Human Papillomavirus Vaccines

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15.1 Burden of HPV-Related Diseases in the Pre-vaccination Era

Human papillomaviruses (HPVs) include more than 100 viral types, with tropism for mucosa or skin. Infection with HPVs may become persistent and progress to precancerous lesions and eventually to invasion, causing cancers in a variety of sites, including the uterine cervix, vulva, vagina, penis, anus, oral cavity, oropharynx, and possibly the skin in patients with epidermodysplasia verruciformis. In order to evaluate the baseline levels of HPV infections and related diseases before universal vaccination programs were implemented, it is necessary to refer to data collected in the years 2003–2012. At that time, HPV infections were estimated to account for 5.2% of all cancers in the world, being responsible for 3% of mouth, 12% of oropharynx, 40% of penis, 40% of vulva/vagina, and virtually 100% of uterine cervix cancers. In particular, HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are classified as group 1 carcinogens by the International Agency for Research on Cancer (IARC). Cervical cancer was the fourth most common cancer in women, and the seventh overall, with an estimated 528,000 new cases in 2012. Most (around 85%) of the global burden occurs in low- and middle-income countries (LMIC), where it accounts for almost 12% of all female cancers. There were an estimated 266,000 deaths from cervical cancer worldwide in 2012, comprising 7.5% of all female cancer deaths. Almost nine out of ten (87%) cervical cancer deaths occurred in the LMIC regions. Mortality varies 18-fold among the different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe, and Australia/New Zealand to more than 20 per 100,000 in Melanesia (20.6), Middle (22.2), and Eastern (27.6) Africa. In addition to causing malignant cancers, HPVs are also the cause of genital warts (GWs), histologically benign lesions that represent the most common sexually transmitted disease in many countries. Several million cases of GWs occur every year in the world in both females and males, with a peak incidence between 20 and 24 years of age for women and between 25 and 29 years among men. HPVs are also responsible for a very rare but extremely debilitating disease, juvenile-onset recurrent respiratory papillomatosis (JORRP), characterized by the growth of recurrent tumors in the respiratory tract, which results from a vertical transmission of HPV from mother to child. Virology studies have substantiated the link between genital condylomas and JORRP. HPV types 6 and 11, which are responsible for 80–90% of the condylomas, are responsible for nearly 100% of JORRP.

European data (2012) (▶ http://www.hpvcentre.net/statistics/reports/XEX.pdf) confirm that the disease burden due to HPV infection is impressive: more than 58,000 new cervical cancer cases are estimated to be diagnosed annually, i.e., the sixth cause of female cancer in Europe overall and the second most common female cancer in women aged 15–44 years. Looking at mortality, more than 24,000 new cervical cancer deaths occur annually in Europe, i.e., the seventh cause of female cancer death overall and the second most common cause of female cancer death in women aged 15–44 years.

Data on other HPV-related cancers are more difficult to obtain, owing to their relatively lower incidence and to a lack of standardization of registries. However, estimates performed using reliable information available for 26 countries in Europe (EU countries not including Greece, Hungary, Luxemburg, and Romania plus data from Iceland, Norway, and Switzerland) show an incidence of about 2700 vulvar cancers, 1100 vaginal cancers, 4600 anal cancers (2900 in females, 1700 in males), 15,200 head and neck cancers (2500 in females, 12,700 in males), and almost 1100 penile cancers. In the same countries, 23,200 cervical cancer cases are estimated to occur every year. Overall, this means that, of the 48,000 HPV-16- and HPV-18-related cancers occurring each year in the selected European countries, 30% are in men. Excluding cervical cancer, of the approximately 23,000 cancer cases due to HPV-16/18, most are seen in men owing to the incidence

of head and neck cancers, which are fivefold more frequent in males than females. New cases of GWs attributable to HPV types 6/11 in the same countries are estimated at between 615,000 and 675,000 each year, with an equal sex distribution.

