
9 Human papillomavirus (HPV)

Key information

Mode of transmission	Skin-to-skin contact, predominantly sexual, with a person with HPV infection.
Links to cancer	HPV is linked to almost all cervical cancers and to about 69% of vulvar, 75% of vaginal, 63% of penile, 90% of anal and 70% of oropharyngeal cancers.
Incidence/prevalence	HPV infection is very common, with initial infection occurring soon after sexual debut and a lifetime risk of over 80%. Recurrent infection and co-infection with multiple types are possible.
Funded vaccine	HPV9 (Gardasil 9) is a recombinant subunit vaccine containing virus-like particles (VLPs). HPV9 contains HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.
Dose, presentation, route	0.5 mL per dose. Pre-filled syringe. Intramuscular injection.
Funded indications and recommended schedules	2 doses, at 0 and 6–12 months for children aged 14 years and under. 3 doses, at 0, 2 and 6 months, for individuals: <ul style="list-style-type: none">aged 15–26 years inclusiveaged 9–26 years inclusive:<ul style="list-style-type: none">with confirmed HIV infection ORwho are transplant (including stem cell) patients. An additional dose for individuals aged 9–26 years post-chemotherapy. NB: Individuals who were previously fully vaccinated with HPV4 are not eligible for HPV9.
Vaccine efficacy/effectiveness	The incidence of HPV infection, precancerous lesions and genital warts is significantly reduced in immunised populations (in women and men). There is evidence for herd immunity (reductions in HPV infection and genital warts in unimmunised populations).

Continued overleaf

Pregnancy	HPV vaccines are not recommended for pregnant women; however, enquiring about the possibility of pregnancy is not necessary before vaccination.
Adverse events to vaccine	Syncope (fainting) is a known injection reaction in adolescents.
Cancer prevention measures	HPV immunisation. Regular cervical screening for women. Safer sex approaches.

9.1 Virology and the causal link to cancer

Human papillomaviruses (HPVs) are small, non-enveloped DNA viruses from the Papillomavirus family. There are about 150 different HPV serotypes. They vary in their preference for infecting squamous epithelium at different sites, thereby causing the various types of HPV infection (eg, common, palmar, plantar or anogenital). More than 40 HPV types can infect the anogenital tract.^{1, 2}

Data from the US cancer registry³ indicates that HPV is causally associated with almost all cervical cancers, about 69 percent of vulvar, 75 percent of vaginal, 63 percent of penile, 90 percent of anal and 70 percent of oropharyngeal cancers (see Table 9.1).

On the basis of their causal link to cancer, HPVs are divided into low-risk and high-risk types. There are approximately 12 high-risk types, which include 16, 18, 31, 33, 45, 52 and 58. Types 16 and 18 are most frequently associated with cervical cancer but are also causally associated with other cancers. In the US, HPV types 16 and 18 are estimated to cause 66 percent of invasive cervical cancers, 80 percent of anal, 49 percent of vulvar, 55 percent of vaginal, 48 percent of penile and 60 percent of oropharyngeal cancers annually³ (Table 9.1).

Low-risk types are predominantly associated with non-malignant lesions, such as genital warts (especially types 6 and 11), and can also cause recurrent respiratory papillomatosis.

Table 9.1: Average annual percentage of cancer cases attributable to HPV, by anatomic site and sex, United States, 2008–2010

Anatomic site ^c	Cancers attributable to any HPV ^{a,b}	Cancers attributable to HPV 16, 18 ^{a,b}	Cancers attributable to HPV 31, 33, 45, 52, 58 ^{a,b}
	%	%	%
Cervix	90.6 ^d	66.2	14.7
Vulva	68.8	48.6	14.2
Vagina	75.0	55.1	18.3
Penis	63.3	47.9	9.0
Anus			
• women	92.5	79.5	10.8
• men	88.7	79.1	3.8
Oropharyngeal			
• women	63.3	50.8	9.5
• men	72.4	63.4	4.4

a Data is from 2008–2010 diagnosis years from population-based cancer registries that participate in the National Program of Cancer Registries and/or the Surveillance, Epidemiology, and End Results Program.

b These estimates do not take into account future changes in incidence, population structure, or the percentage of cancers that are HPV positive.

c International Classification of Diseases (ICD) codes: Cervix C53; Vulva C51; Vagina C52; Penis C60; Anus C21; Oropharyngeal (includes cancers of the soft palate, walls of pharynx, tonsils and base of tongue) C01.9, C02.4, C02.8, C05.1, C05.2, C05.9, C09.0, C09.1, C09.8, C09.9, C10.0, C10.2, C10.8, C10.9, C14.0, C14.2, and C14.8.

d Although HPV is accepted to be a necessary factor in the causal pathway to invasive cervical cancer, HPV is not always detected in tumour specimens from women who receive a diagnosis of invasive cervical cancer due to a variety of reasons, including misclassification of tissue specimens as cervix, quality of tissue specimens, assay sensitivity, and a small proportion of HPV-negative, cervical cancers.

Adapted from: Saraiya M, Unger ER, Thompson TD, et al. 2015. US Assessment of HPV types in cancers: Implications for current and 9-valent HPV vaccines. *Journal of the National Cancer Institute* 107(6), Table 4. DOI: 10.1093/jnci/djv086 (accessed 14 September 2016).

