The Immunisation Advisory Centre

Review of evidence to inform New Zealand National Immunisation Programme, 2023: Human papillomavirus.

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Contents

Figures and Tables

Abbreviations

2vHPV	Bivalent HPV vaccine
4vHPV	Quadrivalent HPV vaccine
9vHPV	nonavalent HPV vaccine
AEFI	Adverse events following immunisation
AESI	Adverse events of special interest
AIN	Anal intraepithelial neoplasia
CDC	Centers for Disease Control and Protection (US)
CIN	Cervical intraepithelial neoplasia
CRPS	Chronic regional pain syndrome
DTaP	Combined diphtheria, tetanus and acellular pertussis vaccine
HepB	Hepatitis B vaccine
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HPV-6/11	HPV genotypes 6 and 11
HPV-16/18	HPV genotypes 16 and 18
HR	Hazard ratio
HSIL	High-grade squamous intraepithelial lesions
IARC	World Health Organization International Agency for Research on Cancer
ICO	Institut Català d'Oncologia
IR	Incidence rate
IRR	Incidence rate ratio
LEEP	Loop electrosurgical excision procedure
MenACWY	Quadrivalent meningococcal conjugate vaccine against groups A, C, W and Y
MSM	Men-who-have-sex-with-men
NZE/O	NZ European and Other ethnicity
OR	Odds ratio
PLHIV	People living with HIV infection
POI	Premature ovarian insufficiency
POTS	Postural orthostatic tachycardia syndrome
NZ	Aotearoa New Zealand
RCT	Randomised controlled trial
RR	Risk ratio
RRP	Recurrent respiratory papillomatosis
SAGE	Strategic Advisory Group of Experts on immunisation
Tdap	Combined tetanus, reduced antigen diphtheria and acellular pertussis vaccine
TGA	Therapeutic Goods Administration (Australia)
UK	United Kingdom
US	United States of America
WHO	World Health Organization

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Summary of evidence

This review of evidence considers the use of human papillomavirus (HPV) vaccines to prevent HPV infection and associated diseases. It includes scientific literature published between 2018 and 2023 around the scheduling of doses and the impact of HPV immunisation programmes on the incidence of HPV-associated diseases, infection and cancers. The aim is to help inform the Aotearoa New Zealand National Immunisation Programme. It is not a systematic review.

Given below are the main areas of focus for this review.

- A general overview of the safety and effectiveness of two- or three-dose schedules of HPV vaccines.
- The impact HPV immunisation programmes have had against HPV-associated disease.
- Review the rationale for one-dose schedules, including evidence around:
    - safety, immunogenicity and effectiveness
    - suggested age-range for one-dose schedules
    - duration of protection of one dose.
- HPV vaccination of specific high-risk groups.
    - Schedule for immunocompromised groups.
    - Off-label use as an adjuvant post-cervical lesion treatment, to prevent reinfection/recurrence and for those aged over 45 years.
    - Prevention of juvenile-onset recurrent respiratory papillomatosis (RRP).

Burden of HPV infection and HPV-associated diseases

Human papillomaviruses are associated with a range of epithelial infections. Twelve genotypes are oncogenic and associated with persistent infections that can progress to invasive cancer.[1] Anogenital warts, caused by types 6 and 11, contribute the most to HPV-associated morbidity, globally. Types 16 and 18 are significantly associated with anogenital cancers, including almost all cervical cancers, and some oropharyngeal cancers. Prevalence of anogenital infection peaks in young adults from the onset of sexual activity. The impact of cervical cancer is greatest in low- and middle-income countries with inadequate access to screening and vaccines. Immunosuppression and human immunodeficiency virus (HIV) infection are associated with an increased risk of persistent HPV infection and hence precancerous lesions.

Aotearoa New Zealand cancer and genital wart epidemiology

Despite vaccination of females since 2008 and males since 2017, HPV-associated cancers continue to be reported, but the highest incidence is in older individuals over the age of 40 years.[2]

Cervical screening has reduced the risk of cervical lesions developing into invasive cancer. The National Cervical Screening Programme became fully operational in 1991 for people aged 20–69 years[3]. As the age range of vaccine-eligible cohorts widened, screening moved to ages 25–65 years in 2019 and in September 2023, HPV self-testing will commence.

In NZ, the incidence of cervical cancer diagnoses sharply increases to the age of 35–40 years then plateaus with a slight decrease to age 50 years. Mortality increases with age and particularly in older age groups after the cervical screening programme ends. Cervical cancer is the 12th leading type of cancer (excluding

non-melanoma skin cancer) and 15th cause of cancer deaths in all females in NZ. In women aged 18-44 years, it is the fourth most common cancer and the third cause of cancer deaths.

Genital wart cases declined substantially following the introduction of 4vHPV vaccine. A further 42 percent decline was seen in reported cases for European and Other ethnicities following introduction of the 9vHPV for both boys and girls in 2017 – this decline was not observed in Pacific and Māori groups.[4] In 2021, the number of diagnosed cases in those aged over 40 years increased, although genital warts cases continued to decline. Except for only a 3 percent reduction for cases in Māori, across the different ethnic groups cases reduced by 17.3–26.4 percent.[4]

HPV vaccination

Based on HPV DNA in histological specimens, globally, the nine-valent HPV (9vHPV) vaccine reduced cervical cancer cases by an estimated 90 percent and by 50 percent for all HPV-related cancer cases.[5] Most vaccination programmes only provide vaccines to women and girls, but HPV also infects men. HPV infection is particularly prevalent in men-who-have-sex-with-men (MSM), who do not benefit from herd protection through the female-only vaccination programmes. Gender-neutral programmes allow for wider vaccine access.

The approved course of 9vHPV vaccine for males or females is:

- two doses given 6–12 months apart for immunocompetent adolescents aged 9 to under 15 years
- three doses at 0, 2 and 6 months for those aged 15–45 years, or for ages 9–45 years if immunocompromised (except with splenic dysfunction).

However, following a World Health Organization (WHO) review and position paper[6], Australia and the UK are now offering one dose of 9vHPV up to the age of 25 years for immunocompetent individuals.

Impact of HPV vaccination programmes

Significant declines in genital wart and abnormal cervical cytology diagnoses have been recorded in New Zealand since the HPV vaccination programme was started in 2008 in vaccine-eligible cohorts.[7, 8]

The population-level impact of HPV vaccination programmes has been systematically reviewed.[9, 10] The key findings of these reviews are listed below.

- Reported reductions in HPV infection, anogenital warts, cervical lesions and penile lesions several years after vaccination.
- Countries with the highest burden of disease see the greatest impact.
- Multi-cohort vaccinations achieve the fastest outcomes, including vaccinating males and females after the age of 16 years.
- Vaccination considerably reduces vaccine-type HPV infections (by up to 96 percent) – which also provides some herd immunity to unvaccinated individuals.
- Countries with the highest vaccine coverage see the largest direct and herd impacts, particularly when vaccinated prior to sexual debut.

Routine two- and three-dose schedules

This review presents evidence to assess how well routine vaccination against HPV performs, using two- and three-dose schedules.

Safety of two- and three-dose schedules

HPV vaccines have well-characterised and excellent safety profiles. Compared with 4vHPV, 9vHPV induces slightly more local and systemic reactions, but like its predecessor, its use has not been causally associated with long-term serious adverse events such as autoimmune or neurological conditions. As with other vaccines, severe allergic reactions/anaphylaxis and syncope are rare immediate responses to vaccination. The estimated incidence rate of anaphylaxis is 15.1 (95% CI 4.9–35.3) and syncope is 54.4 (32.3–86.0) cases per million doses of 9vHPV.[11] The syncope incidence rate in Australia was three times higher in younger adolescents aged 12–13 years than 14–15 years.[12] Although it is recommended to delay vaccination until after pregnancy due to limited data, no safety concerns around giving this non-live vaccine in pregnancy have been identified.[13, 14]

Immunogenicity of two- and three-dose schedules

No correlate of protection is defined for HPV-neutralising antibodies. Non-neutralising antibodies and cellular immune responses are likely to play a greater antiviral role than circulating neutralising antibody levels. The virus-like particles in HPV vaccines make them highly immunogenic and drive a broader response than traditional subunit vaccines. Despite these limitations, serum neutralising antibody levels have been used as a proxy for efficacy in clinical trials and long-term follow-up.[15] Longer intervals between doses, of up to 12 months, gave stronger antibody responses than short intervals of 1 or 2 months. There was no evidence of interference with other routine vaccines.[16]

A phase III study showed sustained antibody levels for at least 7 years in boys and girls vaccinated with two doses of 9vHPV at ages 9–15 years. High seropositivity rates (of over 90 percent) against all vaccine-type HPV genotypes were maintained for least 90 months.[17]

People living with HIV (PLHIV) require three doses since seropositivity declines more rapidly than in those who are HIV-negative. Protection can last for at least 2–4 years.[18]

Vaccine effectiveness of routine two- and three-doses

Following almost two decades of HPV vaccine use in national immunisation programmes, mounting evidence shows that vaccination in males and females prevents:[16, 18, 19]

- persistent HPV infection
- genital warts
- pre-cancerous cervical intraepithelial neoplasia (CIN)
- high-grade cervical cancers
- other anogenital epithelial neoplasia and cancers.[17, 19, 20]

Long-term studies show durable effectiveness of 9vHPV against persistent infection. When stratified by age at vaccination, the effectiveness of one, two or three doses is similar.[21] HPV vaccines are most effective when given prior to the onset of sexual activity.[20, 22, 23]

Conclusions for two- and three-dose schedules

Consistently, safety studies have found no concerns about the long-term safety of these HPV vaccines and no evidence of an association with autoimmune or neurological disease. HPV vaccines are highly immunogenic. They provide long-lasting protection against persistent HPV infection and subsequent pre-cancers. Vaccination prior to onset of sexual activity provides the greatest level of protection. Little

evidence directly compares two or three doses in those aged 16–25 years. Two doses do appear to be highly effective and are likely to be adequate in this age group, if given more than 6 months apart. Protection is less long-lasting in individuals who are immunocompromised, even after three primary doses.

Evidence around the use of a single dose

In 2023, the UK and Australia immunisation programmes introduced a one-dose 9vHPV schedule for immunocompetent individuals aged under 25 years. The following reviews the evidence supporting a one-dose schedule.

Immunogenicity of a single dose

A single dose of 4vHPV or 9vHPV induces a robust, protective response, albeit with lower antibody titres to two or three doses. [24] Low neutralising antibody titres do not necessarily mean that a single dose is inadequately protective. Seropositivity rates were high in all vaccine recipients.[25] One dose appears to be protective for several years post vaccination.[24] Antibody responses against HPV-16 and -18 were sustained for at least two years after one dose.[26, 27] A booster dose of 9vHPV, given 3–8 years after the first dose of HPV vaccine, is adequate to provide further protection against all nine vaccine-HPV types.[28]

Single dose effectiveness

Most of the current data around the use of a single dose has come from multi-dose clinical trials or from individuals partially vaccinated as part of an immunisation programme. One dose of HPV vaccine significantly reduces the frequency of persistent HPV infection compared with no vaccine and is likely to be protective for several years.[25, 29] In an Indian study in which some participants only received one dose, the frequency of cumulative incidence and persistent HPV-16/18 infections were similar and uniformly low in all vaccinated groups (receiving one, two or three doses). These frequencies were significantly higher in an unvaccinated, age-matched control group. Clinical trials are underway to investigate the use of single dose programmes. The KEN SHE study is evaluating single dose 2vHPV and 9vHPV vaccination in Kenyan women. Interim data to 18 months post vaccination has shown that a single dose is highly effective in preventing persistent HPV infections (97 percent against HPV-16/18 infection and 89 percent against all nine 9vHPV types).[30]

Australian women who received one, two or three doses of HPV vaccine had a significantly reduced risk for high-grade cervical intraepithelial neoplasia (CIN) or cancer than those who were unvaccinated in data-linking study. The hazard ratio for one and two doses were comparable to three doses when adjusted for age at time of vaccination. It was proposed that a one-dose schedule or a planned interval of 3–5 years between doses could reduce demand on vaccine and allow time for a full assessment of effectiveness and duration of protection of one dose.[31]

Significant effectiveness against genital warts is seen with one, two or three doses, particularly when vaccination is initiated before the age of 16 years.[21] However, findings supporting one dose were reported as inconsistent in a Cochrane review.[29]

Conclusions for a single-dose schedule

How well a single-dose schedule performs is dependent on:

- vaccine uptake
- herd immunity across both heterosexual and homosexual groups
- ongoing screening for persistent infections

- prompt treatment of lesions that may occur.

There is a moderate certainty that one dose can provide protection against persistent HPV-16/18 infection for at least 10 years, but data is limited for the effectiveness in protecting against HPV-associated cancer. Current evidence suggests that in NZ, extending the interval between doses is likely to be a better option than relying purely on a single dose. One dose provides at least some protection to more people than giving two or even three doses to a smaller, more receptive group. Booster doses could be required.

Preventing HPV recurrence following cervical lesion excision

Evidence around the use of HPV vaccination as an adjuvant treatment following conization and excision of cervical neoplasia is emerging.[32] Ideally, vaccination is best given at a young age before acquiring HPV infection, but when given at the time of CIN treatment or soon after, it appears to moderately reduce the risk of recurrent disease.[33] The effectiveness in women older than 45 years is unclear.

Preventing and treatment of juvenile-onset recurrent respiratory papillomatosis

It is currently unclear, mainly due to the rarity of the condition, whether routine HPV vaccination has significantly reduced the incidence of RRP in children in NZ.[34] Data from larger countries suggest a decrease.[35, 36] Higher HPV vaccine coverage would likely have a greater effect in reducing cases in NZ, when you compare NZ with Australia. Infants who were born to mothers who were vaccinated as adolescents or at least prior to pregnancy are potentially protected by passive transfer of maternal HPV antibodies.[17, 37]

As a treatment or an adjuvant therapy, there appears to be a slowing of recurrence but no evidence yet of prevention of RRP recurrence.[38, 39] With a reduction in genital warts cases, it is hoped that the incidence of juvenile-onset RRP will eventually diminish. Herd immunity from vaccinated males and females will also reduce the spread of HPV-6 and -11 infections to unvaccinated individuals.

Key findings

General overview of two- or three-dose schedules of HPV vaccines, safety and effectiveness against HPV-associated cancer

- HPV vaccination programmes have made significant impacts on the prevalence of vaccine-type HPV infection in vaccine-eligible cohorts.
- Strong evidence of no long-term safety concerns.
- Female-only vaccination provides herd protection to male age-group counterparts, but not to men who only have sex with men.
- Vaccination has the greatest impact when administered prior to sexual debut and acquiring HPV infection.
- Vaccination provides seroprotection for at least 7 years in immunocompetent young people. However, even after three doses, protection does not last as long in those who are immunocompromised.
- Limited data is available to compare two versus three doses in those aged over 16 years. A full three-dose course appears unnecessary to induce good immunogenicity for immunocompetent individuals aged 16–25 years. For this age group, two doses given 6–12 months apart is likely to be optimal.

Review of the rationale for using one-dose schedules

- A single dose induces a lower antibody response than seen after two or three doses, but protection can last for several years, particularly if administered prior to onset of sexual activity and HPV exposure.
- One dose showed comparable effectiveness against CIN or cancer to standard schedules, when adjusted for age at time of vaccination.
- A further dose given 3–5 years after the first dose is likely to be necessary to extend the duration of protection. It is unlikely that further booster doses are required in immunocompetent individuals.
- To improve coverage and to simplify school-based vaccination programmes in NZ, a first dose could be given in school year 7 (age 11 years, ie, last year of primary or first year intermediate school, alongside Tdap). Students in school years 10 or 11 (ages 14–16 years) could be offered a further dose of 9vHPV or as a catch-up for those who missed their first dose.

Specific high-risk groups

- Schedule for immunocompromised groups: immunocompromised groups obtain protection after three doses, but could require a booster dose given 5 years later to maintain that protection. This review did not closely investigate vaccine effectiveness in PLHIV.
- Off-label use as an adjuvant to cervical lesion treatment (conization) provides some protection to reduce the risk of reinfection or lesion recurrence, but limited data is available for those aged over 45 years.
- HPV vaccines can help to prevent juvenile-onset recurrent respiratory papillomatosis in multiple ways: 1) by preventing genital warts to stop infant infection during delivery; 2) maternal antibody gives passive protection to infant; 3) limited evidence has shown that HPV vaccination of children can attenuate the recurrence of infection post-surgery.

Recommendations for the New Zealand immunisation programme

Based on the evidence reviewed, considerations for the NZ programme are as follow:

- **Improving vaccine coverage** for 9vHPV for both boys and girls aged under 15 years will:
    - increase herd immunity for those who are immunocompromised
    - reduce the incidence, morbidity and mortality for HPV-associated cancers and pre-cancers
    - aim to vaccinate prior to acquiring infection through sexual contact.
- **Offering on one dose** could improve HPV vaccine uptake by:
    - simplifying the HPV immunisation programme
    - enabling more capacity to catch-up for those who are unimmunised.
- **Giving a booster dose** given some years after a primary dose could extend the duration of protection of a one-dose schedule. This requires further research.
- **Ensuring** PLHIV and others who are immunocompromised receive no fewer than three doses.
- **Using HPV vaccines for adjuvant treatments** of precancerous lesions and recurrent respiratory papillomatosis needs further evaluation as an off-label use.
- Limited data suggests that **using 9vHPV in adults older than 45 years** (also off-label use) could prevent acquisition of new or persistent infection and genital warts.

Review of literature

Introduction

This review of evidence considers the use of human papillomavirus (HPV) vaccines to prevent HPV infection and associated diseases. It includes scientific literature published between 2018 and 2023 around the scheduling of doses and the impact of HPV immunisation programmes on the incidence of HPV-associated diseases, infection and cancers. The aim is to help inform the Aotearoa New Zealand National Immunisation Programme. It is not a systematic review and has not formally evaluated the quality of evidence.

The review will summarise the epidemiology of HPV infections and associated diseases in New Zealand. It examines the evidence for HPV immunisation programmes and vaccine usage, including:

- a general overview of how the routine two or three dose vaccine schedules have performed against female and male HPV-associated anogenital and oropharyngeal cancers, including:
    - the safety, immunogenicity and effectiveness of HPV vaccines
    - the impact of HPV immunisation programmes on HPV-associated disease.
- investigation of the rationale to change to a one dose schedule, including evidence around:
    - safety, immunogenicity and effectiveness of one dose
    - suggested age range for one dose schedule
    - duration of protection after one dose.

