Current Situation of Human Papillomavirus Vaccines

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Introduction

One of the most outstanding scientific discoveries for vaccine-preventable diseases has been the identification of the causal relationship between the human papillomavirus (HPV) and cervical cancer. This discovery was made in 1977 by Harold Zur Hausen, who was awarded the Nobel Prize in Physiology and Medicine in 2008.[1,2]

Infectious Agent Profile

The human papillomavirus (HPV) is a member of the *Papillomaviridae* family. Its genome consists of double-stranded deoxyribonucleic acid (DNA), containing approximately 8,000 base pairs covered by the major and minor structural proteins, L1 and L2, respectively. The capsid proteins L1 and L2 develop structures that interact with the cellular surface molecules and, therefore, facilitate cell penetration by the virus DNA; moreover, their respective late genes (L) encode the proteins. Early genes (E) control virus replication during the virus cycle. The study of L1 genome sequencing[3,4] has led to the identification of more than 190 virus types, which have high affinity to specific tissue and infect the cutaneous and mucosal epithelium without invading connective tissue or spreading regionally or systemically. The transmission path is mainly sexual, and hard to prevent. The virus incubation period is estimated to be three weeks to eight months; condyloma acuminata may occur at two or three months after infection.[5]

Viruses are classified as low-risk HPV or high-risk HPV, depending on their potential to induce cancer. Currently, the International Agency for Research on Cancer (IARC) defines 12 high-risk virus genotypes associated with cancer in human beings: HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. Additionally, there is some evidence about the oncogenic potential of two genotypes: 68 and 73.[6] Most of the infections are temporary in nature, and about 70% to 90% of them clear within 1 to 2 years.[7,8] Histopathologically, the lesions of the cervix, referred to as cervical intraepithelial neoplasia (CIN), fall into one of three categories: cervical intraepithelial lesion 1 or CIN1, involving mild dysplasia; CIN2 or moderate to severe dysplasia, and CIN3 or severe dysplasia.[9]

Progression of the lesions has been described as a potentially reversible phenomenon up to CIN3, the stage at which neoplastic growth penetrates the basement membrane invading the stroma. Persistent infection and integration of genetic material within the cells are the main factors contributing to oncogenesis.[9-14] Progression from CIN1 to CIN3 may take about 10 years and progression from CIN3 to cervical cancer may take about two years.[10] The etiological role of HPV in cervical cancer has been demonstrated biologically and epidemiologically.[10,13-14]

Epidemiology

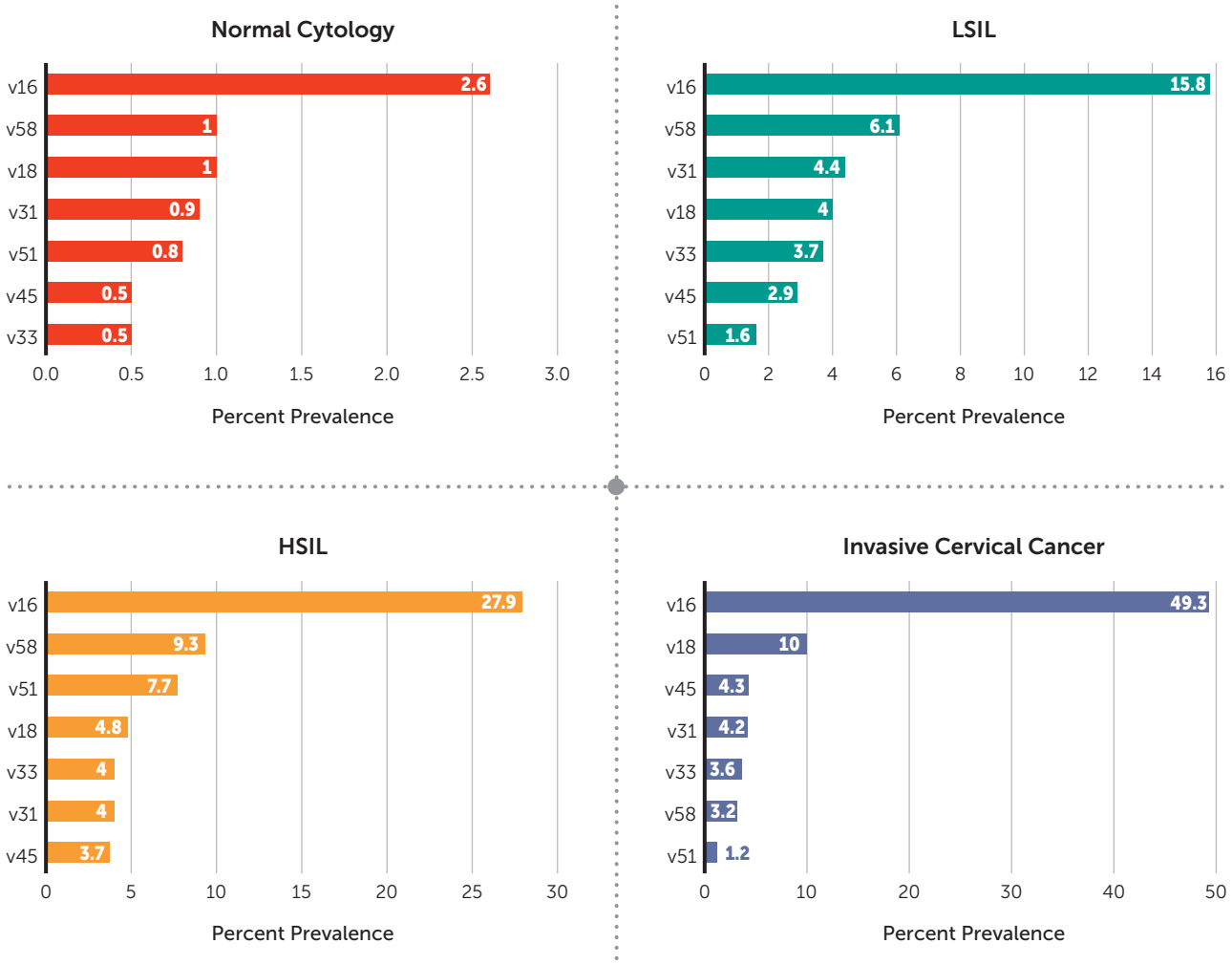
Based on data provided by IARC, over 100,000 cases of HPV-related cancer are diagnosed yearly in Latin America: cervical cancer (80%), oropharynx cancer (6.5%), as well as the remaining HPV-related cancers of the anus, penis, vulva, and vagina.[14]