9.2 Clinical features

9.2.1 Infection

Infection results from skin-to-skin contact, predominantly sexual, with a person with HPV infection. Transmission in the genital region may occur even when condoms are used and does not necessarily require penetrative intercourse. HPV may also be transmitted perinatally, from mother to newborn baby.

Clinically apparent warts are probably more infectious than subclinical infection. The virus penetrates micro-abrasions in the epithelium to reach the basal epithelial cells, where it causes the infected cells to produce proteins that delay cellular maturation. Continued replication of these infected cells in the intermediate epithelial layer, followed by virus replication in the superficial epithelial layer, results in the cellular overgrowth typical of warts.

For most people, HPV infection is transient and becomes undetectable by DNA testing within 6 to 12 months, but in some cases, HPV infection remains latent and may reactivate years later. As it is difficult to detect HPV in its latent stage, it is impossible to know whether in some cases the immune system can completely clear the virus or whether the virus remains latent at undetectable levels, capable of re-emerging later on.

Acquisition of HPV

Infection with oncogenic serotypes of HPV is common, with an estimated 70–80 percent of sexually active individuals becoming infected at some stage during their life. Initial infection occurs soon after sexual debut.

Most episodes of infection become undetectable by DNA testing within two years of acquisition; the average duration of infection is one year. Previous infection does not necessarily create long-term immune memory so does not prevent future re-infection with the same HPV type.

At any one time, approximately 10 percent of women have at least one HPV infection. The HPV serotypes that cause more prolonged infection tend to be those that more frequently result in the development of histological abnormalities.^{4, 5}

The rate of acquisition of HPV is similar in men and women; however, there are differences between the sexes in the immune response to HPV. A smaller proportion of men are HPV-seropositive, and men have lower antibody titres than women.⁶ In contrast to women, for whom the risk for HPV acquisition increases with age through the early 20s and then decreases, studies have demonstrated HPV prevalence in men seems to peak at slightly older ages and remains constant or decreases slightly with increasing age, suggesting persistent HPV infection or a higher rate of re-infection.^{7, 8}

Men who have sex with men, especially those that are HIV-positive, are at higher risk for HPV infection, anal cancer and high-grade anal intraepithelial neoplasia.⁹ In teenage men who have sex with men (aged 16–20 years), early and high per-partner HPV transmission occurred between men soon after their first sexual experiences.¹⁰

Individuals who are immunocompromised (due to medical conditions or treatment) are more likely to develop a persistent HPV infection and to subsequently progress to HPV-related disease.^{11, 12} Those with confirmed HIV infection are more at risk of HPV infection.¹³ HIV-infected individuals who are co-infected with HPV are less likely to become undetectable.^{14, 15} A direct relationship has been identified between low CD4+ cell count and an increased risk of cervical cancer in HIV-infected women.¹⁶

9.2.2 Cervical cancer

HPV rapidly becomes undetectable in the first 6–12 months of acquisition of infection, with 80–90 percent undetectable by two years. Following this, there is a very small fraction of persistent infection that progresses to cervical intraepithelial neoplasia (CIN); these are non-invasive precancerous lesions, which are categorised as either low or high grade CIN. Invasive cervical cancer occurs when the lesions invade the cervical tissue, and is graded from stage I to IV, depending on how far the cancer has spread beyond the cervix into surrounding tissue or organs.

Cervical cancer does not usually develop until decades after acquisition of infection with an oncogenic (cancer-causing) HPV serotype. Persistent HPV infection is detected in almost all women with cervical cancer.

HPV infection, while essential for the development of cervical cancer, is not, by itself, sufficient. Other factors have been described that may be associated with HPV persistence and high-grade lesions including smoking, early onset sexual activity, older age, contraceptive use, multiple sexual partners and genetic factors.^{17, 18}

9.2.3 Other cancers

The clinical features of other HPV-associated cancers and their precancerous lesions in the anogenital and oropharyngeal regions vary, and also depend on the anatomical site.¹⁹ The progression from HPV-associated precancer lesions to cancers in these sites is less well understood than the process in the cervix.

Oropharyngeal cancers

Oropharyngeal cancers include cancers of the soft palate, walls of the pharynx, the tonsils and the base of the tongue. The risk factors for oropharyngeal cancer are similar to those for cervical cancer, including the number of sexual partners, younger age at first sexual intercourse, practice of oral sex, history of genital warts and younger age.²⁰

9.2.4 Genital warts

HPV6 and 11 account for around 90 percent of all genital warts cases. The majority of warts cases are self-limited, although some may persist for several years. Persistence is more common in patients with impaired cell-mediated immunity.¹

9.2.5 Respiratory papillomatosis

Perinatal transmission of HPV virus (usually HPV types 6 or 11) can cause laryngeal infection in infants, which in rare cases can result in recurrent respiratory papillomatosis in children. Respiratory papillomatosis is characterised by multiple warty growths on the mucosal surface of the respiratory tract, which can significantly obstruct the airways.¹⁹

9.3 Epidemiology

9.3.1 Global burden of disease

HPV is an important international carcinogenic infection. The 12 high-risk types are reported to be the second most common infectious cause of cancer worldwide after *Helicobacter pylori*.²¹

Onset of sexual activity

Most HPV infections occur within the first two years of onset of sexual activity, with more than 40 percent becoming infected during this period. The first sexual relationship carries a substantial risk.²²

Cervical cancer

Persistent HPV infection can lead to high-grade CIN. A 2010 study reported more than a quarter (26.7 percent; 95% CI: 21.1–31.8) of those with persistent HPV16 and nearly one in five (19.1 percent; 95% CI: 10.4–27.3) of those with persistent HPV18 develop CIN3 or cancer within 12 years.²³ Approximately one-third of CIN3 progresses to invasive cervical cancer within 10 to 20 years.

