HPV and cancer 1

Present status of human papillomavirus vaccine development and implementation

Rolando Herrero, Paula González, Lauri E Markowitz

Oncogenic human papillomavirus (HPV) infection is the cause of nearly all cervical cancers and a proportion of other anogenital and oropharyngeal cancers. A bivalent vaccine containing HPV 16 and 18 and a quadrivalent vaccine containing HPV 6, 11, 16, and 18 antigens are in use in vaccination programmes around the world. In clinical trials, three vaccine doses provided 90–100% protection against cervical infection and pre-cancer related to HPV 16 and 18 in women aged 15–26 years who were not infected at vaccination. Partial cross-protection against other HPV types has been reported but its duration is unknown. The vaccines were also efficacious at the prevention of HPV 16 and 18 infections at other anatomical sites in both sexes. Immunobridging studies allowed licensing of the vaccines for use starting at age 9 years for both sexes. Two-dose schedules elicit high antibody concentrations, leading to the recommendation of two-dose schedules for girls aged 9–14 years. Pre-licensure and post-licensure studies have provided data supporting vaccine safety. In 2014, a nonavalent vaccine containing HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 antigens was licensed by the US Food and Drug Administration. HPV vaccination was first introduced in high-income countries owing to vaccine cost, logistic challenges, and competing health priorities. Since 2011, vaccine prices have lowered, allowing the introduction of the vaccine in some middle-income countries. Funding of the vaccine by the GAVI Alliance in 2012 led to demonstration projects in some low-income countries. By 2014, more than 57 countries had included the HPV vaccine in their national health programmes. Data from several countries have shown the effect of vaccination on HPV infection and associated disease, and provided evidence of herd immunity. Expansion of programmes to countries with the highest burden of disease is beginning, but further efforts are needed to realise the potential of HPV vaccines.

Introduction

Cervical cancer has historically caused thousands of premature deaths per year in women from the most disadvantaged socioeconomic groups. Worldwide, cervical cancer and maternal mortality each result in about 250 000 deaths per year.1 Until now, approaches for cervical cancer control were complex, expensive, and generally unfeasible in developing areas where the disease is most common. Infection with specific types of human papillomavirus (HPV) causes nearly all cervical cancers, and improvements in the understanding of the natural history of the disease have generated new approaches for primary and secondary prevention, including safe and effective vaccines and powerful screening methods based on viral detection.

Genital HPV infection is very common in sexually active women and men in most areas of the world. The virus is mainly transmitted through sexual intercourse, when epithelial microtrauma is thought to allow interaction of the virus with the basement membrane to establish infection. In 50–70% of women infected, natural infection induces low levels of type-specific neutralising antibodies against the viral capsid (L1), which are able to partly protect against subsequent infection, particularly in people with highest antibody titres.2 Regression of infection and lesions is induced by a local cell-mediated immune response against early viral proteins, mainly E2 and E6. However, when infection is not controlled by the immune system and becomes persistent, dysregulated viral gene expression, cell proliferation, and accumulation of genetic damage can lead to cancer precursors and cancer over several years.

HPV infection is aetiologically associated with about 90% of cancers of the anus, 50% of cancers of the penis, 40% of cancers of the vulva, 70% of cancers of the vagina, and 20–60% of cancers of the oropharynx.3 In high-income countries, anal cancer and HPV-related oropharyngeal cancer are increasing in women and men.4 In the USA, for example, HPV-related cancers are expected to be more common in men than in women in the near future.5 HPV types 16 and 18 are associated with about 70% of cervical cancers and 80–90% of HPV-related tumours in other anatomical sites.4 HPV 6 and 11 are associated with genital warts and recurrent laryngeal papillomatosis, a rare but clinically significant disorder.6

HPV vaccines and immunogenicity

Initial studies7 showing that L1 virus-like particles induce strong immune responses resulted in widespread clinical trials and regulatory licensure of two vaccines against HPV: the bivalent vaccine produced by GlaxoSmithKline (Cervarix) containing HPV 16 and 18 antigens, and the quadrivalent vaccine produced by Merck (Gardasil) containing HPV 6, 11, 16, and 18 antigens. Thus, HPV 16 and 18 are the vaccine types for the bivalent vaccine, and HPV 6, 11, 16, and 18 are the vaccine types for the quadrivalent vaccine. The bivalent vaccine is produced in...
Trichoplusia ni insect cell lines infected with an L1 baculovirus vector and has a special adjuvant called ASO4, consisting of monophosphoryl lipid A and aluminium hydroxide. Monophosphoryl lipid A is a detoxified bacterial lipopolysaccharide and a toll-like receptor-4 agonist associated with the activation of innate and adaptive immune responses. The quadrivalent vaccine, on the other hand, is produced in yeast (Saccharomyces cerevisiae) and has an aluminium hydrophosphate sulfate adjuvant. In 2014, the US Food and Drug Administration (FDA) approved a nonavalent vaccine produced using technology similar to the quadrivalent vaccine. The nonavalent vaccine is directed against nine HPV types (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58; table 1), which together cause almost 90% of cervical cancers and many cervical intraepithelial neoplasms (CINs). CINs associated with these additional HPV types have a lower risk of progression, but are associated with repeat colposcopies and treatment.