Mortality caused by cervical cancer varies in the different regions of the world, presumably due to differences in health care systems, screening and access to health care. The highest mortality rate is observed in Africa, at 27.6 per 100,000 women, and the lowest rates occur in East Asia, Europe, Australia, and New Zealand, at 2 per 100,000 women.[14]

Most sexually-active individuals will have an infection at some point in their lives due to at least one HPV genotype. A meta-analysis published in 2007, which included 157,879 women from 36 countries, estimated a 10% global prevalence of HPV infection in women with normal cytology,[15] with marked geographical differences: higher frequency in Africa (22.9%) and Latin America (18.6%), and less frequency in Southeast Asia (8.3%) and Europe (6.6%). In 2007, HPV-16 was considered the most prevalent genotype in every region (3–4% in North America; 2% in Europe) followed by genotype 18. Similar results were derived from other studies,[16] and from surveillance conducted by IARC in 2005 in women aged 15–74 years from 11 countries.[17] In every region, a peak in the infection rate was observed at age 25, followed by a decrease and a subsequent increase at age 45.[16,17]

The distribution of HPV genotypes is variable amongst the populations even within the same region.[18] A meta-analysis of HPV-infection and HPV-associated cervical cancer surveillance, including reports between 1990 and 2007 in Latin American and Caribbean women, also showed that a comparison of genotype prevalence in women with normal cytology and prevalence in women with a lesion or cervical cancer, yields significant differences in the HPV types detected. In all cases, type 16 was the most frequently identified and accounted for 2.6% in women with normal cytology, 15.8% in low-grade intraepithelial lesions, 27.9% in high-degree CIN, and 49.3% in invasive cancers.[19] Figure 1 illustrates HPV-genotype distribution based on cytology status as established in the meta-analysis. The full report is available online at: www.sabin.org.

Figure 1. Distribution of Prevalence of Specific HPV Genotypes by Type of Lesion or Cytology Status Among Women in Latin America and the Caribbean[19]



Source: Valenzuela MT et al., 2009.[19]

Notes: LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

A similar study published in 2011 regarding HPV prevalence in Canadian women concluded that type 16 was the most common; however, 36 HPV types were isolated in 873 women with CIN and 252 women with cervical cancer. The HPV types identified, and their frequencies, differed based on the extent of the lesion. The most frequent genotypes in order of decreasing frequency were HPV-16, 51, 52, 31, 39, 18, and 56 in women with

CIN1; HPV-16, 52, 31, 18, 51, 39, and 33 in women with CIN2; HPV-16, 31, 18, 52, 39, 33, and 58 in women with CIN3; and HPV-16, 18, 45, 33, 31, 39, and 53 in women with invasive cervical cancer.[20]

In a study regarding the prevalence and genotype distribution of HPV infection in Chinese women who were asymptomatic, HPV was found in 10.3% women (9.5% low-risk types and 1.1% high-risk types). HPV genotypes 16, 52, and 58 were found most frequently in 26.2%, 19.45%, and 13.8% in the study population, respectively.[21]

Prevalence data in men are sparse and difficult to assess. It is estimated that the frequency of infection in men is typically 50%, with a higher rate of low-risk HPV infection when compared to women. However, genotype distribution may change based on the sample collected and the technique used for analysis.[16,22]

Available Vaccines

HPV vaccines are synthesized from the L1 protein. Five proteins are assembled in highly immunogenic, non-infecting virus-like particles (VLPs).[23] In 1993, researchers in the United States from the National Cancer Institute (NCI) discovered a way to synthesize VLPs with the same structure as HPV-16, and it was later used by Merck to manufacture the first quadrivalent vaccine.

Currently, three vaccines have been registered (Table 1), two of them manufactured by Merck/Co., Inc. (quadrivalent vaccine and nonavalent vaccine) and the other one manufactured by GlaxoSmithKline (bivalent vaccine).

As of May 2017, the WHO supports the recommendation for a 2-dose schedule with adequate spacing between the first and second dose (with a 6-month interval) in those aged 9–14 years.[24]

Table 1. Vaccination Characteristics and Schedules for the VLP HPV-16/18, VLP HPV-6/11/16/18, and VLP HPV-6/11/16/18/31/33/45/52/58 Vaccines