It will also review the use of HPV vaccines for specific high-risk groups, including:

- three-dose schedule recommendations in immunocompromised groups
- use as an adjuvant post-cervical intraepithelial neoplasia (CIN) treatment
    - to prevent reinfection / recurrence of CIN
    - as an indication for use in those aged 26–45 years or over 45 years
- prevention of juvenile-onset recurrent respiratory papillomatosis (RRP)
    - maternal passive antibody in infants
    - prevention of genital wart infection of mothers
    - use as an adjuvant treatment to prevent recurrence of RRP following surgery.

World Health Organization human papillomavirus position paper 2022

In relation to HPV, the primary focus of the World Health Organization (WHO) is the prevention of cervical cancer. Vaccination is a fundamental part of the WHO Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem. This strategy aims to prevent 60 million cervical cancer cases and 45 million deaths over the next 100 years. The WHO 2022 position paper on HPV includes updated information around newer HPV vaccines. It covers evidence around the immunogenicity and effectiveness of reduced dose schedules, including off-label recommendations.[6]

As part of its strategy, WHO aims to reduce the burden of cervical cancer through screening and vaccination in low- and middle-income countries. Currently, these countries account for 88 percent of cases worldwide due to poor early cervical cancer detection and survival rates. Globally, cervical cancer was the

fourth leading cause of cancer and cancer deaths in women in 2020. HPV types 16 and 18 are associated with 71 percent of cases. In total, HPV types 16, 18, 45, 31, 33, 52 and 58 account for over 90 percent of all squamous cell carcinomas that are HPV DNA-positive. Persistent infection is more likely to occur in people living with HIV (PLHIV).[6]

The immune response to HPV infection is slow to develop. Because infections are restricted to the mucosal epithelium, they do not induce a rigorous immune response. The median time to seroconversion is approximately 8–12 months. After natural infection, 70–80 percent of women seroconvert and the antibody response is low titre, slow to develop and of low avidity. Men are less likely to respond to infection, few seroconvert and may produce non-protective antibodies.[6] Failure to develop a cell-mediated immune response results in persistent infection and increased risk of cancerous lesions.

WHO recommends all national immunisation programmes contain HPV vaccines to reach 90 percent of girls by the age 15 years (primary target ages 9–14 years). WHO aims to achieve this globally by 2030 by providing multiple opportunities for girls to receive the vaccine doses. WHO recommendations are:

- to use a two-dose programme in both the target age and older age groups, with spacing of 6–12 months between doses. A 12-month schedule is preferred for programmatic and efficiency reasons, as well as resulting in higher antibody titres
- as there is no defined maximum interval between doses, programmes could consider spacing of 3–5 years
- to offer an alternative single-dose schedule for girls and boys aged 9–20 years, as an off-label option
- for individuals who are immunocompromised and PLHIV (regardless of anti-retroviral therapy) to receive at least two doses a minimum of 6 months apart, and where possible three doses
- to conduct further research on the immunogenicity, effectiveness and duration of protection of single-dose schedules in different groups.

Epidemiology and burden

Global burden and epidemiology of HPV

More than 200 types of HPV have been genotyped. Twelve high-risk oncogenic types have been identified. Types 6 and 11 are low-risk non-oncogenic types but are a major cause of morbidity worldwide, causing anogenital warts.[1] HPV prevalence peaks in young adults, across all the world regions. Around one quarter of cases occur under the age of 25 years and prevalence declines in older ages, particularly in Europe and the Americas. Globally, the prevalence of genital HPV infection is highest in men, but persistence is less likely in men than in women. Little is known about the natural history of oral HPV infection, but persistent subclinical infection is likely to precede HPV-driven head and neck cancer. A US study reported oral HPV infection prevalence of 10.1% (95% CI 8.3-12.3%) in men and 3.6% (2.6-5.0%) in women. Oral infection is associated with the number of lifetime sexual partners, current cigarette smoking and older age.[1]

WHO International Agency for Research on Cancer (IARC) presents the incidence and mortality of a range of cancers by global region at https://gco.iarc.fr/today/online-analysis-map. These data, presented in Figure 1 and Figure 2, show that the highest impact of cervical cancer is in low- and middle-income countries. Penile cancer has a high incidence in South America as well as similar incidence to countries affected most by cervical cancer.

Figure 1: Estimated worldwide age-standardised mortality rates for cervical cancer in 2020, from age 10+ years, (source Cancer Today, IARC)

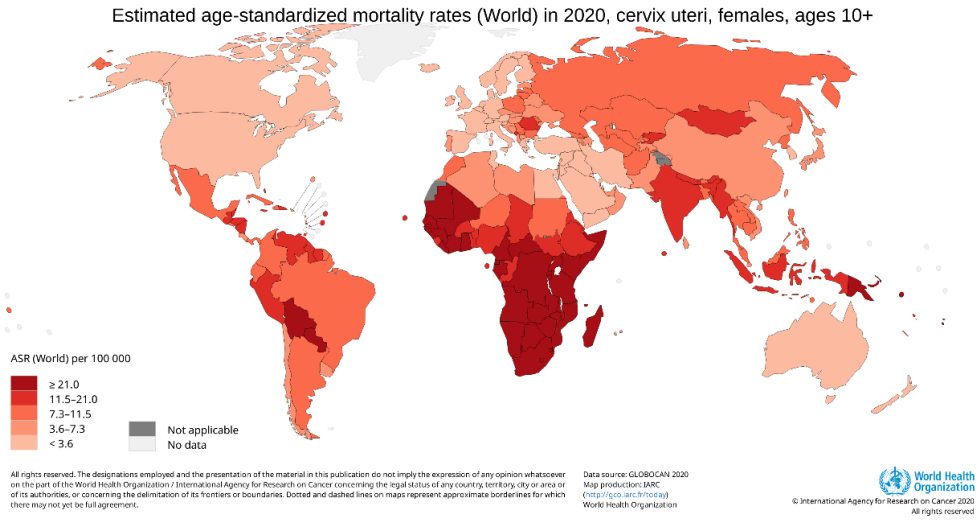
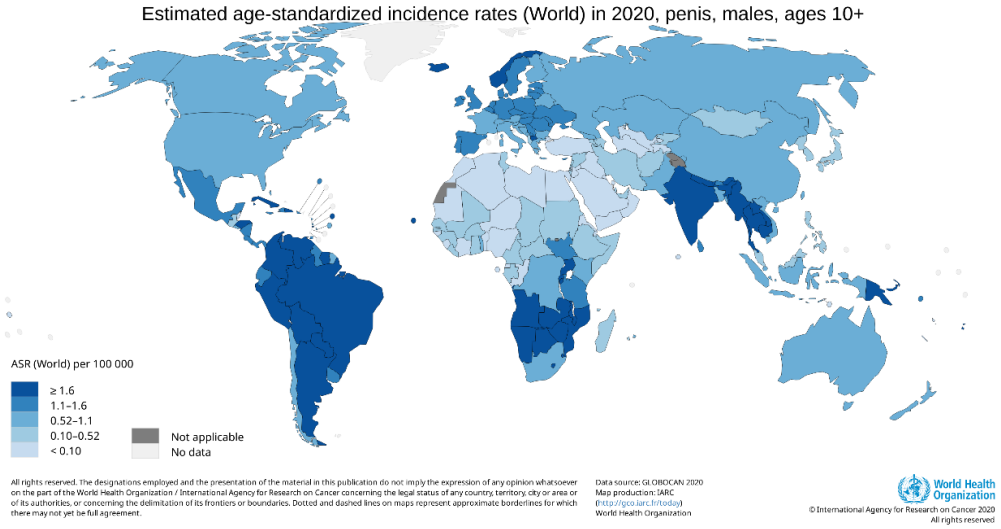
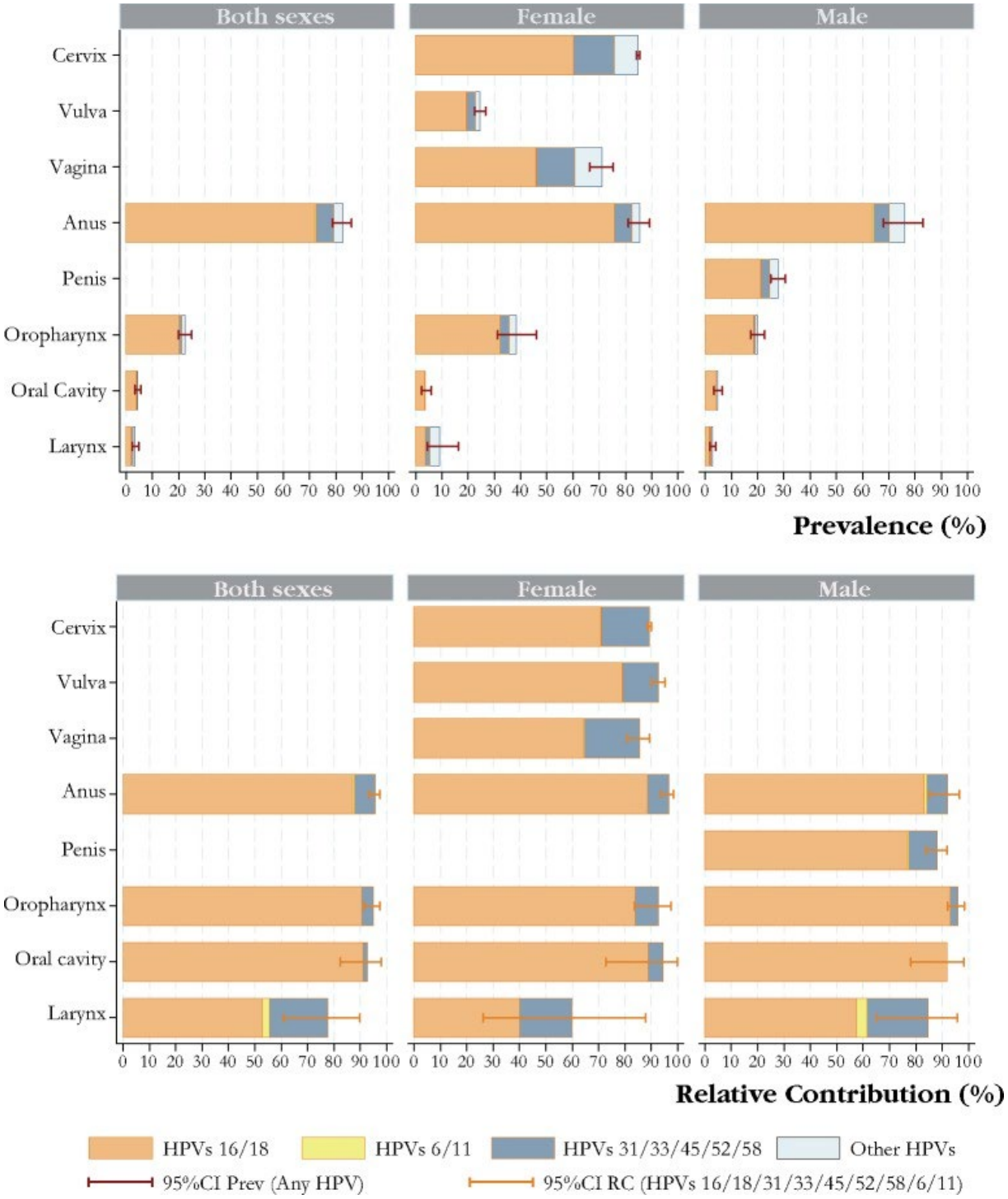


Figure 2: Estimated aged-standardised incidence rates for penis cancer in 2020, from age 10+ years (source Cancer Today, IARC)



The estimated impact of using 9vHPV globally, is a 90% reduction in cervical cancers and 50% reduction in HPV-related cancers. A histological study detected and typed HPV DNA from 18,247 paraffin-embedded specimens collected from 50 countries to examine the additional benefit of 9vHPV vaccine on cancer cases.[5] When comparing world regions, in general, there were slight but not statistically significant regional variations in relative contribution of the nine HPV types. The only exception was for cervical cancer in Africa, Asian and Oceania (World – 89.3%, Africa – 86.3% and Asian and Oceania – 91.2%, $p < 0.05$). In males, the relative contribution of HPV-16/18 was higher in oropharynx cancer than for anal and head and neck cancers ($p < 0.05$) (see Figure 3). Considering the type-specific prevalence estimates in this study and the estimated number of incidences of HPV-related cancer-site cases, the fraction of cancers preventable by 9vHPV vaccine is potentially around 50% worldwide. This includes most cervical and anal cancers, and a high proportion of vaginal, penile, vulvar and head and neck cancers.[5]

Figure 3: Worldwide HPV prevalence and relative contribution in HPV-related cancers, by sex. (de Sanjosé 2018, open access)



95% CI = 95% confidence interval (one-sided, 97.5% CI calculated when appropriate); Cervix = based on HPV DNA; HPV = human papillomavirus; Other locations = based on information on three markers (HPV DNA + (E6*I mRNA or $p16^{INK4a}$)); Prev = prevalence and type-specific relative contribution estimations.

Prevalence of HPV infection in gay and bisexual men

A study investigated the prevalence of HPV types in MSM in a sexual health clinic in Melbourne, Australia. A time-limited catch-up programme in Victoria offered gay and bisexual MSM up to age 26 years 4vHPV vaccination during 2017. Prior to receiving the first 4vHPV doses, more than half (56.5%) of the 496 MSM aged 20–26 years had high-risk HPV types in the anus. Almost half (43.1%) had at least one vaccine-type HPV infection (6, 11, 16 or 18) and 21.0% had HPV-16. Of the participants, 75% had at least one HPV

genotype detected anally and 56% had at least one high-risk HPV type.[40] These results demonstrate that herd immunity from female-only vaccination does not protect all males, and the validity of gender-neutral vaccination programmes.

Epidemiology of HPV-associated disease in New Zealand

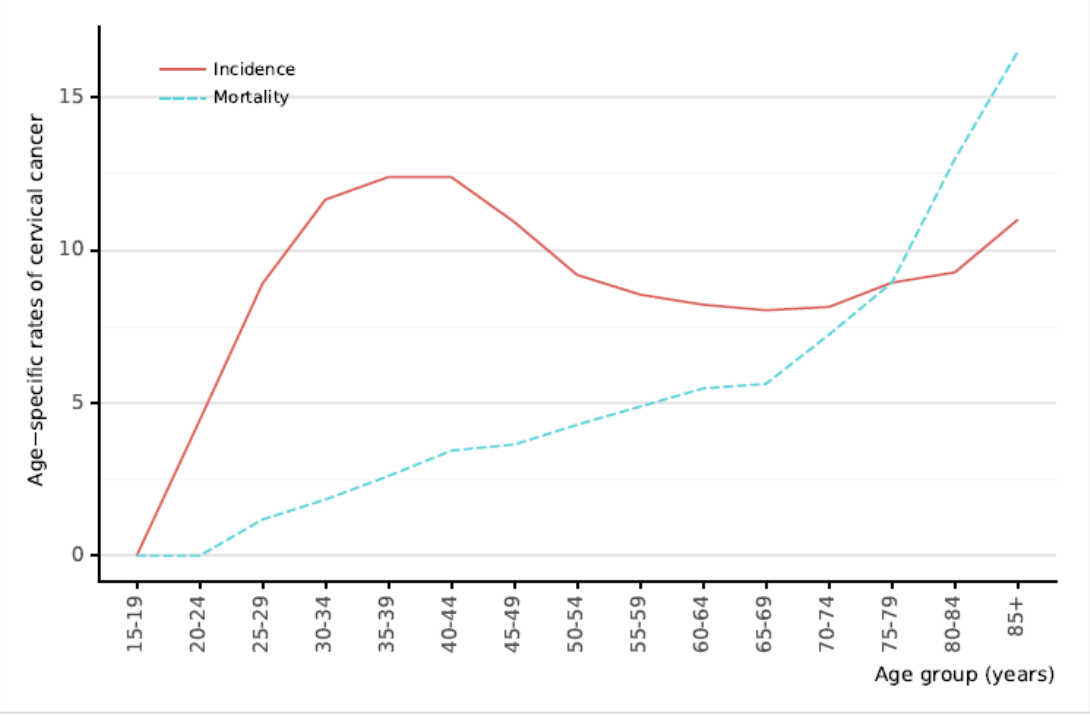
Information about HPV-related cancers in New Zealand is prepared by the HPV Information Centre at the Institut Català d'Oncologia (ICO) in Barcelona, Spain, as part of the World Health Organization International Agency for Research on Cancer (IARC).[2]

In 2021, the estimated HPV vaccine coverage in NZ was 68% for first dose and 48% for last dose.[2]

Cervical cancer

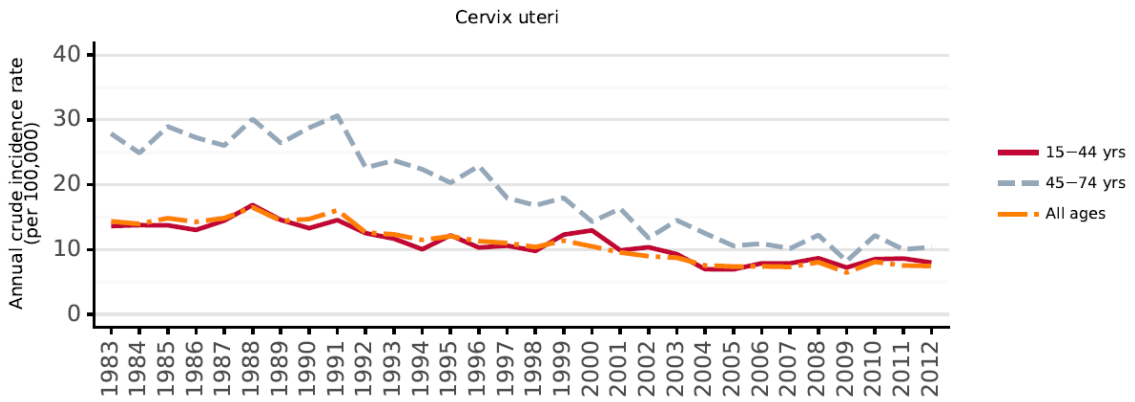
In New Zealand, approximately 2.13 million of women aged from 15 years are at risk for cervical cancer. Annually, as estimated in 2020, there are 174 cervical cancer cases (incidence rate [IR] of approximately 7.1 cases per 100,000 women per year) and 81 cervical cancer deaths (IR 3.3 per 100,000 women per year).[2] Cervical cancer is the 12th leading cause of cancer and 15th leading cause of cancer deaths in all females (excluding non-melanoma skin cancer). In women aged 18–44 years, cervical cancer is fourth most common cancer and third cause of cancer deaths. The age-specific rates of death due to cervical cancer increase with age (see Figure 4), particularly from age 70 years. Cervical cancer incidence has declined (see Figure 5), due in part to the introduction of the National Cervical Screening Programme in 1990 for those aged 20–70 years. Screening moved to ages 25–69 years in 2019. In September 2023, routine screening will change from 3-yearly liquid-based cytology to 5-yearly self-testing for HPV infection.