Regarding precancerous lesions, data collected between 2003 and 2007 in the 31 countries covered by the European Medicines Agency plus Switzerland showed the following ranges in numbers attributable to HPV: Cervical Intraepithelial Neoplasia (CIN) grade 2 or higher (CIN2+) 267,350–510,609; Vulvar Intraepithelial Neoplasia grade 2/3 (VIN 2/3) 12,067–23,977; Vaginal Intraepithelial Neoplasia grade 2/3 (VaIN 2/3) 2442–4521; and Anal Intraepithelial Neoplasia grade 2/3 (AIN 2/3) 1545 in females and 1093 in males.

15.2 Epidemiology and Ways of Transmission

The association between persistent HPV infection and cervical cancer is one of the strongest known in epidemiology, meaning that cervical cancer is necessarily linked to such an infection. HPV types 16 and 18 are responsible for >70% of cervical cancers in the world, the remaining less than 30% being due to the other carcinogenic types. The fraction of noncervical cancers attributable to HPV is variable, being about 83% for anal cancer, 60% for vaginal cancer, 42% for penile cancer, 31% for vulvar cancer, and 22% for oropharyngeal cancer. HPV-16 is also the single most important type to which almost all noncervical cancers due to HPV are attributable.

HPV-6 and HPV-11 are responsible for >90% of genital warts and JORRP cases in the world.

Several co-factors linked to the possible evolution from persistent infection toward precancerous and cancerous lesions have been recognized: smoking, parity, use of oral contraceptives, HIV infection, and other sexually transmitted infections. Male circumcision has been shown to decrease the risk of cervical cancer in female partners.

Transmission of HPV occurs primarily through sexual intercourse, not necessarily implying penetration. As a matter of fact, infection has also been described following manual–genital or oral–genital contact. Condom use may reduce the risk of infection, but is not completely protective.

In addition, nonsexual routes are possible, the most important being mother-to-child vertical transmission, which is a rare but possible event. Transmission through contaminated objects (i.e., surgical gloves or biopsy forceps) has been hypothesized, but has never been definitely proven.

15.3 Human Papillomavirus Vaccines

The development of HPV prophylactic vaccines started after the demonstration of the possibility of producing virus-like particles (VLPs) through self-assembly of antigens codified by the genomic regions L1 and L2 (virus capsid proteins). This property is one of the reasons for the high immunogenicity of HPV vaccines, as recombinant L1 proteins produced in yeast or insect cells reconstitute the external shell structure of the virus.

Infection with HPV is an exclusively mucosal event (no viremia) that does not cause inflammation or cell death. Consequently, natural immunity following infection is usually weak, and reinfection with the same HPV type may occur. Vaccination is given intramuscularly, and a strong primary and secondary response (including immunological memory induction) is obtained after a complete course of immunization.

The mechanism of protection is based on neutralizing antibodies able to prevent virus entry into the target mucosal cell. It is postulated that anti-HPV antibodies produced following active immunization transudate into the cervical mucosal basal layer and into the cervical mucus, where virions are neutralized. However, no minimum protective level of antibodies (correlate of protection) has been defined, also as a consequence of the excellent protection afforded by vaccines. The lack of

such a correlate implies that the protective effect of vaccines needs to be defined clinically. As it is not possible to measure the efficacy of HPV vaccines against cervical and other cancers in clinical trials for evident ethical and temporal reasons, it was necessary to find a surrogate marker of protection afforded by vaccination. Persistent infection with HPV is a possible outcome, but viral clearance can occur spontaneously. Prevention of cervical intraepithelial neoplasia (CIN) grade 2 or higher (CIN2+) is considered the best surrogate, as spontaneous reversion to normal histology, although possible, is very rare.

The demonstration of immunogenicity, efficacy, and safety of the first prototype monovalent vaccine against HPV-16 paved the way for the development and availability of first-generation vaccines, i.e., the quadrivalent vaccine (containing HPV types 6, 11, 16, and 18) and the bivalent vaccine (containing HPV types 16 and 18). Since 2015, a nine-valent HPV vaccine (containing HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) has been approved for use in the USA and Europe.