VACCINE (MANUFACTURER)	Cervarix® HPV-16/18 (GSK)	Gardasil® HPV-6/11/16/18 (Merck)	Gardasil 9® HPV-6/11/16/18/31/33/45/52/58 (Merck)
Vaccination schedule recommended by manufacturers	9–14 years: 2 doses (0.5 mL at 0 and 5–13 months) ≥15 years: 3 doses (0.5 mL at 0, 1, 6 months)	9–13 years: 2 doses (0.5 mL at 0 and 6 months or 0 and 12 months) Alternative 3-dose schedule: (0.5 mL at 0, 2, 6 months)	9–14 years: 2 doses(0.5 mL at 0 and 5–13 months) Alternative 3-dose schedule: (0.5 mL at 0, 2, 6 months) ≥15 years: 3 doses (0.5 mL at 0, 2, 6 months)
WHO recommendation (Global)	Enroll the high priority population: girls 9–14 years of age, before extending coverage to other groups or males. For individuals receiving the first dose before 15 years: 2-dose schedule with a 6-month interval between doses. If the interval between doses is shorter than 5 months, a third dose should be given at least 6 months after the first dose. There is no maximum interval (no more than 12–15 months is suggested). For individuals receiving the first dose ≥15 years: 3-dose schedule (0, 1–2, 6 months). The 3-dose schedule should be used for those younger than 15 years known to be immunocompromised and/or HIV-infected.		
PAHO/WHO TAG recommendation (Americas)	TAG reiterates the importance of prioritizing high coverage in girl cohorts aged 9–14 years to ensure full protection against HPV among girls and induce herd immunity among boy populations. Following the WHO recommendation, countries and territories should implement and monitor the two-dose strategy (with HPV2 or HPV4) with a six-month interval between doses for individuals receiving the first dose before age 15 years. Intervals no greater than 12–15 months are suggested. Three-dose schedules are only recommended for individuals that initiate vaccination at >age 15 years, or those of any age who are immunocompromised and/or HIV-positive.		
Adjuvant	500 µg aluminum hydroxide & 50 µg of 3-O-desacyl-4-monophosphoryl lipid A (AS04)	225 µg amorphous aluminum hydroxyphosphate sulfate (AAHS)	500 µg amorphous aluminum hydroxyphosphate sulfate (AAHS)
Substrate system with recombinant technology	Baculovirus expression system (*Trichoplusia ni cells*)	Yeast substrate (*Saccharomyces cerevisiae*)	Yeast substrate (*Saccharomyces cerevisiae*)
Intramuscular	X	X	X

Source: World Health Organization, 2017.

Bivalent HPV Vaccine

The bivalent vaccine, Cervarix®, includes two antigens: genotypes 16 and 18. The L1 purified proteins in both genotypes are absorbed onto aluminum hydroxide, with the addition of the AS04 adjuvant.[25,26] A special characteristic of this vaccine is the AS04 adjuvant, comprised of deacylated monophosphoryl lipid A (MPL), a non-toxic derivative from *Salmonella Minnesota* R595 lypopolysaccharide, which activates the humoral immune and cell-mediated response and induces the activation of antigen-presenting cells (APC).[27]

The Phase I study of this vaccine was conducted in 49 North American women aged 18–30 years. The results were favorable in terms of immunogenicity and safety.[28]

Phase II studies were conducted in a method similar to studies for the quadrivalent vaccine. The first study was a randomized, double-blind study in 61 women aged 18–30 years.[28] The experimental group received the bivalent vaccine and the control group only received aluminum hydroxide. The second study was also randomized, double-blind in 60 women aged 18–30 years to compare the safety and immunogenicity of the bivalent vaccine with two different adjuvants.[28] One group received the vaccine with AS04 while another group received the aluminum hydroxide vaccine and the third had no addition of adjuvant. In a third study, 209 women aged 18–30 years were randomized to study the effect of dosing.[28] The fourth randomized, double-blind, placebo-controlled study included women aged 15–25 years (560 participants received the vaccine and 553 participants received the placebo).[28,29]

Phase III studies demonstrated an efficacy of 98.1% (95% CI: 88.4–100) against CIN3 caused by HPV-16/18 based on a causality algorithm. In 2010, the bivalent vaccine was registered and recommended by ACIP.[30]

The vaccine is marketed in vials of one or two doses or in pre-filled syringes. It is administered intramuscularly. Each 0.5 mL dose has 20 µg HPV-16 L1 protein and 20 µg HPV-18 L1 protein absorbed onto 500 µg aluminum hydroxide, and 50 µg monophosphoryl lipid A (MPL). The vaccine is indicated for girls starting at 9 years of age for the prevention of premalignant cervical, vulvar, and vaginal genital lesions and type-specific cervical cancer, in a two-dose schedule at 0 and 5–13 months.[24,30] The immune response to the bivalent vaccine is measured through a type-specific enzyme-linked immunosorbent assay (ELISA) using a technology adapted by GSK.[31]

Vaccine efficacy was assessed through the PApilloma TRIal against Cancer In young Adults (PATRICIA) study in three cohorts of women aged 15–25 years. This randomized, double-blind, controlled trial intended to assess vaccine efficacy for type-specific CIN2+ against HPV-16 and 18 (Table 2). Mean follow-up for these cohorts was 34.9 months (SD: 6.4) after the third dose.[32]

Table 2. Results of the PATRICIA Study in Women aged 15–25 Years

Cohorts	ATP*	TVC**	TVC-Naive***
Vaccinated (n)	8,093	9,319	5,822
Controls (n)	8,069	9,325	5,819
Vaccine efficacy (%) **96.1% CI**	92.9 79.9–98.3	30.4 16.4–42.1	70.2 54.7–80.9

Source: Paavonen et al., 2009.[32]

Notes: *According-to-protocol analysis (primary analysis). **Total vaccinated cohort (TVC): included all women receiving at least one vaccine dose, regardless of their baseline HPV status; represents the general population, including those who are sexually active; therefore, it is representative of the general population. ***Total vaccinated cohort: no evidence of oncogenic HPV infection at baseline; represents women before sexual debut.

Additionally, cross-protection against CIN2+ associated with HPV-31, 33, and 45 was seen.

It is possible to extrapolate the efficacy results for both vaccines from studies performed in women over 15 years of age to girls 9 to 15 years of age through immunogenicity bridge studies, since performing efficacy studies in underage girls is unethical. Immunogenicity studies in girls have demonstrated a response in antibody titers at least two folds the levels seen in women over 15 years.

