HPV VACCINE

KEY POINTS

- One HPV vaccine is currently (as of 2024) approved for use (registered) and available in Aotearoa New Zealand: HPV9 (Gardasil 9; Seqirus/MSD); the vaccine is registered for use in males and females aged 9–45 years.
- HPV9 is free for all individuals aged from 9 to 26 years, irrespective of gender. Immunisation is part of the National Immunisation Schedule as a school-based programme in Year 8; those who are not vaccinated at school can receive the vaccine from their local medical clinic.
- Vaccination with HPV9 is recommended for persons with HIV and for transplant recipients aged 27–45 years, and in females of this age, but is not funded in these groups.
- HPV vaccination is also recommended, but not funded, for individuals aged ≥27 years who have had little previous exposure to HPV and are now likely to be exposed, and men who have sex with men (MSM).
- Ideally vaccination should be given prior to the commencement of sexual activity, but should still be given even if sexual activity has commenced.
- Vaccination is effective in individuals with a history of cervical intraepithelial neoplasia (CIN) or genital warts due to its ability to prevent infection with other HPV subtypes.
- Current data indicate that there is no loss of protection over time, and vaccination is expected to provide long-term protection from HPV infection.
- HPV vaccination may reduce the incidence of preterm birth through the elimination of HPV 16/18 infection.
- HPV vaccines have excellent safety profiles.

HPV9 vaccine

The Gardasil™ 9 vaccine contains viral-like particles (VLPs) that are composed of the L1 protein (a component of the virus outer layer) for nine different HPV types (6, 11, 16,

18, 31, 33, 45, 52 and 58); the vaccine does not contain viral DNA and cannot cause infection.[1] Vaccination is associated with antibody responses against the covered HPV strains in nearly all individuals.[2]

Schedules and dosing

In Aotearoa New Zealand, HPV immunisation has been free for everyone aged 9–26 years since 1 January 2017.[3]

- Non-residents must be aged under 18 years to start a funded HPV vaccine course. They can go on to complete the course when aged 18 years or older.
- People eligible for funded healthcare in New Zealand must be aged under 27 years to start a funded HPV vaccine course. They can go on to complete the course when aged 27 years or older.

The vaccine is more effective at a younger age. Therefore, the number of vaccine doses required depends on the age of the individual being vaccinated. The current routine funded HPV immunisation schedule in Aotearoa New Zealand is as follows[2]:

- Age ≤14 years: two doses given 6–12 months apart.
- Age 15–26 years: three doses given at 0, 2 and 6 months.
- Age 9–26 years with confirmed HIV infection or transplant: three doses given at 0, 2 and 6 months.
- Age 9–26 years receiving chemotherapy: an additional dose should be given at least one month after completion of chemotherapy.

A missed dose does not require the schedule to be restarted.[4,5] Although adherence to the vaccination schedule is recommended regarding timing of doses, clinical study data show vaccine efficacy in individuals who have received all three doses within a 1-year period. The second dose should be administered at least 1 month after the first dose, the third dose should be administered at least 3 months after the second dose, and all three doses should be given within a 1-year period.

Effectiveness

A 2016 systematic review evaluated 10 years of real-world experience with the previous quadrivalent form of the HPV vaccine (HPV 4) literature and included 57 publications from nine countries.[6] The greatest impact on HPV infection, genital warts and cervical abnormalities was seen in countries with high vaccine uptake and among girls vaccinated

prior to HPV exposure; reductions of up to 90% were reported for vaccine-type HPV infections (HPV 6/11/16/18) and genital warts.[6]

The HPV9 vaccine extends protection to cover an additional five types of HPV and its efficacy is non-inferior to that of the HPV4 vaccine. The HPV9 vaccine was compared with the HPV4 vaccine in 14,215 women aged 16–26 years in a double-blind, phase 2b-3 trial.[7] Participants received three doses of either vaccine at 0, 2 and 6 months. In the per-protocol efficacy population, the incidence rate of high-grade disease related to HPV-31, 33, 45, 52, and 58 (the five additional HPV types covered by the HPV9 vaccine) was 0.1 per 1000 person-years in the HPV9 group and 1.6 per 1000 person-years in the HPV4 group (1 case vs. 30 cases). HPV9 efficacy was 96.7% (95% confidence interval [CI], 80.9–99.8%).[7] Given that the HPV vaccine has been both widely recommended and introduced in many countries, it is no longer ethical to conduct placebo-controlled trials.