The bivalent and quadrivalent vaccines were originally licensed with a three-dose schedule, and induce strong immune responses against vaccine HPV types and some phylogenetically related non-vaccine types. The main effector of protection is believed to be the IgG antibody, which can reach the site of infection by transudation from serum into the vaginal milieu and by exudation at sites of trauma that expose the basement membrane to infection, as has been shown in animal models. Antibody titres against L1 peak shortly after the third injection and, after an initial drop, plateau at a concentration many times higher than that attained after natural infection. Duration of antibodies has been assessed through about 10 years, and sustained high concentrations have been reported during this time, suggesting that antibodies against both vaccines are likely to last for decades. Boosting with a quadrivalent vaccine a few years after initial vaccination was shown to induce a strong anamnestic response, but whether repeated exposure to the virus is able to induce a boosting effect is still unknown. Antibody concentrations produced by the bivalent vaccine are significantly higher than those produced by the quadrivalent vaccine both for HPV 16 and 18 and for cross-protected types, but the clinical significance of the higher titres has not been established. The minimum concentration of antibodies to achieve protection has not been identified, and the role of avidity maturation and the induction of B-cell memory has not yet been clarified.

### Prophylactic efficacy against cervical outcomes associated with vaccine HPV types

The multicentre vaccine trials for the bivalent and quadrivalent vaccines included more than 20 000 women aged 15–26 years from more than ten countries in four continents. The two main trials of the quadrivalent vaccine are the FUTURE I and FUTURE II trials. The PATRICIA and the Costa Rica vaccine trial, an independent study sponsored by the US and Costa Rican Governments, are the two main trials for the bivalent vaccine. All four trials analysed different cohorts with variable inclusion criteria, making the results not strictly comparable. The differences between cohorts are mainly related to the inclusion of women according to the absence of HPV infection at vaccination, detection of antibodies as indicators of past exposure, number of vaccine doses, and compliance with protocols. Most trials have produced data for vaccine efficacy against advanced cervical cancer precursors (CIN 2, CIN3, and adenocarcinoma in situ) and persistent HPV infection. Some of the studies defined the causal association of their outcomes with specific HPV types on the basis of detection of HPV in exfoliated cells. By contrast, others assessed the presence of specific viral types in histological specimens. Regulatory authorities required protection against clinically significant cancer precursors in the according-to-protocol cohorts for initial licensure.

The quadrivalent and bivalent vaccine trials showed that both vaccines are able to prevent up to 90–100% of new HPV 16 and 18 infections and associated CIN2 or worse in women not infected with HPV 16 or 18 at the time of vaccination (figure 1A and 1B). These findings resulted in licensure and use of the vaccines for cervical cancer prevention interventions, focusing on adolescents as the main target age group.

Despite the strong protection against incident infection and disease, the vaccines do not change the natural history of prevalent infection. In the bivalent vaccine trials, no difference in clearance of HPV 16 and 18 infections...
was reported between participants who received the vaccine and those who did not. Similarly, in the quadrivalent vaccine trials, there was no difference in the incidence of HPV 16 and 18-related CIN2 or worse for women who were seropositive and DNA positive for HPV 16 or 18 before vaccination.

Some studies have reported that the quadrivalent HPV vaccine reduces the occurrence of pre-cancer after treatment with loop electrosurgical procedure and after treatment of anal lesions in men who have sex with men. This reduction was thought to be the result of preventing lesion recurrence; however, it seems to actually be the result of the prevention of new infections by vaccination.

Because other cohorts (eg, intention to treat or total vaccinated cohort) include women with different degrees from prevalent infections at the time of vaccination, the vaccine efficacy is reduced. However, efficacy tends to steadily rise with longer follow-up because lesions originating from the prevalent infections in vaccinated women occur early after vaccination.

Although efficacy trials were done in women aged 15–26 years, both vaccines were initially licensed for women aged 9 years to 25 or 26 years, on the basis of results from immunobridging studies. These results showed that the antibody response of girls aged 9–15 years is non-inferior to that of young adult women, with similar findings for men. In studies of the quadrivalent vaccine, the mean HPV 16 antibody titres 1 month after the third dose in girls and boys aged 10–15 years were twice as high as the titres in women aged 16–23 years. For the bivalent vaccine, the mean antibody titres at month 48 after vaccination for girls aged 10–14 years were six times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.