Cervical cancer is the fourth cause of female cancer in the world. In higher-income countries, it is the second most common cause of female cancer in women aged 15–44 years;²⁴ with an incidence of approximately 10–15 per 100,000 women aged 20–70 years and an annual mortality of approximately 5–8 per 100,000.

Other HPV-related cancers

HPV types 16, 18, 31, 33, 45, 52 and 58 are linked to other cancers in women and men, including vulval, vaginal, penile, anal and oropharyngeal cancers (see Table 9.1).

Anal cancers

Anal cancer remains relatively rare compared to other cancers but the global incidence has increased among both men and women, particularly in high-income regions (the average worldwide incidence is 1 per 100,000 population).²⁴ Women have a higher incidence of anal

cancer than men. The incidence is highest among men who have sex with men, women with history of cervical or vulvar cancer, and immunosuppressed populations, including those who are HIV-infected and patients with a history of organ transplantation.²⁴

Oropharyngeal cancers

There has been an increase in the incidence of head and neck cancers over the past few decades. This increase is mainly due to an unexpected increase in HPV-related oropharyngeal cancers, primarily in males aged 40 to 55 years with exposure to alcohol and tobacco.²⁵

There is wide variability in the reported proportions of oropharyngeal cancers associated with HPV, ranging from 12 to 63 percent, and a lower proportion of oral cancers.¹⁹ Of the oropharyngeal cancers that are HPV-positive, most are associated with HPV types 16 and/or 18 (see Table 9.1).

Genital warts

Genital warts, which are most commonly due to infection with HPV6 or HPV11, have a prevalence of approximately 1 percent of adults in the US.^{26, 27} In Scandinavian countries the reported rates are as high as 10 percent.²⁸

9.3.2 New Zealand epidemiology

Onset of sexual activity

Data from the Youth'12 survey^{29, 30} suggests that approximately 8 percent of New Zealand adolescents may have had sexual intercourse before the age of 13 years. This increases to 24 percent by the age of 15 years and 46 percent by age 17 years.

Compared to 2001, students were more likely to delay sexual debut in 2012 but less likely to use condoms and contraception consistently.³¹ Māori (OR 0.7; 95% CIs: 0.6–0.8) and Pacific (OR 0.5; 95% CIs: 0.4–0.7) students used condoms less frequently than NZ European students; those from socioeconomically deprived communities (school decile 1) used condoms less frequently (OR 0.7; 95% CIs: 0.5–0.9) than students from wealthier communities (decile 10).³¹

Cervical cancer

HPV prevalence in precancerous lesions and invasive cervical cancer

The prevalence of HPV infection and distribution of HPV types among New Zealand women with histologically confirmed CIN 2/3^{32, 33} or invasive cervical cancer³⁴ is broadly consistent with that seen internationally. In women with histologically confirmed CIN 2/3, 97 percent (95% CI: 94–98) were HPV-positive and the prevalence of any high-risk HPV was 96 percent (95% CI: 91–99).³² In women with histologically confirmed invasive cervical cancer, 88.5 percent (95% CI: 83.7–92.4) were HPV-positive, and the prevalence of any high-risk HPV was 87.2 percent (95% CI: 82.2–91.3).³⁴ For both CIN 2/3 and invasive cervical cancer, the overall distribution of HPV types was similar in Māori and non-Māori women, with HPV16 being the most commonly detected HPV type in both groups.^{32, 34}

Cervical cancer registrations and deaths

In 2015 there were 138 new cervical cancer registrations, down from 143 in 2014 (provisional data).³⁵ The age-standardised registration rate was 5.3 per 100,000 population, similar to the 2014 rate (5.5 per 100,000). The registration rate for Māori women was 9.7 per 100,000, 2.1 times greater than for non-Māori women (4.7 per 100,000).

The most recent cervical cancer mortality data is from 2014, when there were 46 deaths (1.4 deaths per 100,000 population).³⁶ The mortality rate for Māori women was 3.0 per 100,000, 2.7 times greater than for non-Māori women (1.1 per 100,000).

Other HPV-related cancers

The most recent New Zealand data available for other HPV-related cancers is from 2014 (see Table 9.2). Note that this data is for new cancer registrations only; the tumours have not been analysed for the presence of HPV.

Table 9.2: Number and age-standardised rate of new registrations for other HPV-related cancers in New Zealand, 2014

Anatomic site*	Number of new registrations	Rate of new registrations (per 100,000)
Vulva	70	2.0
Vagina	20	0.5
Penis	16	0.5
Anus		
• women	54	1.5
• men	32	1.1
Oropharynx		
• women	4	0.1
• men	16	0.6
Tonsils		
• women	13	0.4
• men	57	1.9

* ICD codes: Vulva C51; Vagina C52; Penis C60; Anus C21; Oropharynx C10; Tonsils C09. (Note that in Table 9.1, the US definition for oropharyngeal cancer combines multiple cancers into the definition, using 4-character ICD codes. At the time of writing, New Zealand data for 2014 was only available at the 3-character ICD code level.)