There are a range of variables that influence the effectiveness of a vaccine programme. Therefore, although the positive association between vaccine coverage and effectiveness is clear and consistent, the reported effectiveness in different countries varies. The World Health Organization recommends a 90% vaccination rate for girls aged under 15 years in order to achieve the elimination of cervical cancer.[8] At the time of writing, the Te Whatu Ora HPV vaccination target in Aotearoa New Zealand was 75%.

Impact on cancer endpoints

Vaccine effectiveness and the impact of vaccination on disease becomes evident over time. Cancer endpoints cannot be measured for years after the vaccine has been introduced (whereas changes in the epidemiology of genital warts are evident almost immediately). However, a 2020 large-scale study of women and girls in Sweden who were vaccinated between 2006 and 2017 indicated that HPV vaccination substantially reduced the risk of invasive cervical cancer at the population level.[9]

Impact on incidence of cervical dysplasia, persistent infection and anal infection

The impact of HPV immunisation programmes on the incidence of cervical dysplasia is now evident across multiple countries. There is early evidence for a reduction in the rate of cervical dysplasia in vaccine-eligible cohorts, with younger women showing the strongest evidence of protection after partial doses.[6] Herd immunity is evident for the rate of cervical dysplasia, persistent HPV infection, and incidence of genital warts.[10]

Data from a pivotal randomised, placebo-controlled trial in healthy boys and men showed that the HPV4 vaccine was highly effective at preventing infection with the HPV

types covered and the development of HPV-related external genital lesions.[11] Furthermore, in the subgroup of MSM enrolled in the study, vaccination showed 94.9% efficacy (95% CI, 80.4–99.4%) in protecting against anal infection and associated anal intraepithelial neoplasia.

Impact on incidence of genital warts in Aotearoa New Zealand

New Zealand introduced the HPV4 vaccine (Gardasil®) in 2008. Data from Auckland in 2010 and 2013 showed a steady decline in the rate of genital warts, by 63% and 83% respectively.[12] Nationally, the number of first presentation cases of genital warts has declined from 4,299 in 2008 to 856 in 2019, an 80% reduction.[13,14]

Duration of protection

HPV vaccines are highly immunogenic.[15] They induce robust immunological memory, and mathematical modelling suggests that protection from vaccination is likely to be sustained long-term.[16,17] Stable protective efficacy from HPV vaccination has been shown for at least 10 years.[18-20] A long-term follow-up study in individuals vaccinated with the quadrivalent HPV vaccine showed >90% vaccine effectiveness, with 100% (95% Cl, 94.7–100%) protection against HPV16/18-related high-grade cervical dysplasia at more than 12 years after the first dose.[21] Sustained HPV 6/11/16/18 antibody responses for up to 14 years post-vaccination were also reported.[21] The ongoing performance of HPV vaccines is determined in post-licensing effectiveness studies.

HPV immunisation in special groups

Immunosuppressed individuals

Immunosuppressive conditions are associated with a higher risk for HPV-associated disease. The immunogenicity of HPV vaccine in adult solid organ transplant patients has been shown to be suboptimal when administered early after transplant, and was dependent on the type of transplant and immunosuppression.[22] However, limited data show adequate seroconversion in adolescent kidney and liver transplant recipients, indicating good immune response.[23] In addition, females aged 9–26 years receiving immunosuppressive therapy for inflammatory bowel disease developed antibody responses similar to healthy females.[24] HPV vaccine has also been shown to be immunogenic in HIV-infected men[25] and women.[26] A three-dose vaccination schedule should be used when vaccinating immunosuppressed individuals, regardless of age.

Frequently Asked Questions

Can the vaccine be given to people who are already sexually active or already have HPV infection?

Yes. The HPV vaccine can be offered to people who have HPV. Vaccination protects against infection with HPV genotypes that a person has not previously encountered and/or the development of further disease. Limited data in women shows that vaccination may help to prevent recurrence or reactivation of HPV infection. There is only anecdotal evidence for a therapeutic benefit of HPV vaccination in the context of existing external warts or other HPV disease.[27,28] Overall, the decision to vaccinate older age groups or those who already sexually active should be based on assessment of potential benefit and future risk for each individual.

Can people be tested for infection before getting vaccinated?

