THE NEW ZEALAND HPV PROJECT

Genital, Anal and Throat HPV Infection

SUMMARY OF GUIDELINES

Taken from: **Guidelines for the Management of Genital, Anal and Throat HPV Infection in New Zealand** 10th Edition - 2024

www.hpv.org.nz

The Ministry of Health supports the use of these clinical guidelines, developed by clinical experts and professional associations to guide clinical care.

HPV – Key Overview Points

- Human papillomaviruses (HPV) are extremely common DNA viruses that only infect humans. HPV infects epithelial cells.
- There are more than 100 types of HPV, which can be subdivided into either cutaneous or mucosal categories depending on their tissue preference. There are more than 40 types of HPV that infect the anogenital and oropharyngeal mucosa. These can be broadly split into "high-risk" (hrHPV) and "low-risk" (lrHPV) types based on their association with the development of malignancy.
- Immunisation against HPV infection is available in the form of the nine-valent vaccine (HPV9).
- Most HPV infection is transient (i.e. becomes undetectable by DNA testing after 6–12 months). The majority of HPV infections do not progress. Virus that remains persistent is the key to pathogenesis.
- Individuals should be reassured that a diagnosis of HPV infection does not mean that they will get cancer.
- Low-risk HPV:
    - Infection with lrHPV types causes warty lesions in the anogenital and oral areas.
    - HPV 6 and HPV 11 cause approximately 90% of genital warts and are only rarely associated with precancer or cancer of the lower genital tract.
- High-risk HPV:
    - Persistent infection with hrHPV types causes virtually all cancers of the cervix and a significant proportion of cancers of the anus, oropharynx, vagina, vulva and penis. hrHPV infections are usually subclinical.
    - The 14 most oncogenic HPV types include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Types 16 and 18 are most commonly associated with development of cancer, together accounting for about 70% of invasive cervical cancers. However, not all infections with HPV 16 or 18 progress to cancer. In addition, HPV 16 is strongly associated with anal, oropharyngeal and HPV-associated vulvar cancer.

What's new in the 2024 guidelines

The National Cervical Screening Programme (NCSP) has changed from a cytology-based to primary HPV screening programme. Therefore, rather than including a chapter on cervical screening, we recommend visiting the full NCSP Guidelines.

The World Health Organization has adopted a strategy for cervical cancer elimination as a public health problem through optimal HPV vaccination and cervical screening.

There is an increased focus on the prevention of anal cancer following the publication of the ANCHOR study, which showed that treatment of anal cancer precursors reduces the incidence of anal cancer in those at high risk of invasive disease. HPV-related anal cancer incidence has been increasing, and is highest in HIV-positive MSM, women with a history of vulvar cancers or pre-cancers, and people with immunosuppression (Clifford et al, Int J Cancer, 2021: 148:38-47).

Persistent HPV 16/18 infection has been associated with preterm birth. HPV immunisation has the potential to reduce the incidence of preterm birth.

A recent review of the evidence for sexual transmission of clinical HPV in children has shown that there is no cut-off age to delineate between vertical versus horizontal transmission, and the possibility of sexual abuse needs to be considered in all children with anogenital warts.

Patient information pamphlets

New and updated patient information pamphlets are available free of charge from the HPV website (www.hpv.org.nz).

- HPV and Genital Warts: Key information
- HPV: Cervical screening
- Preventing HPV Cancers by Vaccination: What Everyone Should Know
- HPV and males
- HPV and throat cancer
- HPV and anal cancer

Epidemiology of anogenital HPV infection

- HPV is very common, perhaps universal, amongst sexually active populations. It can be regarded as an inevitable consequence of being a normal sexually active adult.
- On average, 80% of sexually active adults will have some form of HPV infection during their lives.
- The incidence of HPV infection increases in proportion to the number of sexual partners.
- For most people, infection with each HPV type is transient and becomes undetectable by HPV DNA testing within the first 12 months. HPV infection may become latent (undetectable) and reactivate years later, or infection may persist (remains detectable).
- The latency period of anogenital HPV infection is highly variable but is usually 3–6 months. Warts will often appear 3–6 months after HPV infection, but latency periods of many months or even decades have been reported. Evidence for extended latency

periods is seen in immunocompromised and normal individuals who, despite having been sexually inactive for many years, can suddenly develop warts or cervical abnormalities. It is important to emphasise that developing genital warts during a long-term relationship does not necessarily imply the presence of other sexual contacts.