Figure 4: Comparison of age-specific cervical cancer incidence and mortality rates in NZ (estimates for 2020); source ICO/IARC report 2023



Data accessed on 27 Jan 2021
For more detailed methods of estimation please refer to http://gco.iarc.fr/today/data-sources-methods
[a] Rates per 100,000 women per year
Data Sources:
Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I, Bray F (2020). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [27 January 2021]

Figure 5: Time trends showing a decline in cervical cancer incidence in New Zealand (cancer registry data); ICO/IARC report 2023



HPV types 16 and 18 are highly prevalent in cervical cancer lesions in NZ: in 76.6% of cervical cancer, 65.3% of high-grade cervical lesions (CIN-2 or higher), 27.1% of low-grade cervical lesions (CIN-1) and 8.3% of those with normal cytology.[2] HPV types 31, 33, 35, 45, 52 and 58 were detected in 4% – 18% of high grade lesions in NZ in 2014–2015.

Other anogenital cancers

Potentially vaccine-preventable, the presence of HPV DNA has been linked to other anogenital cancers in males and females, including anus, vulva, vagina and penis. Presented in Table 1 are the crude incidence rates of HPV-associated cancer.

Table 1: Crude incidence rates per 100,000 population for HPV-associated cancer in New Zealand (ICO/IARC report 2023)

Cancer type	Male	Female
Cervical	-	7.10
Anal	1.14	1.84
Vulva	-	2.65
Vaginal	-	0.73
Penile	0.89	-
Oropharyngeal	3.08	0.77
Oral cavity	8.78	4.08
Laryngeal	3.71	0.65

Anal cancer is rare, with a global rate of around one case per 100,000 general population. Women have a higher incidence of anal cancer than men generally (45 vs 27 new cases annually in NZ). The highest incidence is in men-who-have-sex-with-men, in women with a history of cervical or vulvar cancer and those who are immunosuppressed (including people living with HIV and organ transplant recipients).[2] Generally, incidence increases with age from around 40 years. The mortality rate of new cases is similar between males and females (crude IR 0.55 per 100,000 men or 0.53 per 100,000 women).

Vulval cancer is rare among women worldwide, accounting for 6% of all gynaecological cancers in 2018, and 60% of identified cases occurring in more developed countries. Two forms are known: basaloid/warty lesions seen in younger women are often associated with HPV DNA detection; and the majority (60%) are

keratinising carcinomas occurring in older women that are rarely associated with HPV. In NZ in 2020, there were 65 new cases (crude IR 2.65/100,000 women per year) and 21 deaths (crude mortality rate 0.86/100,000 women per year) mostly in older women aged over 70 years.[2]

Vaginal cancer represents 3% of gynaecological cancers in the world, with 68% occurring in less developed countries. Around 90% are attributable to HPV. Invasive vaginal cancer is rare in younger women, with a peak in incidences between ages 55–70 years. In 2020 in NZ, there were 18 new cases (IR 0.73/100,000 women) and nine deaths (crude mortality rate 0.37/100,000 women).[2]

Penile cancer rates strongly correlate with those of cervical cancer worldwide. It most commonly affects men aged 50–70 years. Like vulval cancer, HPV is most detected in basaloid/warty tumours and less common in keratinising/verrucous tumours. In 2020, there were 21 new penile cancer cases (IR 0.89/100,000) and four deaths (crude mortality rate 0.17 per 100,000 men per year).[2]

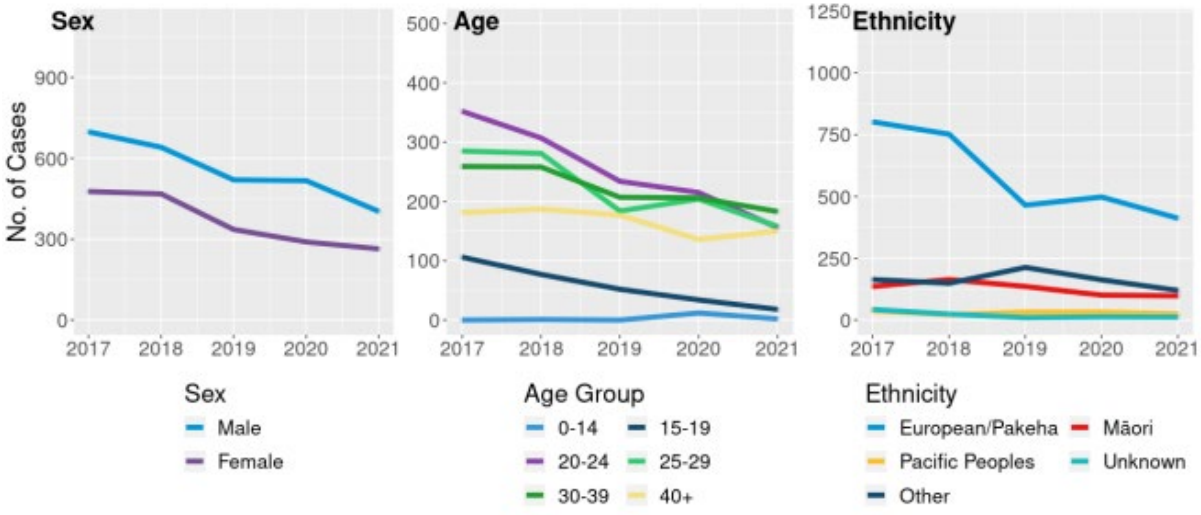
Head and neck cancers

Most head and neck cancers are associated with high tobacco and alcohol consumption. HPV infection has been particularly associated with oropharyngeal cancer and HPV-16 has been associated with cancers of the tonsil, base of tongue and other oropharyngeal sites. Prevalence is higher in males than females in NZ (73 vs 19 new cases annually in 2020; crude IR 3.08 vs 0.77/100,000). Peak age is around 55–59 years. Mortality rate was 0.76 vs 0.33 in men and women, with 18 vs eight deaths in 2020. An association between HPV and laryngeal cancer has not yet been established.[2]

Genital warts

HPV types 6 and 11 are associated with genital warts. Sexual Health and Family Planning clinics report first presentations for genital warts to ESR. During 2017–2019 (see Figure 6), cases numbers among European and Other (NZE/O) ethnicity declined substantially by 42% following the introduction of vaccination of boys. This decline was not observed in Pacific (16% decline) and Māori ethnicities (remained unchanged).[4]

Figure 6: Declines in genital warts cases reported by New Zealand sexual health and family planning clinics, by age, sex and ethnicity from 2017-2021; source ESR 2022.



In 2020, cases of genital warts continued to decline in females but remained steady in males and in all ethnic groups (except NZE/O with a 7% increase between 2019 and 2020).[4] In 2021, 60% of genital wart cases were in males, despite a 20% reduction from 2020 and a 9% reduction in females.[41] Cases increased

for those aged over 40 years. Largest reductions occurred in European (17.3%), Other 26.4% and Pacific (21.9%) ethnicities but only a 3% reduction for Māori.

HPV vaccination in New Zealand

HPV vaccines

The HPV vaccines approved for use in NZ contain recombinant HPV capsid L1 proteins forming virus-like particles grown in yeast cells.[42] The quadrivalent HPV vaccine (4vHPV) was superseded by the nonavalent (9vHPV) formulation in 2017.

- 4vHPV: Gardasil® – HPV types 6, 11, 16 and 18
- 9vHPV: Gardasil 9® – HPV types 6, 11, 16, 18, 31, 33, 45, 52, 58

Also used elsewhere is a bivalent HPV vaccine (2vHPV), Cervarix (GSK), which contains recombinant L1 proteins for HPV types 16 and 18 only in virus-like particles with a proprietary adjuvant.

Timeline of HPV vaccine use in New Zealand

For a summary timeline of HPV immunisation in NZ, see Table 2.

Table 2: Timeline of HPV immunisation in New Zealand, to June 2023

Year	Vaccine	Doses	Funded group
2008	4vHPV	3 doses (at 0, 2, 6m)	Females, aged 12 years, with catch up if born from 1990
2013			Plus, males with HIV <26years, transplant patients
2014			Plus, females aged 9–20 years and all aged <26 with HIV
2015			Plus, other immunocompromising conditions
2017	9vHPV	2 doses for those aged 9 – <15 years (0, 6–12m)	Funding including all males aged 9–26 years; Licensure for females aged 9–45 years
2023		Or 3 doses for those aged ≥15 years or with immunocompromised	Licensure expanded to all males aged 9–45 years (funded to age 26 years)

The first HPV vaccine to become available in Aotearoa New Zealand in 2008 was a quadrivalent HPV (4vHPV; Gardasil® [Merck Sharp and Dohme; supplied in NZ by Seqirus]). It contains virus-like particles expressing four HPV types: low-risk types 6 and 11 that cause genital warts and high-risk oncogenic types 16 and 18 linked to cervical and other anogenital cancers and oral cancers. The initial vaccination programme gave three doses (0, 2 and 6 months) to girls at ages 11 or 12 years in school year 8 with catch-up for those born from 1990. In 2013, 4vHPV became available for transplant patients in hospital and males under the age of 26 years with confirmed HIV infection. In 2014, 4vHPV was recommended and funded for girls and women aged 9–20 years (optimally at age 11–13 years), transplant patients, and all people living with HIV (PLHIV) aged under 26 years. It was recommended but not funded for individuals aged under 26 years with other immunocompromising conditions, men-who-have-sex-with-men and all boys and young men aged under 20 years. Extension of funded vaccine to other immunocompromising conditions commenced in in 2015.

In 2017, a nine-valent vaccine (9vHPV; (Gardasil 9) superseded 4vHPV to provide protection against an additional five high-risk HPV types. All males ages 9–26 years were offered funded 9vHPV. Adolescents

aged 9–14 years receive two doses given 6–12 months apart. Three doses (given at 0, 2, 6 months) are recommended for those aged 15 years and over and all aged 9–26 years with immunocompromising conditions. In 2023, Medsafe extended approval of 9vHPV to males as well as females aged 9–45 years (funded for males and females ages 9–26 years).

International recommendations for HPV vaccine use

Below are examples of recommended schedules in other high-income countries.

Australia

The Australian technical advisory group for immunisation recommends a single dose of 9vHPV for immunocompetent individuals aged 9–25 years (optimally aged 12–13 years). Three doses of 9vHPV (or 2vHPV) given at 0, 2 and 6 months are recommended for those aged 26 years and over and for those at any age who are immunocompromised (excluding asplenia and hyposplenia). HPV vaccination is particularly recommended for men-who-have-sex-with-men (MSM) of any age (as of 30 January 2023[43]).

UK

From September 2023, the UK introduced a single dose schedule of 9vHPV for children aged 12–13 years (school year 8) and for eligible MSM aged under 25 years. Gay, bisexual and other MSM are eligible for two doses of funded vaccine, given 6–24 months apart, from age 25 – 45 years if attending sexual health or HIV health services. Three doses are offered to PLHIV and those who are immunocompromised at the time of vaccination (as of 1 September 2023[44]).

Canada

Two doses of HPV vaccine for immunocompetent males (4v or 9vHPV) and females (2v, 4v or 9vHPV) age 9-15 years given minimum of 6 months apart. Three doses for those aged over 15–26 years and of any age with immunocompromise or PLHIV. Vaccine may be given to men and women aged over 27 years if at ongoing risk of exposure (as of 23 September 2021[45]).

US

The Centers for Disease Control and Prevention (CDC) recommends HPV vaccine routinely at ages 11 or 12 years, starting from age 9. For those initiating vaccination ages 9-14 years, two doses 9vHPV given 0, 6–12 months and three doses for ages 15-45 years and immunocompromised (0, 1-2, 6m) (as of 16 November 2021[46]). The CDC's Academic Committee for Immunization Practices reviewed the evidence for one dose at its meeting in June 2022.[47]

Impact of HPV vaccination programmes

One measure of how a vaccine programme is performing is to assess the population-level impact of the vaccine on the disease incidence before and after the introduction of the vaccine. See Table 8 for a summary of the evidence presented in this section.

Impact of HPV vaccination in New Zealand

The Auckland Sexual Health Service recorded an 83.4% reduction in genital wart diagnoses over five years from 2008–2013, after New Zealand introduced the 4vHPV vaccine to schools in 2009. Vaccination coverage was 56% for the 1993 birth cohort. The modelled relative risk for genital warts for females eligible

for vaccine, from one year to the next, was significantly lower than for those not eligible. In the vaccine-eligible cohorts (ie those aged <20 years at time of vaccine introduction in 2009), the relative risk of a genital wart diagnosis per year was 0.98 (95% CI 0.84–1.13) pre-vaccine, and post-vaccine was 0.77 (0.74-0.81; p=0.004). The modelled relative risk in genital wart diagnoses was not significantly different (p = 0.53) to females in males of an equivalent age to the vaccine eligible and not eligible females.[7]

A retrospective cohort study linked data from the New Zealand National Immunisation Register and the National Cervical Screening Programme between 1 January 2010 and 31 December 2015. It investigated the impact of 4vHPV vaccination on abnormal cervical cytology and histology rates in a total of 104,313 women (374,402 person-years of follow-up) aged 20–24 years.[8] The incidences for high-grade cytology and for high-grade histology were significantly lower in women who had been vaccinated with at least one dose of 4vHPV before age 18 years than those who were unvaccinated: cytology incidence rate ratio [IRR] 0.75, 95% CI 0.70–0.80 (p < 0.001); histology IRR 0.69, 0.64–0.74 (p < 0.001). Overall, and when taking vaccination status into account, the incidence of high-grade histology between Māori and European women did not differ.[8]

Impact of HPV vaccination in other countries

A systematic review conducted by Wang et al (2022) updated an earlier review[48] of evidence of the real-world impact of HPV vaccination (with 2vHPV and 4vHPV).[9] The review included 99 publications with the endpoints of genital HPV infections, anogenital warts and cervical lesions from 1 March 2016 to 31 March 2020. It also included 15 publications with expanded endpoints, including RRP, oral and anal HPV infections, oropharyngeal and anal lesions, from January 2007 to March 2020. The review represented a total of 138 studies from 23 countries. Below are the key findings.

- Australia, Europe, North America and New Zealand recorded reductions in infection, anogenital warts and cervical lesions.
- The updated review also showed a positive impact and effectiveness in low- and middle-income countries, which have the highest burden of disease.
- High vaccination coverage given prior to sexual debut results in the largest benefit.
- Vaccinating males and females beyond adolescent age is beneficial. Implementation of multi-cohort strategies achieves faster outcomes.
- Vaccine-type HPV positivity was reduced by up to 96% in females targeted by national immunisation programmes
    - with evidence of a decrease in HPV infection in unvaccinated females, and
    - more than 70% reduction in vaccine-type HPV among men with high coverage of female-only programmes.

Impact on cervical intraepithelial neoplasia and cervical cancer

As an update of an earlier systematic review and meta-analysis,[49] Drolet et al (2019) investigated the population-level impact of vaccination of women and girls against HPV infection, anogenital wart diagnoses and CIN2+.[10] Published between Feb 2014 and Oct 2018, 65 articles from 14 high-income countries were included, which covered data from 60 million individuals and up to 8 years post-vaccination follow-up. By 5–8 years after vaccination, the prevalence of types HPV-16/18 and HPV-31/33/45 decreased significantly in vaccine-eligible cohorts (see Table 3). Anogenital wart diagnoses significantly reduced in both males and females. CIN2+ prevalence also decreased significantly 5–9 years after vaccination. The review also found

that programmes with multi-cohort vaccination and high vaccination coverage had the greatest direct impact and herd effects when compared with programmes with single-cohort vaccination or low routine coverage.[10] This study was conducted prior to the introduction of 9vHPV, and only some countries had gender-neutral vaccination to include boys.

Table 3: Population-level reductions of HPV-associated disease following HPV vaccination programmes, summary of systematic review and meta-analysis evidence (adapted from Drolet et al, 2019)

HPV-associated infection	Age group	Percentage reduction	Relative risk (95% CI)
HPV 16/18	girls 13-19 years	83%	0.17 (0.11-0.25
	women aged 20-24 years	66%	0.34 (0.23-0.49)
HPV types 31, 33 and 45 (cross-protection)	girls aged 13-19 years	54%	0.46 (0.33-0.66)
Anogenital wart diagnoses	girls aged 15–19 years	67%	0·33 (0·24–0·46)
	women aged 20–24 years	54%	0·46 (0.36–0.60)
	women aged 25–29 years	31%	0·69 (0·53–0·89)
	boys aged 15–19	48%	0·52 (0·37–0·75)
	men aged 20–24	32%	0·68 (0·47–0·98)
CIN2+	screened girls aged 15–19 years	51%	0·49 (0·42–0·58)
	women aged 20–24 years	31%	0·69 (0·57–0·84)

An observational study published in 2021 found that the HPV immunisation programme (2vHPV) in the UK had almost successfully eliminated cervical cancer in women born since 1 September 1995.[50] The study analysed 13.7 million-years of follow-up of women aged 20 to under 30 years to evaluate the incidence of CIN and cervical cancer since the introduction of the HPV immunisation programme. Cervical cancer and CIN3 incidence reduced the most in those offered HPV vaccine at ages 12–13 years. The estimated relative reduction in cervical cancer rates, compared with a reference unvaccinated cohort (born between May 1989 and Aug 1990), was:

- 34% (95% CI 25–41%) for those offered vaccine at age 16–18 years
- 62% (52–71%) for those aged 14–16 years
- 87% (72–94%) for those aged 12–13 years.