Quadrivalent HPV Vaccine

The quadrivalent vaccine has four genotypes: 16, 18, 6, and 11 — the first two being the main high-risk oncogenic viruses and the last two being the low-risk viruses. These VLPs are absorbed onto aluminum hydroxyphosphate.[33-36]

Phase I studies conducted in approximately 290 individuals established that 20 µg, 40 µg, and 50 µg doses generated a significant immune response as compared to 10 µg.[37] Phase II studies for vaccine administration in approximately 6,000 individuals across Europe, Australia, North America, and Latin America, established that the vaccine is safe, and immunogenic as compared to the placebo.[38,39] Subsequently, Phase III studies were conducted in 17,500 individuals in North America, Latin America, Asia, and Australia and established the efficacy and safety of the vaccines.

In 2006, the FDA authorized the first prophylactic HPV vaccine, Gardasil®, which contains the two major oncogenic genotypes, 16 and 18, accounting for about 60% of cervical intraepithelial lesions at risk of progressing to cancer and the two low-risk genotypes, 6 and 11, accounting for approximately 90% of genital warts (i.e., condyloma accuminata) as well as other pathologies such as recurrent respiratory papillomatosis.

The vaccine is marketed in single-dose vials or pre-filled syringes. It is administered intramuscularly and each dose contains 0.5 mL of 20 µg HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 40 µg of HPV-16 L1 protein, and 20 µg of HPV-18 L1 protein absorbed onto 225 µg of adjuvant. The vaccine is indicated for women and men as of 9 years of age for the prevention of premalignant genital lesions (cervical, vulvar, and vaginal), premalignant anal lesions, cervical cancer, anal cancer causally related to oncogenic HPV-16 and 18, and the prevention of condyloma accuminata.[40] The vaccine was registered with a three-dose administration schedule, but is currently being recommended for use with a two-dose schedule with a 6-month interval between doses.[24]

A specific type immunoassay (Luminex) was conducted to assess vaccine immunogenicity.[41] Two Phase III studies, referred to as Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I and II, were conducted to assess efficacy with a mean follow-up of 42 months. The studies demonstrated high efficacy (Table 3): 100% (95% CI: 92.9–100.0) against cervical intraepithelial lesions type 2/3 or CIN2/3 caused by genotypes 16 and 18, in receptors uninfected by HPV. Clinical efficacy against vaginal and vulvar cervical infections and HPV-16 and 18 associated lesions was also demonstrated.[42,43] Intention-to-treat analysis (ITT) demonstrated efficacy significantly lower than 45.1% (95% CI: 29.8–57.3), which could be explained by the inclusion of HPV-infected women.[42]

Table 3. Results of the FUTURE I and II Studies in Women Aged 16–26 Years

Women Aged 16–26 Years	Follow-Up of 42 Months
Impact on Lesions	**Efficacy % (95% CI)**
Cervical intraepithelial lesion 2/3 caused by HPV-16/18	100.0 (93–100)
Vulvar or vaginal intraepithelial lesions 2/3 caused by HPV-16/18	100.0 (82.6–100)
Cervical intraepithelial lesions 1 caused by HPV- 6/11/16 or 18	96.0 (91–98.4)
Vulvar lesions I caused by HPV- 6/11/16 or 18	100.0 (74–100)
Vaginal lesions I caused by HPV-6/11/16 or 18	100.0 (64–100)
Vaginal warts caused by HPV-6 or 11	99.0 (96–100)

Source: Schiller et al., 2012.[43]

In 2007, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommended the vaccine for women of 9 to 26 years of age[44], and the American Cancer Society recommended routine vaccination for women ranging between 9 and 18 years of age.[45]

Nonavalent HPV Vaccine

The nonavalent (9-valent) vaccine, Gardasil 9®, is now available and it adds five new HPV virus genotypes to the four already included in the quadrivalent vaccine. These genotypes are: 31, 33, 45, 52, and 58. An efficacy and immunogenicity study was conducted in women aged 16–26 years, by applying a series of three intramuscular injections on day 1, month 2 and month 6. In connection with antibody response, the demonstrated outcome is non-inferior to the one generated by the quadrivalent vaccine. Regarding efficacy, in an per-protocol analysis, the rate of high-grade cervical, vulvar, or vaginal disease associated with HPV- 31, 33, 45, 52, and 58 was 0.1 per 1,000 person/year in the 9-valent group and 1.6 per 1,000 person/year in the quadrivalent vaccine group, thus demonstrating a 96.7% efficacy (95% CI: 80.9% – 99.8%).[46]

Follow-Up of the Vaccinated Cohorts

The bivalent and quadrivalent vaccines were initially registered with a three-dose schedule and, later on, studies were conducted to assess the presence of neutralizing antibodies. For the bivalent vaccine, 100% of women remained seropositive at 8.4 years of follow-up. For the quadrivalent vaccine, seropositivity measured as IgG class antibodies was 94.3%, 89.4%, 99.5%, and 88.8% for HPV-6,11,16, and 18, respectively at 8 years of follow-up.[47] To date, 9.4–years of follow-up data of the bivalent vaccine have been reported.[48]

Two-Dose Versus Three-Dose Schedule

At the global level, there is interest in simplifying vaccination schedules to increase compliance and the advantages of vaccine adherence, including reduced logistical challenges of vaccinating in schools and lowering related costs and resources.

Studies conducted to demonstrate the non-inferiority of the immune response with a two-dose schedule as compared to a three-dose schedule are valid provided they are conducted concurrently, using the same protocol, in girls and women of the same age, enrolled and randomized to one of the two vaccination schedules.

Non-inferiority of a treatment group is understood as the lower bounds of the multiplicity adjusted 95% Confidence Intervals (CI) for the Geometric Mean Titers (GMT) ratio resulting (girls or women) greater than 0.5. The ratio is estimated for each alternative schedule and every specific genotype.