Table 15.1 Efficacy of the nine-valent human papilloma virus (HPV) vaccine against HPV-31/33/45/52/58 (cervical/vulvar/vaginal disease, persistent infection) – women aged 16–26 years; received all three vaccinations within year of enrolment

Per protocol efficacy population (median follow-up 40 months post dose 33)			
Endpoint	**9vHPV vaccine No. of cases/*n***	**qHPV vaccine No. of cases/*n***	**Efficacy (95% CI)**
≥CIN2/3, VIN2/3, VaIN2/3	1/6016	30/6017	96.7% (80.9, 99.8)
All CIN, VIN, VaIN2	3/6016	103/6017	97.1% (91.8, 99.2)
6-month persistent infection	35/5939	810/5953	96.0% (94.4, 97.2)

1. Joura et al. (2015)
2. Supplement for Joura et al. (2015)
3. Bautista O. V503–001 MEMO – Median Follow-up Time for Efficacy. Data on file. Dr. A Luxembourg ACIP February 2014 Meeting. ► http://www.cdc.gov/vaccines/acip/meetings/slides-2016-02.html

15.4 Bivalent HPV Vaccine

The bivalent vaccine, Cervarix (GSK), is produced in insect cells (derived from the butterfly *Trichoplusia ni*) by recombinant DNA techniques and adjuvanted with the AS04 system, which is composed of aluminum hydroxide and monophosphoryl lipid A, a lipopolysaccharide from the cell wall of *Salmonella* spp. bacteria (Table 15.1). Efficacy data were evaluated in a young adult female population after a three-dose schedule at 0, 1, and 6 months of the vaccine or placebo. Efficacy was primarily in the total vaccinated cohort, which included women who were HPV-DNA-negative and seronegative for HPV-16 and HPV-18 at study entry and who had received at least one dose of vaccine or placebo. Women who had a baseline high-grade lesion or lacking cytology data were excluded from the analysis. The efficacy of the bivalent vaccine in the prevention of CIN2+ associated with HPV-16 and/or HPV-18 was 90.4% (97.9% confidence interval [CI] 53.4–99.3%). Efficacy against the single types was 93.3% (97.9%; CI 47.0–99.9%) for HPV-16 and 83.3% (97.9% CI −78.8–99.9%) for HPV-18. When the analysis was also based on HPV-16 or HPV-18 in the lesion and in preceding cytology samples (post hoc analysis with attribution of the lesion to specific HPV types), efficacy values all became 100% (97.9% CI 74.2–100% for type 16/18; 64.5–100% for type 16; −49.5 to 100% for type 18). The bivalent HPV vaccine showed a cross-protective efficacy, especially against types 31 and 45. An overall efficacy against CIN3+ lesions (irrespective of HPV type in the lesion) of 93.2% (95% CI 78.9–98.7%) was reported at year 4 of follow-up for women involved in the PATRICIA clinical trial. However, it is not possible to define the duration of such a cross-protective effect, also because the clinical trials of HPV vaccines were not powered with the aim of measuring cross-protection. A comparative study on the

immunogenicity of the bivalent and the quadrivalent HPV vaccines showed significantly higher levels of antibodies against both HPV-16 and HPV-18 following administration of the bivalent versus the quadrivalent vaccine. The meaning of such data for long-term protection is as yet unknown.

Following a specifically designed clinical trial to compare the immunogenicity of two doses of bivalent vaccine in girls 9–14 years of age vs three doses given to young women aged 15–25 years, which demonstrated that GMTs after two doses in girls were not inferior to three doses in women, a change occurred in the recommended schedule for young girls, which since 2013/2014 foresees the administration of two doses at 6 months apart for subjects aged <15 years.

15.5 Quadrivalent HPV Vaccine

The quadrivalent vaccine (Gardasil, Merck) is produced in yeast cells by recombinant DNA techniques and adjuvanted with amorphous aluminum salts (Table 15.1). The phase 3 clinical trial was performed in 13 different countries (FUTURE II Study) and involved about 12,000 women, randomly assigned to receive HPV vaccine or placebo according to a 3-dose schedule (0, 2, and 6 months). The composite efficacy result (CIN2, CIN3, adenocarcinoma in situ) after an average 3-year follow-up was 98% (95% CI 86–100%) in the per-protocol susceptible population and 44% (95% CI 26–58%) in the intention-to-treat population, where women already infected were also represented.

