers were measured by different immunoassays throughout the three phases of the HPV-vaccine trials. Proprietary reports of immune responses have used competitive Luminex immunoassay (cLIA) for the quadrivalent HPV vaccine and enzyme-linked immunosorbent assay (ELISA) for the bivalent vaccine. The pseudovirion-based neutralization assay (PBNA), developed by the US National Institute of Health, is considered the most accurate reflection of the neutralizing ability of the induced antibodies [14].

In addition to humoral immunity, cellular immunity is responsible for viral clearance from infected cells and for the resolution of HPV-related lesions. Moreover, there is good evidence that the induction of immune memory, mediated by memory B cells, is the basis for the long-term protection afforded by HPV vaccines [33].

New immunological studies have demonstrated the efficacy and durability of antibody responses with respect to reduced-dosage HPV-vaccine regimens for both vaccines [34-36]. The efficacy of both vaccines have been evaluated through pre- and post-licensure RCTs [37]; the primary end-point for these studies was prevention of CIN 2 or worse disease. The secondary efficacy end-point was prevention of type-specific persistent infection, which is an obligate precursor of cervical cancer [23]. Long-term duration of efficacy (up to 64 years) reported in one of the efficacy studies suggested that antibody concentrations will remain high for at least 20 years [38].

A phase III trial, including greater than 4000 males, suggested the prophylactic vaccination of boys and men with quadrivalent HPV vaccine may reduce the incidence of genital warts [39]. The study of Hillman et al, shows that immune responses to the quadrivalent vaccine are broadly comparable in men and women [40]. Although the risk of acquisition of HPV infection is greatest in young and sexually active women, women older than 25 years are also vulnerable to new infections [41]. The use of quadrivalent HPV vaccine in women between 27 and 45 has been studied and a good level of protection against infection and disease from the HPV types contained in the vaccine was found among those women who were not primarily infected with those of HPV types [42].
Vaccines like other pharmaceutical products, undergo extensive testing including safety, in three phases of clinical trials in human subjects before licensure. A recent review [43], assesses pre-licensure data from more than 60,000 women who received both vaccines, participating in different trials for establishing vaccine safety. Local reactions at the injection site (pain, redness and swelling) were significantly more frequent in vaccine than placebo recipients. Systemic adverse effects following immunization (AEFIs), including fever, nausea and dizziness were observed at a higher frequency than placebo. The most common systemic adverse effects (AEs) following quadrivalent HPV vaccination reported in another study [44] were headache, fever and pharyngeal pain; however, there was no significant difference between vaccination groups and control groups, there were very few serious vaccine-related AEs (0.1%), and they were no more frequent than in those receiving placebo. A recent study [45] on bivalent HPV vaccination subset of women completed and returned safety diary cards documenting symptoms experienced within the first 30 days after vaccination; injection site symptoms and symptoms such as fatigue, headache and myalgia were reported more frequently in the vaccine group than in the control group. The proportion of women reporting new onset chronic disease, Autoimmune disease (AD), and significant medical conditions during their entire duration of the study was similar in both groups. Overall, all pre-licensure studies reported local and general symptoms to be higher in the HPV vaccine groups than in the placebo groups; however most symptoms were transient. Vaccines continue to be monitored for safety after they are licensed. A range of surveillance options can be used to monitor the study of vaccines and immunizations post-licensure [46].

Gardasil is the only HPV vaccine licensed for males, for this reason, all the safety data was referred to this vaccine type. Studies which include the safety of the vaccine in male populations show that the most common AEs reported were injection-site related, and most of these were of mild-to-moderate severity [47]. Safety data set for the US reported by the CDC [48] shows that injection-site reactions are reported less in males than in women, for example pain was reported in 61.4% of men and in 83.9% of women; vaccine related systemic AEs occurred in less than 1% of vaccinated individuals, In the same report, the 3 years follow-up data showed that the same percentage of vaccinated (1.5%) and non-vaccinated men (1.5%) had contributions potentially indicative of ADs, comparable to the prevalence in the general population (1.6%) [49].

Recently, a report [40] described the overall immunogenicity results from a trial of the quadrivalent HPV vaccine in men by presenting serum antibody HPV-6, -11, -16, and -18 responses after completion of the 3-dose vaccination regimen. IN addition, there presented the results stratified by baseline covariates such as age and smoking status, factors that may influence the immune response.
to vaccination. It was demonstrated that the quadrivalent HPV vaccine was highly immunogenic for all vaccine types in heterosexual (HM) men aged 16 to 23 years and men who had sex with men (MSM) aged 16 to 26 years. Almost all subjects seroconverted for vaccine HPV types by month 7. Some interesting differences in immune responses were noted. For example, HM subjects had higher geometric mean titer (GMT) for all the vaccine HPV types at their peak than did MSM. Likewise, black subjects had significantly higher GMTs at month 7 than did both Caucasian and Asian subjects. Consistent with this observation, seroconversion for HPV vaccine types was higher for men residing in Africa than for those in Asia. There was also a suggestion of an age-dependent response, with the vaccine being more immunogenic in younger men than in older men. The vaccine was highly immunogenic in all groups; titers achieved after vaccination were substantially higher than those seen during natural HPV infection. Of note, other potential factors that might have affected immune responses to the vaccine such as tobacco use and lifetime number of sexual partners did not adversely influence month 7 mean GMTs for vaccine HPV types.

In Japan, the HPV-16/18 AS04 adjuvanted vaccine was approved on 16 October, 2009 and was funded by the Ministry of Health, Labor and Welfare until April 2013 under a provisional priority immunization program [50]. In April 2013, HPV vaccination, targeting young girls before sexual exposure, was introduced into the routine immunization schedule for adolescent girls aged 12-16 years, and universal mass vaccination was immediately implemented. A survey conducted in 2011[51] reported that 4.8% of Japanese girls during their latter high school years (16 to 18 year olds). In a randomized, double-blind, controlled study conducted in young Japanese women aged 20-25 years, it was demonstrated that the efficacy of the HPV-16/18 AS04-adjuvanted vaccine against persistent infection with HPV-16 and -18 (6 months as well as 12 months definitions) during 2 years following the first vaccination [52, 53]. Additionally, the vaccine has been shown to provide significant protection against persistent infection associated with a combination of 14 oncogenic HPV types (HPV-16/18/31/33/35/39/45/51/52/56/58/59/66/68) [52]. Persistent infection with the same high-risk HPV type is considered as a predictor for moderate or high-grade cervical dysplasia and cancer.

