



GUIDELINES FOR THE
**MANAGEMENT OF GENITAL, ANAL
AND THROAT HPV INFECTION
IN NEW ZEALAND**

9TH EDITION - 2017



www.hpv.org.nz

Produced by the Professional Advisory Board (PAB) of the
Sexually Transmitted Infections Education Foundation

Sexually Transmitted Infections Education Foundation resources

Helpline

Website

Resources

HPV

Tollfree 0508 11 12 13

www.hpv.org.nz

Health professionals' resources

1. Guidelines for the Management of Genital, Anal and Throat HPV Infection in New Zealand – 9th Edition 2017
Only available online at www.hpv.org.nz
2. Sexually Transmitted Infections – Summary of Guidelines 2017

Patient information pamphlets

1. Some Questions and Answers about HPV and Genital Warts
2. Cervical Smears and Human Papillomavirus Infection (HPV)
3. Preventing HPV Cancers by Vaccination: What Everyone Should Know
4. HPV and Men
5. HPV and Throat Cancer: Common Questions and Answers

HERPES

Tollfree 0508 11 12 13

www.herpes.org.nz

Health professionals' resources

1. Guidelines for the Management of Genital Herpes in New Zealand – 12th Edition 2017
Only available online at www.herpes.org.nz
2. Sexually Transmitted Infections – Summary of Guidelines 2017

Patient information pamphlets

1. The Facts: A guide for people with Herpes Simplex
Includes –
Genital Herpes – The Facts
Herpes and Relationships
Herpes and Pregnancy
Facial Herpes
2. Herpes: Myth vs Facts

Website for youth with information about sexual health and sexually transmitted infections: www.justthefacts.co.nz

JUSTTHEFACTS.co.nz posters are available in A2, A3 and A4 sizes for display, in addition to wallet cards for consumers.

All the above resources are available free of charge from the Sexually Transmitted Infections Education Foundation

Phone: 09 433 6526

Email: info@stief.org.nz

New Zealand Sexual Health Society (NZSHS) resources

Comprehensive STI Management Guidelines and Patient Information handouts are available on www.nzshs.org/guidelines

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1st Edition	1999
2nd Edition	2001
3rd Edition	2002
4th Edition	2004
5th Edition	2007
6th Edition	2010
7th Edition	2013
8th Edition	2015

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ABOUT THIS DOCUMENT

This document is a consensus opinion of the Professional Advisory Board (PAB) of the Sexually Transmitted Infections Education Foundation. The PAB has representation from patients and medical and nursing disciplines involved in the management of people with anogenital HPV and/or genital warts. A process was undertaken to evaluate contemporary international literature and develop best practice regarding the diagnosis, treatment and evaluation of patients with HPV infection/genital warts and their sex partners, in Australasia. The recommendations are based on strong evidence in the literature or reasonable suppositions and opinions of experts. The PAB works on a voluntary basis.

The guidelines' recommendations have been rated under the following evidence-based categories:

GRADE A: Very strong evidence

One or more properly randomised controlled clinical trials.

GRADE B: Fairly strong evidence

One or more well-designed observational studies (i.e. non-randomised clinical trial cohort, case control or time series study, or non-controlled experimental trials).

GRADE C: Weak evidence or firmly held opinion

Opinions of respected authorities that were based on clinical experience, descriptive studies, and/or reports of expert committees.

GLOSSARY OF TERMS AND ABBREVIATIONS

AIN	Anal Intraepithelial Neoplasia
ASC-H	Atypical Squamous Cells – a High-grade lesion cannot be excluded
ASC-US	Atypical Squamous Cells of Uncertain Significance
CIN 1, 2 or 3	Cervical Intraepithelial Neoplasia
HPV	Human Papillomavirus
hrHPV	high-risk Human Papillomavirus
HSIL	High-grade Squamous Intraepithelial Lesion
LBC	Liquid-Based Cytology
lrHPV	low-risk Human Papillomavirus
LSIL	Low-grade Squamous Intraepithelial Lesion
MSM	Men who have Sex with Men
NCSP	National Cervical Screening Programme
PCR	Polymerase Chain Reaction amplification
PIN	Penile Intraepithelial Neoplasia
RRP	Recurrent Respiratory Papillomatosis
SCC	Squamous Cell Carcinoma
SIL	Squamous Intraepithelial Lesion
STI	Sexually Transmitted Infection
TCA	Trichloroacetic Acid
VaIN	Vaginal Intraepithelial Neoplasia
VIN	Vulvar Intraepithelial Neoplasia
VLP	Virus-Like Particle

WHAT'S NEW – CHANGES SINCE THE 2015 GUIDELINES

9-valent vaccine

9-valent vaccine (Gardasil 9 Seqirus/MSD) is registered for use in females 9–45 years and in males 9–26 years.

HPV9 is funded for both boys and girls aged 9–26 years (inclusive).

Those aged 9–14 years will get a two dose schedule and those aged 15–26 years will receive a three dose schedule.

HPV9 is available (but not funded) up to (and including) age 45 for females.

From 1 January 2017

Funded indications and recommended schedules:

Two doses, at 0 and 6–12 months for individuals aged 9–14 years.

Three doses, at 0, 2 and 6 months, for individuals:

- aged 15–26 years inclusive
- aged 9–26 years inclusive:
 - with confirmed HIV infection
 - who are transplant (including stem cell) patients
 - an additional dose for post-chemotherapy patients

Individuals who started with HPV4 may complete their remaining doses with HPV4 or with HPV9 when available.

Individuals who have previously been fully vaccinated with funded HPV4 are not eligible to receive funded HPV9.