Immunological memory against the quadrivalent L1-encoded HPV antigens was demonstrated by a challenge dose administered 5 years after the first dose in fully vaccinated women. A booster response was elicited even if the woman had lost detectable antibodies to some antigen. Interestingly, in the same study, it was possible to highlight that no case of breakthrough infection occurred in women of the vaccine group who became seronegative in the 5-year time interval, whereas ten cases of infection occurred in women belonging to the placebo group. It is not clear whether this means that vaccinated women retained a protective but undetectable level of antibodies to the L1 antigen, or if they were protected through an anamnestic response at the mucosal level. Women belonging to the placebo group were immunized at year 5, and this intervention prevented the possibility of having long-term efficacy data through the comparison of vaccinated vs unvaccinated women. However, data from originally vaccinated women followed through cancer registries in Nordic countries demonstrated no breakthrough infection after 12 years of follow-up, with a trend toward continued protection through 14 years post-vaccination. The quadrivalent vaccine showed a good degree of cross-protection in clinical trials, especially against HPV-31 and HPV-33, the duration of which needs to be further investigated. An independent study comparing the antibody response obtained after two doses administered 6 months apart in girls aged 9–13 years versus young women aged 16–26 years receiving three doses at 0, 2, and 6 months showed non-inferiority of the two-dose schedule, and the two-dose schedule was approved for the quadrivalent vaccine given at age 9–13 years.

15.6 Nonavalent HPV Vaccine

The nine-valent HPV vaccine was developed based on the heritage of the quadrivalent vaccine, with which it shares the same production process and the same adjuvant. It includes the additional HPV types 31, 33, 45, 52, and 58. The foreseen direct impact of the new vaccine is an increase in prevented overall HPV-related cancers from 75% to 89%. About 90% of cervical cancer cases are directly preventable using the nine-valent vaccine (vs 72% with the quadrivalent vaccine), whereas the increase in prevented cases would be more limited for anal cancer (from 87% to 90%).

In a double-blind, randomized, multicenter study, over 14,000 women were randomly assigned to receive three doses of either the nonavalent or the quadrivalent HPV vaccine (comparator) at months 0, 2,

and 6. The nonavalent vaccine turned out to have overlapping (and non-inferior) seroconversion rates and geometric mean titers (GMTs) 1 month after the third dose (month 7). The efficacy of the nonavalent vaccine against precancerous lesions and persistent infection due to HPV types 31, 33, 45, 52, and 58 was directly measured in the trial, as the quadrivalent vaccine lacks VLPs of such HPV types. The overall efficacy data against different endpoints for the five types are reported in Table 15.1 and was invariably >90%, mostly >95%. Table 15.2 reports the 6-month efficacy against persistent infection for the single additional types of the nine-valent vaccine, which ranged from 94.8% to 99.1%.

Table 15.2 Efficacy of the nine-valent HPV vaccine against 6-month persistent infection (PI) due to types 31, 33, 45, 52, and 58. Per protocol population

Endpoint 6-month PI	9vHPV No. cases/ total	qHPV No. cases/total	Efficacy (95% CI)
HPV 31	7/5251	150/5198	95.5% (90.7, 97.9)
HPV 33	1/5553	106/5560	99.1% (95.2, 100)
HPV 45	4/5649	124/5658	96.8% (92.1, 98.9)
HPV 52	11/5263	387/5160	97.3% (95.5, 98.7)
HPV 58	12/5297	225/5284	94.8% (91.0, 97.1)

The nine-valent vaccine was subsequently approved for use with a two-dose schedule at 0–6/12 months in girls and boys aged 9–14 years (► https://www.cdc.gov/vaccines/acip/meetings/downloads/min-archive/min-2016-02.pdf)

15.7 Effectiveness of HPV Vaccines: From Trials to the Real World

Fourteen years after HPV vaccination was implemented in several countries, a considerable amount of disease impact data is available. HPV vaccination programs have been proven to reduce incident and prevalent HPV-related conditions and diseases even a couple of years after vaccination implementation. As those data come from ecological studies, results must be interpreted with care. Below, some of the available data on HPV vaccination effectiveness are reported.

The first diseases on which immunization have an impact are GWs.