Recently, a randomized study was specifically conducted in healthy Malaysian women aged 18-35 years, to evaluate antibody response against HPV-16 and HPV-18 as well as the safety and reactogenicity of the vaccine following each dose [54]. In the study, the HPV-16/18 AS04-adjuvanted vaccine was found to be highly immunogenic in young and adult Malaysian women. All initially seronegative subjects who received HPV vaccine in the study seroconverted at one month post-dose 3, with high antibody titers achieved for both antigens. All initially sero-
positive subjects in the vaccine group not only remained seropositive for HPV-16 and/or HPV-18 antibodies one month post-dose 3 but also developed GMTs comparable to the seronegative study group. This is indicative of the fact that natural infection with HPV from prior exposure does not affect the immune response generated by the HPV-16/18 AS04-adjuvanted vaccine [55-57]. The magnitude of immune response GMTs achieved between different age strata (18-25 and 26-35) in the study were comparable and also consistent with that of a large International phase III clinical study across 14 countries (Australia, Belgium, Brazil, Canada, Finland, Germany, Italy, Mexico, Philippine, Spain, Taiwan, Thailand, UK and USA) in women aged 15-25 years [45].

In the pivotal FUTURE II trial (1095) 12,167 women between the ages of 15 and 26 received three doses of either HPV-6/11/16/18 vaccine or placebo, administered at day 1, month 2, and month 6. Subjects were followed for an average of 3 years after receiving the first dose of vaccine or placebo. Vaccine efficacy for the prevention of HPV 16/18 disease and was 98% in the pre-protocol susceptible population. In addition, the efficacy of the quadrivalent HPV vaccine has previously been demonstrated in women 24 to 45 years of age participating in an International double-blind clinical trial (FUTURE III) [58]. End of the study data (mean follow-up time of 3.8 years) from FUTURE 111 demonstrated quadrivalent HPV vaccine efficacy of 88.7% against the combined incidence of persistent infection, CIN or external genital lesions (EGL) related to vaccine HPV types in the per-protocol population on women aged 24-25 [41].

Recently a study [59] reported the results of two randomized trials evaluating the immunogenicity and safety of two investigational tetravalent HPV L1 VLP vaccines (HPV-16/18/31/45 and HPV-16/18/33/58 vaccines). In these two studies, varying dosages of HPV L1 VLPs (10, 20 or 30µg), adjuvant systems (AS04, AS01 and AS02 [60,61] and dosing regimens (0, 1, 6 months or 0, 3 months or 0, 6 months) were evaluated. For anti-HPV-16 antibodies, the immune interference could be overcome by a change in vaccine formulation (either by increasing the dose of HPV-16 L1 VLPs, or by using a different adjuvant system). In fact, a particularly high anti-HPV-16 antibody response was elicited when the tetravalent HPV-16/18/33/58 vaccine was adjuvanted with AS01 and AS02, compared with the control vaccine. The finding was supported by the detection of higher HPV-16 specific memory-cell responses for formulations containing AS01 and AS02, although these adjuvant systems did not notably impact on HPV-16 specific CD4+ T-cell responses [59]. The nature of the negative immune interference with regard to anti-HPV-18 humoral and cellular immunity was more complex and could not always be overcome by increasing the dose of HPV-18 L1 VLPs, or by using a different adjuvant system. Interestingly, it was observed that increasing the amount
of HPV-31/45 VLPs from 10µg to 20µg did improve the anti-HPV-18 immunogenicity of a tetravalent HPV-16/18/31/45 vaccine, although anti-HPV-18 GMTs were still lower than those elicited by the control vaccine. This was presumably because of enhanced induction of cross-reactive HPV-18 antibodies induced by HPV-45 (both were A7 species of HPV). Although all tetravalent formulations had an acceptable reactogenicity and safety profile, there was a tendency towards an increase in reactogenicity when additional HPV L1 VLPs were added to the vaccine, especially with formulations containing AS01 [59].

In a recent study [62], children 9-11 years of age produced higher concentrations of antibodies to quadrivalent HPV vaccine than children 13-15 years of age; children 12 years of age fell between 2 groups [62]. Another study [63] noted a similar difference between 9-3 years of age, and individuals 15-25 years of age, even when the younger age group was given only 2 doses of vaccine [63]. B-cell memory and T-cell immune responses have also been demonstrated to be stronger in younger adolescents [64].

Recently, a study [65] attempted to evaluate the breadth and magnitude of neutralizing antibodies elicited by both currently available HPV vaccines, using pseudovirus clones representing non-vaccine high risk HPV types, in order to address whether differences in the antibody responses seen would parallel the differences in cross-protection reported from clinical trials of Cervarix and Gardasil and also to ascertain whether cross-neutralizing antibodies could be detected in genital secretions, a prerequisite for investigating neutralizing antibodies as a mediator of cross-protection. There was a strong association between the cross-neutralizing antibody seropositivity reported in the study and available HPV vaccine trial efficacy data against non-vaccine types. Whether this association reflected a casual role for cross-neutralizing antibodies in the vaccine-induced protection against infection and disease, or an association with the immune effector, or neither, can not be deduced from this data alone. The striking association, however suggested that concurrent follow-up of neutralizing antibody seroprevalence and infection rates in post-immunization populations should be of interest. The data demonstrated for the first time that cross-neutralizing antibodies can be detected at the genital site of infection and support the possibility that cross-neutralizing antibodies play a role in the cross-protection against HPV infection and disease that has been reported for the concurrent HPV vaccines.

In Sub-Saharan Africa, prevalent immune-modulating infections such as malaria, and helminthes have been found to reduce the potency of some vaccines such as the bacillus Calmette-Guerrin (BCG) and measles vaccine [66]. It has been suggested that helminthes infection results in Th-2 type cytokine secretion, high and increased CD4+/CD25+ BT regulatory cell population, altering the immunological balance [67]. The Th1 responses (required
for protective immunity) are inhibited as a result of the immunological imbalance, consequently impairing responses to vaccines [67]. Similarly, repeated episodes of infections with malaria can also elicit immunological regulatory responses that may affect immune responses and effectiveness of vaccines [68].

Systemic Lupus Erythematosus (SLE) patients were found to have an increased risk of persistent HPV infection compared to healthy females. They also have a higher risk for developing abnormal cervical smears and squamous intraepithelial lesions (SIL) of the cervix [69]. Recently, a study aimed to evaluate the safety and immunogenicity of the quadrivalent HPV vaccine in female SLE patients aged 12 to 26 years [70]. The recombinant quadrivalent HPV vaccine, Gardasil, was generally well-tolerated and immunogenic in adolescents and young women with SLE. Recombinant quadrivalent HPV vaccine was found to be immunogenic in the study patient population with sero-positivity rates greater than 94% for all four HPV types. This normal immune response to HPV vaccine occurred despite corticosteroid treatment in approximately 60% of patients. Furthermore, the majority of the subjects were being treated also with either azathioprine or mycophenolate mofetil at time of immunization. HPV vaccine was immunogenic, generally safe and well-tolerated in study patient population of adolescents and young women with SLE. Seropositivity to HPV after three doses of the quadrivalent vaccine was greater than 94% in all four HPV types. This excellent response occurred even though the majority of patients were on prednisone and other immunosuppressive medication. Given that the increased risk of persistent HPV infection and its complications in women with SLE is well-established and that quadrivalent HPV vaccine was immunogenic and well-tolerated in the small prospective study, administration of the vaccine series to young females (9-26 years) with SLE should be seriously considered [70].