Source: Ministry of Health. 2016. *New cancer registrations 2014*. URL: <http://www.health.govt.nz/publication/new-cancer-registrations-2014> (accessed 8 February 2017).

Anal cancers

For the period 2003–2007, the age-standardised rate for anal cancer was 0.5 and 1.1 per 100,000 persons per year among men and women in New Zealand, respectively.²⁴ In 2015 the rate increased to 1.1 per 100,000 for men and 1.5 for women (see Table 9.2).

Oropharyngeal cancers

A retrospective review of New Zealand cancer registry data for the period 1981–2010 showed a rapid rise in oropharyngeal cancers in men (mainly in those aged 40 years or older), particularly from 2005 onwards.³⁷ The rate of oropharyngeal cancers was almost four times greater in men (1.87 per 100,000) than in women (0.47 per 100,000). The incidence rates for oral cavity cancer, which is generally associated with alcohol and tobacco consumption, remained relatively stable in

both sexes during that time period. (Note that in this study, oropharyngeal cancers included cancers coded as: C01.9, C02.4, C09.0–C09.9, C14.2 and C10.0–C10.9; oral cavity cancers included: C02.0–C02.3, C02.8, C02.9, C03.0–C03.9, C06.0–C06.2, C04.0–C04.9, C05.0–C05.9, C06.8, C06.9 and C00.3–C00.5).

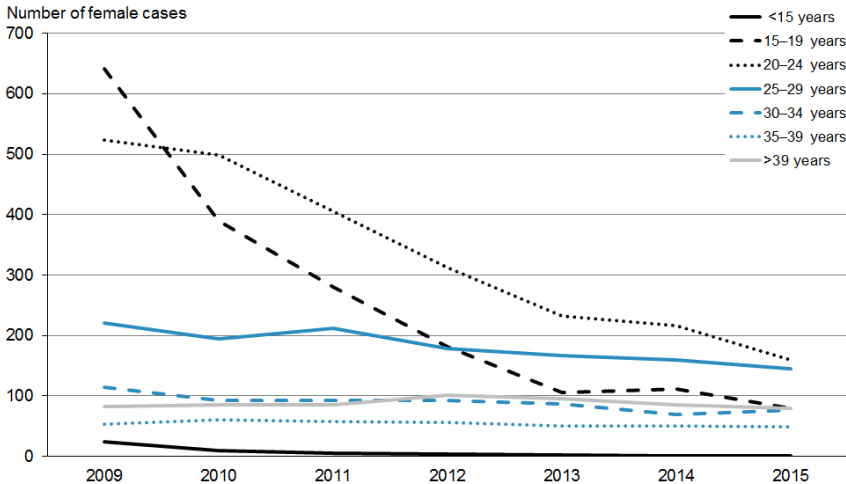
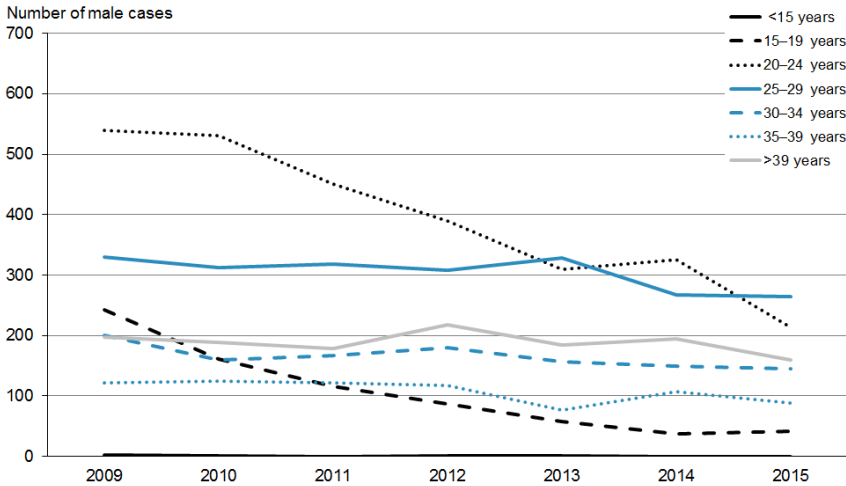
Genital warts

Sexually transmitted infections (STIs) are not notifiable in New Zealand. ESR cautions that the number of cases of STIs reported through the clinic-based surveillance system likely underestimates the true burden of disease in New Zealand because a substantial percentage of STIs are diagnosed by other health care providers.

From 2009³⁸ to 2015³⁹ genital warts clinical case counts reported by sexual health clinics decreased by 54.3 percent (from 3,290 to 1,504 cases) and case counts reported by family planning clinics decreased by 65.6 percent (from 546 to 188 cases). In sexual health clinics there was a decrease in diagnoses in all ethnic groups, except 'Other' ethnicity. In family planning clinics, the number of diagnoses decreased in every ethnic group.

In sexual health clinics, the decrease was most notable in the 15–19 years and 20–24 years age groups, and a moderate decrease in the 25–29 years age group, in both sexes (Figure 9.1). The decrease seen in older age groups, and in males, suggests that immunisation is also providing some herd immunity to unvaccinated individuals. A decline in the number of prescriptions for treating genital warts (imiquimod and podophyllum resin-based products) supports this evidence for a herd immunity effect.⁴⁰ The largest decline was seen in women aged under 20 years.