Results from one clinical trial showed that the quadrivalent vaccine prevents infections in women up to age 45 years. However, although efficacy was reported against a combined endpoint of persistent infection or CIN1 or worse, efficacy against CIN2 or worse was not shown, partly as a result of the low incidence in this age group. A primary vaccination study reported that the bivalent vaccine induces a robust immune response in women up to age 55 years. Although lower than those reported in younger women (15–25 years), antibody concentrations against HPV 16 and 18 in older women (26–55 years) remained several times higher than the concentrations reported in women aged 15–26 years in the PATRICIA trial.
efficacy against a composite endpoint of HPV 31, 33, 45, 52, and 58 high-grade cervical, vulvar, and vaginal lesions was 96.7% (95% CI 80.9–99.8). An immunobridging study in girls and boys aged 9–14 years reported 99% seroconversion and non-inferior antibody titres compared with young women aged 16–25 years receiving the quadrivalent vaccine. More data are needed to assess the additional benefit of the nonavalent vaccine compared with the bivalent vaccine.

Cross-protection and protection against all types of CIN

Both the bivalent and quadrivalent HPV vaccines induce partial cross-protection against phylogenetically related non-vaccine HPV types. The extent and durability of cross-protection afforded by the vaccines is the subject of a continuing debate for public health decision makers. For the bivalent vaccine, significant vaccine efficacies of 88%, 68%, 82%, and 54% were reported in the HPV naive cohort against CIN2 or worse associated with HPV 31, 33, 45, and 51. In the corresponding cohort for the quadrivalent vaccine, a vaccine efficacy of 70% was noted for CIN2 or worse associated with HPV 31 but not for any other HPV type. Protection against HPV 45 could be important since, together with HPV 18, it is the major viral type associated with adenocarcinomas.

CIN3 is probably the best surrogate marker for invasive cancer and overall protection against CIN3 is an important consideration when comparing vaccines. At the end of the PATRICIA trial, efficacy of the bivalent vaccine against CIN2 or worse and CIN3 or worse, irrespective of HPV type, was 64.9% (95% CI 52.7–74.2) and 92.3% (70.9–98.7), respectively in the naive cohort (HPV DNA and serology negative for oncogenic types at baseline and normal cytology). In the final study report of the Costa Rica vaccine trial, overall protection for the bivalent vaccine in the per-protocol cohort against CIN2 or worse, irrespective of HPV type, after 4 years of follow-up was 61.4% (95% CI 29.5–79.8). In the same study, by using an alternative, exploratory definition of type attribution requiring HPV persistence in cases of multiple infection, efficacy against CIN2 or worse was 75.3% (95% CI 48.1–89.3) irrespective of HPV type and 82.4% (57.0–94.0) against any oncogenic HPV. However, the study did not have sufficient power to assess vaccine efficacy against CIN3. The efficacy estimate of the quadrivalent vaccine was 42.7% (95% CI 23.7–57.3) against CIN2 or worse and 43.0% (13.0–63.2) against CIN3 in the naive cohort irrespective of HPV type. Many possible explanations exist for the differences in efficacy between the two vaccines (bivalent and quadrivalent) against cervical cancer precursors irrespective of causal HPV type, including the serological or DNA detection methods used to define the naive cohorts, differences between baseline characteristics of participants, differences in type-specific HPV prevalence in the population, or higher levels of cross-neutralising antibodies of the bivalent vaccine. Whether duration of protection against non-vaccine types will be comparable with duration of protection against vaccine types remains unclear.

Efficacy in non-cervical sites

Efficacy of the vaccines at other anatomical sites in both sexes has been reported. The quadrivalent vaccine has been shown to offer 100% vaccine efficacy against vulvar and vaginal disease associated with vaccine HPV types in per-protocol cohorts (figure 1B). In men, the quadrivalent vaccine has shown to reduce 90% of HPV 6, 11, 16, and 18-associated penile, perianal, and perineal (all sites combined) external lesions and 69% of persistent infection, and 100% of penile intraepithelial lesions associated with vaccine HPV types. In another study in men who have sex with men, the quadrivalent vaccine prevented 95% of persistent anal infections with vaccine-related types and 78% of anal intraepithelial lesions (figure 1C).

For the bivalent vaccine, the evidence of protection at extracervical sites comes from ad-hoc analyses of young women in the Costa Rica vaccine trial. An 84% reduction in prevalent HPV 16 or 18 anal infection was reported 4 years after vaccination in women who were HPV DNA negative at the cervix at enrolment. Since vulvar lesions have become increasingly common, the efficacy of the bivalent vaccine against vulvar infections was also investigated in the Costa Rica vaccine trial in a subset of about 1000 women. In the intention-to-treat cohort, a 50% reduction in HPV 16 and 18 vulvar infections was detected. However, efficacy against vulvar infections has not been reported from the large PATRICIA trial. In another intention-to-treat analysis, exfoliated oral cells of more than 5000 vaccinated and unvaccinated women were tested for HPV. Of the vaccinated women, only one had HPV 16 or 18 infection; whereas 15 of the control participants were infected, providing an estimated vaccine efficacy of 93% for this cohort against prevalent oral HPV infection 4 years after vaccination (figure 1A).