These appears to be an association between human immune-deficiency virus (HIV) and HPV infection [71-73], with the cervical c and HIV infection epidemics having a strong geographic correlation in Sub-Saharan Africa. There are an estimated 22.5 million people living with HIV in Sub-Saharan Africa, representing 68% of the global HIV burden [74]. The majority of people living with HIV in Sub-Saharan Africa are female, mainly girls and women aged 15-24 years, with approximately 21% of women aged 20-24 years known to be infected with HIV. In a case-control study in South Africa, HIV-positive women were 5 times more likely to be infected with high-risk HPV types than HIV seronegative women [75]. The HPV-16/18 AS04-adjuvanted vaccine is well-tolerated, immunogenic and highly effective against persistent HPV infection and associated cervical lesions in HIV-negative young women [22,76-78]. Recently, a study assessed the safety and immunogenicity of the HPV-16/18 AS04 adjuvanted in young women with HIV infection from South
Africa [79]. The HPV-16/18 AS04- adjuvanted vaccine was found to be well-tolerated and immunogenic in HIV-infected women in South Africa. HPV-16/18 prophylactic vaccination before sexual debut offers the potential to decrease the incidence of cervical cancers and related mortality in developing countries where risk may be increased by the high prevalence of HIV infection.

A study conducted in USA examined the immunogenicity and safety of the quadrivalent HPV vaccine in HIV-infected young women [80]. Immune responses were robust among those who were HPV DNA and HPV seronegative for vaccine-type HPVs at the time of vaccination and received all 3 vaccine doses within specific timeframes. Among HIV-infected women or antiretroviral therapy (ART), GMTs and seroconversion rates did not differ significantly from those of a historical comparison group of HIV-uninfected young women in the same age range. These findings suggested that treatment with ART could have a positive influence on response to vaccination, and provide support for current recommendations of the ACIP to vaccinate HIV-infected individuals. The study data demonstrated that the quadrivalent HPV vaccine was immunogenic and was generally safe and well-tolerated in HIV-infected adolescent and young adult women, supporting current recommendations to vaccinate HIV-infected individuals. Some young women not on ART, suggested that ART may improve response to vaccination in HIV-infected young women.

Human Papilloma Virus Vaccine Recommendations

Since 2007, recommendations have been issued in many industrialized countries on subjects to whom vaccination should actively be offered. Actual implementation was highly dependent on national factors, such as organization of the healthcare system and ways chosen to reimburse vaccination offer [81]. In 2013, a record-low price for HPV vaccines was negotiated by the Global Alliance for Vaccines and Immunization (GAVI) for countries eligible for support, opening the door for millions of girls in the world’s poorest countries to be immunized against HPV [82]. GAVI’s support for HPV vaccines will enable a bridging of the gap between rich and poor countries, by making HPV vaccines available where girls need them the most, thus preventing the infection that causes this disease.

ACIP recommends routine vaccination at age 11 or 12 years with HPV 4 or HPV 2 for females and with HPV 4 for males [11,83]. The vaccination series can be started beginning at age 9 years. HPV 4 and HPV 2 are each administered in a 3-dose schedule. The second dose should be administered 1-2 months after the first dose. Vaccination also is recommended for females aged 13 through 26 years and for males aged 13 years through 21 years, who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be
vaccinated. If females or males reach age 27 years before
the vaccination series is complete, the second and/or third
doses of vaccine can be administered after age 26 years to
complete the vaccination series. Prevention assessments
(e.g., pap testing or screening for high-risk HPV DNA,
type-specific HPV DNA tests, or HPV antibody tests) to
establish the appropriateness of HPV vaccination are not
recommended [48]. The minimum interval between the
first and second doses of HPV vaccine (either HPV 4 or
HPV 2) is 4 weeks. The minimum recommended interval
between the second and third dose of vaccine is 12 weeks,
The minimum interval between the first and third dose is
24 weeks. Inadequate doses or vaccine doses received after
a shorter-than-recommended dosing interval should be
re-administered. If the vaccine schedule is interrupted for
either HPV 4 or HPV 2, the vaccine series does not need
to be restarted. If the series is interrupted after the first
dose, second dose should be administered, and the second
and third doses should be separated by an interval of at
least 12 weeks. HPV vaccine (either HPV 4 or HPV 2) can
be administered at the same visit as other age-appropriate
vaccines, such as tetanus, diphtheria, and acellular pertus-
sis and quadrivalent meningococcal conjugate vaccines.
Administering all indicated vaccines together at a single
visit increases the likelihood that adolescents will receive
each of the vaccines on schedule. Each vaccine should be
administered by using a separate syringe at a different an-
tomic site [48].

The CDC and ACIP subsequently recommended
routine vaccination of females aged 11-12 years, as well
as catch-up vaccination for females aged 13-26 years and
vaccination of ages 9-10 years at the provider’s discretion
[48,84]. Despite these recommendations, HPV vaccina-
tion rates remain suboptimal, with only 44.3% of 13-17
year olds receiving at least one dose in 2009 [85]. Data
from the 2008 National Health Interview Survey indi-
cated 14.7% of 11-12 year olds and 25.4% of 13-17 year
olds received at least one dose of the HPV vaccine, and
only 5.5% of 11-12 year olds and 10.7% of 13-17 year olds
received all 3 doses [86]. Although patient factors includ-
ing concerns about vaccine safety [87], moral or ethical
concerns [88, 89], and insurance/access to care issues [90]
have been cited, another equally important factor with re-
gard to vaccine uptake among children [91-93] and adults
[94-97] is physician recommendation [98].

First nationally representative survey of US provider
recommendation of HPV vaccination [99] was conducted
to determine the prevalence of physician recommenda-
tion of HPV vaccination in early (ages 11-12), middle ages
(13-17), and late adolescent/young adult (18-26) female
patients by specialty among a nationally representative
sample of US physicians. Given that females aged 11-12
years are the primary target group for routine vaccination,
the second aim was to identify factors associated with rec-
ommendation of vaccination for early adolescents. Across
the main specialties involved in HPV vaccination, the
prevalence of “always” recommending vaccination was lowest for early adolescents (34.6%) and increased slightly to approx 50% for middle (52.7%) and late adolescents/young adults (50.2%). That practice is not in compliance with ACIP recommendations which designates girls aged 11-12 years as the primary target, ideal age group for routine vaccination [48,84]. These results pointed to the need to intervene with physicians as one approach to increase dissemination of HPV vaccination in females [99]. In addition to specialty, physicians aged 40-49 years were more likely to recommend HPV vaccination than physicians in younger or older age group. Compared to physicians who reported high perceived barriers to vaccination, those who reported low perceived barriers were more likely to recommend vaccination to early adolescents.