Treatment options for genital warts by indication/site

Indication/site	**Treatment(s)**
Cervical or vaginal warts	• Consider no treatment (natural resolution rate is high; recheck after 6 months and refer if still present) • Possible cryotherapy • Surgery
Vulval warts	• Cryotherapy - can be repeated weekly until clearance (this is the only suitable treatment in pregnancy) • Imiquimod
Urethral meatal warts	• Cryotherapy with cryoprobe (technically difficult with liquid nitrogen) • Possible use of imiquimod or podophyllotoxin (but data limited) • Consider referral for specialist management as there is a risk of stenosis with over-zealous treatment • Surgery
Penile warts	• Imiquimod or podophyllotoxin • Cryotherapy
Anal warts	• Cryotherapy (open-sided anoscopes and bent probes can be used to target lateral areas) • Surgery • Intra-anal warts should be referred for specialist management
Mons Pubis	• Imiquimod or podophyllotoxin • Cryotherapy
Oral warts	• Cryotherapy • Surgery

HPV FAQs

What are the consequences of HPV infection?

- Most HPV infections are asymptomatic and of no consequence.
- HPV causes all anogenital warts – 90% of which are caused by non-oncogenic HPV 6 or 11.
- Persistent infection with oncogenic HPV types such as HPV 16 and 18 is responsible for a portion of intraepithelial neoplasia and cancers of the anogenital tract and oropharynx (cervical 100%, vaginal 90%, anal 80%, penile 50%, vulval 40%, oropharynx 26%).
- Although genital warts and genital tract cancers are declining, HPV-associated head and neck cancers and anal cancers are increasing – especially in men.

Does natural infection induce protective immunity?

- Not always. Current evidence suggests that naturally-acquired immunity is unlikely to be effective in preventing reinfection because of the ability of the virus to evade the immune system; this does not appear to be the case with vaccine-derived immunity.
- Naturally-acquired immunity to reinfection: the seroresponse to natural infection varies depending on the anatomical site infected and the individual themselves. There is some evidence that there is a reduced risk of reinfection with the same HPV type, but not other types (i.e. no cross-protection).
- Naturally-acquired immunity to persistent infection: once an infection has become established, resolution is largely dependent on innate and cell-mediated immunity. Reactivation of previously latent infection is common in women who become immunosuppressed.
- Naturally-acquired immunity to tumorigenesis: because natural immunity is very slow to develop, CIN can develop during the period of persistent infection.

Does reactivation of latent HPV occur?

- For most people HPV infection is transient and becomes undetectable by DNA testing within 6-12 months. HPV infection can remain latent and may reactivate years later. It is not possible to detect HPV in its latent state so it is not possible to know whether in some cases the immune system has completely cleared the virus or whether the virus remains latent in an undetectable level.

Can asymptomatic people be tested for HPV?

- There is no available test to determine the HPV status of a person.
- Current laboratory assays for HPV DNA detect only particular high risk types (in order to guide clinical management in cervical screening) so cannot be used as a screening test for 'all HPV types'.

What are the important points to know about HPV associated anal cancer?

- The incidence of anal cancer is increasing and the burden of disease is highest in men who have sex with men and HIV positive MSM. There is no effective method (including anal cytology/smear) for screening for anal cancer. Annual digital anorectal examination

(DARE) is recommended for HIV positive MSM who are aged 35 years or over (see https://analcancerscreening.guidelines.org.au/). HPV vaccination is the most effective method of prevention.

What are the important points to know about HPV-associated oropharyngeal cancer?