A study conducted in Vietnam[49] was intended to assess the non-inferiority of alternative vaccination schedules by comparison with the standard three-dose schedule using the quadrivalent vaccine in girls aged 11–13 years. The alternative schedules with the quadrivalent vaccine were administered at 0, 3, 9 month intervals; 0, 6, 12 month intervals; and 0, 12, 24 month intervals. Non-inferiority criteria were met with the first two schedules for the four vaccine genotypes; however, this criterion was not met for genotypes HPV-16 and HPV-6 a month upon conclusion of the schedule at 0, 12, and 24 month intervals. The cohort of girls was followed for 36 months to establish the duration of the antibodies based on these three different schedules. Results demonstrated that there was no inferiority in the response to the alternative schedules as compared to the standard schedule.[50]

In another study, a two-dose versus a three-dose schedule in girls aged 9 and 13 years was compared as well as the response to the two-dose schedule in girls and the three-dose schedule in women aged 16–26 years. The GMT were measured at 7, 18, 24, and 36 months after the last vaccine dose. The results established that the only differences observed in terms of inferiority were in girls that received the two-dose schedule versus the girls that received the three-dose schedule against genotype 18 as of the 18 month and against genotype 6 as of the 36 month. The antibodies response expressed as GMT was non-inferior in a two-dose schedule in girls as compared to a three-dose schedule in women.[51]

In May 2017, the WHO stated the current evidence supports the recommendation for a 2-dose schedule with adequate spacing between the first and second dose in those aged 9–14 years.[24]

Vaccine Impact

Vaccination impact data is derived from information on HPV epidemiology before and after vaccination and vaccine coverage (even with one or two vaccine doses higher than 50%). A recently published meta-analysis reports the following data: A) in girls aged 13–19 years, infections caused by HPV-16/18 have decreased by 64 % (p = 0.01); infections caused by HPV-31/33/45 have decreased by 28% (p= 0.44); infections caused by HPV-31/33/45/52/58 show basically no decrease (p = 0.32); B) in women aged 20–24 years, infections caused by HPV-16/18 have decreased by 31% (p=0.00001). [52]

Australia is the country with the most extensive HPV vaccination experience, since their National Immunization Program started administering the quadrivalent vaccine in girls and boys in 2007. Five years after vaccination, the condyloma acuminata in women under 21 years of age decreased from 11.7% in 2007 to 0.85% in 2011.[53] Another researcher in Australia measured HPV genoprevalence amongst women aged 18–24 years who attended family-planning centers. The 2005–2007 pre-introduction data was compared to the 2010–2011 post-introduction data. The number of infections caused by HPV-16/18/6/11 decreased from 28.7% to 6.7%, p<.001; infections caused by high-risk genotypes were reduced from 47.0% to 34.2%, p<.05.[54]

In the United States, prevalence of HPV-16 and 18 in CIN2/3 and adenocarcinoma in situ (CIN2+) in women has been compared via the epidemiological surveillance system through population-based sentinel centers from 2008 to 2012. The prevalence of CIN2+ lesions caused by HPV-16/18 decreased from 53.6% to 28.4% amongst women who had received at least one vaccine dose. This decrease, however, was observed in unvaccinated women (57.1% vs 52.5%). Estimation of vaccine efficacy in the prevention of CIN2+ was 21% (95% CI: 1–37); 49% (95% CI: 28–64) and 72% (95% CI: 45–86) in women who had initiated the schedule 25–36 months, 37–48 months, and more than 48 months before screening, respectively. [55]

These findings confirm the following:

1. An extended vaccination schedule administered at 0, 1 and 12 month intervals or at 0, 2 and 12 month intervals does not yield lower immunogenicity than a traditional schedule administering the last dose at 6 months. Moreover, higher GMT levels may be obtained with an extended schedule.
2. A two-dose schedule administered at 0, 2 months vs. 0, 6 months shows that the latter with a 6-month interval had higher Geometric Mean Concentrations (GMC) in girls aged 9–14 years.

Immune Response

The HPV infection caused by any genotype is quite common. Between 50% and 80% of women are expected to be infected at some point in their lives.[56] After infection, the first barrier the virus encounters is innate immunity — phagocytes, soluble proteins (such as cytokines and the epithelial barrier) — which clears the virus in almost 90% of infections. However, innate immunity does not demonstrate specific memory. The other defense mechanism, adaptive immunity, is activated by natural immunity, which is characterized by high-specificity and immune memory. Antibody response to L1 after vaccination affords protection against HPV infection via adaptive immunity. The antibody-mediated humoral immunity can prevent viral reinfections, while cell-mediated immune responses are key to clearing temporary infections. CD4(+) T-lymphocytes play a central role in humoral immunity and cell-mediated immunity. Seroconversion and generation of antibodies against the major virus proteins or the L1 protein occur simultaneously upon activation of cell-mediated immunity or shortly thereafter.[5]

The generation of the secondary antibody response to exposure as well as the preservation of antibody levels at all times are the main roles of memory B cells. High levels of memory B cells, for example, may represent a biomarker indicative of high levels of long-lasting serum antibodies.

Natural immune responses to HPV infection are weak due to HPV evasion mechanisms. The natural infection does not cause viremia or the elimination of cells thus resulting in a minimally inflammatory process.[57]

To date, no protection marker or antibody concentration indicative of protection has been established. [57]

In connection with the HPV-vaccine-induced immune adaptive response, the following has been described[58]:

1. The VLPs, with no viral genome, activate CD4(+) helper lymphocytes which go into a proliferation and differentiation state and interact with B cells. The activated CD4(+) lymphocyte cytokines contribute to maturation of B cells, which generate specific antibodies against the virus VLPs.
2. Virus-specific T-lymphocytes and memory B cells are generated for the VLPs.
3. On the next contact with the virus VLP or HPV, a T-cell dependent immune response is generated in a short period ranging between 24 and 48 hours.
4. The VLPs in HPV vaccines generate a significant immune response, with antibody titers 10 to 100 folds higher than the response induced by natural infection.[59]
5. Immune response in girls aged 9–14 years is higher than in women over 15 years. A significant difference has been shown to exist between receptors in girls and receptors in adult women, with a higher number of memory B cells in the former group, suggesting that at least for the purpose of inducing memory B cell creation, immunization of girls aged 9–13 years could be advantageous to maximize the response to HPV vaccines and to obtain higher efficacy.[59-61]
6. The bivalent vaccine which has an aluminum hydroxide-adjuvant with the addition of AS04 generates a higher antibody response than the quadrivalent vaccine.[62–65]
7. A "head-to-head" study comparing the immune response generated by the bivalent versus the quadrivalent vaccine against HPV-16 and 18 demonstrated that the bivalent vaccine generated 3.7 and 7.3 folds more neutralizing antibodies respectively in women aged 18– 26 years at 7 months after the introduction of the three-dose schedule. After 48 months of follow-up, the GMT remained 2.0 and 5.2 folds higher against HPV-16 and HPV-18, respectively. However, to date there is no clarity as to the clinical impact these differences may have, i.e., how it translates clinically into protection against infection.[63,66]

Adverse Events

The World Health Organization (WHO), through its Global Advisory Committee on Vaccine Safety, concluded in March 2014 that available HPV vaccines have an excellent safety profile.[67] The vaccine efficacy studies have included an assessment of potential short-term (assessments at 7 and 30 days after vaccination) and long-term (follow-up of 39 months) adverse events.[48,68] Local events at the HPV injection site, including pain and edema, occur more frequently and some systemic events, such as fatigue and headaches, are less frequent when compared to the control group.[69] However, no statistically significant differences have been shown in the occurrence of other adverse events as a result of HPV vaccination as compared to the control group.[68] Some reports have related the onset of some autoimmune diseases to vaccination; however, properly conducted population-based studies have ruled out such associations. In a study published in the British Medical Journal in 2013, no difference was observed in the number of autoimmune diseases, neurological changes or thromboembolic vein disease in 300,000 girls who received the HPV quadrivalent vaccine when compared to the control group.[70]

Vaccine safety and efficacy in individuals less than 9 years has not been established. As a precautionary measure, the vaccine is not recommended for administration in pregnant women.

Vaccine Coverage in Latin America

In July 2017, the Technical Advisory Group (TAG) on Vaccine-preventable Diseases of the Pan American Health Organization (PAHO) provided an update on the use of HPV vaccines in the Region of the Americas. As of June 2017, 29 countries and territories in the Americas have introduced the vaccine into their national immunization programs. Through routine immunization, an estimated 80% of the adolescent female cohort has access to the HPV vaccine. The worldwide administration of approximately 1.7 million HPV doses has been reported, yet there is a paucity of country-level vaccination coverage data, including in the Region.[71]

Per the 2017 TAG meeting report, "In 2016, only 14 of 29 countries and territories reported HPV vaccination coverage for the full recommended series in their national schedules, either two or three doses. Among these countries, the highest full-series coverage reported was 86% and the lowest 6%, with a median range of 47–55%. There is confusion regarding the selection of denominator populations for each dose in the series as well as additional challenges in making inter- or intra-country comparisons because of differing target populations."[71]

Conclusion

The role of HPV as a cause of cervical cancer and the risk attributable to this virus on other types of cancers such as oropharynx, penis, anal, vulvar, and vaginal cancers are undisputable. Cervical cancer is one of the main causes of death amongst women in every region of the world, with the highest impact in Africa. This complex virus has more than 190 genotypes, out of which 12 are high-risk based on their oncogenic potential. The epidemiology of the infection is also complex since it progresses to cervical cancer in only a small percentage of infected women and most infections are temporary.

Given that HPV-associated diseases are a public health priority, the development of vaccines against HPV has been long-awaited by clinicians, epidemiologists, civil society, and national and international public health authorities.

Currently, there are three vaccines available that differ in the number and type of genotypes they include. The bivalent vaccine includes two oncogenic genotypes, 16 and 18; the quadrivalent vaccine includes two low-risk genotypes, 6 and 11 and two high-risk genotypes, 16 and 18; and more recently the 9-valent vaccine has added five new genotypes to the ones included in the quadrivalent vaccine: HPV-31/33/45/52/58.

The recommended age of HPV vaccination in most immunization programs is in girls aged 9–13 years, since the immune response obtained in this age group is several folds higher than the response obtained in women over 15 years, which is potentially due to lack of exposure to the virus and higher memory B cell induction capacity in the former group.

Regarding dosing, scientific evidence has demonstrated that the antibody levels expressed as GMC in the two-dose schedule were non-inferior to the ones attained with the three-dose schedule in individuals less than 15 years. These findings have led to the recommendation for a two-dose schedule. Regarding the interval between the first and the second dose, scientific evidence has demonstrated that the response at 6 months and up to 12–15 months is higher in individuals less than 15 years as compared to schedules with a one or two month

interval. The three-dose schedule continues to be recommended for women aged 15 years and older, as well as immunocompromised or HIV-infected patients.

A number of developed countries have included the HPV vaccine in their routine immunization programs, and the effectiveness of the intervention has already been assessed. For instance, as the first country to adopt the vaccine, Australia has reported that between 2007 and 2011, prevalence of condyloma acuminatum has diminished from 11.7% to 0.85%. The United States has reported a reduction in the prevalence of CIN2+ caused by HPV-16 and 18 from 53.6% to 28.4%.

In late September 2015, the WHO reported that more than 65 countries had adopted the HPV vaccine into their immunization programs and more than 200 million doses had been distributed exhibiting a safety profile. In the Americas Region, the TAG reported that 29 countries had included the vaccine and approximately 80% of adolescent girls had access to it as of June 2017.

Since there is still a long way to go, countries need to implement epidemiological surveillance and permanent monitoring prior to the introduction of HPV vaccines into their immunization programs.

References

1. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. *The Lancet* 2013; 382(9895): 889–899.

2. zur Hausen H. Human papillomaviruses and the possible role in squamous cell carcinomas. *Berlin Heidelberg: Springer* 1977.