The corresponding risk reductions for CIN3 were 39% (36–41%), 75% (72–77%), 97% (96–98%), respectively.[50] Vaccine coverage for at least one dose ranged from 60.5 to 88.7%, and for all three doses from 44.8 to 84.9% (including catch-up vaccinations) in the vaccine-eligible cohorts.[50]

Impact on penile HPV infection

Following the implementation of school-based HPV vaccination in males as well as females in Australia, a study conducted between 2014 and 2017 investigated the prevalence of penile HPV infection in sexually active heterosexual males.[51] Males aged 17–19 years were genotyped for 37 HPV types, including 13 high-risk types.[51] The prevalence ratios were adjusted between two periods: 2014–2015 (preceding vaccination of males, n = 152) and 2016–2017 (males eligible for school-based vaccination, n = 146). The investigators used the National HPV Vaccination Programme Register to confirm vaccination status. A national school-

based HPV vaccination programme began in 2007 for girls aged 12–13 years with a three-year catch-up programme for those aged up to 26 years (with three doses). In 2013, vaccination was extended to boys aged 12–13 years with a catch up to age 15 years until end of 2014. The study included nine (5.9%) males vaccinated during the pre-male vaccination period and 81 (55.5%) vaccinated with at least one dose of 4vHPV when boys were eligible for vaccination. Compared with the 2014/15 period, the prevalence of penile 4vHPV types in 2016/17 was lower but not statistically significant (0.7% [95% CI 0–3.8%] vs 2.6% [0.7–6.6%] p = 0.371). The prevalence of any of the 37 HPV types (11.6% vs 21.7%; p = 0.021) and the 13 high-risk HPV types (7.5% vs 15.8%; p = 0.031) was significantly lower in 2016/17 than 2014/15. However, after adjusting for age and source of recruitment, there was no statistically significant difference in HPV prevalence across all groups, between those recruited in 2016/17 and 2014/15, and across the whole study period between those partially or fully vaccinated and those who were unvaccinated. It appeared that herd immunity from the female vaccination programme reduced prevalence in heterosexual males. Prevalence of 4vHPV types was 22% in 2006/2007 in those aged ≤21 years. This study only investigated heterosexual men. The impact of universal HPV vaccination is likely to be of greatest benefit to gay and other MSM who may not receive herd protection from female-only programmes and are at high risk of anogenital cancer.[51]

Conclusions of the impact of vaccination programmes

The HPV vaccination programme has made a positive impact in New Zealand on genital wart and cervical dysplasia diagnosis. Systematic reviews of international literature also support these observations with larger populations.

- Reported HPV infection, anogenital warts, cervical lesions and penile lesions have reduced.
- Countries with the highest burden of disease see the greatest impact.
- Multi-cohort vaccinations achieve the fastest outcomes, including vaccination beyond adolescence for males and females.
- Vaccination considerably reduces vaccine-type HPV infections (by up to 96 percent). This also provides some herd immunity to unvaccinated individuals.
- Countries with the highest vaccine uptake, particularly when vaccinated prior to sexual debut, see the largest direct and herd impacts.

Vaccine safety

The safety of HPV vaccines has been well characterised across multiple studies and meta-analyses over the last almost two decades. As reviewed previously, HPV vaccines have demonstrated excellent safety profiles and extensive post-licensure studies have found no safety signals of concern.[52] Vaccine reactogenicity and adverse events following immunisation (AEFI) that were identified in licensure clinical trials are well characterised and have not been presented in this review. See Table 5 for a summary of the evidence presented below.

Systematic reviews of vaccine safety

The pivotal clinical trials for 9vHPV and a systematic review by Bergman et al (2019) found that 9vHPV was slightly more reactogenic than its predecessor 4vHPV. It had a slightly increased the risk of local (RR 1.07, 95% CI 1.05–1.08) and common systemic adverse events (1.01; 0.98–1.04) in males and females.[15] Empirical studies have not found any serious adverse outcomes causally associated with 2vHPV, 4vHPV or 9vHPV vaccination. These outcomes included postural orthostatic tachycardia syndrome (POTS), chronic regional

pain syndrome (CRPS),[53, 54] premature ovarian insufficiency (POI)[55] or demyelinating diseases[56] in girls, and autoimmune disorders in girls[11, 57] and boys.[58]

A systematic review and meta-analysis by Willame et al (2020) found no clear association between HPV vaccines and these conditions.[59] The review included 22 post-licensure observational studies on HPV vaccination and autoimmune and other rare adverse events. The meta-analysis covered 35 diseases that corresponded to 48 pooled risk estimates, the majority of which (43/48) showed no significant risk. The most frequently assessed were type-1 diabetes (11 studies), immune thrombocytopenia purpura and thyroiditis disease (eight studies each). Studies observed positive and negative associations with a range of diseases, but interpretation of the findings requires caution due to diversity in methodological approaches, age groups and vaccine comparisons. There was no evidence of a consistent safety signal for autoimmune conditions associated with HPV vaccination.[59]

Real-world safety surveillance data

No new safety concerns have been related to 9vHPV vaccination. The safety profile of this vaccine is consistent with that established in previous HPV vaccine studies and surveillance.

A retrospective cohort study compared the risk of emergency department visits and hospitalisation during defined intervals soon after vaccination with 9vHPV and later.[11] A total of 330,774 doses of 9vHPV were given to 215,965 male and female Kaiser Permanente Northern California members aged 9 years or over who received at least one dose of 9vHPV, and of these, 140,628 had no prior HPV vaccination. Conditional logistic regression compared the odds of events in the post vaccination risk intervals (days 0–14 and 0–60) and the odds of events during control intervals (days 61–75 and 61–120). Also characterised were prespecified events (allergic reaction and syncope) on the day of vaccination and all deaths during the study period. The median age for the first dose was 12–13 years and 77% received at least one concomitant vaccine. Of the 18 event categories that were significantly elevated, findings for most were either previously known, preceded vaccination or had other causes. Rates of allergy (five cases, all received other vaccines concomitantly) and syncope (18 cases, 11 with other vaccines) were infrequent but potentially related to vaccination. The estimated incidence rate for post-vaccine allergic reactions was 15.1 (95% CI 4.9–35.3) per million doses of 9vHPV and syncope was 54.4 (32.3–86.0) per million doses. The rate of deaths was consistent with the background rate and none were considered related to 9vHPV.[11]

Therapeutics Goods Administration (TGA) in Australia conducted surveillance over 11 years following 9 million doses of 4vHPV (from 2007 to 2017 for females and 2013 to 2017 for males). It included enhanced surveillance during 2013–2014 to monitor the addition of HPV vaccination in males to the immunisation programme.[12] From 4,551 AEFI reports, no unexpected patterns of concern were found. The data were consistent with similar surveillance internationally. TGA rarely received reports of adverse events of special interest, which were not causally associated with vaccination (including spontaneous reporting of POTS CRPS, Guillain-Barré syndrome, POI, venous thromboembolism). There were 856 reports of syncope (overall rate 9.11 per 100,000 doses) and 30 reports of anaphylaxis (overall rate 0.32 per 100,000 doses, six of these were cases given concomitant vaccines DTaP, HepB and/or influenza). More than half of the syncope cases were reported during a period of enhance surveillance (n = 453; rate 29.6 per 100,000 doses). Syncope reporting was three times higher in those aged 12–13 years compared with the rate in 14–15-year-olds (10.7 per 100,000 doses in enhanced surveillance).[12]

Inadvertent HPV vaccination in pregnancy

Few studies have evaluated exposure to 9vHPV in pregnancy. A systematic review and meta-analysis conducted by Dousti et al (2023), based on almost 1.4 million individuals across seven articles, did not show

an increased risk for miscarriage (risk ratio [RR] 1.18 [0.58–23.8]) or stillbirth (2.01; 0.66–6.13) in those who were vaccinated with HPV vaccines during pregnancy [note, these numbers were taken from Forrest plot figures, not as given in text, as they differed slightly]. However, it is recommended to wait until after pregnancy to vaccinate while data is limited.[13]

Further supporting previous studies, an evaluation of the safety of inadvertent vaccination with 4vHPV in pregnancy found no associations between vaccination and adverse pregnancy or infant outcomes. Out of 90,600 pregnancies, in women aged 17–28 years on active US military duty between 2007 and 2014, approximately 2% were exposed to 4vHPV during pregnancy (including 1,775 pregnancies and 1,441 infants).[60]

A cohort study using the Vaccine Safety Datalink network in the US found no increased risk for pregnancy or infant outcomes when 9vHPV is administered around the time of or during pregnancy. The study included 1,493 pregnancies among women with a mean age 23.9 years (standard deviation ± 2.9). Of these, 445 (29.8%) received 9vHPV during pregnancy, 496 (33.2%) during peri-pregnancy and 552 (37.0%) received 4HPV or 9vHPV distally to pregnancy. Vaccine administered in pregnancy compared with those distally exposed was not associated with an increased risk of miscarriage (spontaneous abortion, hazard ratio 1.12, 0.66–1.93) nor for perinatal exposure (RR 0.72, 0.42–1.24). Among the live births (n = 1,409), there was no increase in risk for premature birth (RR 0.73, 0.44–1.20) or small-for-gestation-age (RR 1.31, 0.78–2.20) when vaccinated in pregnancy. Neither did the risk of preterm birth (RR 0.72, 0.45–1.17) and small-for-gestational-age (RR 1.10, 0.65–1.88) increase when vaccinated peri-pregnancy.[14]

Conclusion

Multiple global studies have assessed safety since the first approval for use of HPV vaccines. The findings have been consistent:

- These vaccines are not associated with long-term safety concerns and there is no evidence of association with autoimmune or neurological disease.
- Immediate adverse responses are rare. Estimated rate of severe allergic reactions is 15.1 million doses. Estimated syncope rate is around 50 cases per million doses of 9vHPV. Most reported cases concurrently received other vaccines.
- Syncope is likely to be an immunisation stress-related response in teenagers and can lead to fall-related injuries if not precautious.
- There are no concerns around receiving HPV vaccines in pregnancy, but ideally out of an abundance of caution, wait until after delivery before vaccinating a pregnant person.

Routine schedule with two or three doses

Immunogenicity

Many studies have used immunogenicity of antibody responses and seroconversion rates as a proxy for efficacy when comparing vaccines, dose numbers and timing. However, no serological correlate of protection is defined, and other components of the immune system are likely to play roles in the long-term, vaccine-induced immunity against HPV. It has been postulated by J Brotherton (NCIRS webinar, May 2023)[61] that the vaccine virus-like particles behave more like whole virus than a free subunit vaccine, inducing a broader and stronger immune response.

Since there is no correlate of protection for HPV-neutralising antibodies, it is not clear if: [62]

a) the quantity of neutralising antibody induced by a single dose drops below a protective threshold faster than multiple doses

b) low levels of antibody, below assay detection levels, are adequate for long-lasting protection

c) non-neutralising antibodies play a role in immunity to kill HPV-infected cells

d) cellular immune responses driven by the inflammatory response to intramuscular injection play a greater role in HPV immunity than humoral antibody responses.[62]

Presented below is a selection of published immunogenicity data, based on putative seroprotection levels and antibody titres, upon which a proxy for efficacy has been based. See Table 6 for summary of evidence.

A Cochrane systematic review by Bergman et al (2019) compared different types and schedules of HPV vaccine in males and females aged 9–26 years. The evidence to September 2018 included 20 RCT with 31,940 participants and follow-up ranged from 7 months to 5 years.[15] The review found that most studies comparing two or three doses focussed on immune response rather than infection or disease outcomes. The immunogenicity of two doses was similar to three doses. Longer intervals between the doses (up to 12 months) gave stronger antibody responses than shorter intervals and to at least 36 months follow-up post vaccination.[15]

Co-administration with other vaccines

A systematic review and meta-analysis by Li et al in 2019 found no evidence of interference between the immune response of HPV vaccines (2vHPV, 4vHPV and 9vHPV) and the other routine vaccines, including combined hepatitis A and B vaccine, Tdap, Tdap-IPV or MenACWY, when given concurrently to 9–25-year-olds. HPV vaccines are highly immunogenic.[16]

Long-term immunogenicity

The long-term immunogenicity after vaccination with three doses of 9vHPV was followed up for 8 years in girls and boys vaccinated between ages 9–15 years (n = 1,272). Sustained anti-HPV antibody responses were observed for at least 7 years. Seropositivity rates of over 90% remained for each of the 9vHPV types to at least 90 months post vaccination. GMTs peaked at around 7 months and sharply declined for the first 12 months, then plateaued around 24 months with a gradual decrease out to 90 months.[17]

Immunogenicity in people living with HIV

People living with HIV are highly recommended to receive at least two, preferably three doses, of HPV vaccine due to immunocompromise, regardless of antiretroviral therapy status.[6] A systematic review and meta-analysis conducted by Staadegaard et al (2022) found evidence that seropositivity declines with time following three doses of 2vHPV, 4vHPV and 9vHPV more rapidly in those who are HIV-positive compared with those who are HIV-negative. Pooled proportion of seropositivity at 28 weeks following three doses was around 100% for those who received 9vHPV vaccine against HPV-16 and HPV-18 types. The evidence suggested that seropositivity declines with time after vaccination but can last for at least 2–4 years in PLHIV.[18]

Conclusions

HPV vaccines induce a strong immune response, with most recipients demonstrating seroconversion to vaccine-type anti-HPV IgG antibodies. Long-term immunogenicity of two or three doses lasts for at least 8 years in immunocompetent young people. Seropositivity declines more rapidly, within 2–4 years, in PLHIV who received three doses 9vHPV.

Vaccine effectiveness of two or three doses

Early data on HPV vaccine effectiveness focused on genital wart incidence and rates of persistent HPV infection. Given sufficient time, studies investigated the protection against high-grade cervical lesions. After almost two decades of use, data is now available looking at the prevention of cervical cancer, other anogenital intraepithelial neoplasia and head and neck cancers. Presented below are recent data and systematic reviews of 4vHPV and 9vHPV vaccine efficacy and effectiveness. See Table 7 for a summary of the evidence.

Significant reductions have been shown in the incidence of HPV infection and related diseases, especially in countries with high vaccine uptake prior to HPV exposure.[63] The effectiveness for one or more doses of HPV vaccine is estimated to be 83.0 – 96.1%. Maximal reductions have been reported of approximately 90% for persistent HPV-6, 11, 16 and 18 infections, 90% for genital warts, 45% for low-grade cytological cervical abnormalities and 85% for histologically proven high-grade cervical abnormalities.[63]

Most of the studies included in the Cochrane systematic review by Bergman et al (2019), which compared different types and schedules of HPV vaccine in males and females aged 9–26 years, focussed on the immune response to HPV vaccines rather than disease and infection outcomes.[15] No studies had evaluated the efficacy of 9vHPV in males. With moderate certainty of evidence, one reviewed study found that 4vHPV given to men aged 16–26 years provided better protection than control against external genital lesions and genital warts (for up to 3 years follow-up). In females aged 16–26 years, three doses of 4vHPV and 9vHPV provided equivalent levels of protection against cervical, vaginal and vulvar precancer lesions and cancer (high-certainty, at up to 4.5 years follow-up).[15]

Vaccine-type HPV infection

Markowitz et al (2022) conducted a systematic review of data published between 2007–2021 from national immunisation programmes. They examined the effectiveness of HPV vaccine by the number of doses, against a range of endpoints including HPV types 16 and 18 infection, anogenital warts and cervical abnormalities. The review included 35 studies, which were all deemed to have a high risk of bias. A confounder for bias included the demographics, age, and age of commencement of sexual activity in girls who had fewer than the recommended three doses. Most studies found the highest estimate of effectiveness following three doses. Eighteen out of 30 studies that evaluated single doses and 19 out of 29 studies that evaluated two doses demonstrated significant effectiveness. When studies were adjusted or stratified by age at vaccination, effectiveness was similar for three, two and one doses.[21]

An interim follow-up analysis assessed the durability of vaccine effectiveness against persistent infection after approximately 8 years, as part of a long-term extension of a phase III study. In the immunogenicity and safety study (NCT00943722), boys and girls were vaccinated at ages 9–15 years with three doses of 9vHPV.[17] No cases of vaccine-type HPV-related high-grade intraepithelial neoplasia or genital warts were observed in 1,107 participants for a median of 7.6 years (8.2 years maximum) after dose three. The incidence of six-month-persistent vaccine-type HPV infection or disease (49.2 per 10,000 person years in females and 37.3 per 10,000 person-years in males) was similar to that reported in other RCTs, and was significantly lower than seen in control groups in those RCTs.[17] Further data from this study is presented in the Medsafe Gardasil 9 datasheet. It shows that no cases of high-grade intraepithelial neoplasia or genital warts were observed for up to 11 years post dose three in girls (median follow-up 10 years) and to 10.6 years for boys (median 9.9 years).[42]

A study in the Netherlands found that the effectiveness of at least one dose of 2vHPV was 89.9% (95% CI 63.0% – 97.2%) against anal HPV-16/18 infection. It included 548 women aged 16–24 years visiting sexual health clinics.[19]

A systematic review by Harder et al (2018) evaluated the efficacy of HPV vaccination in males. Based on limited relevant data from seven studies, the review found that vaccination in males was moderately effective against persistent anogenital HPV infection at 46.9% (28.6 – 60.8%). But against persistent oral infections (88%; 2 – 98%), wide error bars were due to a lack of data. Vaccination prior to infection had the highest effectiveness and supported early vaccination before the onset of sexual activity.[22]

HPV-associated disease in females and males

Follow-up of 14,251 women who received three doses of 9vHPV or 4vHPV vaccines was part of a phase IIb/III RCT (NCT00543543). It found the efficacy of 9vHPV was 96.7% (95% CI 80.9% – 99.8%) against the additional five HPV types in this vaccine. The antibody response to 9vHPV against the 4vHPV-types (6, 11, 16, 18) was non-inferior to 4vHPV vaccination.[64] The rate of high-grade cervical, vulvar or vaginal disease, irrespective of HPV type (included and not included in the vaccines), was 14.0 per 1,000 person-years in both groups. This included participants with and without prevalent infection or disease. For those in the 9vHPV group, the rate of disease related to the additional HPV types (31, 33, 45, 52, 58) was 0.1 per 1,000 person-years and in the 4vHPV group was 1.6 per 1,000 person-years. Vaccination with 9vHPV did not prevent infection and disease beyond the nine types covered by the vaccine.[64]

A cohort of 602 healthy MSM aged 16–26 years from a larger double blind RCT were investigated for the efficacy of 4vHPV against anal intraepithelial neoplasia (AIN) compared with placebo.[65] Efficacy against AIN associated with HPV types 6, 11, 16 or 18 was 50.3% (25.7–67.2%) in the intention-to-treat population (who received at least one dose of 4vHPV) and 77.5% (29.6 – 93.3%) in the per-protocol population (who received three doses at months 0, 2, 6). The risks of persistent anal 4vHPV-type infection were reduced by 59.4% (43.0 – 71.4%) in the intention-to-treat group and 94.9% (80.4 – 99.4%) in per-protocol population.[65]