In Australia, 5 years after implementation of HPV vaccination, a 93% reduction of GWs irrespective of vaccination status was registered in women aged <21 years and a 100% reduction in women who declared that they had been vaccinated. GW incidence in heterosexual men also decreased by indirect effect. Such an effect was not visible in the homosexual male population. In Denmark, after introduction of the vaccination program, the incidence ratio (IR) of GWs in 16- and 17-year-old women between 2008 and 2013 decreased from 1071 to 58 per 100,000 person-years and was reduced from 365 to 77 per 100,000 person-years in men.

Also, the prevalence of vaccine-type HPV DNA decreased significantly in Australian females aged 18–24 years: 4vHPV prevalence decreased from 29% to 7% in partially and to 2% in fully vaccinated women; a lower prevalence of vaccine-targeted types in unvaccinated women (19%) suggested herd immunity. Furthermore, in a country using the bivalent vaccine, such as Scotland, from a total of 4679 samples tested, a significant reduction in prevalence of HPV-16 and HPV-18 from 29.8% (95% CI 28.3, 31.3%) to 13.6% (95% CI 11.7, 15.8%) was registered in the 5 years after vaccination implementation.

Precancerous lesions have also decreased significantly following implementation of immunization strategies. Australian data updated to March 2014, with a vaccine coverage around 70% for three doses, showed a

reduction of high-grade precancerous lesions (CIN2/3) of 50% in women aged <21 years. In Scotland, a significant reduction of CIN diagnoses in women who received three doses of vaccine vs those not vaccinated was registered: for CIN 1, adjusted RR was 0.71 (95% CI 0.58–0.87; $P = 0.0008$). For CIN 2, adjusted RR was 0.5 (95% CI 0.4–0.63; $P = 0.0001$) and for CIN 3, adjusted RR was 0.45 (95% CI 0.35–0.58; $P = 0.0001$).

In 2020, first direct evidences collected in Sweden on the effectiveness of HPV vaccines against cervical cancer were published. Girls and women were evaluated for cervical cancer until their 31st birthday. Cervical cancer was diagnosed in 19 women who had received the quadrivalent HPV vaccine and in 538 women who had not received the vaccine. The cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated. After adjustment for age at follow-up, the incidence rate ratio for the comparison of the vaccinated population with the unvaccinated population was 0.51 (95% confidence interval [CI], 0.32–0.82). After additional adjustment for other covariates, the incidence rate ratio was 0.37 (95% CI, 0.21–0.57). After adjustment for all covariates, the incidence rate ratio was 0.12 (95% CI, 0.00–0.34) among women who had been vaccinated before the age of 17 years and 0.47 (95% CI, 0.27–0.75) among women who had been vaccinated at the age of 17–30 years.

Further data from 4 Nordic European countries (Denmark, Iceland, Norway, and Sweden) at the end of 14 years of follow-up after enrollment in FUTURE II were available in 2021. Young women (16–23 years of age) who received three qHPV vaccine doses during the randomized, double-blind, placebo-controlled FUTURE II base study were followed for effectiveness for an additional ≥10 years through national registries. The observed incidence of HPV-16/18-related high-grade cervical dysplasia was compared with recent historical background incidence rates in an unvaccinated population. No cases of HPV-16/18-related high-grade cervical dysplasia were observed in the per-protocol effectiveness population ($N = 2121$; 24,099·0 person-years of follow-up) during the entire study. Vaccine effectiveness of 100% (95% CI 94.7–100) was demonstrated for ≥12 years, with a trend toward continued protection through 14 years post-vaccination.

15.8 Safety of HPV Vaccines

All HPV vaccines showed a good safety profile in clinical trials. Local reactions (pain, swelling, induration, redness, etc.) are frequently reported side effects. Systemic reactions included fever, headache, vertigo, and nausea.

Post-marketing surveillance data include, as expected, reports of a wide range of adverse events following immunization (AEFIs). Causality assessment is a complex process that implies the verification of the simultaneous presence of different criteria, and not simply temporal association.

Several diseases of uncertain etiology have been reported after HPV vaccination; however, none of them was demonstrated to be causally associated with immunization.