Efficacy and immunogenicity of fewer than three doses

The strong immune response to the vaccine resulted in an investigation of whether vaccination with fewer than three doses would be able to reduce disease incidence. A proof-of-principle study in the Costa Rica bivalent vaccine trial, which included a group of women who did not receive all their vaccine doses and who were HPV DNA negative at baseline, reported a vaccine efficacy for prevention of persistent HPV 16 and 18 infection that was similar for women who received one, two, or three doses. Antibody response was investigated in a subgroup, and 100% of women, irrespective of the number of doses, remained HPV 16 and 18 seropositive at 4 years. HPV 16 and 18 antibody titres in women receiving two doses at least 6 months apart were non-inferior to the three-dose group. HPV 16 antibody concentrations were at least 24 times higher in the one-dose vaccine group than in the two-dose vaccine group and nine times higher in the one-dose vaccine group compared with
natural infection. Notably, antibody concentrations after one dose remained stable over 4 years.49

Additionally, several studies have reported that the immunogenicity of two doses of both vaccines, particularly in girls aged 9–14 years, and when the doses are separated by 6 months, is non-inferior to that of three doses in women aged 15–26 years, for whom vaccine efficacy has been proven.46,47 In the position manuscript on HPV vaccines reported in October, 2014, WHO recommends the use of a two-dose schedule of either vaccine for girls younger than 15 years.50 This new recommendation is likely to have a strong effect on the cost and logistics of HPV vaccination programmes. Nevertheless, follow-up is needed to ensure that long-term efficacy is similar to that of a full course of three doses and decide whether further doses are needed long term. An International Agency for Research on Cancer randomised clinical trial in India investigating the efficacy of two versus three doses of the quadrivalent vaccine in which vaccination was interrupted will provide an opportunity to assess the vaccine efficacy of one and two doses. However, the efficacy of only one dose warrants formal testing in carefully planned clinical trials (Sankaranarayanan R, International Agency for Research on Cancer, personal communication).

**Safety**

Pre-licensure trials included more than 20 000 women aged 9–26 years for the quadrivalent vaccine and more than 30 000 women aged at least 10 years for the bivalent vaccine. The most common injection-site reaction was pain for both vaccines.48 No differences in serious adverse events, new onset autoimmunity and chronic diseases, or deaths between vaccine and control groups for either vaccine were recorded.6,49 None of the rare deaths was judged to be vaccine related. Because of initial concerns about potential vaccine effects on pregnancy outcomes for the bivalent vaccine, a pooled analysis of PATRICIA and Costa Rica trial data was recommended by the FDA. The analysis showed no evidence of a significant rise in miscarriages in women vaccinated with the bivalent vaccine compared with controls.6 Post-licensure studies based on pregnancy registries have not identified any concerns for either vaccine.6,49

Substantial data are available on post-licensure safety. By the end of 2013, more than 144 million doses of the quadrivalent vaccine (Kouter B, Merck, personal communication) and about 41 million doses of the bivalent vaccine had been distributed worldwide.6 Post-licensure monitoring includes both passive surveillance and active monitoring systems. Data from passive systems are available from several countries,6,48 but have limitations, including reporting of events occurring coincidentally after vaccination and incomplete reporting.50 The most widely reported adverse events following immunisation have been injection-site reactions, dizziness, and headache.6,48,51 For the quadrivalent vaccine, post-vaccination syncope is one of the most common adverse events following immunisation reported to the US Vaccine Adverse Events Reporting System.52 In the UK and the Netherlands, where the bivalent vaccine was introduced, presyncope and syncope were also among the most frequent adverse events following immunisation recorded.53 In these countries, syncope has been reported after administration of other vaccines to adolescents. Although various serious outcomes and deaths have been reported to these passive systems, none have been attributed to the vaccines. Further assessments of specific outcomes in epidemiological studies have not identified concerns.