3. Reference clones at International HPV Reference Center. https://ki.se/en/labmed/international-hpv-reference-center. Accessed January 18, 2016.

4. Bernard H-U, Burk RD, Chen Z, van Doorslaer K, Hausen H zur, de Villiers E-M. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* 2010; 401(1):70–79. doi:10.1016/j.virol.2010.02.002.

5. Stanley M. Immune responses to human papillomavirus. *Vaccine* 2006; 24:S16-S22. doi:10.1016/j.vaccine.2005.09.002.

6. Franceschi S, Plummer M, Clifford G, et al. Differences in the risk of cervical cancer and human papillomavirus infection by education level. *Br J Cancer* 2009;101(5):865-870. doi:10.1038/sj.bjc.6605224.

7. Bernard H-U, Burk RD, Chen Z, van Doorslaer K, Hausen H zur, de Villiers E-M. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. *Virology* 2010;401(1):70–79. doi:10.1016/j.virol.2010.02.002.

8. Beutner KR, Tyring S. Human papillomavirus and human disease. *Am J Med* 1997;102(5):9–15.

9. Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst* 1999; 91(3):252–258.

10. Goodman A, Wilbur DC. Case 32-2003: A 37 year-old woman with atypical squamous cells on a papanicolaou smear. *N Engl J Med* 2003; 349(16):1555–1564.

11. Walboomers JMM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189(1):12–19. doi:10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F.

12. Münger K, Baldwin A, Edwards KM, et al. Mechanisms of Human Papillomavirus-Induced Oncogenesis. *J Virol* 2004;78(21): 11451-11460. doi:10.1128/JVI.78.21.11451-11460.2004.

13. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55(4):244–265.

14. Fact Sheets by Cancer. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed January 18, 2016.

15. De Sanjosé S, Diaz M, Castellsagué X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis* 2007;7(7):453–459.

16. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: A meta-analysis update. *Int J Cancer* 2007;121(3):621–632. doi:10.1002/ijc.22527.

17. Clifford G M. Worldwide distribution of human papillomavirus types in citologically normal woman in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet* 2005;366(9490):991–998.

18. Valdivia IM, Aguayo F, Pruyas M, Snijders PJ, Corvalán A, Ferreccio C. Genotipos de virus papiloma humano (VPH) en pacientes con cáncer cervico-uterino en un hospital público y una clínica privada de Santiago, Chile. *Rev Chil Infectol* 2010;27(1):11–15.

19. Valenzuela MT, Pío de la Hoz F, Koumans E, Nazzarena M, Koss C, Posso H, Cavada G, Urquidi C, et al. Human Papillomavirus (HPV) and Related Burden of Disease in Latin America and the Caribbean. January 2009.

20. Coutlée F, Ratnam S, Ramanakumar AV, et al. Distribution of human papillomavirus genotypes in cervical intraepithelial neoplasia and invasive cervical cancer in Canada. *J Med Virol* 2011;83(6):1034–1041. doi:10.1002/jmv.22081.

21. Xue H, Lin X, Li T, Yan X, Guo K, Zhang Y. Prevalence and genotype distribution of human papillomavirus infection in asymptomatic women in Liaoning province, China: Prevalence and Genotype Distribution. *J Med Virol* 2015;87(7):1248–1253. doi:10.1002/jmv.24029.

22. Dunne EF, Nielson CM, Stone KM, Markowitz LE, Giuliano AR. Prevalence of HPV infection among men: a systematic review of the literature. *J Infect Dis* 2006;194(8):1044–1057.

23. Baker TS. Structures of bovine and human papillomaviruses. Analysis by cryoelectron microscopy and three dimensional image reconstruction. *Biophys J* 1991;60:1445–1456.

24. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017–Recommendations. Vaccine 2017 Oct 13;35(43):5753–5.

25. Monie A, Hung C-F, Roden R, Wu TC. Cervarix™: a vaccine for the prevention of HPV 16, 18-associated cervical cancer. *Biol Targets Ther* 2008;2(1):107.

26. Harper DM, Franco EL, Wheeler C, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *The Lancet* 2004; 364(9447):1757–1765.

27. Garçon N, Chomez P, Van Mechelen M. GlaxoSmithKline Adjuvant Systems in vaccines: concepts, achievements and perspectives. *Expert Rev Vaccines* 2007;6(5):723–739. doi:10.1586/14760584.6.5.723.

28. Cervarix Clinical Review — ucm237976.pdf. http://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm237976.pdf. Accessed January 19, 2016.

29. De Carvalho N, Teixeira J, Roteli-Martins CM, et al. Sustained efficacy and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine up to 7.3 years in young adult women. *Vaccine* 2010;28(38):6247–6255. doi:10.1016/j.vaccine.2010.07.007.

30. Centers for Disease Control and Prevention (CDC). FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and updated HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010;59(20):626–629.

31. Koenig S IS, Shaw A. Chapter 11: HPV vaccines: Commercial Research & Development. *Vaccine* 2006:S3/99-SE/105.

32. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *The Lancet* 2009;374(9686):301–314.

33. Padmanabhan S CS. Intellectual property, technology transfer and manufacture of low-cost HPV vaccines in India. *Nat Biotechnol* 2010;28(7):671–678.

34. Cho HJ KY. Advances in human papilloma virus vaccines: a patent review. *Expert Opin Ther Pat* 2011;21:295–309.

35. McNeil C. Who invented the VLP cervical cancer vaccines? *J Natl Cancer Inst* 2006;98(7):433.

36. Harper DM. Review of Gardasil. *Vaccines Vaccin* 2010;1:pii 1000107.

37. Merck conducted six phase 1 and phase 2 clinical studies between 1997 and 2004–2006.

38. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;6(5):271–278.

39. Gardasil, INN-human papillomavirus vaccine [Types 6, 11, 16, 18] (Recombinant, adsorbed)-WC500021142.pdf. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000703/WC500021142.pdf. Accessed January 18, 2016.