For the quadrivalent vaccine, a review of 15 published post-marketing studies based on both passive and active surveillance showed an excellent record of safety on >1 million vaccinated subjects around the world. The US Institute of Medicine published a review on HPV vaccination, autoimmune disease, and acute disseminated encephalomyelitis (ADEM), which stated that the vaccine is not associated with an increased risk of multiple sclerosis or other demyelinating diseases.

The most recent threat to HPV vaccination programs was the report of some cases of complex regional pain syndrome (CRPS) and of postural orthostatic tachycardia syndrome (POTS) in vaccinated girls, following which vaccination coverage dramatically fell in Japan. Following a Danish request of review for evidence of possible causality, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) stated that available evidence does not show any causal relationship between HPV vaccination and the two

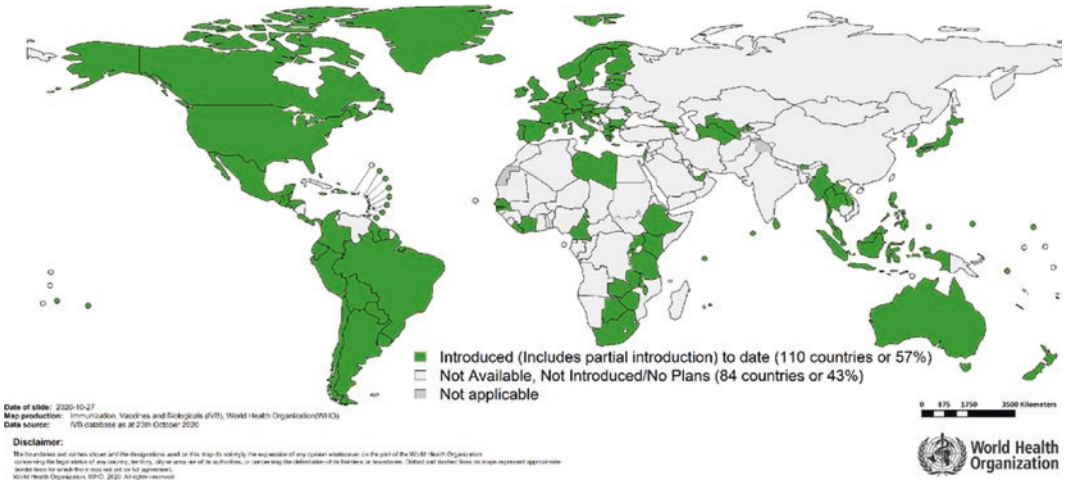

Fig. 15.1 Countries that include human papilloma virus (HPV) vaccine in their national immunization program. (Data source: WHO/IVB Database, as of 23rd October 2020. Map production Immunization Vaccines and Biologicals (IVB), World Health Organization; The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement. ©WHO 2020. All rights reserved)

syndromes. Such a conclusion was endorsed officially by the EMA on November 20, 2015. In December 2015, the WHO Global Advisory Committee on Vaccine Safety confirmed that no such causal association exists, calling for efforts by Japan health authorities to restore vaccination coverage.

15.9 Vaccination Programs in the World

Vaccination for HPV has been recommended and implemented in the adolescent female population of several countries for about 14 years, starting from industrialized areas and achieving different coverage results (Fig. 15.1). In May 2018 the WHO Director-General made a global call for action toward the elimination of cervical cancer as a public health problem, aiming to reduce the annual incidence below 4 cases per 100,000 globally. In August 2020, the World Health Assembly passed a resolution calling for elimination of cervical cancer and adopting a strategy to make it happen.

Countries with limited resources have been involved in vaccination demonstration projects and, in some cases, have launched a national program with the help of international agencies and alliances (Fig. 15.2). Extension of the immunization offer to adolescent male subjects has become an important additional opportunity for several countries, also because the progressive decrease of vaccine costs and the possibility of administering two doses only in adolescents have made universal HPV immunization a cost-effective option in many instances. Special attention is needed for homosexual men with HIV infection, who are at a particularly increased risk for HPV-related diseases and deaths. However, it seems unlikely that a high vaccination coverage is reached in such a risk group, universal (female and male) adolescent programs being the real solution. An extension of female age groups involved in the active offer of immunization to include young adults would allow a faster impact of vaccination programs on HPV-related cancers and precancers.