Population-based studies have investigated specific adverse events and allow possible associations between vaccination and adverse events following immunisation to be assessed. In the USA, the Vaccine Safety Datalink assesses adverse events that might be associated with HPV vaccines compared with a control group.52 In an investigation of about 600 000 doses of quadrivalent HPV vaccine given to females, no significant risk of the prespecified endpoints (Guillain Barré syndrome, stroke, venous thromboembolism, appendicitis, seizures, syncope, allergic reactions, and anaphylaxis) was reported.6 Two studies, which were part of a manufacturer post-licensure commitment to the FDA, included a general safety assessment investigating outcomes in 189 000 female participants receiving at least one dose of the quadrivalent vaccine. One study53 noted same-day syncope and skin infections in the 2 weeks after vaccination that were associated with the vaccination. In the other study,52 rates of 16 autoimmune disorders in the vaccinated population were not increased compared with a matched population of non-vaccinated women and girls. A population-based cohort study54 in female participants in Denmark and Sweden analysed more than 696 000 doses of the quadrivalent vaccine. No consistent evidence supporting causal associations between exposure to the quadrivalent vaccine and disorders investigated was reported. In a case-control study in France investigating autoimmune disorders, no association was reported between receipt of the quadrivalent vaccine and idiopathic thrombocytopenic purpura, central demyelination or multiple sclerosis, Guillain Barré syndrome, connective tissue disorders (including systemic lupus erythematosus, rheumatoid arthritis, and juvenile arthritis), type 1 diabetes mellitus, and autoimmune thyroiditis.55

Various reviews of safety data have been done, including one by the US Institute of Medicine, which reviewed data for quadrivalent vaccine safety in 2011.56 WHO’s Global Advisory Committee on Vaccine Safety reviewed safety data for both the quadrivalent and bivalent HPV vaccines many times, most recently in March, 2014. These reviews continue to affirm the safety of HPV vaccines.57

**Status of vaccine introduction and policy**

After the first HPV vaccine was licensed in 2006, the first countries to introduce the HPV vaccine were the
USA, Australia, Canada, and some European countries. Cost prevented the introduction of the vaccines into middle-income and low-income countries. Further impediments to the introduction of HPV vaccines included the challenges of the target age group and competing health priorities. Starting in 2011, tiered pricing of vaccines and lower vaccine prices obtained through the Pan American Health Organisation’s Revolving Fund allowed vaccine introduction in some middle-income countries. Funding of the HPV vaccine by the GAVI Alliance starting in 2012 (with vaccine costs of less than US$5 per dose) and donation programmes resulted in HPV demonstration projects in some low-income countries (table 2). By September, 2014, more than 57 countries worldwide had introduced the HPV vaccine into their national immunisation programmes (figure 2).

Although all HPV vaccination programmes target young adolescent girls, specific target age groups and catch-up vaccination recommendations differ between countries. In 2009, WHO recommended targeting just one birth cohort between the ages of 9 and 13 years. Country-level vaccination policies have evolved owing to the availability of additional data from clinical trials and new regulatory approvals. Whereas both HPV vaccines were first licensed for girls and women, the quadrivalent vaccine was later licensed for boys and men in some countries. Two countries have included boys and young men in their national vaccination programmes, the USA in 2011, and Australia in 2013. Austria also recommends the HPV vaccine for boys and men, but does not provide national funding.

Some countries introduced two-dose or delayed three-dose schedules after data became available showing that two doses separated by 6 months elicited a non-inferior immune response in young adolescent girls compared with the licensed three-dose schedules at 0, 1–2, and 6 months in women. The delayed three-dose schedule (0, 6, and 60 months) allowed countries to assess the two-dose schedule and decide whether the third dose would be needed. In April, 2014, the WHO’s Strategic Advisory Group of Experts recommended a two-dose HPV vaccination schedule for adolescent girls if the vaccination series is initiated before age 15 years. A three-dose schedule is recommended for those initiating vaccination at 15 years or older and for immunocompromised individuals.

### Country-specific examples

#### High-income countries

Two countries that introduced vaccination shortly after the vaccines were first licensed and achieved high coverage were the UK and Australia. In the UK, the bivalent vaccine was introduced in a publicly funded, school-based immunisation programme in 2008, for girls aged 12–13 years. A catch-up programme for girls to age 17 years, both in and out of school, was offered for 2–3 years. Three-dose coverage for girls aged 12–13 years has exceeded 90% in Scotland and 80% in England. The catch-up programme in Scotland was mainly school-based, resulting in high coverage. The UK changed to the quadrivalent vaccine in their national programme in 2012 and to a two-dose schedule in 2014.

In Australia, a publicly funded programme started in 2007 using the quadrivalent vaccine. The programme included school-based vaccination of girls aged 12–13 years and a 2 year catch-up programme (2007–09) for those aged 13–17 years, which was delivered through schools. During that time, a 2 year catch-up programme was offered to women not in school and aged up to 26 years. The school-based vaccination programme in Australia resulted in greater than 70% three-dose coverage of girls in the targeted age groups. Of women in the catch-up age group aged 18–26 years, 55% received at least one dose and 32% three doses.

In the USA, HPV vaccination was introduced at the end of 2006 for girls and at the end of 2011 for boys. The target age group is 11–12 years for both sexes. Vaccination is through primary care providers and the vaccine is funded by the Federal Vaccines for Children Program or private medical insurance. Coverage with at least one dose of HPV vaccine in girls aged 13–17 years increased from 25% in 2007 to 57% in 2013; however, coverage with three doses in 2013 was only 38%. In 2013, coverage with at least one dose of HPV vaccine in boys aged 13–17 years was 35%, and with three doses was 14%.