Individuals who have previously been vaccinated with HPV4 which was self-funded are eligible for funded HPV9, up until age 27.

New patient information pamphlet

One new patient information pamphlet is available from the HPV website (www.hpv.org.nz) – **Preventing HPV Cancers By Vaccination: What Everyone Should Know.**

HUMAN PAPILLOMAVIRUS (HPV) – OVERVIEW

KEY POINTS

- More than 40 HPV types infect the anogenital area and throat (pharynx and larynx) and the majority are sexually transmitted.
- Divided into low-risk (LrHPV) types, which are not associated with precancer or cancer, and high-risk (hrHPV) types, which are associated with precancer and cancer.
- Patients should be reassured that a diagnosis of HPV infection does not equate to cancer.
- 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.
- Warty lesions in the anogenital and oral areas are usually caused by LrHPV.
- hrHPV infections are usually subclinical.
- Immunisation against HPV infection is available in the form of the nine valent vaccine (HPV9).

Human papillomaviruses (HPV) are extremely common DNA viruses that only infect humans. HPV infect epithelial cells. Infection with low-risk HPV types causes external genital warts. Persistent infection with high-risk HPV types causes virtually all cancers of the cervix and a significant proportion of cancers of the anus, oropharynx, vagina, vulva and penis. There are more than 100 types of HPV, which may be subdivided into either cutaneous or mucosal categories depending on their tissue preference. There are more than 40 types which infect the anogenital and oropharyngeal mucosa. These can be broadly split into “high-risk” and “low-risk” types based on their association with the development of malignancy.

- Low-risk HPV (LrHPV) – 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 (hrHPV) – 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 and throat cancer.

Clinical presentations

- Genital warts (condyloma acuminata). HPV infects the penis, scrotum, perineum, anal canal, perianal skin, vaginal introitus, vulva, cervix.
- Squamous intraepithelial lesions (SILs) of the vagina, cervix, anus, penis. HPV infection has been clearly linked to nearly all SILs and cancers of the cervix and anus. HPV is also linked to a subset of penile, vulval and vaginal cancer.
- Oropharyngeal cancer (see [page 23](#)).
- Infection of respiratory mucosa also occurs, particularly but not exclusively in children.

Subclinical HPV infection

- Subclinical means not visible to the naked eye. May be hrHPV and/or LrHPV.
- Subclinical HPV infection is most commonly detected by cervical cytology or biopsy specimens.
- HPV DNA testing is currently available only as an adjunct to cervical cytology. HPV DNA testing has no clinical utility in sexually transmitted infection (STI) screening. hrHPV testing has been shown to be effective as a primary screening test to reduce cervical cancer rates for both unvaccinated and vaccinated women.¹ The NCSP is in the process of redeveloping the programme towards primary screening with the HPV test, in line with a number of other international cervical screening programmes. Vaccination is the first line of prevention and regular screening with hrHPV testing is the second line of prevention. There are no screening tests clinically available for HPV detection from oropharyngeal, anal, or male genital specimens. Neither are there any approved serologic or blood tests.

EPIDEMIOLOGY OF ANOGENITAL HPV INFECTION

KEY POINTS

- 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.
- Most anogenital HPV infections are subclinical.
- On average, 80% of sexually active adults will have some form of HPV infection during their lives.
- HPV infection increases in incidence 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 extremely variable; usually 3–6 months, but latency periods of many months or even decades have been reported.² Evidence for such extended latency periods is seen in immunocompromised and normal patients 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.

Epidemiology in females

Generally speaking the same HPV genotypes cause cervical cancer everywhere in the world with very little variation from region to region.³ There is no evidence of a significant population based or genetic predisposition for cervical cancer. This means that risk is directly related to amount and timing of exposure to HPV infection, the likelihood of persistence and access to preventative health care. 10.5% of women worldwide are positive for HPV DNA in the cervix.⁴ Smoking is an independent risk cofactor which may increase the risk of the development or progression of lesions once HPV infection has occurred. In an international meta analysis, the highest prevalence is in young women (20–25% around age 20) falling to 10% at age 30 and falling slightly thereafter,⁵ while a study in the United Kingdom reported a prevalence of 40% in 20–24 year olds falling to 7% by 50 years of age.

Rates of HPV infection in young women are high following first sexual contact. 28% after 1 year with one sexual partner, increasing to 49% after 36 months, and remaining high with the acquisition of each new partner.^{6,7}

Most HPV infection occurs after initiation of sexual activity and is transient, although in some cases HPV infection remains latent and may reactivate years later.⁸ There is a rapid loss of detectable HPV in the first 6–12 months, with 80–90% becoming undetectable by 2 years. The key step in cervical carcinogenesis is overt measurable hrHPV persistence, which after a year or two strongly increases the risk of the development of high grade CIN or AIS.^{9,10} Some infections may become quiescent (latent) or undetectable¹¹ however, the fraction of HPV infections that become latent is unknown. In older women, detection of new HPV infection is likely to represent reactivation of infection rather than acquisition of a new, recent infection.^{12,13} Reactivation is also proposed as a main source of newly detected HPV infection in HIV-positive and immunocompromised women who reported no new sexual partners.¹⁴

Studies of anal HPV infection in women suggest that it is far more common than originally thought.^{15–17} Women with a history of vulval or cervical high-grade SIL or cancer are also at increased risk of anal HPV infection and HPV-related disease. In these studies anal intercourse was not a consistent risk factor with either anal HPV infection or anal SIL.¹⁸