There is no test to determine an individual's HPV status. Blood serology is not reliable and 'swabs' cannot be used for this purpose. Current HPV DNA testing is only used to detect particular high-risk types to guide clinical management in cervical screening, so cannot be used as a screening test for "all HPV" types.

Does natural infection induce protective immunity?

Not always. Current evidence suggests that naturally-acquired immunity is unlikely to be effective in preventing reinfection because of the ability of the virus to evade the immune system; this does not appear to be the case with vaccine-derived immunity.

Naturally-acquired immunity to reinfection: the seroresponse to natural infection varies depending on the anatomical site infected and the individual themselves. There is some evidence that there is a reduced risk of reinfection with the same HPV type, but not other types (i.e. no cross-protection).

Naturally-acquired immunity to persistent infection: once an infection has become established, resolution is largely dependent on innate and cell-mediated immunity. Reactivation of previously latent infection is common in women who become immunosuppressed.

Naturally-acquired immunity to tumorigenesis: because natural immunity is very slow to develop, CIN can develop during the period of persistent infection.[29-33]

Will cervical screening still be needed?

Yes. Irrespective of whether someone with a cervix has been vaccinated, routine cervical screening will need to continue for the foreseeable future. This is because of possible

prior infection with HPV types that cause CIN, or new infection with other HPV types not covered by vaccination.

What if the vaccine is given to a pregnant person?

The HPV vaccine is not currently recommended for use in pregnancy. However, enquiry about possible pregnancy is not required before vaccination. Completion of the vaccine course should be deferred if a person is found to be pregnant. However, there are no safety concerns with the use of non-live vaccines in pregnant women and a number are routinely recommended in this group. Also, there is no clinical trial evidence that the HPV vaccine adversely affects fertility, pregnancy, or infant outcomes; many pregnancies occurred in the trial participants.[34,35] The key message is: don't get the HPV vaccine if you are pregnant, but if you find out that you were pregnant at the time of vaccination then don't worry about it. Women can safely breastfeed if they receive the HPV vaccine during that period.

Could less common genotypes replace types 16 and 18?

In theory, widespread vaccination may allow less common HPV genotypes to replace those covered by the current vaccine, but expert opinion considers this to be unlikely.[36] Emergence of less common genotypes can occur where different strains or types of an agent compete with each other, such as with pneumococcal vaccination, but this is not the case with HPV. A person can be co-infected with several types at one time. Programmes will be monitoring changes in HPV genotyping to ensure that prevention continues to be effective.

Can people be tested to check immunity after vaccination?

There is no clinically useful test for immunity after vaccination. The minimum level of antibody required to provide protection is currently unknown and not likely to be important.

Does the quadrivalent vaccine provide any cross-protection against non-vaccine types?

Yes. The quadrivalent vaccine provided statistically significant levels of protection against type 31 and serum neutralising antibody to types 33 and 52, none of which were specifically targeted by that vaccine.[37]

Can the HPV vaccine be given with other vaccines?

Yes, the HPV vaccine can be co-administered with other non-live and live vaccines. Separate injection sites should be used.

Is the vaccine safe in patients who are on biologic agents?

Yes, because it is not a live vaccine.

How safe is the vaccine?

Very safe. The HPV vaccine has an excellent safety profile and is well tolerated in all age groups. In pivotal clinical trials, the majority of adverse events reported were of mild or moderate severity, with injection site reactions being the most common.[38]

No safety signals have been identified since the vaccine was licensed. A summary of the published post-licensing safety data on the HPV4 vaccine from both active and passive surveillance studies to 2015 included data from more than one million preadolescents, adolescents and adults.[28] Syncope, and possibly skin infections, were reported to be associated with administration of the vaccine; more detailed analysis of the "infections" suggested some were likely to be injection site reactions. Serious events were carefully examined, and there was no increase in incidence over background rates.[28] These data for the HPV4 vaccine were confirmed by another post-licensing study (to 2016).[27] With the exception of syncope, which is reaction to the injection rather than the vaccine, no safety signals were identified.[27]

The HPV9 vaccine was found to be as safe in female individuals as the quadrivalent vaccine.[39] More recently, no safety concerns were identified related to the HPV9 vaccine based on US data from 215,965 individuals aged ≥9 years who received at least one vaccine dose between October 2015 and September 2017.[40]

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