Figure 9.1: Number of genital warts (first presentation) in sexual health clinics, by sex and age group, 2009–2015



Source: ESR

9.4 Vaccines

9.4.1 Available vaccines

Two HPV vaccines are approved for use (registered) and are available for distribution (marketed) in New Zealand: HPV9 (Gardasil 9, Seqirus/MSD) and HPV4 (Gardasil, Seqirus/MSD).

Both vaccines are registered for use in females aged 9–45 years and in males aged 9–26 years. HPV9 is registered as a two- or three-dose schedule in individuals aged 14 years and under, and as a three-dose schedule in older individuals. HPV4 is registered as a three-dose schedule for all age groups, but may be used as a two-dose schedule for those aged 9–14 years.

Both vaccines contain HPV virus-like particles (VLPs), which are composed of the L1 protein (a component of the virus outer layer) aggregated into clumps that mimic the outer structure of the HPV virion. The VLPs do not contain viral DNA and are incapable of causing infection. The L1 proteins are produced by genetically engineered yeast cells.

Funded HPV vaccine

Each 0.5 mL dose of HPV9 vaccine (Gardasil 9, Seqirus/MSD) contains:

- 30 µg of HPV6 L1 VLP, 40 µg of HPV11 L1 VLP, 60 µg of HPV16 L1 VLP, 40 µg of HPV18 L1 VLP, 20 µg of HPV31 L1 VLP, 20 µg of HPV33 L1 VLP, 20 µg of HPV45 L1 VLP, 20 µg of HPV52 L1 VLP, and 20 µg of HPV58 L1 VLP
- 500 µg of aluminium hydroxyphosphate sulphate.

The vaccine does not contain any preservative or antibiotics.

Other vaccine

HPV4 was the vaccine used prior to the 1 January 2017 introduction of HPV9 (see also section A1.3.4 in Appendix 1 for the history of HPV vaccines in New Zealand).

Each 0.5 mL dose of HPV4 vaccine contains:

- 40 µg of HPV16 L1 VLP, 20 µg of HPV18 L1 VLP, 20 µg of HPV6 L1 VLP and 40 µg of HPV11 L1 VLP
- 225 µg of aluminium hydroxyphosphate sulphate.

The vaccine does not contain any preservative or antibiotics.

9.4.2 Efficacy and effectiveness

The efficacy of HPV vaccines can only be studied in older age groups due to the sexual naivety of the younger age group; protection against persistent HPV infection and related disease is the main target for vaccination. Immunological bridging is therefore used to infer efficacy in the younger age group; that is, by comparing the antibody responses (immunogenicity) between the younger and older age groups. Because the antibody responses are non-inferior to those seen in older age groups, efficacy is inferred for the younger age group.

Immunogenicity

Although there is no known correlate of protection (that is, the antibody level required for protection against HPV-related disease), HPV vaccines generate excellent antibody responses in most recipients.

HPV4

Immunisation with three doses of HPV4 vaccine produces antibody responses against HPV16, HPV18, HPV6 and HPV11 in more than 99 percent of vaccine recipients. The height of the antibody titres following three doses of HPV vaccine is greater than that following natural infection.

Differences in seroconversion rates and antibody titres were seen in immunocompromised individuals. The immune response to HPV4 among immunocompromised children appears adequate,^{41, 42} although antibody titres were lower than those in healthy children of the same age groups.⁴¹ Seroconversion among HIV-infected individuals has been demonstrated to be robust and higher among those with lower HIV loads or on antiretroviral therapy.^{43, 44, 45}

While some immunosuppression regimes can attenuate the immune response to HPV4, patients with autoimmune diseases generally appear to respond well to the vaccine.⁴⁶ In contrast, adult solid organ transplant recipients produce suboptimal responses to HPV4.⁴⁷

The immunogenicity of three doses of HPV4 vaccine has been established to be robust and long-lasting.^{48, 49, 50} Anamnestic responses have been demonstrated out to 8.5 years.

Two doses of HPV4 are more immunogenic in recipients aged between 9 and 15 years than in older age groups and comparable to three doses in older recipients.⁵¹ In young females, two doses have been found to be non-inferior to three doses, particularly when the interval between doses is at least six months.⁵²

HPV9

The immunogenicity of HPV9 was initially assessed in women aged 16–26 years.⁵³ Antibody responses generated by the HPV9 vaccine to HPV types 6, 11, 16 and 18 were non-inferior to those generated by the HPV4 vaccine. HPV9 has also demonstrated non-inferiority to HPV4 in girls and boys aged 9–15 years.⁵⁴

Antibody responses to all nine vaccine HPV types in girls and boys aged 9–15 years and men aged 16–26 years were non-inferior to women aged 16–26 years.^{55, 56}

Men who have sex with men appear to produce lower antibody titres than heterosexual men (although seroconversion rates to all nine vaccine types were greater than 99 percent in both groups).⁵⁵ This lower antibody response is possibly due to greater exposure to the virus, highlighting the importance of vaccination at a young age.

The immunogenicity of two doses of HPV9 in girls and boys aged 9–14 years was compared with three doses in women aged 16–26 years,⁵⁷ the age group in which efficacy was demonstrated. Antibody responses in girls and boys after two HPV9 doses were non-inferior to the antibody responses in women who received three doses.