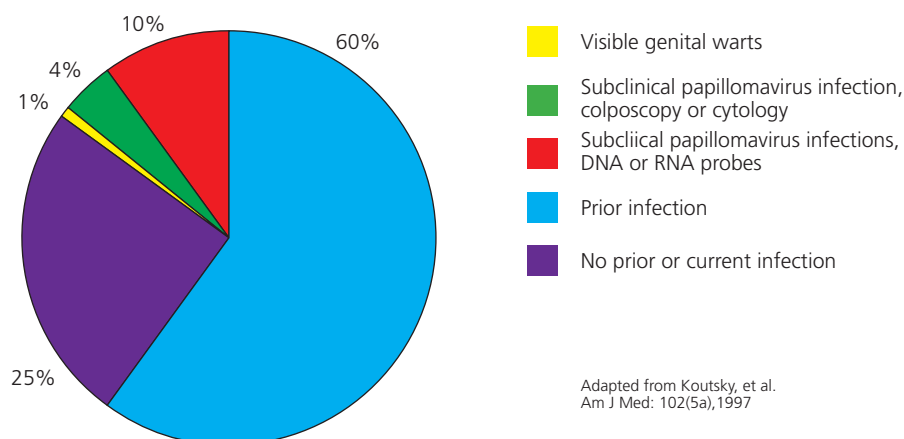


Figure 1: Estimated prevalence of genital HPV infection among men and women 1–49 years of age in the US (1994).

Epidemiology in males

Reported genital prevalence of specific HPV types and their clearance in men vary widely, males have a lower seroconversion rate than for women of the same age, this may mean they have a higher risk of reinfection throughout life.¹⁹

Heterosexual men

HPV infection is common among heterosexual men. At any one time, the prevalence of anogenital HPV of any type was 53%. The overall median time to becoming HPV undetectable was 7.5–12 months.^{20,21} Few studies have evaluated the frequency of anal HPV in heterosexual men. In a study that included 1305 heterosexual men, anal HPV was detected in 12%.²²

Men who have sex with men (MSM)

The burden of anogenital HPV infection is highest amongst MSM, particularly HIV positive MSM.²³

An American study on urban HIV-negative MSM showed an overall prevalence of anal HPV infection of 57% with the most common type being hrHPV-16.²⁴ Prevalence did not vary across age groups. Anal HPV was independently associated with a history of receptive anal intercourse (odds ratio 2.0) and with more than five sex partners in the preceding 6 months (odds ratio 1.5). The most common site of HPV recovery in HIV-negative MSM is the anal canal.²⁵ Anal HPV has been associated with an increased risk of HIV acquisition in MSM.²⁶

TRANSMISSION OF ANOGENITAL HPV INFECTION

KEY POINTS

- HPV is spread from close skin-to-skin contact.
- Transmission in the genital region may occur even when condoms are used and does not necessarily require penetrative intercourse.
- If one member of a stable partnership has anogenital HPV infection, the other is likely to be either infected or immune to that infection.
- Condoms provide limited protection against HPV infection, but their use is recommended to prevent other sexually transmitted infections.
- Because of variable latency, HPV infection may develop during a long-term relationship and does not necessarily imply other sexual contacts.

Sexual transmission

HPV infection results from skin-to-skin contact and can be transmitted by penetrative as well as non-penetrative sexual contact²⁷ (genital-genital, oral-genital, anal-genital, oral-anal). Other types of contact may also play a role; such as spread during sexual activity through fingers or sex toys from genital areas infected with HPV.²⁸ Anal intercourse is not required for spread to the anal canal. The prevalence of HPV infection is much lower in virgins (4% vs 22% in sexually active women in a report from Sweden).²⁹ The virus is not transmitted via blood or body fluid, e.g. semen. Transmission occurs frequently because subclinical infections are common and asymptomatic, and warty lesions often go unnoticed, particularly in areas that are not easily inspected for the presence of warts. Among heterosexual couples, type specific concordance (both partners infected with the same HPV type) is common,³⁰ almost 25%.

It is generally believed, although not proven, that clinically visible warts offer the greatest possibility for transmission, and that treating warts decreases that possibility.

Anogenital HPV infection can be transmitted to the mouth through oral sex.³¹ The mouth appears to be a less hospitable environment for genital strains of HPV than the genital area.³²⁻³⁵

Immunity from natural infection is generally poor. Naturally produced antibodies provide partial protection, although many people do not seroconvert.^{36,37} Previous infection does not necessarily create long-term immune memory so does not prevent future re-infection with the same HPV type.

Non-sexual transmission

Vertical transmission in utero is very rare³⁸ (see Pregnancy and Breastfeeding section, **page 21**). Autoinoculation may occur rarely.³⁹ While HPV DNA has been found on fomites (inanimate objects), there is no evidence to suggest that transmission occurs.^{40,41}

For management of HPV infection in children, see **page 25**.

Condom use

Consistent condom use has been shown to reduce the risk of acquisition of HPV infection and genital warts (in the order of 30-60% reduction).⁴²⁻⁴⁴ They may reduce recurrence when both partners are infected,⁴⁵⁻⁴⁷ although the extent to which recurrence is due to re-infection is not known.

Vaccine

HPV vaccine is a very effective method of preventing HPV acquisition – see HPV Vaccines section, **page 28**.

EXTERNAL GENITAL WARTS – CLINICAL PRESENTATION AND DIAGNOSIS

KEY POINTS

- Genital warts vary widely in appearance and distribution in the anogenital area.
- The differential diagnosis includes normal anatomical findings such as vestibular papillomatosis and pearly penile papules, dermatoses, and intraepithelial neoplasia.
- Diagnosis is generally made by visual inspection.
- Genital warts which are atypical in appearance should be biopsied to exclude alternate diagnoses, particularly intraepithelial neoplasia.
- The use of HPV DNA testing for anogenital wart diagnosis is not recommended, because test results do not confirm the diagnosis and do not assist with genital warts management.
- The application of 3–5% acetic acid which might cause affected areas to turn white, is not a specific test for HPV infection and is not recommended.