- Although oral cavity cancers associated with smoking and alcohol are decreasing, HPV-associated oropharyngeal cancer is increasingly common – especially in men.
- In common with anogenital HPV-related disease, a viral aetiology for oropharyngeal cancer raises questions for the patient, their partner and health practitioners. There is no clinically apparent premalignant condition and no reliable laboratory screening test. Common concerns are how the virus is acquired, whether there have been sexual partners outside of the couple and how to manage an ongoing sexual relationship. It is important to emphasise that a diagnosis of HPV-related cancer does not necessarily imply multiple sexual partners or other partners outside the relationship. There is no need to alter sexual activity with a stable partner, as sharing of HPV would have occurred long before the clinical appearance of the cancer. Female partners are not known to be at higher risk of developing cancer (at any site) themselves, but should follow standard cervical screening guidelines. A useful guide to discussing these issues includes a printable patient information sheet.[1] At the time of writing there is no clear evidence for transmission of HPV through kissing.

HPV Vaccination FAQs

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

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

Will cervical screening still be needed?

- Yes. Irrespective of whether someone with a cervix has been vaccinated, routine cervical screening will need to continue for the foreseeable future. This is because of possible prior infection with HPV types that cause CIN, or new infection with other HPV types not covered by vaccination.

[1] Fakhry C, D'Souza G. Discussing the diagnosis of HPV-OSCC: common questions and answers. Oral Oncol. 2013;49:863-71.

What if the vaccine is given to a pregnant person?

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

Can the HPV vaccine be given with other vaccines?

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

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

- Yes, as it is not a live vaccine.

How safe is the vaccine?

- Very safe. The HPV vaccine has an excellent safety profile and is well tolerated in all age groups. In pivotal clinical trials, the majority of adverse events reported were of mild or moderate severity, with injection site reactions being the most common.
- No safety signals have been identified since the vaccine was licensed. A summary of the published post-licensing safety data on the HPV4 vaccine from both active and passive surveillance studies to 2015 included data from more than one million preadolescents, adolescents and adults. Syncope, and possibly skin infections, were reported to be associated with administration of the vaccine; more detailed analysis of the "infections" suggested some were likely to be injection site reactions. Serious events were carefully examined, and there was no increase in incidence over background rates. These data for the HPV4 vaccine were confirmed by another post-licensing study (to 2016). With the exception of syncope, which is reaction to the injection rather than the vaccine, no safety signals were identified.
- The HPV9 vaccine was found to be as safe in female individuals as the quadrivalent vaccine. More recently, no safety concerns were identified related to the HPV9 vaccine based on US data from 215,965 individuals aged ≥9 years who received at least one vaccine dose between October 2015 and September 2017.

Can people be tested to check immunity after vaccination?

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

Key information for patients about HPV

There is a balance to be reached between 'over-normalising' a diagnosis of a viral STI and failing to empathise with the potential psychological impact of a diagnosis. It is important to address any concerns generated by the individual by the proactive provision of information and education, e.g. handouts, directing the individual to reputable sources of information (www.hpv.org.nz) and referral to a sexual health specialist if required.

- Vaccination against HPV has been available for many years and everyone who is eligible should have it.
- 80% of unvaccinated adults will get infected with HPV at some point in their life. Given that infection is asymptomatic in most infected individuals it is easily shared through sexual (including oral) skin-to-skin contact.
- There is no need to alter sexual activity with a stable partner because sharing of HPV would have occurred long before the clinical appearance of lesions or an abnormal smear result. There is no way to know which partner infected an individual with HPV or how long ago infection occurred. Having HPV does not mean that a person or their partner is having sex outside the current relationship.
- In most people the virus is harmless and causes no symptoms and will not develop into warts, pre-cancer or cancer.
- In a few people, HPV causes genital warts which are harmless and different from the types of HPV that cause abnormal cells or cancer.
- In a few people, HPV can cause abnormal cells which can sometimes lead to cancers in both men and women, including cervical, vaginal, vulval, anal and head and neck cancers and penile cancers.
- Partners will inevitably share HPV. There is no way to know which partner it came from or how long ago. Having HPV does not mean that a person or his/her partner is having sex outside the relationship.
- There are treatments for genital warts and abnormal cells.
- There is no treatment to eliminate HPV; where infections resolve, this is due to elimination by the body's immune system.
- HPV does not affect fertility.
- HPV does not stop you having a normal sex life.
- There is no HPV test to check HPV status. This means there is no test that can help answer the questions "Do I have HPV?", "Does my partner have HPV?", "Has my HPV gone?", "Can I have the vaccine?"