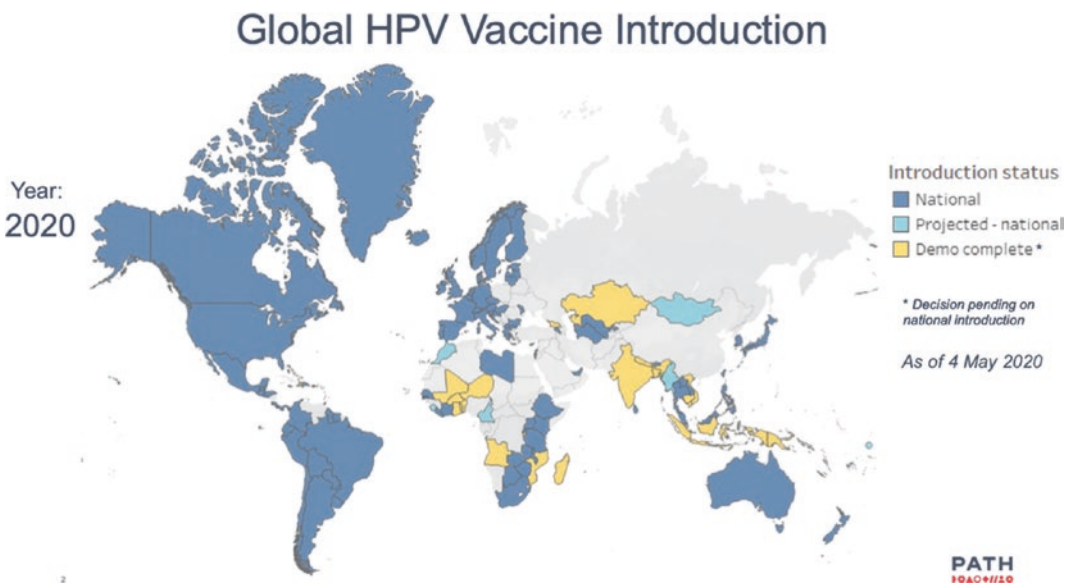

Fig. 15.2 Global HPV National Vaccine Introduction Projected National Introduction, and Completed Demonstration Projects as of May 4, 2020. (▶ https://path.azureedge.net/media/documents/Global_HPV_Vaccine_Intro_Overview_Slides_webversion_2020May.pdf)

Furthermore, it must not be forgotten that reaching high coverage with HPV vaccines can have a deep impact on the organization of screening programs. In the presence of a high coverage against HPV vaccine types in the population, it would be possible to extend HPV DNA testing as a primary screening test, and fewer screening rounds during a woman's lifetime would be sufficient to provide almost complete protection against HPV.

	Bivalent vaccine	Quadrivalent vaccine	Nonavalent vaccine
Antigens (virus-like particles – VLPs)	20 μg HPV-16 20 μg HPV-18	40 μg HPV-16 20 μg HPV-18 20 μg HPV-6 40 μg HPV-11	60 μg HPV-16 40 μg HPV-18 30 μg HPV-6 40 μg HPV-11 20 μg HPV-31 20 μg HPV-33 20 μg HPV-45 20 μg HPV-52 20 μg HPV-58
Expression system	Baculovirus expression vector system in *Trichoplusia ni* Rix4446 cell substrate	*Saccharomyces cerevisiae* yeast	*Saccharomyces cerevisiae* yeast
Adjuvant	AS04 Adjuvant system [50 μg MPL and 500 μg $Al(OH)^3$]	225 μg amorphous aluminum hydroxyphosphate sulfate	500 μg amorphous aluminum hydroxyphosphate sulfate
Administration schedule	2 doses 5–13 months apart from 9 to 14 years 3 doses at month 0, 1, 6 in subjects ≥15 years	2 doses at month 0 and 6 from 9 to 13 years 3 doses at month 0, 2, 6 in subjects ≥14 years	2 doses 5–13 months apart from 9 to 14 years 3 doses at month 0, 2, 6 in subjects ≥15 years

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