Genital warts are visible lesions that occur in the anogenital area and there is good correlation between physical findings and histological studies.

There are four variants of genital warts:

1. Skin-coloured filiform warts (condyloma acuminata) occur on moist mucosal skin.
2. Skin-coloured raised papules with a rough warty surface (verruca vulgaris) arise on drier areas of genital skin.
3. On either dry or moist skin, smooth flat-topped papules which may be pink, red, brown or black, can develop (carpet warts).
4. Giant condyloma up to 4cm in size with a cauliflower surface and red or pink in colour usually arise on dry genital skin.⁴⁸

Genital warts are frequently multifocal (one or more lesions at one anatomic site, e.g. vulva), or multicentric (lesions on disparate anatomic sites, e.g. perineum and cervix).⁴⁹⁻⁵¹ It is important to examine the entire lower genital tract for the presence of multicentric visible warts before treatment.

Perianal lesions are common in both sexes, including heterosexual men. They are not exclusively associated with anal sex, due to the regional spread of HPV infection. They are, however, seen more commonly in MSM.

Lesions can also occur on the vagina, cervix, urethral meatus and anal canal.

Differential diagnosis

Most warts are clinically recognisable. However, some require examination under magnification (e.g. with a dermatoscope or colposcope) to distinguish from other lumps (e.g. vestibular papillomatosis or molluscum contagiosum). For many patients, the psychological impact of warts is significant. If the diagnosis is uncertain, it is useful to get a second opinion (either from a colleague or a specialist).

The differential diagnosis of genital warts includes:

- Normal anatomic variants in women such as vestibular papillae, prominent sebaceous glands (Fordyce spots) and skin tags (acrochordans).
- Normal anatomic variants in men such as sebaceous glands (Tyson's glands), pearly penile papules, skin tags, angiofibroma.
- Infections such as molluscum contagiosum, condylomata lata (syphilis).
- Dermatoses and benign neoplasms such as seborrhoeic keratoses, melanocytic naevus, angioma, lymphangioma, psoriasis and lichen planus.
- High-grade squamous intraepithelial lesion (HSIL) (previously called VIN, vulval intraepithelial neoplasia).⁵² HSIL usually presents as white, red or pigmented papules or plaques which may be pruritic, but can be asymptomatic. The lesions may have a warty surface and can be unifocal or multifocal. A lesion may be small and discrete or may be an extensive plaque covering most of the vulval or perianal skin. It may be clinically indistinguishable from the papular form of external genital warts, but appears more disorganised.^{53,54} Histological examination of these lesions shows high-grade intraepithelial neoplasia. HSIL is usually associated with HPV type 16 infection.
- Vulval cancer. This may arise from HSIL as a tumour or ulcer.

A number of clinical variants of PIN are recognised; many are associated with HPV type 16⁵⁵ (see [page 39](#) for pictures).

Penile and anal cancer usually present as a small nodule which may be ulcerated. Untreated, it will progress to a large ulcerated plaque. On the penis the most common sites are the glans, coronal sulcus and prepuce.

TREATMENT OF EXTERNAL GENITAL WARTS

KEY POINTS

- The primary goal of treatment is to eliminate warts that cause physical or psychological symptoms. Non-treatment is an option for asymptomatic warts and the cure should not be worse than the disease.
- There is no definitive evidence that any one treatment is superior to the others and no single treatment is suitable for all patients or all warts.⁵⁶ Methodological difficulties in designing RCTs and the frequency of spontaneous regression means that there is limited evidence to inform best practice.
- The method of treatment should be determined by patient preference, available resources and the experience of the practitioner. Other factors include the size, number and site of the warts, the age of the patient and whether the patient is pregnant.
- All treatments have significant failure and relapse rates.
- People with a small number of low volume warts, irrespective of type can be treated with either ablative therapy or topical treatment. Podophyllotoxin for 4 weeks or imiquimod for 16 weeks are suitable home treatments for patients. The patient should be given a demonstration on lesion finding, treatment application and advice about discomfort and local skin reactions from the treatment.
- Soft, non-keratinised warts respond well to cryotherapy, imiquimod or podophyllotoxin. Dry, keratinised warts may be better treated with ablative methods such as cryotherapy, excision or electrocautery. Aggressive ablative therapy should be avoided over the clitoris, glans penis, urinary meatus, prepuce, in uncircumcised men.
- If there is no significant response within 4–6 weeks, an alternative diagnosis, change of treatment modality, or onward referral should be considered.
- Patients should be given information about all the treatment options (including no treatment) in order for them to make an informed decision about their preferred choice.
- Not undertaking treatment may be an option, given that about 30% of patients will experience spontaneous clearance of warts over a 6-month period. However, many patients will seek treatment, to remove the discomfort, anxiety, social stigma and fears about transmission. Lack of response to therapy should be referred to a Sexual Health Specialist to review diagnosis and management options.
- Although treatment can result in disappearance of genital warts, the underlying viral infection may or may not persist. The elimination of external visible warts may not decrease infectivity since the warts may not represent the entire viral burden, as internal sites and clinically normal skin may act as reservoirs for HPV infection. Warts rarely progress to cancer. There is no specific treatment for subclinical HPV infections, most of which resolve spontaneously.⁵⁷
- Because all available treatments have shortcomings, some clinics employ combination therapy (e.g. provider-administered cryotherapy with patient-applied topical therapy between visits to the provider). However, limited data exist regarding the efficacy or risk of complications associated with combination therapy.
- If warts are in the pubic region avoid shaving or waxing as this may facilitate local spread by autoinoculation of HPV into areas of microtrauma.