In Canada, specific target age groups vary by province and territory. All offer the quadrivalent vaccine to girls through school-based programmes in at least one of grades 4–8 (about 9–13 years of age). A modified schedule was implemented in two provinces. In 2009, Quebec implemented a two-dose schedule, with the doses given 6 months apart for 9–10 year olds with an option to give the third dose 5 years later. In 2013, Quebec decided to convert to a two-dose schedule for girls vaccinated in grade 4 (about 9–10 years of age). British Columbia changed from a three-dose schedule at 0, 2, and 6 months to an extended three-dose schedule for girls in grade 6 (about 11–12 years of age) in 2010 and to a two-dose schedule in 2014 for the same age group.

#### Low-income and middle-income countries

Table 2: GAVI-funded national introductions of HPV vaccine and demonstration projects in some low-income countries, 2013 and 2014

<table>
<thead>
<tr>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>National introductions</td>
<td>Uganda and Uzbekistan to introduce in 2015, Rwanda to switch from manufacturer to GAVI support</td>
</tr>
<tr>
<td>Demonstration projects</td>
<td>Benin, Burundi, Cameroon, Côte d’Ivoire, Gambia, Liberia, Mali, Senegal, Solomon Islands, and Toogo</td>
</tr>
<tr>
<td>HPV=human papillomavirus.</td>
<td>Rwanda introduced the HPV vaccine into their national programme in 2012 through a manufacturer donation.</td>
</tr>
</tbody>
</table>

Table 2: GAVI-funded national introductions of HPV vaccine and demonstration projects in some low-income countries, 2013 and 2014
Middle-income and low-income countries

The first middle-income countries to introduce HPV vaccination into their national immunisation programmes were Panama and Mexico in 2008.59 By mid-2014, 18 countries in Central and South America offered the HPV vaccine through public immunisation programmes.59 Bhutan and Rwanda were the first low-income countries to introduce HPV vaccination nationwide. Rwanda obtained the vaccine through an industry donation in 2011.57 By use of a school-based programme, three-dose coverage of 93% was achieved in girls in grade 6 (about 12–13 years of age, but often of a wider age range). Although the GAVI Alliance prioritised the HPV vaccine in 2009, it was not until 2012 that both HPV vaccines were first made available to GAVI-eligible countries.58 Countries can apply for HPV vaccines through two pathways: national introduction if the country has the ability to deliver a complete three-dose series to at least 50% of the target vaccination cohort; or, if countries do not meet this requirement, they can apply for HPV vaccine demonstration projects. In 2013, 11 countries received funding for demonstration projects and ten additional countries in 2014 (table 2). Although few countries have been awarded funds for national introduction of an HPV vaccine, the demonstration projects will provide an opportunity for countries to gain experience with HPV vaccine delivery and make plans for national introduction. Most countries are choosing to implement HPV vaccination through school-based programmes; however, the issue of reaching girls who do not attend school needs to be addressed.78

Vaccine impact and effectiveness

Within a few years of vaccination introduction, data from various countries showed positive outcomes of HPV vaccination on HPV-associated disease and infection.79 Early and intermediate HPV-associated outcomes being monitored include HPV prevalence,67,68,80–82 genital warts,83–91 and cervical lesions (table 3).92,93–95,97,98,102

The earliest indication of the effect of the quadrivalent vaccine was from post-licensure monitoring studies in Australia. An ecological investigation in a sexual health clinic in Melbourne reported a sharp reduction in new genital warts in young women within 2 years after vaccine introduction.95 Subsequent studies at additional clinics reported decreases in genital warts in women targeted for vaccination, and in men.96 Within 5 years of vaccine introduction, the proportion of women younger than 21 years and 21–30 years of age diagnosed with genital warts was reduced by 93% and 73%, respectively.95 A reduction was recorded for heterosexual men (82% in men younger than 21 years and 51% in men aged 21–30 years), but not in men who have sex with men, suggesting a possible effect of herd immunity. Furthermore, a fall in vaccine-type HPV prevalence from 28–7% to 6-7% was reported in women aged 18–24 years seen at family planning clinics,103 and a reduction was seen in high-grade lesions in girls younger than 18 years.103

In Denmark, a cohort study based on national registry data reported a significant fall in the incidence of genital warts compared with the pre-vaccine era, with the largest reduction in the younger birth cohorts analysed.104 Of girls aged 16–17 years a yearly average reduction of 45% was seen between 2008 and 2011. Reductions in cervical lesions were reported too.105

In both England and Scotland, where high coverage was achieved with the bivalent vaccine, a fall in HPV 16 and 18 prevalence was reported. In England, vaginal swabs submitted from women screened for chlamydia at sexual health services,106 showed a decrease in HPV 16 and 18 prevalence from 19-1% to 6-5% in the vaccine-eligible young women aged 16–18 years. No reduction was reported in women aged 22–24 years, an age group not targeted for vaccination. In Scotland, a fall in HPV 16 and 18 prevalence was reported from 28-8% to 16-7% in women aged 20–21 years attending cervical cancer screening between 2009 and 2012.107 Furthermore, the data suggested some cross-protection against HPV types 31, 33, and 45.