Various studies have examined healthcare provider barriers to recommending the HPV vaccine. Daley et al, found that the need to discuss sexuality before recommendation and prior vaccine refusals were barriers to recommendation among adolescents in the target vaccination age range [100]. Another study found that inadequate reimbursement was solely related to not recommending vaccination for adolescent girls of all ages [101]. Other studies found that negative parental perceptions of the vaccine, HPV knowledge deficits, lack of support for mandatory vaccination, lack of office coordination, and difficulty determining insurance coverage were barriers to recommendation [102-104]. Provider recommendation of the HPV vaccine does not necessarily guarantee uptake, some research suggests that such recommendations play an important role in whether an individual initiates and completes the three dose vaccine series [105,106]. Thus, identifying barriers to recommendation is vital, especially among populations at greater risk for both non-vaccination and downstream negative health outcomes [107,108].

The focus on HPV vaccine recommendation patterns for low-income adolescents can help frame strategies to increase recommendation, and ultimately vaccination, for this vulnerable population. Discomfort discussing STIs with parents was negatively associated with HPV vaccine recommendation for all groups, except the late catch-up group. That is, the more discomfort physicians felt discussing STIs with the parents of their early, target and early catch-up adolescent patients, the less likely they were to report recommendation of HPV vaccination. In contrast, a positive association was found for discussion of STIs with adolescent girls. The more discomfort physicians felt discussing STIs with their early and target adolescent patients, the more likely they were to report recommendation of the HPV vaccine. One possible explanation for this finding was that physicians may be more likely to incorporate the HPV vaccine into the immunization schedule for younger adolescents making discussion of HPV specifically less of a priority. Difficulty ensuring completion of the three-dose vaccine series, which is typi-
cally administered over a six month period, was negatively associated with vaccine recommendation only for early adolescent girls. The more difficulty physicians perceived it was for early adolescents to complete the vaccine series, the less likely they were to recommend vaccination. Concern about HPV vaccine efficacy was negatively associated with HPV recommendation only among target group adolescent girls. It appeared that providing physicians’ information about HPV vaccine efficacy is an important component of interventions to increase recommendation for adolescent females in the target group. Physicians who reported higher levels of time constraints were also less likely to recommend HPV vaccination to target group adolescent girls. In this situation, preparatory and supplemental patient-focused educational materials or training of mid-level providers to discuss vaccination may alleviate this barrier without compromising comprehensive care to patients. Concerns that teens will practice risky sexual behaviors was negatively associated with recommendation of the HPV vaccine for early catch-up adolescent girls only. Physicians who reported higher concerns that teens would practice risky sexual behaviors were less likely to report vaccine recommendation. Physicians who reported that the majority of their parents were of non-Hispanic Black race were less likely to recommend vaccination compared to those who saw a majority of non-Hispanic white patients for target adolescents only. This finding highlighted the potential impact of non-disparate recommendation patterns among low-income adolescent girls regardless of race/ethnicity. Family medicine physicians compared to pediatricians were less likely to report recommendation of vaccination for all groups except the early vaccination group. As family medicine physicians may see patients across the spectrum of vaccination categories, it is important that efforts to increase recommendation of HPV vaccines extend beyond the pediatrician [109].

Healthcare providers face a number of barriers to recommending HPV vaccine, some of which are interpersonal in nature. For example, some providers express difficulty discussing sexual health issues that may attend HPV vaccination particularly with younger adolescents in the target age range for vaccination [99,100]. Others perceive parents as being opposed to the vaccine and are reluctant to strongly recommend the vaccine due to concerns about initiating time-consuming or confrontational debates [100,110]. A very recent study [111] described healthcare providers’ HPV vaccine recommendation practices to explore their perceptions of and approaches to addressing, HPV vaccine hesitancy among parents of 11-12 year old youth. Healthcare providers in the sample perceived parental HPV vaccine hesitancy to be common; about half of respondents reported that parents frequently request to delay or sometimes wish to refuse HPV vaccination. The findings suggested that perceptions of parental hesitancy may discourage providers from delivering recommendations according to guidelines and that the providers’ self efficacy to address parental HPV vaccine
hesitancy and their outcome expectations may also influence their recommendation practices. It was found that respondents with lower levels of confidence in addressing concerns and who felt they were not influential or able to convince parents to get the vaccine were less likely to routinely recommend HPV vaccination in either males or females. Respondents in the sample perceived parents’ association between HPV vaccine and sexual activity to be an especially common source of hesitancy. Provider training or other tools may be particularly helpful if aimed at helping to convey that HPV vaccination is most beneficial before the onset of sexual activity and that HPV is highly prevalent. Effective and efficient ways of assessing and addressing parents’ vaccine concerns are needed, and many providers in this study indicated a screening questionnaire to identify parental concerns would be helpful for counseling HPV vaccine hesitant parents. The findings highlighted differences in HPV vaccine recommendation practices based on provider specialty.

HPV vaccination rates are low among socioeconomic disadvantaged groups, and in states and regions with low cervical cancer screening participation and greater cervical cancer morbidity and mortality [112]. Uninsured and low-income women suffer disproportionate cervical morbidity, mortality and late-stage diagnosis [113,114]. Provider recommendation is a key facilitator to vaccination among low-income medically underserved population [115,116]. However, little is known about vaccine recommendations, or beliefs regarding the anticipated impact of the vaccine on cervical cancer outcomes among providers who serve medically underserved women [117]. Focused surveys and interventions are necessary to develop appropriate and effective messages and outreach methods for uptake of HPV vaccination [118]. To better facilitate the adoption of HPV technologies in a medically underserved population, the CDC launched the Cervical Cancer (Cx3) study [119], a pilot study that assessed patient and provider knowledge, attitudes and practices related to cervical cancer screening and HPV vaccination. One study [120] presented the HPV vaccine recommendations and beliefs of Cx3 study providers in a cross-sectional survey [120]. The study found that primary care providers working in 6 Federally Qualified Health Centers across Illinois were generally supportive of, and routinely recommended the HPV vaccine for their patients. However, they made fewer recommendations to vaccinate females aged 9-12 years (which includes the target age for vaccination), compared to older adolescents and adults (13-26 years of age). While it is preferable to administer the vaccine before exposure to HPV through sexual activity, those already exposed to HPV and have HPV-associated outcomes (for example, females with Pap test abnormalities and persons with a history of genital warts) should also be vaccinated, making Pap test results, HPV test results, and number of sexual partners irrelevant to determining vaccination. It was not surprising that one-third of providers sometimes to al-
ways use sexual history to determine vaccination because these same providers also reported the number of their patient’s current (71%) and lifetime (67%) sexual partners as important factors to consider when determining her cervical cancer screening interval [121]. More than half of providers reported they would not change their screening and management practices for females who have been vaccinated; encouraging since current screening guidelines do not differentiate between vaccinated and non-vaccinated women, however this may change with new surveillance data and more being vaccinated. Of concern were the more than one quarter of providers who would change their patient care after vaccination.