For a summary of treatment by anatomic site and treatment options, see Tables 1 and 2, pages 11-12.

Efficacy of Treatments

A Cochrane review assessed trials comparing the use of self-applied imiquimod with other patient-applied or provider-applied treatment modalities. The quality of trials was very low and the findings should therefore be interpreted with caution. Compared to other self-applied treatments it was not possible to determine if there was any difference between clearance and recurrence rates. Compared to other provider-applied treatments it was unclear whether there were differences in regression rates but there were less recurrences at 6 months with the use of imiquimod.⁵⁸

Treatment of genital warts, particularly complex cases, is an art. Specialist consultation is recommended for cases which are difficult to treat.

Self-applied treatments (home therapy)

Imiquimod

Imiquimod is available as a 5% cream on prescription and is fully subsidised. These applications may lead to an increase in adverse skin reactions.⁵⁹

Imiquimod 3.75% is not currently available in New Zealand.

Mechanism of action: An immune enhancer that stimulates production of interferon and other cytokines. It appears to have an advantage of reduced recurrence rate.⁶⁰

Suitable for: Women, and some men with foreskin-associated warts. Particularly useful for 'carpet warts' (smooth, flat-topped and joined-up), where the female introitus and perianal area are involved.

Precautions: Not currently recommended in pregnancy. There are limited case reports of its use in pregnancy.

Application: Careful application of imiquimod cream is important.

Apply onto fingertip and rubbed onto clean, dry, wart area until cream vanishes, once daily, three times per week, prior to normal sleeping hours and after sexual activity (imiquimod weakens condoms and vaginal diaphragms). Wash off next morning (including from skin folds) or after 6–10 hours. The standard duration of treatment is 16 weeks, although the majority who clear their warts will do so by 8 weeks. There is no data on use of imiquimod beyond 16 weeks and non-responders by 12–16 weeks should be switched to an alternative treatment.

The manufacturer recommends that a sachet be used for single use to cover an area of up to 20cm².

Side effects: Imiquimod frequently causes localised erythema, swelling and/or (rarely) superficial ulceration of the treated area which is due to the direct therapeutic action of the agent, i.e. switching on the immune response, rather than to hypersensitivity. These local skin reactions can be managed by having a break from treatment for a few days. Skin reactions result in discontinuation of the treatment in less than 2% of patients. Hypopigmentation may occur. Imiquimod can also cause flu-like symptoms in a small percentage of patients.

Imiquimod should be used with caution (it is not a contraindication) in patients with autoimmune conditions, or those on systemic immunosuppressive drugs, although systemic absorption from topical treatment is likely to be negligible.

Podophyllotoxin

Podophyllotoxin is dispensed as a 0.5% solution (Condyline™). The 0.15% cream is not available in New Zealand. These contain purified podophyllin in a more standardised form. Podophyllotoxin has been extensively studied in randomised and placebo-controlled trials. It is licensed for 4- to 5-week courses and supervision by medical staff is recommended when the lesion area is greater than 4cm².

Mechanism of action: The active moiety is an antimitotic and causes localised tissue necrosis. Localised epidermal pallor, caused by intracellular oedema, can usually be seen within 48 hours of application.

Suitable for: Men with external warts that can be visualised. May be less effective for keratinised warts.⁵⁹

Not for use in women because of difficulty in application.

Contraindications: A history of hypersensitivity (incidence approximately 1%). They are not used in pregnancy or lactation, or in children. Should not be used on warts which cannot be visualised, on internal warts, and they are not recommended for extensive wart areas (>10cm²).

Application: Patients must be able to visualise, identify and reach their warts, and if necessary should be shown what is wart and what is normal skin, using a mirror. Podophyllotoxin solution should be applied carefully to the warts using one of the applicators enclosed with the product, taking care that the solution does not come into contact with healthy skin and allowing drying after application to avoid inadvertent spreading of the solution. Applying Vaseline or zinc ointment on healthy skin around the wart(s) can be protective. The solution should be applied twice daily for 3 consecutive days followed by 4 days rest each week until the warts have resolved, or for a maximum of 5 consecutive weeks.

Side effects: Mild erythema with slight pain and/or superficial ulceration of the treated area can be expected. More severe skin ulceration, erosions, erythema, irritation, scarring, phimosis, pain, burning and soreness can occur. These effects are usually only mild to moderate in severity and resolve when the warts necrose.⁵⁹

Physician-applied treatments

Cryotherapy

Mechanism of action: Destroys the wart tissue by freeze/thawing, resulting in sloughing and wart destruction.

Suitable for: External and internal warts. Dry and moist warts. Can be used in pregnancy.

Application: Adequate training and expertise in this technique is required. Effective cryotherapy may be achieved by a cryoprobe or application of liquid nitrogen by spray or by loosely wound cotton on a wooden applicator (not with tightly wound, typical cotton swabs). The full thickness of the wart should be frozen until there is whitening of the surrounding skin area for 2mm. (Note: It is difficult to visualise the lesion using a cotton bud method of application and a spray method is preferred.) Treatment is repeated weekly until the warts have resolved. Some sexual health clinics have facilities for more focused freezing using fine probes with nitrous oxide or carbon dioxide cryoguns. Patients can be referred for treatment.