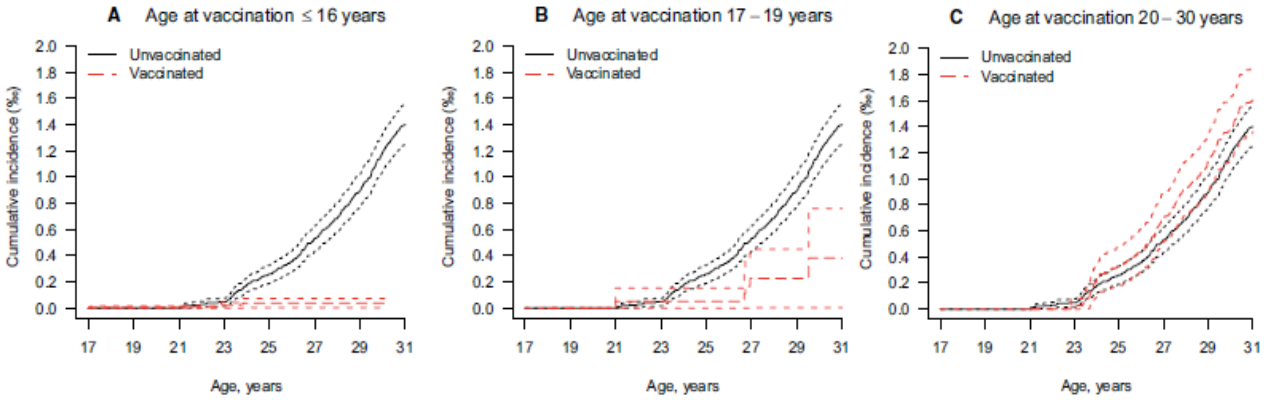
Cervical cancer

A Swedish study found that 4vHPV substantially reduced the risk of invasive cervical cancer in young women and girls (considered vaccinated if received at least one dose 4vHPV). The study followed an open population of almost 1.7 million women and girls aged 10–30 years from 2006–2017 through demographic and health registers. It assessed an association between HPV vaccination and risk for invasive cervical cancer.[20] The cumulative incidence of cervical cancer was 47 cases per 100,000 among vaccinated women and 94 cases per 100,000 among those unvaccinated (diagnosed in 19 women who received HPV vaccine vs 538 who had not). After adjustment for age at follow-up, the incidence rate ratio (IRR) was 0.51 (0.32–0.82). After adjustment for all covariates, IRR in those who had been vaccinated before the age of 17 years was 0.12 (0.00–0.34) versus 0.47 (0.27–0.75) for those vaccinated between ages 17–30 years, supporting vaccination at a younger age.[20]

A Danish study comprised a cohort of 867,689 women aged 17–30 years. It found that, compared with unvaccinated women, the IRR for cervical cancer was 0.14 (95% CI 0.04–0.53) for those who initiated vaccination aged ≤16 years (36.3% of cohort), and 0.32 (0.08–1.28) for those vaccinated between ages 17–19 years. For those vaccinated at age 20–30 years, compared with unvaccinated women, adjusted IRR was 1.19 (0.08–1.79) but with a 4-year buffer period (in which these women were counted as unvaccinated until 4 years after vaccination), adjusted IRR was reduced to 0.85 (0.55–1.32).[23] Women were followed from 1 October 2006 or their 17th birthday, whichever was later, until first diagnosis of cervical cancer, death, emigration or 31 December 2019, whichever was sooner. Of the vaccinated women, 78.5% received three

doses, 15.7% received two doses and 5.8% received one dose. The lack of immediate effect for older women indicated the importance of vaccination at an early age. During over 5.5 million person-years, out of a total of 504 women who developed cervical cancer, 325 were unvaccinated and 179 were vaccinated (crude IR 11.3 vs 6.7 per 100,000 unvaccinated vs vaccinated women). See Figure 7 for cumulative incidence by age group.[23]

Figure 7: Vaccination at a young age reduced the cumulative incidence of cervical cancer. For women vaccinated at A) age ≤16 years, B) 17–19 years and C) 20–30 years, by attained age and stratified by age at vaccination. (Kaejer et al 2021, open access)



Conclusion of the review of routine two- or three-dose schedules

HPV vaccination is highly protective against HPV-associated disease, particularly with high vaccine uptake prior to HPV exposure when aged under 16 years. The evidence shows that:

- Reductions of over 85–90% in persistent HPV infections, genital warts and high-grade CIN in vaccinated cohorts.
- The effectiveness of one, two or three doses were similar when adjusted or stratified by age at time of vaccination.
- Three doses of 9vHPV are highly protective (80.9–99.8%) against its additional five HPV types.
- Vaccine efficacy was 59% in MSM given at least one dose of 4vHPV and after three doses, efficacy was 95% against persistent anal vaccine-type HPV infection.
- Vaccination prior to exposure to HPV at an earlier age clearly provides the greatest protection.
- Data directly comparing two doses and three doses in those aged 17–25 years is limited. It is likely that two doses are more than sufficient for this age group to provide long lasting protection.

Evaluating the use of a single dose

Immunogenicity of a single dose

Studies specifically designed to compare one dose of HPV vaccines versus two or three doses are underway. Presented below are some of the interim results. Also available is observational data through earlier clinical trials and other studies for those who did not complete the full course.

One small study in Québec, Canada, found that all participants (n = 31) remained seropositive to each of the 4vHPV serotypes 3–8 years (mean 5.4 years) after one dose of 4vHPV. Furthermore, 58–87% of participants who had received only 4vHPV had cross-protective antibodies to the five other HPV types in

the 9vHPV vaccine.[28] These participants were subsequently given a dose of 9vHPV at age 13–18 years (mean 15.5 years). At one month after the 9vHPV dose, all participants were seropositive for all nine HPV types and had a 36.1–89.1 fold increase in antibody GMT against the nine vaccine-type HPVs (24.3–82.1 fold for those who were seropositive pre-9vHPV and 62.1–263.0 fold in those who were seronegative).[28]

In 2020, a systematic review by Secor et al found that a single dose of HPV vaccine (2vHPV or 4vHPV) did not meet immunogenicity non-inferiority compared with standard dose schedules in females aged 9–26 years.[24] Robust immunogenicity was demonstrated across all the multi-dose schedules and standard doses (three doses, 0, 2 and 6 months) (see Figure 8). However, not meeting non-inferiority criteria did not necessarily mean that the single dose will not confer adequate protection, since this study used GMT levels as a basis for the correlate of protection. Also, none of the studies were designed to assess single dose immunogenicity specifically.[24]

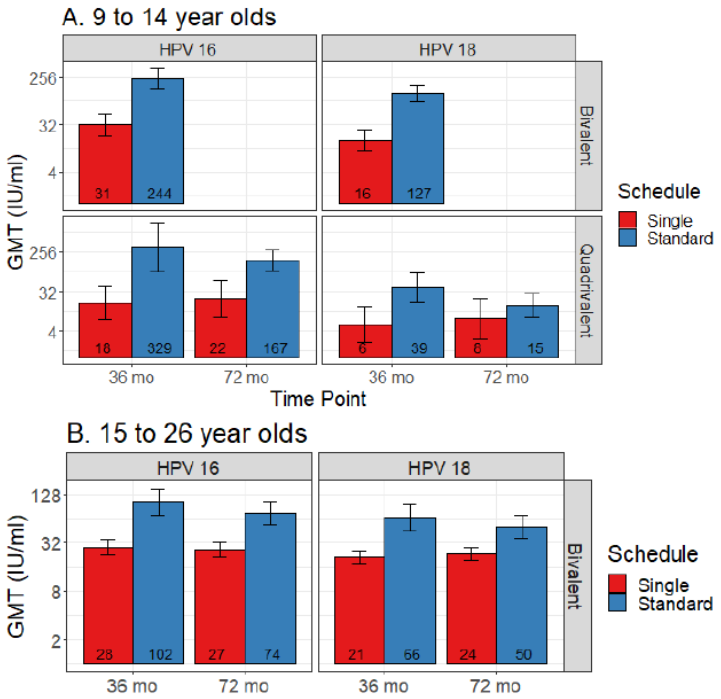
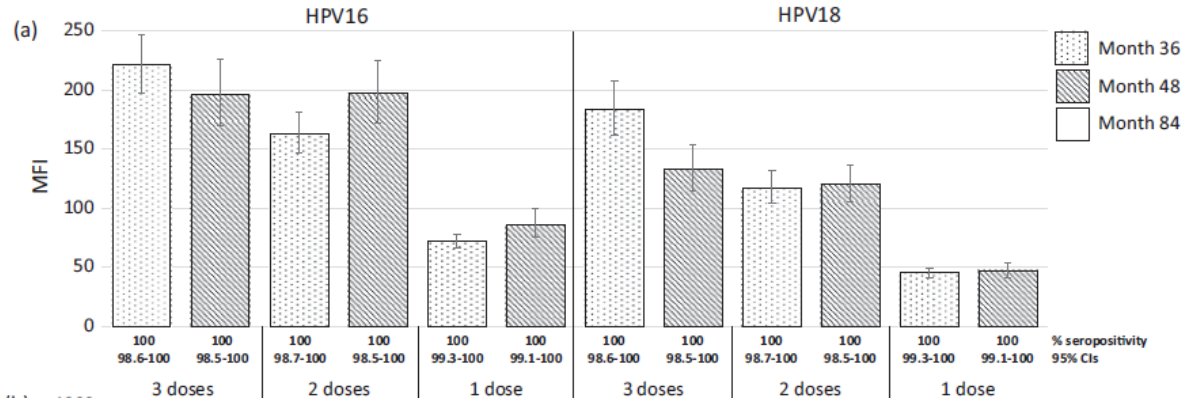


Figure 8: Lower geometric mean titres (GMT) for single dose compared with standard schedule of HPV vaccine (95% error bars) among A) 9–14-year-olds, and B) 15 – 26-year-olds (Secor et al 2020, open access)

Another systematic review by Whitworth et al (2020) found that the HPV-16/18 seropositivity rates were high in all HPV vaccine recipients (100% in three out of four studies reporting this endpoint). But antibody levels were lower in those who received one dose compared with two or three doses. The decline in antibody following vaccination was less pronounced for the one-dose arm and appeared more stable through follow-up than two or three doses. Antibody avidity against HPV-16 and 18 was comparable between groups, although neutralising antibody levels were lower in the reduced-dose schedule (see Figure 9). This review assessed clinical trial data to compare the immunogenicity of a single dose of HPV vaccination with no doses and multi-dose schedules in vaccinated participants.[25]

Figure 9: Magnitude of anti-HPV16 and 18 antibody responses at 36- and 48-months post vaccination with 3, 2 or 1 doses of 4vHPV in IARC India trial, with seropositivity rates and 95% CI. (Whitworth et al 2020; open access)

MFI = mean fold antibody increase



During a cluster randomised trial in India (IARC India) and unrelated to the study, suspension of 4vHPV vaccination in April 2010 resulted in four study groups (two by design and two by default) of per protocol participants (given two or three doses) and partially vaccinated girls aged 10–18 years.[66] All of the vaccinated participants seroconverted to HPV-16 and -18 and remained seropositive for at least 48 months regardless of the number of doses received.[66]

Serological data from an open-label phase III Dose Reduction Immuno-bridging and Safety (DoRIS) study, showed that a single dose of HPV vaccine induced a strong IgG antibody response. The response was sustained for at least 2 years after vaccination. The study assessed two HPV vaccines (2vHPV and 9vHPV) in 930 healthy HPV-naïve Tanzanian girls aged 9–14 years. Seropositivity at 24 months after one dose was compared with two or three doses of the same vaccine.[26] Antibody GMCs were significantly lower after one dose of 9vHPV than in those who received two or three doses. But seroconversion for both vaccines for anti-HPV-16 at 24 months was non-inferior to two or three doses. For anti-HPV-18 antibodies, at least 98% of girls who had received one dose were seropositive at 24 months for both vaccines. Antibody GMCs remained constant over time, from 7 to 24 months after vaccination, for those who received one dose. As shown in Figure 10, no significant difference in vaccine avidity index was seen for any dose schedule or vaccine.[26]

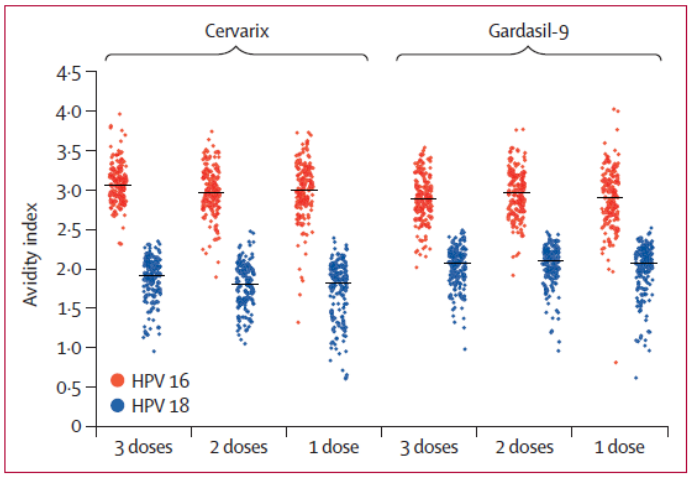


Figure 10: The distribution of HPV-16 and HPV-18 antibody avidity index at 24 months after HPV vaccination is not dependent on the number of doses. (Watson-Jones, 2022, open access)

Each data point represents a single individual and the lines through the date points represent the median avidity index.

One dose of HPV vaccine in young girls provided sufficient protection against persistent HPV infection in an immunobridging analysis of the Tanzanian DoRIS study (ages 9-14 years). In those who received one dose of 2vHPV or 9vHPV vaccines, the HPV type 16 and 18 antibody responses and seropositivity at 24 months were non-inferior to historical vaccine recipients. The historical groups received one dose only of 2vHPV

from a Costa-Rican study (women ages 18–25 years) and 4vHPV from an IARC India study (girls ages 10–18 years), respectively, and for whom efficacy had previously been reported.[27]

Table 4: Comparable GMCs and seroconversion rates at 24 months after single-dose HPV vaccination in DoRIS immunobridging study with historical cohorts (per-protocol population). (Baisley, 2022, open access)

	Participants*	GMC (IU/mL)†	Seroconversion‡
HPV 16 IgG antibody			
DoRIS (2-valent vaccine)	148	22·9 (19·9–26·4; 14·7–40·0)	147 (99%)
CVT (2-valent vaccine)	97	17·7 (13·9–22·5; 7·3–38·7)	96 (99%)
DoRIS (9-valent vaccine)	145	13·7 (11·9–15·8; 8·9–21·4)	144 (99%)
Aged <15 years (post hoc)	145	13·7 (11·9–15·8; 8·9–21·4)	144 (99%)
India (4-valent vaccine)	131	6·7 (5·5–8·2; 3·3–16·1)	121 (92%)
Aged <15 years (post hoc)	68	9·7 (7·7–12·1; 5·0–21·1)	68 (100%)
HPV 18 IgG antibody			
DoRIS (2-valent vaccine)	141	9·9 (8·5–11·5; 5·7–17·7)	139 (99%)
CVT (2-valent vaccine)	97	8·0 (6·4–10·0; 3·7–15·5)	96 (99%)
DoRIS (9-valent vaccine)	136	5·7 (4·9–6·8; 3·0–10·8)	133 (98%)
Ages 15 years (post hoc)	136	5·7 (4·9–6·8; 3·0–10·8)	133 (98%)
India (4-valent vaccine)	129	2·2 (1·9–2·7; 1·2–4·1)	99 (77%)
Ages <15 years (post hoc)	69	2·7 (2·1–3·4; 1·4–4·5)	57 (83%)

Data are n, GMC (95% CI; IQR), or n (%), unless otherwise stated. CVT=Costa Rica Vaccine trial. DoRIS=Dose Reduction Immunobridging and Safety Study. HPV=human papillomavirus. IARC=Institutional Agency for Research on Cancer. GMC=geometric mean concentration. *Includes DoRIS and CVT participants who were ELISA antibody negative and HPV DNA negative, and IARC India participants who were ELISA antibody negative, at baseline (before vaccination) for the HPV genotype under analysis. †ELISA serum antibody GMC. ‡Seroconversion was defined as concentrations greater than or equal to the laboratory determined cutoff (HPV16=1·309 IU/mL; HPV18=1·109 IU/mL) among girls who were seronegative for the HPV genotype at baseline.

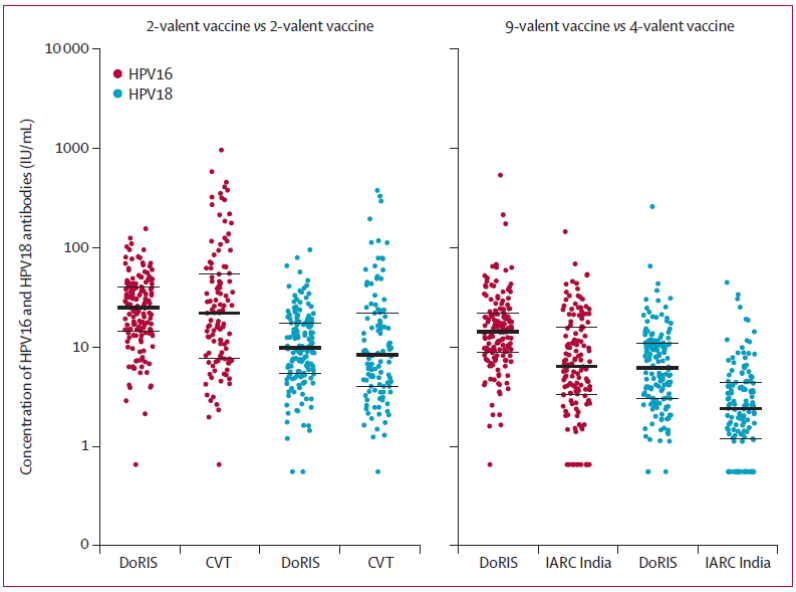


Figure 11: Distribution of HPV-16 and HPV-18 antibody concentrations at 24 months after a single dose of HPV vaccine, by total vaccinated cohort in DoRIS immunobridging study. (Baisley, 2022, open access)

Each datapoint represents a single individual and the line through the data points indicates median concentration with error bars showing interquartile range.