Quadrivalent HPV vaccine trials have demonstrated high levels of immunogenicity, reductions in genital warts, and potential reductions in precancerous anogenital lesion sin males [122,123]. Thus, vaccination has significant primary prevention benefits for all males [124], but particularly for those from racial/ethnic and sexual minority groups, who are disproportionately affected by HPV-related diseases [125,126]. Recently, a study [127] explored factors associated with US physicians’ HPV vaccine recommendations to early (ages 11-12), middle (13-17), and late adolescent/young adult (18-26) males. The study offered insight into physician practices while HPV vaccine was available, but not universally recommended for males. Findings suggested that most family physicians (FPs) and Pediatricians did not consistently recommend HPV vaccination to males during the ACIP’s permissive recommendation period. Results from the study highlighted key variables associated with physicians’ HPV vaccine recommendation practices while permissive guidelines were in effect. Pediatricians were more likely than FPs to recommend HPV vaccination to males. In accordance with the Diffusion of Innovations theory [128], physicians who self-identified as being among the first to use a newly recommended vaccine (i.e., innovations/early adopters) were more likely to ‘always’ recommend HPV vaccine when permissive guidelines were in effect compared to later adopters. Innovators/early adopters have more favorable attitudes toward change [128] and are likely more knowledgeable about innovations. Innovators/early adopters in the study may have been routinely offering HPV vaccine to males despite only permissive guidance from the ACIP because they may have been more knowledgeable about promising results from clinical trials of HPV vaccine in males [129] and anticipated expanded ACIP guidelines. Innovators/early adopters also may be more receiving reimbursement for vaccinating male patients. Identifying and supporting innovators/early adopters may facilitate diffusion of male HPV vaccination given these physicians are watched by colleagues as they test evidence-based changes [130] (for example, feasibility of implementing the new guidelines in clinical practice) and could influence other physicians’ support (for example, strength of recommendation) for HPV vaccination. The assessments of physicians’ barriers related to
immunizing patients against HPV was neutral with regard to patient sex and, because the ACIP guidelines for males were permissive at the time of the survey, physicians may have responded to the barrier items with their female patients in mind. Overall rates of recommendation were low, and possibly influenced by the permissive nature of the ACIP recommendation. Additionally, identifying and supporting innovators/early adopters may help diffuse HPV vaccination guidelines and encourage later adopters to support guidelines.

**Human Papilloma Virus Vaccine Coverage**

Persistent infection with the high risk (HR) HPV type is a necessary cause of cervical cancer, and has been shown to be associated with other cancers in men and women [131]. Two of these HR-HPV types, HPV 16 and HPV 18 are present in around 70-80% of cervical cancer [132,133]. In late 2008, the UK began providing HPV vaccination, free at the point of delivery, routinely to 12 year old females, and catch-up vaccination to females up to and including 17 year olds. The bivalent vaccine was offered until September 2012 when the programme changed to offer the quadrivalent vaccine. Throughout the UK, over 80% of females eligible for routine vaccination each year have completed the three dose course[134-136]. Three dose coverage within the catch-up ages has been lower, with average coverage of 73% for individuals aged 14-15 years, and 45% for 16-17 years [134], although this is still higher in most other countries [137-139]. In 2013, a study reported the findings of surveillance of type-specific HPV infections in sexually active young females in England, showing evidence of substantially lower HPV16/18 prevalence in the first 4000 post-vaccination period specimens tested compared with pre-vaccination prevalence[140]. Recently, the similar survey reported further findings from ongoing HPV surveillance (over 7000 post-vaccination specimens) in the high coverage population, including changes in vaccine and non-vaccine types [141]. The survey was aimed to determine to what extent any such observed changes were likely to have resulted from vaccination rather than be due to methodological reasons (for example, assay performance) or a result of other factors such as changes in sexual behavior overtime. This surveillance of young sexually active women undergoing Chlamydia screening has demonstrated continuing reductions in the prevalence of the HPV vaccine types following the introduction of a high-coverage national HPV vaccination program as well as some evidence of overall reductions in HPV 31 (the clearly related HPV type with strongest evidence of cross-protection from the bivalent vaccine trials [78]). Encouragingly, these reductions were more marked in the later post-vaccination period with higher estimated vaccination coverage. The percentage reductions between the post-vaccination and pre-vacci-
nation periods among the youngest two age groups were very similar to the estimated vaccine coverage. If all the reduction in prevalence was due to a direct effect of vaccination, consistent with close to 100% vaccine effectiveness. Such high vaccine effectiveness unlikely given that women included in this surveillance were largely vaccinated as part of the catch-up program, and almost certainly some of those vaccinated would have had an existing HPV infection. This surveillance made use of a large sample of residual specimens taken for Chlamydia screening and tested anonymously for HPV-DNA infection. Young women attending for Chlamydia screening had higher risks of Chlamydia, and therefore, probably for HPV infection, than the general population. The reductions in the HPV vaccine types (HPV16/18) was observed, therefore, reassured that benefits of HPV vaccination had not been inequitably biased to lower risk individuals. The observations that the reductions in HPV16/18 were only seen in the age groups eligible for national HPV vaccination, and reduced further in the later post-vaccination period (i.e., were proportionate to estimated vaccination coverage), strongly suggests that the changes seen are attributable to vaccination. Comparison of HPV prevalence between the pre-vaccination and post-vaccination periods were adjusted for age, venue type and Chlamydia positivity (as a marker of sexual behavior). However, other changes in the population characteristics (on sexual behaviors not captured by Chlamydia positivity) might have resulted in a change in prevalence of the non-vaccine HR-HPV types. If women in the post-vaccination period were at a higher risk of HPV infection then this could have underestimated the potential effect of HPV vaccination on the HPV vaccine types. In the USA, reductions in the prevalence of HPV vaccine types were 56% in individuals aged 14-19 years, despite a low self-reported vaccination coverage (34% with one or more doses) [9]. In Scotland, where cervical screening is offered from age 20 years, a 54% reduction in the vaccine types has been shown in individuals aged 20 years, as well as a 48% reduction in cross-protection types HPV 31, 33 and 45 [142]. In 2008, a study [143] was performed related to type-specific HPV prevalences in Southern Sweden to establish prevalences of 16 HPV types at a time when the vaccination coverage was still low [143]. To evaluate whether the program was effective in preventing the circulation of vaccine-type HPV infection or whether it was associated with changes in prevalences of non-vaccine types, the 2008 baseline HPV prevalences in Southern Sweden in 2012 and 2013, two time points after the launch of the organized vaccination program when the HPV vaccination in Southern Sweden had increased [144]. It was considered essential that monitoring studies should make an effort to include the most sexually active women, as it is possible that vaccination programs may preferably reach women from high socio-economic groups that may be at low risk for HPV infection [145], resulting in that effectiveness of HPV control can not be directly inferred from vaccination coverage. 16 different
HPV types were monitored, but only the four vaccine HPV were significantly decreased after the launch of the organized vaccination program. The decline was seen for all of the vaccine HPV types (HPV 6, 11, 16, and 18). The fact that the decline was seen only among women in the analyzed age groups with high vaccination coverage (below 23 years of age) suggested that the decline is a result of the vaccination. None of the nanovaccine types showed any significant decrease in prevalence, suggested that the cross-protection known to be induced by vaccination was less effective for reducing the HPV spread in this population [146]. The effect of the HPV vaccination programs on the population was not only dependent on protection of vaccinated individuals, but was also affected by population immunity (herd immunity). At a vaccination coverage of 80%, the vaccine effectiveness at the population level had been estimated to be 78% for HPV 16 and 96% for HPV 18 [147]. In the age groups with highest coverage, the results of the study were, in principle, in agreement with these predictions. Indirect protection of unvaccinated men has been predicted to be about 42%, if 80% of all girls are vaccinated [147]. Although a decline of HPV vaccine types was found among men also, the decline among men was based on few observations and was not specific to HPV vaccine types, suggested that it’s not an effect of the vaccination, but due to some other causes. HPV 31 was the only non-vaccine type that tended to decrease in this study. Although this tendency was not significant, it was only observed in the age groups with high vaccination coverage (women younger than 23 years). The quadrivalent vaccine has significant efficacy against HPV 31[148], but if cross-protection is reason for the tendency for lower HPV 31 prevalence will need to be further evaluated. The results suggested that even very early after the launch of the vaccination program, a significant reduction of prevalences of HPV 6, 11, 16 and 18 can be seen.