Efficacy

HPV-related cancers

No studies have yet been undertaken to look for protection against invasive cervical cancer because these would require extremely long periods of follow-up and because study participants who develop precancerous lesions (CIN 2/3 or adenocarcinoma *in situ*) require treatment to prevent progression to invasive cancer. However, protection against CIN 2/3 or adenocarcinoma *in situ* is widely accepted as a surrogate for protection against invasive cancer. Bivalent and quadrivalent HPV vaccines have been shown to be highly effective in preventing these HPV16- and HPV18-related precancerous lesions in females.^{2, 58} In the pivotal efficacy trial in women aged 15–26 years,⁵⁹ HPV4 vaccine efficacy for the prevention of precancerous lesions related to HPV16 or HPV18 was 98 percent (95% CI: 26–58) in the per-protocol susceptible population.

Studies in males, including men who have sex with men, have shown that HPV4 vaccine is efficacious against anal HPV infection and associated precancerous lesions.^{6, 60, 61}

HPV9 efficacy was studied in women aged 16–26 years and compared with HPV4.⁵³ HPV9 prevented cervical, vulvar and vaginal disease and persistent infection related to HPV types 31, 33, 45, 52 and 58 (the five additional serotypes in HPV9). The antibody response and incidence of disease related to HPV types 6, 11, 16 and 18 were similar in the two vaccine groups.

Effectiveness

A 2016 systematic review of published literature⁶² summarised the global experiences with HPV4 from 1 January 2007 to 29 February 2016. It assessed the global effect of HPV4 vaccine on HPV infection, genital warts and cervical abnormalities based on 57 publications across nine countries. The greatest impact was seen in countries with high vaccine uptake and among girls vaccinated prior to HPV exposure. Maximal reductions of around 90 percent were reported for vaccine-type HPV infections (6, 11, 16, 18) and genital wart cases.

Duration of protection

As vaccination programmes have only been in place for a maximum of 10 years, the duration of protection is not yet known. Follow-up studies 8–10 years after HPV vaccination have shown no waning of protection.² Long-term studies are ongoing to determine the duration of efficacy for all HPV vaccines.

Herd immunity

Australia has seen a reduction in the prevalence of vaccine-type HPV infections (6, 11, 16, 18) in unvaccinated young men after the introduction of the vaccine to young women, supporting the role of herd immunity.^{63, 64, 65} There was also a significant decrease in the prevalence of vaccine-type HPV infections in unvaccinated women (aged 25 years or younger).⁶⁶

In a study of data from a sexual health clinic in Melbourne,⁶⁵ the researchers noted the near disappearance of genital warts in women and heterosexual men aged under 21 years. In addition, the data indicated that the basic reproductive rate (see section 1.2.1) had fallen below one. This reduction in cases occurred without any corresponding reduction in women aged over 30 years, men who have sex with men, and non-residents. Similar trends were noted in the data from the Australian genital warts national surveillance network.

Previous exposure to HPV

While efficacy is unclear, there are no safety concerns in offering vaccination to women who have had HPV-related disease and would like to use the vaccine to reduce the risk of further disease.

A retrospective analysis of the HPV4 vaccine's pivotal efficacy trial data (Future I and Future II) studied a group of women who were vaccinated before they had their first treatment for HPV-related disease.⁶⁷ This showed a reduction in subsequent HPV-related disease in vaccinated women aged 15–26 years who had received treatment for cervical, vulvar or vaginal disease during the trial. The study showed a 46.2 percent reduction (95% CI: 22.5–63.2) after cervical surgery of any HPV-related disease and 35.2 percent reduction (95% CI: 18.8–51.8) after diagnosis of genital warts or vaginal or vulvar disease.

In contrast, a systematic review⁶⁸ explored efficacy against CIN3+ precancers in women with evidence of prior vaccine-type HPV exposure in three randomised controlled trials and two post-trial cohort studies and showed no evidence that HPV vaccines were effective in preventing vaccine-type HPV-associated precancer in pre-exposed women. Despite these findings, it was concluded that longer-term benefits in preventing re-infection could not be excluded; ie, the vaccine is not therapeutic but may prevent future infection, emphasising the importance of vaccination prior to sexual debut.

International recommendations

The WHO recommends a two- or three-dose HPV4 schedule for individuals aged under 15 years and a three-dose schedule for older individuals.⁶⁹

HPV9 was registered for use as a two- or three-dose schedule for individuals aged under 15 years and a three-dose schedule for older individuals by the European Medicines Agency⁷⁰ in June 2015 and by the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) in July 2016.

Since October 2016, the US Advisory Committee on Immunization Practices has recommended a two-dose HPV schedule for individuals aged 9–14 years and a three-dose schedule for those aged 15–26 years or who are immunocompromised.

9.4.3 Transport, storage and handling

Transport according to the *National Standards for Vaccine Storage and Transportation for Immunisation Providers 2017*.⁷¹ Store in the dark at +2°C to +8°C. Do not freeze.

9.4.4 Dosage and administration

The dose of HPV vaccine is 0.5 mL, administered by intramuscular injection in the deltoid area (see section 2.2.3).

Co-administration with other vaccines

HPV vaccine may be co-administered with any live or inactivated vaccine indicated at the same visit.²

Interchangeability

All HPV vaccines may be used interchangeably for completion of a course.⁷²

9.5 Recommended immunisation schedule

9.5.1 Recommended and funded

From 1 January 2017 males and females aged 26 years and under become eligible for HPV vaccine. Including males in a routine vaccination programme is expected to increase the benefit to the population in terms of reduction for both HPV-related cancer outcomes and genital warts.