The study concluded that a single-dose schedule could alleviate vaccine supply constraints and costs of vaccine and delivery; therefore, expand access of HPV vaccination to countries that most need it. A clinical trial with one dose is also underway in Tanzania evaluating the addition of vaccination of males to female HPV vaccinations (Add-Vacc study).[27]

Immunogenicity of extending intervals between vaccine doses

The systematic review by Secor et al also reviewed the use of extended intervals between doses. Robust immunogenicity was shown across all multidose groups, but non-inferiority was mixed across vaccines, HPV types 16 or 18 and timepoints when dosing intervals were extended (>12 months).[24] For girls given 9vHPV after an extended interval of 3–8 years, following dose of 4vHPV at ages 9-14 years, the antibody response was non-inferior to the standard dosing schedule for HPV-16 and -18 at one month after the last dose.[28] The small Canadian study (n = 31) appeared to show that a single dose of 4vHPV primed the response to all nine HPV types in 9vHPV vaccine. It concluded that one dose of 9vHPV is sufficient to complete the immunisation of those who only received one dose of 4vHPV, when given several years later.[28] The systematic review concluded that extended dosing-interval schedules confer non-inferior immune response. These could be an effective alternative to the current schedules or single dose schedules, enabling greater HPV vaccine uptake.[24]

Conclusion

A single dose of 4vHPV or 9vHPV induces a robust protective response, albeit with lower antibody titres to two or three doses, that appears to last for several years post vaccination. Most recipients demonstrate seroconversion. A booster dose of 9vHPV given 3–8 years after a single dose of 4vHPV or 9vHPV is adequate to provide further protection against all nine vaccine HPV types.

Effectiveness of a single dose

Systematic reviews evaluating single doses.

A systematic review by Whitworth et al (2020) found that the evidence from clinical trials supported the use of one dose of HPV vaccine, which was likely to be as effective as multi-dose schedules.[25] The review compared the efficacy of a single dose of HPV vaccination with no vaccination or the standard two or three dose schedules. The review used data from the 2vHPV studies in Costa Rica CVT and multinational PATRICIA trial and the IARC India 4vHPV trial. It found that the frequency of HPV-16/18 infection up to 7 years post vaccination was low (<1% for 12-month-persistent infection) and did not differ significantly by the number of doses ($p > 0.05$). Compared with those who were unvaccinated, the frequency of infection was significantly lower in those who received one dose ($p < 0.01$ for all infection endpoints in each study). In the IARC India study (detailed below), rates of persistent HPV-16/18 infection at 7 years post vaccination with 4vHPV (ages 17–25 years) were:

- 0% each in two-dose and the single-dose arms
- 0.2% (0.0–0.9%) in the three-dose arm
- 1.2% (0.7–2.1%) in unvaccinated women.[25]

A Cochrane systematic review was presented at the WHO Strategic Advisory Group of Expert in Immunisation (SAGE) meeting in April 2022. It compared the effectiveness of one dose with two or three doses, or no vaccine, for a range of clinical outcomes and groups vaccinated. When compared with no vaccine, certainty was high that one dose resulted in short-term (up to 18 months) reduction in persistent HPV-16/18 infection with moderate certainty of a reduction for up to 10 years. There is limited evidence on the incidence of abnormal cytology or CIN. The data mostly came from observational studies with a high risk of confounding bias and should be interpreted cautiously. Similarly, when comparing one dose with two or three doses, the evidence is limited.[29]

Single-dose clinical trial data

An ongoing RCT (KEN SHE study), involving 2,275 Kenyan women aged 15–20 years, is evaluating the vaccine efficacy of a single dose of either 2vHPV (n = 760) or 9vHPV (n = 757) against persistent HPV infection.[30] Interim findings at 18 months found that single doses of 2vHPV and 9vHPV are highly effective in preventing persistent HPV infections (primary outcome).[30] At 18 months- and 36 months-follow-up, the study is comparing infection rates in those who receive HPV vaccine immediately with those who have delayed 2vHPV or 9vHPV vaccination (a meningococcal vaccine was given as control). The participants were tested for HPV DNA at enrolment, and then undergo six-monthly cervical swabs and a month-three vaginal swab. Serum samples are tested for HPV antibodies.[30, 67] Interim data reported vaccine efficacy of one dose of 9vHPV of 97.5% (95% CI 81.7–99.7%, $p \leq 0.0001$) against HPV-16/18 persistent infections and 88.9% (68.5–96.1%, $p < 0.0001$) against all nine HPV types in the 9vHPV vaccine. The rate of HPV infection in the control group was high at 9.42 per 100 woman-years and a third higher than in previous clinical trials, highlighting the need for vaccination in this population in whom cervical cancer is a leading cause of cancer mortality of women aged under 50 years.[30]

Data from the IARC India clinical trial demonstrated that a single dose of HPV vaccine provides similar protection to two or three doses against persistent HPV-16 and 18 infections. During the study, an unrelated suspension of 4vHPV vaccination in April 2010 resulted in four study groups, two by design and two by default, consisting of per-protocol (two or three doses) and partially vaccinated girls aged 10–18 years.[66] Over 7 years of follow-up (2009–2017), the frequencies of cumulative incidence and persistent HPV-16/18 infections were similar and uniformly low in all the vaccinated groups: age-standardised incidence HPV16/18 was 1.5%, 95% CI 1.1–2.0; and for HPV-31/33/45 was 5.4%, 4.7–6.2%. Incidences were significantly higher in unvaccinated age-matched control: HPV-16/18 incidence was 10.8%, 6.5–15.1%; and HPV-31/33/45 was 13.7%, 9.2–18.1%. The frequency of non-targeted HPV types was also similar in the vaccinated groups and higher in unvaccinated controls.[66]

Data-linking studies evaluating single-dose HPV vaccination

One dose of 4vHPV showed comparable effectiveness to two or three doses against high-grade cervical disease in a high-coverage setting.[31] A national cohort study was conducted in Australia to assess the effectiveness of 4vHPV against CIN2+, adenocarcinoma-in-situ (AIS) and cancer by the number of doses for up to 7 years post vaccination. The study linked data in cervical screening registers from eight jurisdictions with the national HPV vaccination registry, death index and cancer registries. This included 250,648 women who were aged 15 years or under when eligible for vaccine (born 1992 or later) and who were screened between April 2007 (when vaccinations commenced) and 31 December 2014. Of those women, 19.5% were unvaccinated, and 69.8% had received three doses, 7.3% had two doses and 3.4% had one dose of 4vHPV. The data were compared with a historical cohort to exclude herd protection.[31] The vaccinated women had a lower risk for high-grade CIN or cancer than the unvaccinated women: adjusted hazard ratio for one dose = 0.65 (0.52-0.81), two doses 0.61 (0.52-0.72) and three doses 0.59 (0.54-0.65). When adjusted for age at time of vaccination, HR for one and two doses were comparable to three doses. Consistent findings were shown using multiple sensitivity analyses.[31] The authors proposed that a one-dose schedule or a planned interval of 3–5 years between doses could reduce demand on vaccine globally. Thus, allowing time to confirm the equivalence of effectiveness and duration of protection of one dose.[31]

Effectiveness of single doses against genital warts

In a systematic review, Markowitz et al (2022) examined the effectiveness of HPV vaccination on anogenital warts by the number of doses and the buffer period after vaccination.[21] Effectiveness estimates of one or

two doses were generally high when using longer buffer periods, decreasing the differences between the number of doses. One study showed that with a three-month buffer, there was significant effectiveness for three, two and one doses: adjusted IRR =0.20 (0.17-0.23); 0.32 (0.26-0.40) and 0.54 (0.43-0.68), respectively. When the buffer period was 12 months in those who initiated vaccination at ages 10–16 years, differences between the number of doses were not statistically significant.[21]

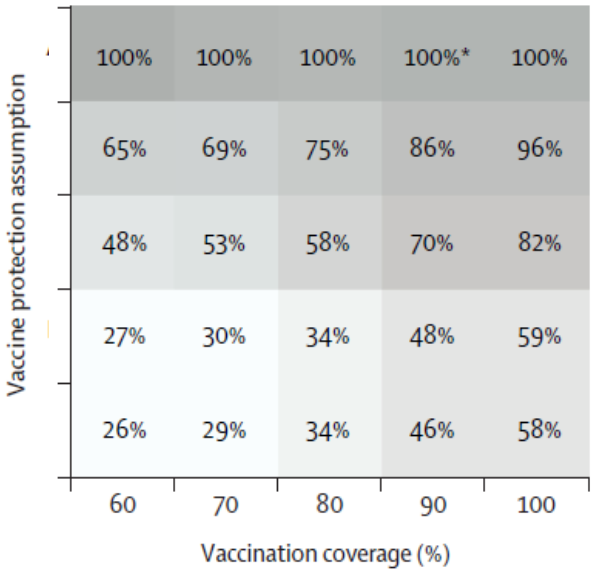
The Cochrane systematic review, presented at the WHO SAGE meeting in April 2022, found that the unadjusted results were inconsistent for the effect of one dose against genital warts. All the estimates were in favour of one dose compared with no vaccine.[29] When comparing one and two doses of HPV vaccine, around half of the studies demonstrated a greater reduction in risk when two doses were given, particularly when vaccinated over the age of 16 years. The results were inconsistent with longer follow up. Across three studies, three doses appeared to be more effective than one dose in preventing genital warts. The review found limited evidence of a difference between one and two or three doses. However, the estimates of effect come from observational studies with a high risk of bias due to confounding.[29]

Predicted impact of a single dose

Based on 90% coverage in girls aged 10 years and life-long protection from one or two doses of HPV vaccine, a modelling study in India predicted HPV vaccination could reduce the prevalence of HPV-16/18 in 50 years by 97% (80% uncertainty interval 96–99%). The life-time risk of cervical cancer was reduced by 71–78%.[68] To assess the impact of a single-dose HPV vaccination compared with no vaccine or two-dose schedule, the modelling used an adapted HPV transmission model (EpMetHeos) on Indian data on sexual behaviour, HPV prevalence and cervical incidence. It found that a single-dose catch-up was more likely to be impactful than two doses without catch-up (see Figure 12).[68] By allocating the same number of doses, the model predicted reductions in lifetime risk of cervical cancer of 39–65% for single doses given to ten catch-up birth cohorts (aged 11–20 years) versus 38% across the first ten routine vaccination birth cohorts. However, expanding the age range for catchup (to 26–30 years) resulted in marginal gain because of increased sexual exposure at older ages. For example, catch-up for girls aged 11–15 years with 60% coverage could reduce the lifetime risk of cervical cancer by 50–57%; whereas, catch-up of women aged 26–30 years only reduced life-time risk by 12–16%. Assuming waning in vaccine protection, the model predicted a 21–100% higher per-dose efficacy for one-dose than two-dose vaccination.[68]

Figure 12: Estimated relative efficiency in cases prevented per dose of HPV vaccine is greater for a single dose than two doses, based on routine vaccination at age 10 years without catch-up. (Man et al, 2022, open access)

* Base-case scenario in India.



Conclusions of single dose effectiveness

How the single dose performs is dependent on vaccine uptake. It is also dependent on herd immunity across both heterosexual and homosexual groups, ongoing screening for persistent infections and prompt treatment of lesions that may occur. Studies show vaccination with one dose of HPV vaccine to be protective against HPV-16/18 persistent infection for at least 7 years in Costa Rica (vaccinated at age 18-25 years, 2vHPV) and Indian (vaccinated at age 10–18 years, 4vHPV).

One-dose recipients may require a booster dose some years later. One dose provides at least some protection to more people than is achievable by giving two or even three doses to a smaller albeit more receptive group. Indian data modelling anticipated that a single dose of HPV vaccine with a catch-up programme up to age 20 years to have a greater gain in impact on high-risk HPV infections than two doses without catch-up. However, this does not necessarily reflect the NZ population.

The current limited evidence suggests that extending the interval between doses is likely to be a better option in NZ than relying purely on a single dose.

Preventing HPV recurrence following cervical lesion excision surgery

Vaccination after conization treatment of women with cervical intraepithelial neoplasia (CIN) lesions could prevent recurrence of HPV infection and reduce the risk of developing further lesions. Although loop electrosurgical excision procedure (LEEP) helps to treat cervical lesions, the recurrence or residual disease rate after treatment is up to 17% with a life-long risk of cervical cancer and other HPV-related cancers.

A handful of clinical trials are underway to investigate the potential effectiveness of 9vHPV in addition to LEEP to prevent recurrent or residual CIN and to reduce the need for repeated LEEP treatments.[69] These include two phase III studies: NOVEL Trial (NCT03979014) and HOPE9 study (NCT03848039). Already conducted studies used bivalent and quadrivalent HPV vaccines post CIN treatment. See Table 9 for a summary of this evidence.

A systematic review and meta-analysis by Jentschke et al (2020) showed a significant reduction in risk (RR 0.41, 95% CI 0.27–0.64) of developing recurrent CIN2+ after 4vHPV or 2vHPV vaccination. It compared surgical excision and vaccination with 4vHPV or 2vHPV with excision alone, independent of HPV type. An age-dependant analysis found no difference between women aged under 25 years and older women (RR 0.47 [0.28-0.80] vs 0.52 [0.41-0.65]). The number of women needed to be vaccinated before or after conization to prevent one case of recurrent CIN2+ was found to be 45.5.[32]

The meta-analysis included the following studies:

- A Spanish retrospective review reported that HPV vaccination immediately before or after conization reduces risk of disease recurrence.[70] The study was conducted with 242 patients (median age 36 years; range 18 – >45 years) undergoing LEEP for CIN2/3 with three-monthly follow-up for up to 24 months. Of these women, 42.6% received 2vHPV or 4vHPV immediately before or after conization. Multivariate analysis showed vaccination to be a protective factor for CIN2/3 recurrence (OR 0.36; 95% CI 0.125–1.032, $p < 0.03$). Neither vaccine type nor timing of vaccination showed significant association with recurrence onset.[70]
- A statistically non-significant lower risk of CIN2+ among 2,074 Danish women was shown in those who were vaccinated with 4vHPV three months before (median age 29 [17–49] years) or up to 1 year after (median age 28 [17–51] years) conization. These were compared with 15,054 unvaccinated women (median age 32 [17–51] years; adjusted HR 0.86, 0.67–1.09).[71] The retrospective study concluded that

vaccination could be a clinically effective adjunct to conization to decrease the risk of recurrent high-grade cervical neoplasia. The authors noted that those who were vaccinated 0–3 months before conization tended to have less severe lesions.[71]

- A study involving 265 women (mean age 39.8 ± SD 10.3 years) in Catalonia, Spain, found that HPV vaccination was associated with a significant reduction (4.5-fold) in the risk of developing persistent or recurrent high-grade squamous intraepithelial lesions (HSILs) after conization. It also demonstrated that vaccination prevented acquisition of a new HPV infection after treatment (in those who were HPV-negative at first conization).[72] During January 2013 to July 2017 in Spain, women diagnosed with any SIL/CIN requiring treatment were recommended but not funded HPV vaccination (two doses of 2vHPV or three doses of 4vHPV). From July 2017, Spain funded 9vHPV for all women undergoing conization for HSIL/CIN2+. All unvaccinated women who had undergone conization due to high-grade lesions in the previous 12 months (2016–2017) were recalled for vaccination.[72] Significantly more of the women treated for cervical lesions after July 2016 were vaccinated (36% vs 79.1%; $p < 0.001$). At the end of follow-up, a multivariate analysis found that persistent low-grade SIL/HPV infection and HSIL at the first conization significantly increased the risk of persistent/recurrent HSIL (OR 4.3 [1.3–14.3] and OR 21.0 [3.6–123.5], $p = 0.018$). Conversely, HPV vaccination significantly reduced the risk of persistent/recurrent HSIL at the end of follow-up (OR 0.2; 0.1–0.7, $p = 0.01$).[72]
- Univariate analysis of an Italian single institution study found that HPV vaccination given within 4 weeks of LEEP was a protective factor against cervical dysplasia requiring further LEEP (OR 0.4, 0.2–0.8; $p = 0.02$). The overall rate of recurrence within 2 or more years was 10.5%. Of these women, 17/103 (16.5%) were unvaccinated and 13/182 (7.1%) were vaccinated; $p = 0.01$.[73] These data supported the role of HPV vaccination as an adjuvant treatment after cervical hyperplasia excision.

Not included in the Jentschke review, an Italian retrospective study concluded that vaccination is a modifiable factor that could improve the outcomes of women with high-grade cervical dysplasia. The study analysed the charts of women undergoing LEEP conization (aged 39 years; range 17 – 89): 1,914 had known vaccination status, of which 116 (6.1%) were vaccinated after conization (with narrower age range 24 – 45 years) and 1,798 (93.9%) had conization alone.[33] Of the patients with available data, 1,371 (94.7%) had detectable high-risk HPV. The five-year recurrence rate of HSIL was 1.7% (n = 2) and 5.7% (n = 102) for those vaccinated and unvaccinated after conization, respectively ($p = 0.068$). Most of those vaccinated had received 4vHPV (93%) and the remainder had 2vHPV.[33]

Conclusions of HPV recurrence prevention

There is emerging evidence for the use of HPV vaccination as an adjuvant treatment following conization and excision of cervical neoplasia. Ideally, it is best to vaccinate at a young age before acquiring HPV infection. But when given at the time of treatment or soon after, vaccination appears to moderately reduce the risk of recurrent disease. The effectiveness in women older than 45 years is unclear. Studies do not describe adjuvant treatment in those requiring conization who were previously vaccinated.

Prevention and treatment of recurrent respiratory papillomatosis

Infants born to mothers with genital warts are at increased risk of recurrent warty growths in their airways known as recurrent respiratory papillomatosis (RRP). Prophylactically, HPV vaccine can prevent genital warts in mothers. Another potential role is as adjuvant therapy for preventiing recurrence of infection following surgical removal.