In the USA, analysis of data from the National Health and Nutrition Examination Survey, a nationally representative survey, showed a 56% reduction in population prevalence of vaccine-type HPV in self-collected cervicovaginal samples from girls aged 14–19 years in the 4 years after vaccine introduction.108 This fall is despite substantially lower vaccine coverage than in other countries where declines have been reported. An analysis of private health insurance claims data in the USA showed a significant 38% reduction in genital warts claims by women aged 15–19 years between 2006 and 2010, and a smaller reduction in women aged 20–24 years between 2009 and 2010. There were no reductions in genital warts claims by women aged 25–39 years.109

In addition to studies of population effect, vaccine effectiveness has been investigated.110,111,112,113,114 The vaccine was reported to be most effective in individuals vaccinated at a younger age, which is to be expected. For example, Leval and colleagues115 reported vaccine effectiveness...
<table>
<thead>
<tr>
<th>Vaccine type, country of study, and study outcome are listed in first column. Studies with vaccine history available also provide data for estimated vaccine effectiveness. HPV=human papillomavirus. CIN=cervical intraepithelial neoplasia. *Several studies have assessed genital warts in Australia and not all are included in the table.</th>
<th>Vaccination history</th>
<th>Population, data source, or specimen</th>
<th>Selected findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bivalent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine-type prevalence, England</td>
<td>No</td>
<td>Young women aged 16–24 years undergoing chlamydia screening in sexual health centres (vulva or vaginal swabs)</td>
<td>HPV 16 and 18 prevalence decreased from 19·1% in 2008 to 6·5% in 2010–12 in young women aged 16–18 years</td>
</tr>
<tr>
<td>Vaccine-type prevalence, Scotland</td>
<td>Yes</td>
<td>Women aged 20–21 years attending cervical cancer screening programmes (liquid-based cytology) linked to vaccination records</td>
<td>HPV 16 and 18 prevalence decreased from 28·8% in 2009 to 16·7% in 2012 in women aged 20–23 years; vaccine effectiveness assessed</td>
</tr>
<tr>
<td>Cervical lesions, Scotland</td>
<td>Yes</td>
<td>Women aged 20–21 years attending cervical cancer screening programmes linked to vaccination records</td>
<td>Decrease in incidence of CIN lesions in vaccinated cohorts; vaccine effectiveness assessed</td>
</tr>
<tr>
<td><strong>Quadrivalent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine-type prevalence*</td>
<td>Yes</td>
<td>Women aged 18–24 years attending cervical cancer screening programmes in family planning clinics (liquid-based cytology)</td>
<td>HPV 6, 11, 16, and 18 prevalence decreased from 28·7% in 2005–07 to 6·5% in 2010–12 in women aged 18–24 years; vaccine effectiveness assessed</td>
</tr>
<tr>
<td>Genital warts*</td>
<td>No</td>
<td>Women and men assessed in a sentinel network of sexual health clinics</td>
<td>Proportion of women and girls aged &lt;21 years diagnosed with new genital warts decreased from 11·5% in 2007 to 0·85% in 2011; proportion of heterosexual men and boys diagnosed with new genital warts aged &lt;21 years decreased from 12·1% in 2007 to 2·2% in 2011</td>
</tr>
<tr>
<td>Cervical lesions*</td>
<td>No</td>
<td>Women attending cervical cancer screening from the Victorian Cervical Cytology Registry</td>
<td>Incident of high-grade cervical lesions decreased by 38% in girls aged &lt;18 years from 2003–07 to 2007–09</td>
</tr>
<tr>
<td>Cervical lesions*</td>
<td>Yes</td>
<td>Cohort using linked screening and vaccination registry data</td>
<td>Vaccine effectiveness assessed</td>
</tr>
<tr>
<td>Cervical lesions*</td>
<td>Yes</td>
<td>Case-control study using linked administrative health datasets</td>
<td>Vaccine effectiveness assessed</td>
</tr>
<tr>
<td>Denmark</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital warts36</td>
<td>No</td>
<td>Danish National Patient Register</td>
<td>Genital warts decreased from 381 per 100 000 person-years in 2008 to 39·8 per 100 000 person-years in 2011 in girls aged 16–17 years</td>
</tr>
<tr>
<td>Cervical lesions37</td>
<td>No</td>
<td>Nationwide Pathology Data Bank</td>
<td>CIN 2/3 decreased by 15% annually in women aged 18–20 years during 2010–13</td>
</tr>
<tr>
<td>Cervical lesions38</td>
<td>Yes</td>
<td>National health and pathology registries</td>
<td>CIN 2/3 and CIN 3 decreased in vaccinated cohorts; vaccine effectiveness assessed</td>
</tr>
<tr>
<td>Sweden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital warts39</td>
<td>No</td>
<td>People aged 10–44 years living in Sweden during 2006–10 from national registries</td>
<td>Genital warts decreased by &gt;25% between 2006 and 2010 in girls aged 17–18 years</td>
</tr>
<tr>
<td>Genital warts40</td>
<td>Yes</td>
<td>Open cohort using national registries</td>
<td>Vaccine effectiveness assessed</td>
</tr>
<tr>
<td>Genital warts41</td>
<td>Yes</td>
<td>Open cohort using national registries</td>
<td>Vaccine effectiveness assessed</td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccine-type prevalence42</td>
<td>Self-report</td>
<td>Women and girls aged 14–59 years from the National Health and Nutrition Examination Survey (self-collected vaginal swabs)</td>
<td>HPV 6, 11, 16, and 18 prevalence decreased from 11·5% in 2003–06 to 5·1% in 2007–10 in girls aged 14–19 years</td>
</tr>
<tr>
<td>Vaccine-type prevalence43</td>
<td>Yes</td>
<td>Young women aged 13–26 years in clinic settings</td>
<td>HPV 6, 11, 16, and 18 prevalence decreased from 31·8% in the pre-vaccine era to 9·9% in vaccinated women and girls and 15·4% in unvaccinated women and girls in 2009–10</td>
</tr>
<tr>
<td>Genital warts44</td>
<td>No</td>
<td>People aged 10–39 years from commercial health insurance claims data</td>
<td>Genital warts decreased from 2·9 per 100 000 person-years in the pre-vaccine era to 1·8 per 100 000 person-years in 2010 in girls aged 15–19 years</td>
</tr>
<tr>
<td>Genital warts45</td>
<td>No</td>
<td>People aged from &lt;21 years to &gt;30 years in four age groups from claims data</td>
<td>Genital warts decreased from 0·9% in 2007 to 0·6% in 2010 in women and girls aged &lt;21 years</td>
</tr>
<tr>
<td>Cervical lesions46</td>
<td>Yes</td>
<td>Women aged 18–31 years with high-grade cervical lesions diagnosed in sentinel sites</td>
<td>Vaccine effectiveness assessed for HPV 16 and 18-related lesions</td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital warts47</td>
<td>No</td>
<td>People aged 10–79 years from a health insurance database</td>
<td>Genital warts decreased from 316 per 100 000 person-years in 2007 to 242 per 100 000 person-years in 2008 in girls aged 15–19 years</td>
</tr>
<tr>
<td>New Zealand</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genital warts48</td>
<td>No</td>
<td>People seen at a sexual health clinic</td>
<td>Proportion of girls aged &lt;20 years diagnosed with genital warts decreased from 13·7% in 2007 to 5·1% in 2010</td>
</tr>
</tbody>
</table>