See Table 9.3 for HPV vaccine recommendations and schedules. Children aged 14 years and under receive two doses of HPV vaccine, at 0 and 6–12 months – provided the second dose is administered before their 15th birthday, see Table 9.3 below. However, three doses are required for this age group if they have confirmed HIV infection or are transplant or chemotherapy patients, or if the minimum dosing interval is not met (see below). Older individuals receive three doses of HPV vaccine, at 0, 2 and 6 months.

Table 9.3: HPV vaccine recommendations and schedules

Note: HPV vaccine may be offered from age 9 years, but the usual Schedule will be at age 11/12 years (school years 7/8). Funded recommendations are in the shaded rows. See the Pharmaceutical Schedule (www.pharmac.govt.nz) for any changes to the funding decisions.

Recommended and funded	Doses	HPV Schedule ^a
Children aged 14 years and under	2 ^b	0 and 6–12 ^c months
Individuals aged 15–26 years ^{d,e}	3	0, 2 and 6 months ^f
Individuals aged 9–26 years:	3	0, 2 and 6 months
<ul style="list-style-type: none"> with confirmed HIV infection^g transplant (including stem cell) patients^g post-chemotherapy patients^g 	An additional dose	At least 1 month after the last dose
Recommended but not funded	Doses	HPV Schedule
Individuals aged 27 years and older: ^{d,e,h}	3	0, 2 and 6 months ^f
<ul style="list-style-type: none"> who have had little previous exposure to HPV and are now likely to be exposed who are men who have sex with men with HIV. 		

- a Individuals who started with HPV4 may complete their remaining doses with HPV9. Those who were fully vaccinated with HPV4 are not eligible for HPV9.
- b Regardless of the age at the 1st dose, if the 2nd HPV dose is given at age 15 years or older a 3rd HPV dose is recommended and funded. Give the 3rd HPV dose at least 4 months after the 2nd.
- c For children aged 14 years and under, the 2nd dose is preferably given at least 6 months after the 1st. However, if the 2nd dose is given less than 5 months after the 1st, a 3rd HPV dose is recommended and funded. Give the 3rd HPV dose at least 6 months after the 1st.
- d The decision to vaccinate older age groups should follow an assessment of the potential benefits of vaccination – based on their likely previous HPV exposure and future risks.
- e Individuals who were under age 27 years when they commenced HPV vaccination are currently funded to complete the 3-dose course, even if they are older than 27 years when they complete it.
- f If a shortened schedule is required, give the 2nd dose at least 1 month after the 1st dose and the 3rd dose at least 3 months after the 2nd dose.
- g See section 4.3.3 for more information.
- h HPV vaccines are registered for use in females aged 9–45 years and in males aged 9–26 years. However, there are no theoretical concerns that the efficacy or safety of HPV vaccine in males up to the age of 45 years will differ significantly from females of the same age or younger males.

Immunisation should be completed before the onset of sexual activity. The optimal time for HPV administration is at age 9–13 years, as most males and females in this age group would be naïve to all HPV types. However, individuals who have begun sexual activity may still benefit from vaccination. The decision to vaccinate older age groups should follow an assessment of the potential benefits of vaccination – based on their likely previous HPV exposure and future risks.

Note:

- For the two-dose HPV schedule for children aged 14 years and under:
 - the second dose is preferably given at least 6 months after the first; however, if the second dose is given less than 5 months after the first, a third HPV dose is recommended and funded – give the third HPV dose at least 6 months after the first
 - if the second dose is given at age 15 years or older, a third HPV dose is recommended and funded – give the third HPV dose at least 4 months after the second.
- Individuals who started with HPV4 may complete their remaining doses with HPV9.
- HPV9 is not funded for those individuals who were previously fully vaccinated with HPV4.
- Non-residents who were under age 18 years when they commenced HPV vaccination are currently funded to complete the course, even if they are older than 18 years when they complete it.

9.5.2 Recommended but not funded

Individuals aged 27 years and older

The decision to vaccinate older age groups should follow an assessment of the potential benefits of vaccination – based on their likely previous HPV exposure and future risks.

The data from the pivotal studies for HPV4 has demonstrated potential benefit to some women older than 25 years. HPV4 has been shown to be effective at preventing infection and disease from the vaccine types in women aged 24–45 years who were uninfected at baseline.⁷³ However, pre-vaccination testing for cervical cytological abnormalities or for HPV infection is not recommended.

HPV9 and HPV4 vaccines are registered for use in females aged 9–45 years and in males aged 9–26 years. However, there are no theoretical concerns that the efficacy or safety of HPV vaccine in males up to the age of 45 years will differ significantly from females of the same age or younger males.

9.5.3 Pregnancy and breastfeeding

HPV vaccines are not recommended for pregnant women; however, enquiring about the possibility of pregnancy is not necessary before vaccination.⁷⁴

Data to date shows no adverse effects of HPV vaccines on pregnancy outcomes.^{2, 75} However, if a vaccine dose has been administered around the time of conception or during pregnancy, health professionals are advised to report this to CARM (see section 1.6.3) and the vaccine manufacturer to assist with ongoing safety monitoring. If a woman is found to be pregnant after starting the HPV vaccine schedule, the remaining doses should be delayed until after pregnancy.