Impact of HPV vaccination programmes on recurrent respiratory papillomatosis

A retrospective review at Starship Children's Hospital in New Zealand investigated the incidence of juvenile-onset RRP before and after the commencement of the national HPV immunisation programme over a 14-year period.[34] First, the incidence of RRP in children over ten years prior to introduction of 4vHPV during September 1998 to August 2008 was compared with incidence after its introduction (September 2008 to August 2022). Second, the review compared RRP incidence pre-vaccination with the most recent six years when vaccination became more widely available (ie. from 2016, including following the introduction of 9vHPV for males and females). Over the whole period, Starship treated 31 children for RRP. The mean incidence prior to vaccine introduction was 0.21 per 100,000 children per year (nine cases in 1998–2008). with no significant difference after the vaccine introduction (rate 0.23 per 100,000 per year; 14 cases during 2008–2022; p = 0.90). Over the latter six years (2017–2022), a non-significant reduction of 0.06 cases per 100,000 per year was observed (0.15 per 100,000 children per year; four cases 2017–2022; p = 0.56). The authors proposed that this smaller reduction in incidence may be explained by a low HPV vaccination rate (≤70%) in New Zealand compared with countries with a higher vaccine uptake.[34]

A study conducted by the Australian Paediatric Surveillance Unit reported that, over 5 years to the end of 2016, the rates of RRP declined from 0.16 per 100,000 in 2012 to 0.02 per 100,000 in 2016 (p = 0.034).[36] Of the genotyped cases, four cases had HPV-6 and three cases had HPV-11 infections. Twenty percent of cases had maternal history of genital warts, 60% were first born and 13/15 cases were born vaginally. None of the mothers had HPV vaccination during pregnancy.[36]

The US also observed a decline in juvenile-onset RRP incidence from 165 cases born during 2004–2005 (prior to 4vHPV vaccine introduction in 2006) to 36 cases born during 2012–2013. The incidence rate per 100,000 births declined from 2.0 cases in 2004/5 to 0.5 cases in 2012/13 (IRR 0.2, 95% CI 0.1–0.4). These data were collected from 26 tertiary medical centres in 23 US states and 576 cases born between 2004–2013 were identified.[35]

Passive antibody protection

As well as preventing genital warts in the mother, a potential mechanism to provide protection to infants from HPV-6 and 11 infections is through the transplacental transfer of antibodies from vaccinated mothers. The levels of HPV-6/11 antibodies were measured in peripartum maternal blood and cord blood of infants born to women who received 9vHPV or 4vHPV as part of an earlier pivotal efficacy RCT.[37] The median time for collection of serum samples after vaccine dose one was 22 months (range 9–34 months). All vaccinated mothers' and paired infants' samples were seropositive for anti-HPV-6 and -11 antibodies. Geometric mean titres between mothers and their infants were comparable and not significantly different between the two vaccines. Maternal anti-HPV antibody titres were highly positively correlated to those in the infant. The Pearson correlation coefficients for anti-HPV-6 and anti-HPV-11 antibodies were 0.94 and 0.93 in the 9vHPV group and 0.99 and 0.77 in the 4vHPV group, respectively.[37] As mentioned above, the maternal antibody levels appear to be maintained for at least 8 years following three-dose vaccination with 9vHPV,[17] and therefore, infants are potentially passively protected against acquiring HPV infection. The presence of maternal antibodies, particularly when vaccination takes place prior to sexual debut, provides twice the opportunities to protect infants:

1) reduces risk of acquiring HPV-6/11 infection leading to genital warts and perinatal HPV transmission during delivery
2) passive protection for the infants from maternal antibodies adds an extra layer of protection against infection in the airways during delivery.

Adjuvant therapy or treatment

Several studies have been conducted around the therapeutic use of HPV vaccine as a treatment or adjuvant therapy after surgery to prevent RRP recurrence in children and adults.

Goon et al (2023) conducted a meta-analysis of the use of HPV vaccine as adjuvant therapy for RRP in adults.[74] Based on a total of 101 patients in three studies, an overall reduction of 0.12 (95% CI 0.06–0.18) recurrences or surgeries per month was reported. Studies included in the Rosenberg systematic review[39] described below were excluded in this meta-analysis.

In another systematic review, which included 12 studies (case studies and non-randomised studies), Park et al (2022) found that, although the use of HPV vaccine as a treatment for juvenile-onset RRP has shown some promise, the certainty of its effectiveness remains unclear with the available data.[38]

An earlier systematic review by Rosenberg et al (2019) looked at the use of HPV vaccine as an adjuvant therapy after surgery. It identified a significant reduction in the number of surgeries per month after vaccination compared with before (estimated mean 0.06 vs 0.35) and the mean inter-surgical interval was significantly increased (7.0 months [range 0.3–45] before vs 34.5 months [range 2.7–82 months] after vaccination).[39]

Conclusions around the use of HPV vaccination for preventing recurrent respiratory papillomatosis

It is currently unclear, mainly due to the rarity of the condition, whether the routine HPV immunisation programme has significantly reduced the incidence of RRP in children in NZ. Data from larger countries suggest a decrease. Higher HPV vaccine coverage would likely have a greater effect in reducing cases in NZ, when you compare NZ with Australia. There is also a potentially protective role for passive transfer of antibodies in infants born to mothers vaccinated as adolescents or at least prior to pregnancy.

As a treatment or an adjuvant therapy, there appears to be a slowing of recurrence but no evidence yet of prevention of RRP recurrence. With a reduction in genital warts, together with herd immunity from vaccinated males and females to reduce the spread of HPV-6 and -11 infections to unvaccinated individuals, the incidence of juvenile-onset RRP will hopefully and eventually diminish.

Summary of evidence tables

Table 5: Table of evidence for vaccine safety

Outcomes	Ref	Participants	Results	Findings
Serious adverse events of special interest (AESI)				
Chronic regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS)	53	European Medical Agency PRAC review of CRPS and POTS in young women receiving HPV vaccines.	Background rates of CRPS and POTS ~150 cases of each per million females aged 10–19 years. No evidence that overall rates differed in those vaccinated.	No evidence of serious adverse outcomes due to HPV vaccination, including POTS and CRPS
Passive surveillance	12	Passive surveillance, 9 million doses 4HPV given to males (2013–2017) and females (2007–2017) in Australia.	4,551 passive AEFI reports. Syncope rate overall 9.11 per 100,000 doses; during enhanced surveillance rate of syncope was 3 times higher in younger adolescents (~30 vs 10 per 100,000 doses). Anaphylaxis rate overall 0.32 per 100,000.	AESI rare and not causally associated with vaccine. No unexpected patterns of concern. Syncope and anaphylaxis rare, known responses to vaccination.
Premature ovarian insufficiency (POI)	55	Systematic review (SR) to Sept 2022, four studies, 1.25 million patients. HPV vaccinated compared with unvaccinated controls or other childhood vaccines.	POI RR 0.47 (0.14-1.59) between vaccinated and both controls. Between HPV vaccinated and unvaccinated - RR 0.75 (0.22-2.49). Between 4vHPV and 2v/9vHPV - RR 0.93 (0.33-2.64)	No significant risk overall between 4vHPV vaccination and controls for POI risk. No differences between HPV vaccines.
Central demyelinating diseases – multiple sclerosis, Guillain-Barré syndrome, optic neuritis.	56	SR (to May 2017) out of 2,863 articles, 11 selected for meta-analysis.	Pooled OR 0.96 (0.77-1.20) for central demyelinating disease, similar odds for MS and ON. Data too limited for GBS for meta-analysis.	Findings strongly support no significant association between HPV vaccination and demyelinating diseases

Outcomes	Ref	Participants	Results	Findings
Autoimmune disease and other rare events	59	SR (to April 2019) – 22 studies included Meta-analysis 35 disease = 48 pooled-risk estimates. 4vHPV most used.	43/48 pooled estimates shown no significant effect Three negative associations – paralysis (OR 0.52; 0.35-0.77), ITP (0.55; 0.34-0.88), CFS (0.77; 0.62-0.97) Two positive associations – Hashimoto (OR 1.25; 1.09-1.44) and Raynaud's (OR 1.63; 1.21-2.20)	Absence of clear association between HPV vaccine and autoimmune/other rare diseases.
Females	57	Meta-analysis on six studies for 2v and 4vHPV vaccines: incl 243,289 vaccinated and 248,820 controls.	Pooled OR 1.038 (0.689-1.562) for HPV vaccination and autoimmune disease.	No correlation identified between 2vHPV or 4vHPV vaccination and risk of autoimmune disorders.
Males	58	65,606 males received ≥1 dose 4VHPV, 55,670 matched controls in US.	Vaccinated group: 35 cases among 39,735 person-years (IR 0.88; 0.61-1.23). Controls: 47 cases 58,215 person-years (IR 0.81, 0.59-1.07) RR: Overall 1.09 (0.70-1.69); rheumatological/haematological 0.49 (0.10-2.42; gastroenterological 1.26 (0.58-2.71); endocrinological 1.11 (0.61-2.02); neurological 1.46 (0.21-10.40).	Incidence of autoimmune conditions among males similar between those receiving 4vHPV and those unvaccinated.
	22	SR to April 2017, seven articles included, only one RCT for safety.[75]	Data from a large RCT showed nine SAE in vaccinated group (2,202 male participants) and 11 in placebo group (2,029): RR 0.73 (0.25-1.99) risk difference (-0.2, -0.7 to 0.3). None of the SAE judged to be vaccine related.	Limited data presented on safety, but no serious adverse events associated with vaccine.
Allergy and syncope on day of vaccination	11	215,965 KPNC members in US received ≥1 dose 9vHPV, males and females; 140,628 had received no previous doses.	18 event categories significantly elevated; skin-disorders (OR 1.88, 1.00-3.53) and ill-defined conditions (incl abdominal pain, allergic reactions, syncope; OR 1.36, 1.13-1.64). Deaths were consistent with background rate. Post vaccine five cases of day 0 allergic reactions 15.1 (4.9-35.3) per million doses (one case anaphylaxis); 18 events day 0 (5 possibly related to vaccine) of syncope 54.4 (32.3-86.0) per million doses.	No new safety concerns related to 9vHPV in males or females. Data were consistent with other studies.
Inadvertent vaccination in pregnancy				

Outcomes	Ref	Participants	Results	Findings
Pregnancy and infant outcomes	13	SR (2009-2019) of seven articles and meta-analysis of three articles.	Miscarriage: RR 1.18 (0.58-23.8) p=0.065, I^2 91% or stillbirth (2.01; 0.66-6.13), p=0.22; I^2 68% .	None of the studies show increased risk or statistical difference for miscarriage or stillbirth following vaccination with HPV vaccine.
HPV4	60	US military women aged 17–28 years, ≥ 1 pregnancy during 2007–2014. Total of 90,600 pregnancies and 75,767 singleton infants; 2% exposed to 4vHPV when pregnant. Comparison with those who received 4vHPV 4–12 months prior to LMP as perinatal exposure (distal to pregnancy) and those unexposed to 4vHPV.	Miscarriage: vaccinated in pregnancy vs no vaccine in pregnancy: aHR 1.05 (0.94-1.18) and vs perinatal vaccine (RR 1.05; 0.93-1.20) Premature birth aRR 0.87 (0.71-1.07) and 0.91 (0.72-1.13).	No association between HPV vaccine exposure in pregnancy and adverse pregnancy or infant outcomes.
HPV9	14	Vaccine Safety Datalink data, pregnancies ending Oct 2015–Nov 2018; pregnant women aged 12–28 years (mean 23.9); receipt 9vHPV during pregnancy (LMP to 19 weeks gestation); comparators distal receipt of 4v or 9vHPV vaccine (22–16 weeks before LMP) and 9vHPV peri-pregnancy (from 42 days before LMP).	1493 pregnancies, mean age 23.0 ± 2.9 years; 445 vaccinated in pregnancy, 496 peri pregnancy, 552 distal vaccination. Miscarriage HR 1.12 (0.66-1.93) vaccine in pregnancy vs distal; peri pregnancy RR 0.72 (0.42-1.24) Premature birth: 9vHPV in pregnancy vs distal RR 0.73(0.44-1.02) and 0.72 (0.45-1.17).	Vaccination with 9vHPV was uncommon during or around the time of pregnancy and not associated with increased risk of spontaneous abortion (miscarriage) or adverse birth outcomes.

Abbreviations: AEFI – adverse event following immunisation; AESI – adverse events of special interest; CRPS – chronic regional pain syndrome; HR – hazard ratio; IR – incidence ratio; ITP – immune thrombocytopenia purpura; LMP – last menstrual period; OR – odds ratio; POTS – postural orthostatic tachycardia syndrome; POI – primary ovarian insufficiency; RR – relative risk / risk ratio; SR – systematic review

Table 6: Table of evidence for vaccine immunogenicity

Outcomes	Ref	Participants	Results	Findings
Immunogenicity of two or three doses				
Two doses	15	Cochrane SR (Sept 2018) comparing HPV vaccine types and schedules in males and females aged 9-26 years. Included 20 RCT with 31,940 participants, up to 5 years follow-up.	Longer interval between first two doses of 9vHPV and 2vHPV resulted in higher and non-inferior GMTs compared with shorter intervals.	Immunogenicity of two doses similar to three doses. Longer intervals between two doses gave stronger response.

Outcomes	Ref	Participants	Results	Findings
Long term immunogenicity	17	Follow-up for ≥8 years of 1,272 boys and girls aged 9–15 years, 9vHPV.	GMTs peaked at 7 months, sharply decline to 12m and after 24m slowly decrease.	Seropositivity rates remain >90% for each HPV type to ≥90 months post vaccination.
Coadministration	16	SR / meta-analysis (to Dec 2018), concurrent vaccination in those aged 9–25 years. Included 13 papers with 11,657 participants.	The seroconversion rates for antibodies against all vaccine HPV types was the same between concomitant administration and non-concomitant administration groups (pooled RR = 1.00).	No evidence of interference for HPV vaccines or routine vaccines (2v, 4v, 9vHPV, HepA/B, Tdap, Tdap-IPV, MenACWY).
People living with HIV	18	SR / meta-analysis (to Feb 2021); 3 doses HPV vaccine.	Seropositivity declines with time more rapidly in those who are HIV positive than HPV negative. Pooled proportion seropositive at 28 weeks after three doses 9vHPV 100% for HPV-16 and 18.	Seropositivity declines with time but can last for 2-4 years in PLHIV.
Immunogenicity single dose				
	28	31 girls aged 13-18 years (mean 15.5 years) previously vaccinated with 4vHPV from 3-8 years (mean 5.4) earlier.	All participants were seropositive to 4HPV types and 58-87% had antibodies to the other five HPV types in 9vHPV. Dose of 9vHPV increased 9vHPV GMTs 24.3-82.1-fold in those seropositive and 62.1-236.9-fold in those previously seronegative.	Seropositivity against 4vHPV types was maintained for at least 5 years after vaccination in young females. Priming with 4vHPV produced cross-reactive protection against 5 non-vaccine types. A single dose of 9vHPV induced a robust booster response in 4vHPV primed individuals.
	24	SR (to April 2019) 23 studies included in females aged 9-26 years. Non-inferiority between alternative/standard schedule by age groups 9–14 and 15–26 years.	Robust immunogenicity demonstrated across multi-dose groups. Single dose did not meet non-inferiority criteria for any comparison (at 36 and 72 months after first dose).	Single dosing may provide economic and health benefit.
	25	SR (Jan 1999 – Aug 2018), four studies included immunogenicity comparing one dose to other schedules.	Antibody titres were significantly lower with one than two or three doses, decline in antibody was less pronounced in one-dose arm – more stable through follow-up. Antibody avidity comparable but neutralising antibody levels lower in reduced dose schedules.	Although evidence indicated that magnitude of antibody responses is lower following a single dose, the clinical significance may be limited.
	26	Open label Phase III DoRIS study, Tanzania, 930 HPV-naïve girls aged 9-14 years given 2v or 9vHPV	Seropositivity at 24 months after one dose was ≥98%. GMTs were significantly lower after one dose 9vHPV but anti-HPV16 seroconversion was non-inferior to two or three doses. Antibody levels remained on constant from 7–24 months.	A single dose of 2vHPV or 9vHPV can induce a strong and sustained IgG response for at least 2 years after vaccination in girls.

Outcomes	Ref	Participants	Results	Findings
	27	Immunobridging study – comparing DoRIS immunogenicity with other clinical trials (Costa Rica 2vHPV, ages 18–25 years; India 4vHPV, ages 10–18 years).	Antibody responses of a single dose of 2VHPV or 9vHPV at 24 months in DoRIS study were non-inferior to those in other clinical trials.	One dose of HPV vaccine in young girls was demonstrated to provide sufficient protection against persistent HPV infection.
Extended dosing interval	28 24	31 females (originally given 4vHPV at age 9–14 years). Antibody levels measured at 1 month, given 3–8 years after a dose of 9vHPV.	Robust immunogenicity demonstrated across multi-dose groups, but mixed non-inferiority with extended interval (≥12m between doses). The extended interval to a second dose 9vHPV was non-inferior to the standard dosing schedule for HPV-16 and -18 (at 0, 6 or 0, 2, 6 months).	Extended interval dosing schedules may be effective alternative to the standard schedule. A second dose given years after first may be sufficient to complete vaccination of those who only received one dose.

Abbreviations: GMT – geometric mean titre; PLHIV – people living with HIV; SR – systematic review

Table 7: Table of evidence for vaccine efficacy and effectiveness

Outcomes	Ref	Participants	Results	Findings
Two or more doses				
Genital lesions and genital warts	15	Cochrane review	4vHPV protected against external genital lesions and genital warts in men aged 16–26 years for up to 3 years follow-up. In females, 4vHPV and 9vHPV provided equivalent levels of protection against cervical, vaginal, vulvar precancerous lesions and cancer.	
Range of endpoints (HPV-16/18 infection, anogenital warts, cervical abnormalities)	21	SR between 2007-2021, 35 studies.	When adjusted or stratified for age, it found similar effectiveness for one, two or three doses.	
Cervical cancer	23	Danish cohort study. 867,689 women, 36.3% vaccinated <age 17 years. 78.5% received three doses, 15.7% received two doses and 5.8% received one dose.	IRR cervical cancer compared with unvaccinated (325 events): vaccinated ≤16 years (six events) = 0.14 (95% CI 0.04-0.53); age 17-19 years (five events) = 0.32 (0.08-1.28); age 20-30 years (168 events) = 1.19 (0.08-1.79).	HPV vaccination reduced the incidence rate of cervical cancer by 86% and 68% among females vaccinated at age ≤16 years or age 17-19 years. Supports vaccination at a younger age.