It has been reported that 79 million persons aged 15-59 years in the United States are currently infected with HPV, and approximately 14 million new cases diagnosed each year [149]. In 2013, in the US, the median HPV vaccination coverage levels for female adolescents among commercial and Medicaid plans were 12% and 19%, respectively (ranges 0%-34% for commercial plans; 5%-52% for Medicaid plans) [150]. The Healthcare Effectiveness Data Information Set (HEDIS) HPV vaccination measure was publicly reported for the first time in 2013, approximately 7 years after the quadrivalent HPV vaccine was licensed in the US and recommended by the ACIP for use in female adolescents [151], allowing healthcare providers time to adapt to the recommendations. Despite this, results from this study indicated that health plans are performing poorly overall with regard to HPV vaccination rates in female adolescents aged 13 years. In the US, HPV vaccination coverage has been lower than observed for other vaccines recommended for adolescents [152],
Characterizing the strategies and best practices used by higher performing plans will be important for improving HPV vaccination at the recommended ages of 11 or 12 years, before most adolescents are exposed to the virus, can ensure are protected against HPV infections [150].

The Uganda Ministry of Health in collaboration with Program of Advancement Through Health and Education (PATH), an International non-profit organization, carried out an HPV vaccination demonstration project using existing human resources, structures, and systems of the Expanded Program on Immunization (EPI) from 2008 to 2009 to explore the feasibility of two HPV vaccine delivery strategies: 1) A stand-alone school-based strategy that selected girls based on their enrollment in primary grade 5 (P.5) (known as ‘grade based’ strategy), and 2) a strategy that combined delivery of HPV vaccine for girls selected based on their age (10 year olds) with the distribution of medication and Vitamin A through the existing Child Days Plus (CDP) programs (called the ‘aged-based strategy’) [153]. Recently, a qualitative study explored the feasibility of the two delivery strategies from the prospective of health workers, district leaders and staff of the Uganda National Expanded Program on Immunization utilizing in-depth interviews and focus group discussions [154]. The study found factors that facilitated successful delivery of HPV vaccine included: coordination between health and education officials for implementation in schools (as done through the micro-planning exercise in this program); designing delivery strategies based on a good understanding of the current system and opportunities for synergy (as was identified by prior formative research); teacher involvement when vaccinating at schools; and implementation through the regular EPI system, structure, and human resources, with visible government endorsement and ownership of the program. Preparing the health and education systems in terms of cold chain and resource allocation was a key component for the HPV vaccine demonstration project in Uganda, as this helped identify gaps in advance and defined training needs for key personnel.

In France, it is recommended to limit the use of HPV vaccines to 14 year old girls and use them as ‘catch-up’ in 15-23 year old young women who have never had sexual relations or at the latest 1 year after their first sexual relations. The vaccination protocol providing maximum efficacy includes three doses to the administered over a 6 month period [155-157]. However, the High Council for Public Health has recently revised this recommendation and advised that vaccination takes place between 11 and 14 years of age [158]. France has no organized HPV vaccination program. Vaccination is therefore opportunistic and left to the initiative of parents or the young women themselves. Yet it has been shown that the epidemiological impact on uterine cervical cancer is highly dependent on the level of vaccine coverage [159]. Recently, a study was conducted to estimate the vaccination coverage of young women in Picardy, France, for the 2009-2010 period based
on data from the reimbursements for vaccine dose delivered and to study certain socio-economic factors that could be influential [160]. HPV vaccination coverage in Picardy in 2009-2010 is low and continues to decrease compared to 2008. Compliance with the vaccination protocol is mediocre, resulting in a substantial financial loss for the National Health Insurance and a loss of opportunity for the young women concerned and for the entire population. Compliance is better if the young woman begins vaccination early, a valuable observation for future attempts to improve vaccination coverage by lowering the vaccination age. The arrival of vaccination may raise the fear of less use of screening measures for cervical cancer in young vaccinated women. However, the High Council for Public Health recommends that all means be deployed to reach high vaccination coverage, particularly in young women living in socio-economic conditions at risk for not benefitting from optimal conditions of regular cervical cancer screening.