Side effects: Pain and necrosis following application of cryotherapy are fairly universal, and blistering may occur. The treatment of large warts or areas at one time can create wound care problems. Adverse effects include irritation, local oedema, necrosis, ulceration and pain, especially when the treated area thaws. Both hypo- and hyperpigmentation can occur, but this is usually temporary. Although the use of injected local or topical anaesthesia (e.g. tetracaine hydrochloride gel 4% cream) is rarely necessary, it may facilitate cryotherapy by reducing pain when a large number or area of warts is present.

Curettage and scissor or scalpel excision

Mechanism of action: Directly remove genital warts.

Suitable for: Exophytic warts.

Contraindications: Known bleeding abnormality. Can be used in pregnancy.

Technique: Direct removal with extension of the wound only into the upper dermis. Haemostasis can be secured with an electrosurgical unit or a chemical styptic (e.g. silver nitrate sticks); suturing is rarely required or indicated when removal is done properly.

Side effects: Localised pain, for which mild analgesics may be required, and bleeding. If operating-room surgery is required there are the additional hazards of a general anaesthetic.

Electrocautery or diathermy (hyfrecation)

Mechanism of action: Coagulates proteins of treated tissues.

Suitable for: Anogenital and oral warts.

Contraindications: None. Can be used in pregnancy.

Technique: Both electrocautery and laser therapy require masks and a smoke evacuator to prevent inhalation of aerosol HPV and oropharyngeal transmission. Advanced training and expertise is required to minimise scarring. Once anaesthesia is attained, physical destruction of warts can commence. Usually, no additional haemostasis is required.

Side effects: Local pain and possible infection. Scarring is more common than after cryotherapy.

Laser therapy

Mechanism of action: Vaporisation of warts.

Suitable for: Vulval, vaginal, cervical and perianal warts. Not considered first-line treatment because of expense. Can be considered if there are obstructive or large lesions.⁶¹

Contraindications: None. Can be used in pregnancy.

Technique: Advanced training and expertise required. Specialist only.

Side effects: Local pain. Scarring and hypo- or hyperpigmentation can be minimised by controlling depth and avoiding treatment beyond the dermal papillae.

Trichloroacetic acid (TCA)

Mechanism of action: TCA is a caustic agent that destroys warts by chemical coagulation of proteins. Treatment solution concentrations have not been standardised and saturated concentrations of 85–95% have been used.

Suitable for: Small warts on moist surfaces.

Application: Specialist clinic settings only. Training is necessary before applying this treatment. TCA solutions should be applied sparingly and allowed to dry before the patient sits or stands. If there is intense pain, the acid can be neutralised with soap and sodium bicarbonate. TCA solution has a low viscosity (comparable to that of water), and if over-applied can spread rapidly and 'run', damaging a significant area of normal tissue.

Contraindications: Nil, but most suitable for small moist warts. Can be used in pregnancy.

The following treatments are not recommended because of side effects, toxicity and difficulty in application:

- Podophyllin resin
- 5% fluorouracil cream
- Systemic interferon

Selecting treatment(s) for individual patients (see Table 3, page 13)

Many patients require a course of therapy rather than a single treatment. Studies have not systematically evaluated the factors that influence the selection of therapy, although a survey found that patients expressed a desire for topically applied therapies that may be used at home. **As no one treatment is ideal for all patients or all warts, consideration should be given to a change of treatment modality or onward referral if there is no significant response within 4–6 weeks.** Most treatment modalities are eventually effective in eliminating small numbers of warts. Patients with limited disease (i.e. one to five warts) may benefit most from cryotherapy or simple office surgery. Ablative therapy (cryotherapy) should be considered in those with large or extensive areas of warts to at least debulk their warts.

For self-applied therapeutic modalities, treatment beyond the manufacturer's recommendations is not advisable and concurrent use of multiple therapeutic modalities on a single wart is not recommended as routine treatment. **It should be borne in mind that a continuing lack of response to therapy might indicate other pathology and referral for assessment should be considered in such cases.**

Continually evaluate the response to treatment to avoid over-treatment and a therapeutic course worse than the disease itself. Persistent hypo- and hyperpigmentation is a possible complication of ablative therapeutic modalities. Depressed or hypertrophic scars rarely occur. Ablative treatment, especially to the introitus, can result in disabling chronic pain syndrome or hyperaesthesia at the treatment site.

Surgical removal of warts, by diathermy, laser ablation or excision under local or general anaesthesia, may render the patient wart-free, usually in a single visit. However, the disadvantages are that significant training, a moderate amount of equipment, and a longer patient visit are required. Although surgery is obviously of most benefit when warts are present in large numbers or over large surface areas, it can be used for average cases. While the cost of a single surgical visit may be greater, surgery can accomplish in one visit what other ablative modalities often require multiple visits to accomplish, which may result in greater cost effectiveness for some patients. However, recurrence rates may be the same as other therapeutic modalities and the morbidity of treatment may be greater with increased risk of pain, infection and scarring.

Combination treatment

Although treatments are commonly combined, few studies have been published to show that clearance rates or recurrence rates are improved. Possible combinations include:

- Cryotherapy and podophyllotoxin versus cryotherapy alone.
- Cryotherapy applied once followed by topical agent such as podophyllotoxin.
- A combination of laser and imiquimod has been shown to be safe and well tolerated.⁶²

Symptomatic therapy

- For ongoing management by the GP or health professional, the patient should be advised to return weekly for treatment until all the warts have gone. Patients may be referred to a specialist or sexual health clinic when there is a poor response to treatment, or warts continue to recur after 3 months.
- Saltwater baths are a useful thing the patient can do to help soothe and heal the genital area during treatment. Two handfuls of plain salt per bath or two tablespoons in a large bowl, preferably twice daily, and dry with hairdryer.
- Lignocaine gel 2% (Xylocaine™) is a useful local anaesthetic to put on raw areas 2 minutes prior to micturition and defaecation.
- A concomitant thrush infection is common. Local imidazole preparations often help, and/or oral fluconazole.
- For large areas made raw by wart ablations, 1% silver sulphadiazine cream is useful.