40. World Health Organization. Human papillomavirus laboratory manual. 2009.

41. Schiller JT, Castellsagué X, Garland SM. A Review of Clinical Trials of Human Papillomavirus Prophylactic Vaccines. *Vaccine* 2012;30:F123-F138. doi:10.1016/j.vaccine.2012.04.108.

42. Dillner J. On behalf of the future i/ii Study Group Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. *BMJ* 2010;341:c3493.

43. Schiller JT, Castellsagué X, Garland SM. A Review of Clinical Trials of Human Papillomavirus Prophylactic Vaccines. *Vaccine* 2012;30:F123-F138. doi:10.1016/j.vaccine.2012.04.108.

44. Quadrivalent Human Papillomavirus Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP). http://francais.cdc.gov/mmwr/preview/mmwrhtml/rr5602a1.htm. Accessed January 18, 2016.

45. Saslow D, Castle PE, Cox JT, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin* 2007;57(1):7–28.

46. Joura E, Giuliano A, Iversen E, Bouchard C, Mao C, Mehlsen J, Moreira E, et al. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. *N Engl J Med* 372(8):711–723.

47. Romanowski B. Long term protection against cervical infection with the human papillomavirus: Review of currently available vaccines. *Hum Vaccin* 2011; 7(2):161–169. doi:10.4161/hv.7.2.13690.

48. Naud Ps, Roteli-Martins CM, De Carvalho NS, Teixeira JC, de Borba PC, Sanchez N, Zahaf T, Catteau G, Geeraerts B, Descamps D. Sustained efficacy, immunogenicity, and safety of the HPV-16/18 AS04-adjuvanted vaccine: final analysis of a long-term follow-up study up to 9.4 years post-vaccination. *Hum Vaccin Immunother* 2014; 10:2147–2162.

49. Neuzil KM, Thiem VD, Janmohamed A, et al. Immunogenicity and reactogenicity of alternative schedules of HPV vaccine in Vietnam: a cluster randomized noninferiority trial. *Jama* 2011; 305(14):1424–1431.

50. LaMontagne DS, Thiem VD, Huong VM, Tang Y, Neuzil KM. Immunogenicity of Quadrivalent HPV Vaccine Among Girls 11 to 13 Years of Age Vaccinated Using Alternative Dosing Schedules: Results 29 to 32 Months After Third Dose. *J Infect Dis* 2013;208(8):1325–1334. doi:10.1093/infdis/jit363.

51. Dobson SR, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *Jama* 2013;309(17):1793–1802.

52. Drolet M, Bénard É, Boily M-C, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *Lancet Infect Dis* 2015; 15(5):565–580.

53. Ali H, Donovan B, Wand H, Read T, Regan D, Grulich A, Fairley Ch, Guy R. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. 2013/4/18. 346.

54. Tabrizi SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis* 2014; 14(10):958–966.

55. Hariri S, Bennett NM, Niccolai LM, et al. Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States — 2008–2012. *Vaccine*. 2015;33(13):1608–1613. doi:10.1016/j.vaccine.2015.01.084.

56. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine* 2006;24 Suppl 1:S1-S15. doi:10.1016/j.vaccine.2005.09.054.

57. Stanley M. Immunobiology of HPV and HPV vaccines. *Gynecol Oncol*. 2008;109(2):S15-S21. doi:10.1016/j.ygyno.2008.02.003.

58. Toh ZQ, Licciardi PV, Fong J, Garland SM, Tabrizi SN, Russell FM, Mulholland EK. Reduced dose human papillomavirus vaccination: an update of the current state-of-the-art. Vaccine 2015 Sep 22;33(39):5042–50.

59. Block SL. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 28) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics* 2006;118:2135–2145.

60. Dobson SR. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *Journal of the American Medical Association* 2013; 309:1793–1802.

61. Smolen K, Gelinas L, Franzen L, Dobson S, Dawar M, Ogilvie G, Krajden M, Fortuno E, Kollmann T. Age of recipient and number of doses differentially impact human B and T cell immune memory responses to HPV vaccination. *Vaccine* 2012; 30:3572–3579.

62. Einstein MH. 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 randomized study of healthy women aged 18–45 years. *Human Vaccines* 2011;7:1343–1358.

63. Einstein MH. Comparison of the immunogenicity and safety of Cervarix and Gardasil human papillomavirus (HPV) cervical cancer vaccines in healthy women aged 18–45 years. *Human Vaccines* 2009; 5:705–719.

64. Toft L. Comparison of the immunogenicity of Cervarix and Gardasil human papillomavirus vaccines for oncogenic non-vaccine serotypes HPV-31, HPV-33, and HPV-45 in HIV-infected adults. *Human Vaccines and Immunotherapeutics* 2014; 10:1147–1154.

65. Barzon L. Neutralizing and cross-neutralizing antibody titres induced by bivalent and quadrivalent human papillomavirus vaccines in the target population of organized vaccination programmes. *Vaccine* 2014; 32:5357–5362.

66. 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.

67. World Health Organization. Global Advisory Committee on Vaccine Safety Statement on the continued safety of HPV vaccination. 2014. http://www.who.int/vaccine_safety/committee/topics/hpv/GACVS_Statement_HPV_12_Mar_2014.pdf.

68. Angelo MG, David MP, Zima J, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme: POOLED SAFETY FOR HPV-16/18-VACCINE. *Pharmacoepidemiol Drug Saf* 2014;23(5):466–479.

69. Paavonen J, Jenkins D, Bosch FX, et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomized controlled trial. *The Lancet* 2007; 369(9580):2161–2170.

70. Arnheim-Dahlström L, Pasternak B, Svanström H, Sparén P, Hviid A. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *Bmj* 2013 Oct 9;347:f5906.

71. Pan American Health Organization. Technical Advisory Group on Vaccines and Immunization (TAG) XXIV Meeting Report, July 2017.