HPV vaccines have been found to have high efficacy and safety and programs have been implemented in various countries throughout the world, including Canada, Australia, the United Kingdom, and the United states. HPV vaccination programs have nevertheless aroused some controversy. The vaccine is expensive, raising questions about alternative public health gains in countries with existing cervical cancer screening programs which could have been obtained for the same investment. Non-substantiated fears have been raised by some, about the impact of the vaccine on sexual behavior; parents who believe the vaccine might have a negative influence on sexual behavior are less likely to intend to vaccinate daughters [161]. Other commentators [162] have pointed out that this vaccine is unique, in that it could potentially lead to the decreased utilization of the cervical screening program, already established as effective, by women uncertain about the vaccine’s incomplete coverage of oncogenic viral genotypes [163,164], thereby paradoxically increasing the future burden of invasive cervical cancer from the much less common non-vaccine strains. A root cause of inequity in cervical cancer is poverty, mediated biologically by increased risk of sexual exposure to HPV and reduced detection, appropriate follow-up and treatment for preclinical abnormalities. Cervical cancer is also a disease of poverty via psycho-social mechanisms, such as a lack of power for women around sexual relations (in many societies, but generally associated particularly with lower levels of female education) and lack of understanding of the disease [165]. Recently, a study aimed to find out whether it is possible using a simple approach to discover, plausible scenarios in which corresponding population subgroups could be at increased risk of invasive cervical cancer following the implementation of an HPV vaccination program, thereby potentially increasing inequity in the whole population [166]. Unlike many other vaccines, even if the herd immunity effect led to an indirect impact on invasive cancer of vaccine strains, the outcome could still
be poorer in some scenarios in which a subgroup of the population may find itself, because the overall impact of the program depends on other factors, including screening uptake and the prevalence of non-vaccine genotypes. But some scenarios remain in the minority. For instance, if the prevalence of circulating vaccine strains fell by 60%, then the outcome would be better for 88% of subgroups, as long as vaccination effectiveness and coverage were fixed at 90%. If the fall in vaccine strain prevalence were only 20% then the outcome would still be better in 82% of scenarios, showing that if herd immunity effects are modest, this could be compensated far by declines in other parameters. Although many vaccination programs result in herd immunity which protects everyone, vaccinated or not, they may not benefit everyone equally and, indeed may increase inequity in health. Such iatrogenic inequity receives less attention than inequities observed in other areas of public health because the overwhelming success of vaccination programs produces such a large absolute reduction in most individuals’ (and therefore the population-level) risk of disease. HPV is highly transmissible, implying that to achieve significant herd immunity will require not only high effectiveness but also coverage that is significantly higher than the levels of around 50% seen in jurisdictions such as Ontario [167,168].

Australia was the first country worldwide which in 2007 introduced HPV vaccination free of charge for adolescents aged 12-13 years to the national immunization program. In 2009, a catch-up program for young females from 13 to 26 years old was implemented. Vaccination for younger adolescent is offered within school-bases immunization program, thus vaccination coverage in this group is 75%. The percentage of vaccinated young females aged 18-26 years is lower, amounting to 38% [169].

At the end of 2006, HPV vaccination started to be funded by the government of the United States. The highest vaccination coverage (32%) was reported in persons aged 13-17 years and living in north-eastern States. Vaccination outcomes depend substantially on the State’s health policy [9]. Having approved the use of HPV vaccine in 2006 in Canada, it was recommended for girls aged 9-26 years. Since 2010, HPV is also recommended for males at the age of 9-26 years. Irrespective of the similarities regarding vaccination funding between the United States and Canada (public resources), vaccination coverage rates in Canada are higher: 75% and 1% in public schools and catholic schools, respectively [170].

In Mexico, HPV vaccination was introduced in 2008 to the National Public Health program for girls aged 12-16 years. A total of 125 communities of the lowest human development index, classifying as areas of the highest incidence of cervical cancer, were enrolled into the program. As many as 81% of girls were vaccinated with three doses of HPV vaccine. In 2011, the National Immunization Council has approved the augmentation of the recommendations by HPV vaccination for ll 9 year old girls.
within a ‘school-based vaccination program [171].

In developing countries, HPV infections account for 86% of all STIs [172]. Haiti is one of such countries. There, HPV vaccination is funded by the PAHO Revolving Fund (Pan American Health Organization). Only 31% of girls aged 9-13 years benefited from such an opportunity. Little interest in vaccination among parents results from the lack of information on HPV infection and its association with cervical cancer that should be provided by medical personnel and schools [173].

HPV vaccination coverage rates in adolescents in South American countries are high with examples being Brazil and Bolivia with 85% and 77% girls aged 10-16 years and 9-13 years, respectively [172].

Low- and middle-income African countries frequently meet serious obstacles in introducing new vaccines to National Immunization Program. In Uganda, high vaccination coverage rate in adolescents (83%) was achieved as vaccines administered in schools [173]. In Tanzania, a total of 76% of adolescent received three doses of the vaccine within the project of the introduction of HPV vaccination [174].

Asian countries succeeded in achieving high HPV vaccination coverage rates in adolescents. Vietnam is one of such countries where high vaccination coverage rate (96%) was achieved in girls aged 9-14 years due to a pilot immunization program within PATH, 2008-2009 [172].

European countries which first introduced HPV vaccination in 2007 were: Belgium, France and Germany. In the successive year, vaccination was introduced to Greece, Luxembourg, the Netherlands, Italy, Spain and Switzerland. In 2009, HPV vaccination for girls was also introduced in Denmark, Norway, Portugal, San Marino, Macedonia and Great Britain [175]. The highest vaccination coverage rates are reported in Western Europe and Scandinavia [145]. In England, where vaccines are funded from public resources, 80% of girls aged 12-13 years were vaccinated while in Scotland, vaccination coverage rate in adolescents was 92% [176].

HPV vaccination was adopted into the German routine immunization schedule for 12 to 17 year old girls in March 2007 [177]. A cross-sectional survey was conducted three years after initiation of routine HPV immunization [178] to assess: 1) HPV vaccine uptake among women aged 18-20 years at the country-level and 2) knowledge on post-vaccination cervical cancer screening and condom use in this age group [178]. In multivariate analysis, only low educational status was use would be associated with the misconception that condom use would be dispensable after HPV vaccination. In contrast, low educational status, not being vaccinated against HPV, and never/seldom being concerned about health-related issues were factors independently associated with the misconception that HPV
vaccination would obviate the need for participation in cervical cancer screening. The results of the survey indicated that there is an urgent need for the implementation of a corticosteroid program for adolescents to facilitate easy access to vaccination, including balanced information tailored to this age group, particularly for less educated population subgroups.

There is a clear evidence that parental resistance is a barrier to HPV vaccination for children in the recommended age range of 1-12 years. One study found that parents are increasingly hesitant about vaccinating young daughters; parents are three times more likely to initiate vaccination in daughters between ages 16 and 18 than in daughters between ages 10 and 12 [179]. Among adolescent boys of the same age group, vaccine initiation increases by age up to age 15 and then fluctuates thereafter [179]. The major issue in convincing parents to vaccinate their pre-teen children seems to be the negative connotation associated with vaccinating young children against a virus that is transmitted through sexual contact [180,181].

**Discussion**

HPVs are a large family of small double-stranded DNA viruses that infect squamous epithelia including the skin and the mucosae of the ano-genital tract and upper-respiratory tract [182]. The FDA-approved vaccines Cervarix and Gardasil have shown excellent efficacy in past and recent trials in prevention of neoplasia and pre-neoplastic lesions associated with HPV infection and will likely continue to play a major role in HPV prevention among young females and males. With the recent promising results of therapeutic HPV vaccines, treatments for those with existing HPV infections may be on the horizon [4].