Table 1: Treatment by site

(For details of individual therapies, see Table 2, page 12)

Site	Treatment	Use in Pregnancy
External genital warts	Patient-applied Imiquimod (Aldara 5% cream); OR Podophyllotoxin solution. Provider-administered Cryotherapy; OR Trichloroacetic acid; OR Surgical removal; OR Laser; OR Diathermy.	No Yes
Cervical warts Vaginal warts	Colposcopy is not indicated Cervical smear is not indicated unless due Consider no treatment as an option as rate of natural resolution is high Cryotherapy is possible with liquid nitrogen Follow-up recommended 6 months. Refer if still present	Yes
Urethral meatal warts	Cryotherapy with Cryoprobe (technically difficult with liquid nitrogen). N.B. Risk of stenosis if overzealous treatment. Note: Podophyllotoxin and imiquimod have been used, but limited data.	Yes No
Anal warts	Cryotherapy. Special open-sided anosopes and bent probes are available to permit treatment laterally; OR Surgical removal.	Yes
Oral	Cryotherapy; OR Surgical removal.	Yes

Table 2: Summary of treatment options

Note: All treatments have wide response and recurrence rates. Not all treatments are funded in New Zealand.

Forms of Treatment	Usage	Application Frequency/Duration	Advantages and Disadvantages	Use in Pregnancy
Patient-applied				
Imiquimod (Aldara) 5% cream	External genital warts	Patient should apply once daily at bedtime, 3 times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours post application.	Immune enhancer. May be more effective on moist warts e.g. introitus and perianal areas. Relatively low recurrence rate.	Not recommended.
Podophyllotoxin Condyline (solution)	External genital warts for males. Not for use in women because of difficulty in application.	Patient should apply podophyllotoxin solution with the supplied applicators, protecting surrounding skin with Vaseline. The cream is applied with a finger, to visible external warts, twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, up to 4 cycles. The total wart area should not exceed 10cm ² , and the total volume of podophyllotoxin solution should not exceed 0.5 ml/day. If possible, the initial treatment should be demonstrated by the health care provider.	Results are dependent on patient compliance and correct application of treatment. Not for large (>10cm ²) wart areas and may be less effective on dry warts. Overzealous use can cause painful ulceration. The solution should be used on readily visible warts, particularly in men.	Contraindicated in pregnancy.
Provider-administered				
Cryotherapy (Cryoprobe or liquid nitrogen on prepared swabs)	External anogenital, cervical, urethral, anal or oral warts	Weekly. Freeze full thickness of wart, whitening the surrounding skin area up to 2mm. The size of the swab should be tailored to the size of the lesions e.g. use of orange stick and wrap-around cotton wool to obtain correct size.	Effective for moist and dry warts, pain can be reduced by use of local anaesthetic, gel/cream. Safety and efficacy highly dependent on skill level, equipment and experience. Risk of over or under application with liquid nitrogen.	Yes
Electrocautery or diathermy (Hyfrecation)	External anogenital or oral warts	Single treatment.	Prompt wart-free state, results depend on skill level and training, requires equipment, longer clinic visit, local anaesthesia is mandatory. Skin bridges should be left in between sites to aid healing and minimise scarring.	Yes
Laser therapy	Extensive anogenital warts	Single treatment.	Prompt wart-free state, may require general anaesthetic. Expensive and only available in a few major centres.	Yes
Surgery	Extensive anogenital, oral or anal warts	Removal by tangential scissor excision, tangential shave excision, curettage or electrosurgery. Treatment can be repeated as required.	Prompt wart free state, results depend on skill level and training, requires equipment, longer clinic visit. Anaesthesia mandatory. Particularly useful for pedunculated warts, and small numbers of anatomically accessible warts.	Yes
Trichloroacetic acid (TCA)	External anogenital, vaginal or anal warts	A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. If an extra amount of acid is applied, the treated area should be powdered with sodium bicarbonate, or liquid soap preparations to remove unreacted acid. Surrounding skin can be protected with petroleum jelly. Can be repeated weekly as required.	Inexpensive, effective for moist and dry warts. Needs careful application by a trained health professional. Not for large areas of friable warts. Low viscosity may result in spreading if over applied, which can cause painful iatrogenic ulceration.	Yes

Table 3: Factors that may influence the selection of treatment for warts

Patient preferences and characteristics
Preference for self-applied or administered treatments.
Ability to identify accurately and physically reach warts.
Cognitive ability.
Cost of treatment.
Duration of treatment and/or number of visits, distance and work.
Tolerance of pain.
Age
Safety and efficacy of treatments for warts have not been studied in paediatric populations.
When treating, attention should be paid to avoiding and controlling pain associated with treatment. Requiring a parent or guardian to apply a treatment that may be painful is questionable.
Variations in the rate of psychosocial development in adolescence should be taken into account (i.e. cognitive ability to understand and carry out any treatment programme, particularly patient-applied therapy).
Pregnancy
Podophyllotoxin is not recommended and the safety of imiquimod in pregnancy is not known. 5-fluorouracil is a teratogen.
Disease presentation
Wart size and count: in general, provider-administered topical treatments are not ideal for large areas of warts, although they may have a debulking effect.
Anatomic location and circumcision status (men): Warts on moist (partially keratinised) surfaces and intertriginous areas appear to respond better to topical treatments than do warts on dry (fully keratinised) surfaces and open areas. Aggressive ablative or surgical therapy should be avoided over the clitoris, glans penis, urinary meatus, prepuce, and prepuce cavity in uncircumcised men.
Health care provider preferences and characteristics
Clinical training and experience.
Financial and physical resources.
Scheduling limitations.
Immunologic status
Immunocompromised patients may have lower response and higher recurrence rates.