Outcomes	Ref	Participants	Results	Findings
	20	Swedish data linking study, 1.7 million women and girls aged 10–30 years during 2006-2017.	Cumulative incidence cervical cancer 19 cases vaccinated vs 538 unvaccinated: aIRR 0.37 (0.21-0.57); aIRR 0.12 (0.00-0.34) vaccinated at ages <17 years vs 0.47 (0.27-0.75) vaccinated ages 17–30 years.	9vHPV substantially reduces risk of invasive cervical cancer in young women.
Persistent infection	17	Durability of VE up to 8 years follow up in 1,107 boys and girls vaccinated with three doses 4vHPV aged 9–15 years.	No cases of vaccine-type HPV-related intraepithelial neoplasia or genital warts – median 7.6 years follow up. IR 6-month persistent infection females 49.2 (26.9-82.6) and males 37.3 (7.7-109.1) /10,000 person-years); comparable to RCTs and significantly lower than placebo controls in those trials.	9vHPV provides durable protection from persistent vaccine-type HPV infection and associated disease.
	64	Follow-up of 14,251 women who received three doses 9vHPV or 4vHPV in RCT. Genital swabs taken 6mthly after first dose to 59 months.	Efficacy of 9vHPV was 96.7% (95% CI 80.9-99.8) against infection with the additional HPV types in this vaccine and antibody response against 4vHPV-types (6, 11, 16, 18) was non-inferior to 4vHPV.	9vHPV prevents cervical, vulvar and vaginal disease and persistent infection associated with additional five HPV-types.
	19	Netherlands, 548 females aged 16–24.	VE of at least one dose 2vHPV was 89.9% against anal HPV-16/18 infection.	Vaccination against HPV-16/18 can prevent anal HPV infection in women.
Disease in males	65	602 MSM aged 16-26 years; per-protocol three doses 4vHPV.	Efficacy of ≥1 dose 4vHPV against AIN associated with vaccine-type HPV 50.3% (25.7-67.2) [ITT]; efficacy of three doses 77.5% (29.6-93.3) [PP]. Persistent infection – reduced by 59.4% (43.0-71.4) and 94.9% (80.4-99.4), respectively.	4vHPV vaccine helps to reduce the risk of anal cancer in men.

Outcomes	Ref	Participants	Results	Findings
Single dose				
HPV infection	25	SR (Jan 1999 – Aug 2018), four studies included, comparing efficacy against infection for one dose to standard two or three dose schedules or no vaccination (for any HPV vaccine)	The frequency of HPV-16/18 infection was low (<1% for 12-month persistence) in all vaccinated participants up to 7 years post vaccination and did not significantly differ by number of doses. Frequency of persistent infection was significantly lower in those who received one dose than those unvaccinated (p<0.01).	Vaccination was protective against persistent vaccine-type HPV infection for up to 7 years with one, two or three doses.
	30	KEN SHE study: 2,275 women in Kenya aged 15–20 years. One or two doses of 2vHPV or 9vHPV. With 18 and 36-months follow-up. Control meningococcal vaccine. Study ongoing.	VE at 18 months for one dose of 9vHPV = 97.5% (95% CI 81.7-99.7%, p≤0.0001) against HPV-16/18 persistent infections and 88.9% (68.5-96.1%, p<0.0001) against all nine HPV types.	Single dose of 2vHPV or 9vHPV were highly effective against persistent HPV infections in a population with a high rate of HPV infection.
High grade cervical disease	31	Registry linking study in 250,648 women born since 1992 and aged <15 years at time of 4vHPV vaccination: 48,845 (19.5%) were unvaccinated, 174,995 (69.8%) received three doses, 18,190 (7.3%) two doses and 8,618 (3.4%) one dose.	aHR for CIN2+/cervical cancer risk up to 7 years post vaccination: one dose= 0.65 (0.52-0.81), two doses 0.61 (0.52-0.72) and three doses 0.59 (0.54-0.65). One and two doses were comparable to three doses when adjusted for age.	One dose of 4vHPV was shown to have comparable effectiveness to two or three doses against high-grade cervical disease in a high coverage setting.
	66	IARC India study: out of 17,729 girls aged 10–18 years, 4,950 (28%) received one dose 4vHPV. Other groups received three doses (day 1, 60 180+) and two-doses (day 1 and 60 or day 1 and 180+).	Age-standardised cumulative incident HPV 16/18 infections over 7-year period (2009-2017): one dose = 1.5 (0.8-2.2); all vaccinated = 1.5 (1.1-2.0); unvaccinated =10.8 (6.5-15.1). Persistent HPV infections: one dose zero cases, all vaccinated = 0.1 (0.0-0.3); unvaccinated = 1.2 (0.7-2.1).	One dose provides lasting protection against HPV-16 and 18 infections, similar to two and three dose schedules. One dose is preferable to no vaccination in low-income countries.

Abbreviations: AIN – anal intraepithelial neoplasia; aHR – adjusted hazard ratio; aIRR – adjusted incidence rate ratio; ITT – intension to treat population; MSM – men-who-have-sex-with-men; PP – per-protocol population; RCT – randomised controlled trial; SR – systematic review; VE – vaccine effectiveness/efficacy

Table 8: Table of evidence for impact of HPV vaccination programmes

Outcomes	Ref	Participants and study design	Results	Findings
Reduction in genital warts	7	Modelling study. NZ new genital wart diagnoses, five years 2007-2013 Auckland Sexual Health Service, female 4HPV vaccination 56% coverage.	Pre and post vaccination introduction for vaccine-eligible females genital warts diagnosis per year RR = 0.95 [0.91-0.98] vs 0.77 (0.74-0.81); p=0.004 Males of same age – no significant difference	An 83.4% reduction in genital warts diagnoses was recorded over five years from introduction of 4vHPV in schools for girls.
High-grade lesions	8	Retrospective cohort data linkage study 2010–2015 impact on cervical cytology in 104,313 women aged 20–24 years.	Incidence rate ratio [IRR] for high-grade abnormal cervical cytology in those vaccinated with ≥1 dose 4vHPV = 0.75 (0.70-0.80, p<0.001) and for high-grade histology IRR = 0.69 (0.64-0.74, p<0.001).	The incidence for high-grade cytology was lower in women who had been vaccinated with at least one dose of 4vHPV before age 18 years than those who were unvaccinated.
Reduction in infection, anogenital warts and cervical lesions	9	SR (to March 2020), 99 publications for HPV infection and cervical lesions, 15 for RRP, oral and anal infections and lesions.	Key findings: • Reductions in infection, anogenital warts and cervical lesions were identified in Australia, Europe, North America and New Zealand. Updated review also showed an impact and effectiveness in low- and middle-income countries, which have the highest burden of disease. • Largest benefit achieved with high vaccination coverage given prior to sexual debut. • Benefits are seen in vaccinating males and females above adolescent age and faster outcomes are achieved by implementing multi-cohort strategies. • Up to 96% reduction in vaccine-type HPV positivity in females targeted by national immunisation programmes. Evidence of decrease in unvaccinated females. >70% reduction in vaccine-type HPV among men with high coverage of female-only programme.	
	10	Follow-up SR /meta-analysis including 60 million individuals and up to 8 years post-vaccination, 65 articles published literature from Feb 2014 – Oct 2018.	Showed a substantial impact of HPV vaccination programmes after 5-<9 years on HPV infections (54-83% decrease) and CIN2+ (31-51%) in girls and women and on anogenital warts in males and females (31-67%). High vaccination coverage and multicohort vaccination had great direct and herd impacts.	
Cervical cancer	50	Observational study, UK with 2vHPV 13.7 million-years follow-up women aged 20 – <30 years.	Relative reduction in cancer rates: 34% (25-41) offered vaccine at ages 16–18 years; 62% (52-71) for ages 14–16 years; and 87% (72-94) for ages 12–13 years, compared with a reference unvaccinated cohort (born between May 1989 – Aug 1990); risk reduction by age offered vaccine for CIN3 was 39% (36-41), 75% (72-77), 97% (96-98), respectively.	HPV immunisation programme in UK with 2vHPV almost successfully eliminated cervical cancer in women born since 1 September 1995. Greatest impact for those vaccinated at a young age.
Penile infection	51	Cross-sectional study. Penile HPV infection, sexually active heterosexual males between 2014-2017 (2014–15 before male vaccination, 2016-17 males	Heterosexual males - nine vaccinated with 4vHPV prior to male vaccination period and 81 vaccinated with ≥1 dose as part of programme.	Despite significant differences in HPV prevalence before age/source of recruitment adjustment, there was no statistically significant differences in

Outcomes	Ref	Participants and study design	Results	Findings
		eligible for 4vHPV vaccination in Australia) aged 17–19 years.	Prevalence of 4vHPV types lower in 2016/17 than 2014/15 – 0.7% (0-3.8%) vs 2.6 (0.7-6.6%) p=0.37.	HPV prevalence (all 37 types or 13 high-risk types) in any cohort. Herd immunity from female programme reduced HPV prevalence in males from 22% in 2006/7.
Impact of a single dose	68	Modelling study to assess impact of single dose HPV vaccination compared with no dose or two doses in India.	Predicted life-time risk of cervical cancer of 39–55% for single doses given to those aged 11–20 years (ten catchup birth cohorts) compared with 38% for the first ten routine vaccination cohorts. Expanding age range to 26–30 years had marginal gain. Assuming waning protection, 21–100% higher per-dose efficacy was projected with single-dose than a two-dose vaccination.	A single-dose catch-up was likely to be more impactful than two doses without catch-up. Projections suggest that by using single-dose HPV vaccination, the cervical cancer burden in India could be substantially reduced.

Abbreviations: IRR – incidence rate ratio; RR – relative risk; SR – systematic review

Table 9: Table of evidence for vaccine effectiveness as adjuvant therapy for prevention of SIL/CIN recurrence

Outcomes	Ref	Participants	Results	Findings
Recurrent CIN2+	32	Meta-analysis including three prospective, three respective, three post-hoc RCT, one cancer registry study.	Significant reduction in risk (RR 0.41, 95% CI 0.27-0.64) of developing recurrent CIN2+ after vaccination with 4vHPV or 2vHPV with surgical excision compared with excision alone, independent of HPV type. No significant difference between women aged under 25 years and older women (RR 0.47 [0.28-0.80] vs 0.52 [0.41-0.65]). NNT to prevent one case of recurrent CIN2+ = 45.5.	
	70	Retrospective review, Spain. 242, patients (median age 36 years, range 18->45 years) undergoing LEEP for CIN2-3 follow-up 3 monthly for 2 years, 42.6% received 2v or 4vHPV vaccination around time of conization.	Vaccination a protective factor for CIN2/3 recurrence: OR 0.63 (0.125-1.032; p<0.03).	HPV vaccination immediately before or after conization reduces risk of disease recurrence.
	71	Retrospective study, including 2,074 women in Denmark vaccinated 3 months before or immediately after CIN2+ conization (median age 29 [17–29] years) and ≤1 year after (28 [17–51] years) vs 15,054 unvaccinated women (median age 32 [17-51] years).	Non-significant, lower risk of CIN2+: vaccinated aHR 0.86 (0.67-1.09) vs unvaccinated. Those vaccinated 0-3 months before conization tended to have less severe lesions.	Study concluded that vaccination could be a clinically effective adjunct to conization to decrease the risk of recurrent high-grade cervical neoplasia.

Outcomes	Ref	Participants	Results	Findings
Persistent HPV infection or high-grade intraepithelial lesion	72	265 women, Catalonia, median age 39.8 ± 10.3 years. 9vHPV vaccination funding began for high-risk CIN during study period (from July 2017); from 2013–2017 2vHPV or 4vHPV recommended not funded for those requiring treatment for any SIL/CIN.	Persistent LSIL/HPV infection and HSIL at the first conization significantly increased the risk of persistent/recurrent HSIL (OR 4.3 [1.3-14.3] and OR 21.0 [3.6-123.5], p = 0.018). HPV vaccination significantly reduced the risk of persistent /recurrent HSIL at the end of follow-up (OR 0.2; 0.1-0.7, p = 0.01).	HPV vaccination was associated with a 4.5-fold reduction in risk of developing persistent or recurrent infection and prevented acquisition of new HPV infection.
Cervical dysplasia	73	Italy, 103 unvaccinated and 182 unvaccinated women receiving cervical hyperplasia excision (LEEP).	HPV vaccination given within 4 weeks of LEEP was a protective factor against cervical dysplasia requiring further LEEP (OR 0.4, p = 0.02). The rate of recurrence within ≥2 years overall was 10.5%; of these women 17/103 (16.5%) were unvaccinated and 13/182 (7.1%) were vaccinated; p = 0.01).	Supports a role for HPV vaccination as an adjuvant treatment after cervical hyperplasia excision.
High-grade lesion	33	Italy, retrospective study, chart analysis women ages mean 39 years (range 17-89) undergoing LEEP conization. 116/1,914 (6.1%) vaccinated (93% with 4vHPV) after conization aged 24–45 year and 1,798 (93.9%) conization alone. 94.7% had detectable high-risk HPV DNA.	The five-year recurrence rate of HSIL after conization was 1.7% (n = 2) of those vaccinated and 5.7% (n = 102) unvaccinated, respectively (p = 0.068).	Vaccination is a modifiable factor that could improve the outcomes of women with high-grade cervical dysplasia

Abbreviations: AIN – anal intraepithelial neoplasia; aHR – adjusted hazard ratio; CIN – cervical intraepithelial neoplasia; HSIL – high-grade squamous intraepithelial lesion; ITT – intension to treat population; LEEP – loop electrosurgical excision procedure; LSIL – low-grade squamous intraepithelial lesion; MSM – men-who-have-sex-with-men; OR – odds ratio; PP – per-protocol population; RCT – randomised controlled trial; SR – systematic review; VE – vaccine effectiveness/efficacy

Table 10: Table of evidence of incidence and treatment of recurrent respiratory papillomatosis

Outcomes	Ref	Participants	Results	Findings
Impact of HPV vaccination programmes on incidence				
New Zealand	34	Retrospective review Starship Children's Hospital, incidence of juvenile-onset recurrent respiratory papillomatosis (RRP) prior to 4vHPV (1998–2008) and following HPV vaccination programme (2008–2022; 9vHPV in 2016).	No significant difference incidence of RRP when vaccine introduced in NZ from 0.21 per 100,000 per year (nine cases 1998–2008) to 0.23 per 100,000/year (14 cases 2008–2022; p = 0.9). Since 9vHPV used in males and females, non-significant reduction to 0.15 per 100,000/year (four cases 2017–2022; p = 0.56).	A lower reduction in juvenile-onset RRP was seen in NZ than reported in other countries with higher HPV vaccine uptake.
Australia	36	Australian Paediatric Surveillance Unit study over 5 years to end 2016.	RRP rates declined from 0.16 per 100,000 in 2012 to 0.02 per 100,000 in 2016 (p = 0.034)	
US	35	Data from 26 tertiary medical centres in 23 US states.	Incidence rate of RRP declined from 2.0 cases per 100,000 births in 2004–2005 (165 cases prior to vaccine introduction) to 0.5 cases per 100,000 births in 2012–2013 (36 cases): IRR 0.2 (0.1-0.4).	Declines in RRP likely due to HPV vaccination.
Protection from maternal antibody	37	Antibody levels of HPV-6/11 antibodies were measured in peripartum maternal blood and cord blood of mothers who had received dose one of 9vHPV or 4vHPV 9–34 months (median 22 months) prior to sample collection.	Maternal anti-HPV-6 and 11 antibodies were highly correlated with those in the infant: 9vHPV group – correlation coefficient = 0.94 and 0.93, respectively; 4vHPV group – 0.99 and 0.77.	Placental transfer of maternal antibodies could provide additional protection to infants from RPP as well as preventing genital warts in the mother.
HPV vaccine as adjuvant treatment for RRP				
Children	38	SR included 12 studies	Some promise has been shown for use of HPV vaccine in treatment of RRP in children, but certainty of evidence is low with currently available data.	
Adults	74	Meta-analysis use of HPV vaccine as adjuvant therapy for RRP in adults.	Over three studies and 101 patients, an overall reduction of 0.123 (0.062–0.183) was reported in recurrences or surgeries per month.	
	39	SR use as HPV vaccine as adjuvant after surgery.	Significant reduction in number of surgeries per month comparing rate before and after vaccine treatment (estimated mean 0.35 vs 0.06). Mean inter-surgical interval was also significantly increased from 7.0 months (range 0.3–45) before vs 34.5 (range 2.1–82) months.	Supported the use of HPV vaccine as an adjuvant treatment of RRP.

Abbreviations: IRR – incidence rate ratio; RR – relative risk; RRP - recurrent respiratory papillomatosis; SR – systematic review

Search terms

Medline

▼ Search History (5)

# ▲	Searches	Results
1	Papillomavirus Vaccines/ and Papillomavirus Infections/ and Vaccination/	3234
2	limit 1 to (english language and yr="2018 -Current")	1691
3	one dose.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	9629
4	limit 3 to yr="2018 -Current"	3654
5	2 and 4	61

Selected 30

# ▲	Searches	Results
1	Papillomavirus Vaccines/ and Papillomavirus Infections/ and Vaccination/	3234
2	limit 1 to (english language and yr="2018 -Current")	1691
3	one dose.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	9629
4	limit 3 to yr="2018 -Current"	3654
5	2 and 4	61
6	vaccine effectiveness.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	4653
7	limit 6 to (english language and yr="2018 -Current")	2757
8	2 and 7	54
9	nine-valent.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	88
10	nonavalent.mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	325
11	9 or 10	410
12	2 and 11	58

Selected 93 in total

Scopus

TITLE-ABS-KEY ("human papillomavirus" AND "vaccine") AND PUBYEAR > 2016 AND (EXCLUDE (EXACTKEYWORD , "Animal Experiment")) 5724 documents

TITLE-ABS-KEY ("human papillomavirus" AND "vaccine") AND PUBYEAR > 2017 AND PUBYEAR < 2024 AND (EXCLUDE (EXACTKEYWORD , "Animal Experiment")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "IMMU") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "MULT") OR LIMIT-TO (SUBJAREA , "HEAL")) 4,599 documents

(TITLE-ABS-KEY ("human papillomavirus" AND "vaccine") AND TITLE-ABS-KEY ("single dose")) AND PUBYEAR > 2017 AND PUBYEAR < 2024 AND (EXCLUDE (EXACTKEYWORD , "Animal Experiment")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "IMMU") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "MULT") OR LIMIT-TO (SUBJAREA , "HEAL")) 60 documents

Selected: 36, removed 8 duplicates.

Cochrane

Human papillomavirus title/abstract/keyword 2018 – 2023 – 20 selected 3,

Pubmed

vaccine safety HPV review 2017–2023, meta-analysis, systematic review 58 results, selected 18

Additional literature was found through articles reviewed and grey literature.

Total Endnote library 253 including journal articles, reports, webpages, press-releases and electronic book chapters.

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