In females, the risk of cervical cancer and the potential for prevention of this devastating disease served as the impetus for widespread adoption of the vaccine. The increase in male genital lesions, penile cancer as well as oropharyngeal and ano-genital cancers helped to extend the indications for the vaccine for both males and females up to 26 years of age. There also reported benefits to male patients regarding a marked decrease in sexually transmitted lesions from female sexual partners who have been vaccinated. One study presented the early evidence of population impact of HPV vaccines with moderate reductions in HPV associated pathology in the vaccinated groups [183]. Preliminary data from Australia showed that herd immunity may be an added benefit from the vaccine group [184]. The best and the ideal time to begin the vaccine series in both genders is before the age of commencing sexual contact [185].

The safety and immunogenicity profile of HPV vaccines have been conducted in large scale trials and the results suggested that vaccine has an excellent safety profile, well tolerated and induces a sustained immune responses [76,186-189].
Vaccine effectiveness against HPV 16 and 18 related CIN 2 or worse was estimated by calculating the expected incidence of CIN 2 and 3 or worse in an non-vaccinated cohort using historical registry data. Using passive cancer registry based follow up of HPV vaccinated, placebo vaccinated, and non-vaccinated reference cohorts for long term HPV vaccine efficacy is feasible as was already stated in the proof of principle Finland study [190]. The efficacy of quadrivalent HPV vaccine in preventing infection and genital disease in males has been assessed in the randomized, double-stranded, placebo-controlled V501-P020 trial in 4,065 healthy boys or men aged 16-26 years with a follow up of 3 years. The safety and tolerability of HPV vaccines have been evaluated in many studies with similar profiles in the vaccinated and control groups, irrespective of ethnicity or age. The most common AE reported for both vaccines in trials and clinical experience is injection-site reaction, particularly described as pain, swelling and erythema in 95% of cases of moderate intensity [191], which has been confirmed by a recent study [192], on both vaccines in post-marketing experience. From registered trials, both HPV vaccines have been classified as pregnancy category B by FDA. Therefore, the vaccine is not recommended for pregnant women, because there is no enough data to ensure safety to the fetus [193,194].

Vaccination stimulates the immune system to produce antigen specific immunity. Because AD etiologies also involve stimulation of the immune system, it has been suggested that vaccination may trigger Ads. Head-to-head studies of the two HPV vaccines have provided evidence that the bivalent HPV vaccine induces a stronger immune response than the quadrivalent vaccine, with high levels of neutralizing antibodies maintained at 2 years post-vaccination [25,195]. It has been showed by a recent study of the bivalent HPV vaccine that levels of neutralizing antibodies against both HPV 16 and HPV 18 remain several times above natural infection levels up to 9 years after vaccination [196]. In contrast, where the immune response against HPV 16 is maintained with the quadrivalent vaccine up to 5 years, the response against HPV 18 seems to lower in time when measured by the competitive Luminex Immunoassay (cLIA) [197]. In this regard, it has to be noted that efficacy of the quadrivalent against clinical endpoints associated with HPV 18 is maintained at 5 years, despite waning antibody levels [198].

HPV vaccine is recommended for patients within the indicated age group, who are candidates for transplantation or post-transplant in those who have not vaccinated previously [199]. Many transplant centers may choose to prescribe vaccination for persons of any age that are transplant candidates or recipients. Recently, a prospected cohort study, the only study that determined the immunogenicity of quadrivalent HPV vaccine in a young adult post-transplant population [200]. This study showed that the vaccine has suboptimal immunogenicity in the post-transplant setting. It was found that patients who were early post-transplant and lung transplant recipients had especially low vaccine responses. Therefore, vaccinating
patients at later time-points post-transplant may be more beneficial with respect to immunogenicity. The results of the study provided an insight into factors to be considered while decision-making for vaccine providence for transplant recipients and counseling patients at risk.

Of various factors that influence HPV vaccination, the role of healthcare providers is perhaps the major one. Receiving a providers’ recommendation is reported to be the most consistent predictors of HPV vaccination [201,202]. Improving HPV vaccine recommendation may be especially important for raising coverage among boys since parents are less likely to know that the vaccine is available for their sons [202]. Missed opportunities present a substantial barrier to achieving widespread HPV coverage [203,204]. Reflecting the importance of preventing missed opportunities, a recent report found that if all missed opportunities had been eliminated then, more than 90% of girls would have achieved at least one dose of the HPV vaccine [205]. Missed opportunities result from primary care providers failing to strongly recommend the vaccine at visits [99,206], parents refusing or delaying vaccination [207], and adolescents presenting to acute visits instead of preventive care [208-210]. A recent survey conducted by the New York City (NYC) Health Department in 2007 among NYC providers identified a combination of financial, insurance and parental concerns as barriers to HPV vaccination [211]. Parental concerns included vaccine safety, duration of protection, and fears that vaccination encourages early sexual activity. Despite the safety and efficacy of HPV vaccine [212,213], the literature suggests that parents lack knowledge and accurate information about HPV vaccine dissuading them from immunizing their children [116]. Recent assessments of barriers to HPV vaccination suggest that there are male specific barriers [214] especially lack of office visits by adolescent male patients [116] and physicians’ belief that vaccinated males are not worth the cost or effort [215].

HIV-infected women are disproportionately affected by HPV-related ano-genital disease compared with HIV-uninfected women [216,217]. Despite the immunologic reconstitution associated with the use of combination antiretroviral therapy, the prevalence of ano-genital HPV infections and diseases remain high [218,219]. A recent study conducted to determine the immunogenicity and safety of quadrivalent HPV vaccine in HIV-1-infected women [220] showed that quadrivalent vaccine is safe and immunogenic among HIV-infected women aged 13-45 years who were seronegative for the HPV types included in the vaccine and for the women seropositive for the HPV types prior to the vaccination series, the vaccine induced a significant increase in antibody levels.

Cost-effectiveness studies support the implementation of HPV vaccination of preadolescent and adolescent girls before sexual onset including lower resource settings provided the vaccines are affordable; the cost-effectiveness in lower resource settings is heavily influenced by the unit cost of vaccine [221-225].
Conclusion

HPV vaccines have been shown and reported to be highly effective in preventing HPV acquisition and diseases in both the sexes, especially if administered prior to HPV exposure. Studies have reported excellent results on safety, immunogenicity and high efficacy of the HPV vaccine in both the sexes. In spite of the promising results of the HPV vaccination, the coverage rates are estimated to be well below the health goals in majority of countries; in order to achieve the high coverage rates in all the countries, it is necessary to obtain the meaningful public health benefits of HPV vaccination, parents need to acquire more knowledge through instructions by the healthcare providers regarding the safety and efficacy of HPV vaccine. Improvements in provider communication with the patients and their parents about vaccine safety and efficacy and counsel vaccine recipients about the prevention of STIs could substantially contribute to HPV vaccination during early adolescence becoming truly routine.

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