HPV vaccines may be given to breastfeeding women.¹⁹

9.6 Contraindications and precautions

See section 2.1.3 for pre-vaccination screening guidelines and section 2.1.4 for general contraindications for all vaccines.

9.6.1 Contraindications

HPV vaccine should not be administered to people with a history of an anaphylactic reaction to a prior dose of HPV vaccine or to a vaccine component. HPV vaccines contain HPV proteins produced by genetically engineered yeast cells. They should not, therefore, be given to people with a history of an immediate hypersensitivity to yeast.

9.6.2 Precautions

Pregnancy is a precaution – see section 9.5.3.

9.7 Expected responses and AEFIs

HPV vaccines have excellent safety profiles internationally. There have been no safety signals raised since the vaccines were licensed, and a number of large investigations have been carried out to assess specific outcomes, particularly autoimmune conditions.^{76, 77, 78, 79, 80}

Post-marketing surveillance systems globally continue to monitor the safety of HPV vaccination programmes.^{81, 82, 83} The WHO's Global Advisory Committee on Vaccine Safety has systematically reviewed HPV vaccine safety and has not found any safety issue that would alter its recommendations for use.⁸⁴ The main challenge with HPV vaccine is communicating its excellent safety profile.⁸⁵ (See also the HPV discussion in section 3.2.4.)

Syncope (fainting) occurs frequently in adolescents following vaccination, but this is an injection reaction, not a reaction to the vaccine.^{1, 86}

Safety has been evaluated in approximately 15,000 subjects in the HPV9 clinical development programme.⁷² The vaccine is well-tolerated, and most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity. The safety profiles were similar in HPV4 and HPV9 vaccinees. Female HPV9 recipients had more injection site adverse events than female HPV4 recipients, including swelling (40.3 percent compared to 29.1 percent in HPV4 recipients) and erythema (34 percent compared to 25.8 percent in HPV4 recipients). Injection site adverse events were similar in males following either vaccine. Male recipients had fewer injection site adverse events. Rates of injection-site swelling and erythema both increased following each successive dose of HPV9.

In summary, HPV9 is well-tolerated in all age groups, although it is slightly more reactogenic than HPV4.^{53, 55, 72} The most common adverse events are pain, swelling, erythema, pruritus, headache and pyrexia.

9.8 Cancer prevention measures

For women, HPV immunisation is part of a three-pronged approach to cervical cancer prevention that also includes regular cervical screening and safer sex approaches. For men, HPV immunisation and safer sex approaches are expected to contribute to the prevention of HPV-related cancers and disease that affect men, as well as cervical cancer prevention in women.

9.8.1 HPV immunisation

A vaccine that can prevent infection with oncogenic HPV types has the potential to reduce the incidence of precursor lesions and cancer. Vaccination needs to be administered before HPV infection occurs in order to prevent atypia and malignancy. Because genital HPVs are so common and so readily transmitted, in practical terms vaccination should be offered before the onset of sexual activity; that is, during early adolescence.

HPV immunisation does not reduce the progression of established disease but can be used in therapeutic situations by preventing the reactivation of latent infection.

9.8.2 Regular cervical screening for women

A successful HPV immunisation programme for men and women will reduce the community prevalence of HPV infection and thus the incidence of cervical cancer in women. However, HPV immunisation will not completely eliminate cervical cancer because some women will not have been vaccinated, a few will not develop immunity despite vaccination, and some will be infected prior to vaccination or with oncogenic types not present in the vaccine.

Consequently, women will need to continue to undergo regular cervical screening to detect those precancerous lesions that occur despite vaccination. Cervical screening programmes are based on regular cytological screening or HPV testing to detect, monitor and treat at an early stage precancerous lesions, or CIN. These programmes have been successful in reducing invasive disease and mortality.

Although the frequency of abnormal cytology is lower in the vaccinated group, women who have received HPV immunisation should still take part in the National Cervical Screening Programme. Three-yearly cervical smears are recommended for women between the ages of 20 and 70 years who have ever been sexually active.

9.8.3 Safer sex approaches

To minimise the risk of HPV infection (plus other sexually transmitted infections), practitioners should remind individuals of safer sex approaches, including sexual abstinence, monogamous relationships, delayed sexual debut, and minimising the number of sexual partners.² Consistent and correct use of condoms can decrease the risk of anogenital HPV infection when infected areas are covered or protected by the condom. However, HPV transmission in the genital region may occur even when condoms are used and does not necessarily require penetrative intercourse.

9.9 Variations from the vaccine data sheets

HPV vaccines are registered for use in females aged 9–45 years and in males aged 9–26 years. However, there are no theoretical concerns that the efficacy or safety of HPV vaccine in males up to the age of 45 years will differ significantly from females of the same age or younger males (see section 9.5.2).

For the three-dose schedules, the HPV vaccine data sheets recommend that all three doses are given within a 12-month period. The Ministry of Health recommends that if the three-dose schedule has been interrupted, prior doses do not need to be repeated regardless of how long ago the previous doses were given (see Appendix 2).

The HPV9 data sheet states that there are no studies on the interchangeability of HPV vaccines. The Ministry of Health recommends that all HPV vaccines may be used interchangeably for completion of a course.⁷² Those individuals who started with HPV4 may complete their remaining doses with HPV9.

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