Table 3: Post-licensure studies of HPV vaccine population effect and effectiveness by country
against genital warts of 93% in female individuals in Sweden vaccinated before age 14 years compared with only 48% in those vaccinated at age 18–22 years. Some effectiveness studies have shown protection against non-vaccine targeted but related HPV types.10,11

Conclusion

Highly immunogenic, safe, and effective vaccines are now available to control HPV-related diseases with proven efficacy against disease at many anatomical sites where they have been investigated, including the cervix, vulva, vagina, anus, and penis. Although data are not available on effectiveness for prevention of oropharyngeal disease, data from trials show vaccine efficacy for prevention of oral HPV infection.12 Many countries around the world have implemented national HPV vaccination programmes. Although some countries have achieved high coverage, particularly those with school-based vaccination programmes, vaccine uptake has been low in other countries. Studies are already reporting a significant effect on early disease endpoints, and evidence of herd immunity in men and boys in female-only vaccination programmes has also been shown. Achieving links between vaccine administration and cervical screening and cancer registries would facilitate intermediate-term and long-term outcome monitoring.

Expansion of vaccination programmes to countries where the burden of disease is highest is beginning, but further efforts are needed in these areas to realise the full potential of HPV vaccination. Vaccination policies have evolved since the first HPV vaccine was licensed in 2006; continued assessment of vaccination programmes, data from trials, and post-licensure monitoring will provide additional information for optimum use of these highly effective vaccines.

Contributors

RH contributed to the scientific literature search, data interpretation, and writing and revising of the article. PG and LEM contributed to the scientific literature search, writing and revising of the article, and figure preparation. All authors have approved the final submitted version.

Declaration of interests

We declare no competing interests.

Acknowledgments

The findings and conclusions in this Series paper are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References