Post-treatment follow-up

The benefit, frequency, interval and type of follow-up care necessary after treatment of warts has not been studied. Follow-up evaluation can provide the opportunity for education and counselling of patients. The need to monitor for complications of therapy will vary greatly on the basis of the patient's experience and cognitive ability, the number and location of warts, and the treatment modality used. Patients concerned about recurrences could be offered an evaluation 3 months after successful treatment, since most recurrences occur during this period. In immunosuppressed patients, recurrences of warts are much more common and periodic follow-up evaluation may be necessary.

Patients with genital warts are at risk of other sexually transmitted infections (STIs). Management of genital warts must include careful assessment and testing for other STIs as appropriate, depending on the patient's sexual history.

Treatment recommendations

- The goal of treatment for genital warts is the removal of visible warts. **GRADE C**
- Standard therapies for genital warts can eventually remove most warts, although no one treatment is ideal for all warts or all patients. **GRADE A & C**
- Clinicians should be knowledgeable about, and have available to them, at least one patient-applied treatment and one health care provider-administered therapy. **GRADE C**

Emerging or alternative therapies

A number of ablative therapies have been trialled in the destruction of anogenital warts. Sinecatechins (an active product of green tea extract) inhibits telomerase production via its role in cell signalling pathways. Sinecatechins ointment is approved for use in the US.⁶³ Trials of photodynamic therapy and intralesional immunotherapy are being evaluated.⁶⁴

Use of HPV vaccine as therapy

Does vaccination of persons already infected alter the natural history of the virus i.e. does vaccination result in faster clearance (or undetectability), reduce persistence or prevent recurrence of disease? The data to answer these questions conclusively is not yet available.

Immunocompromised patients

Persons who are immunocompromised because of HIV or other reasons may not respond as well as immunocompetent persons to therapy for genital warts, and they may have more frequent recurrences after treatment. Immunosuppressed women should have annual cervical screening, with early referral for colposcopy if abnormalities are detected. Squamous cell carcinomas arising in squamous intraepithelial lesions resembling genital warts occur more frequently among immunosuppressed persons.

Imiquimod should be used with caution (it is not a contraindication) in patients with autoimmune conditions, or those on systemic immunosuppressive drugs, although systemic absorption from topical treatment is likely to be negligible.

Treatment options depend on underlying condition.

Management of immunocompromised patients should be in consultation with a Sexual Health Specialist as well as other specialists involved in the patient's care.

Assessment of sex partners

HPV-related disease raises questions for the patient, their partner and health practitioners regarding mode of transmission and ongoing intimacy.

There is no reliable way to inform partners if they have HPV or not. HPV DNA tests cannot be used for 'routine' screening because commercial assays are only used to detect high-risk HPV types and do not detect low-risk HPV or latent (i.e. undetectable) HPV. The use of acetic acid applied to the skin is not a useful test for subclinical HPV infection.

It is important to emphasise that a diagnosis of HPV does not necessarily imply multiple sexual partners or other concurrent sexual partners.

At the time of writing, there is no evidence that cancer can be transmitted to a partner through sexual activity.

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 lesions or abnormal smear result. For further counselling messages, see **pages 32-33**.

ANOGENITAL HPV AND CANCER

KEY POINTS

- hrHPV plays a significant role in lower genital tract precancers and cancers: cervical almost 100%, vaginal ~90%, anal ~80%, penile ~50%, vulval ~40%.⁶⁵
- Most women with hrHPV will not develop cervical cancer and in many the hrHPV will resolve spontaneously.
- HPV 16 and 18 result in a higher risk of progression to precancerous lesions than infection with other high-risk types. It is thus important to identify these two genotypes of hrHPV to support management.
- Anyone with a cervix who has ever been sexually active should receive cervical cancer screening, including women with female partners and trans-men who have not had genital affirming surgery
- Anal cancer is a rare cancer globally; the attributable fraction due to HPV is about 80%. Although it remains an uncommon cancer, the incidence of anal cancer is increasing and the burden of disease is highest in MSM and HIV-positive MSM.²³
- 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 50 years or over (see www.ashm.org.au/hiv/management-hiv/anal-cancer).

Cervical cancer

Epidemiology

Most sexually active women will acquire HPV infection at some point in their life, but only a few women will go on to develop cervical cancer. HPV infection typically occurs in the younger age groups whereas cervical cancer typically develops later in life. Hence it usually takes many years for a precursor lesion to develop into a cancer. This is reflected in the epidemiology of HPV and cervical cancer. Cervical cancer is the fourth most common cancer in women worldwide, with an Age Standardised Rate of over 30/100,000 women in high risk regions (Eastern Southern and Middle Africa, Melanesia).⁶⁶ The evidence linking HPV to cervical carcinoma is extensive, with HPV 16 accounting for approximately 50% of cases and HPV 18 for 20%. HPV 16 and 18 account for about 70% of all cervical cancers worldwide.⁶⁷⁻⁷⁰ The prevalence of HPV 16/18 in confirmed high-grade disease in New Zealand is comparable to that observed in Australia and European countries.^{71,72} The prevalence of HPV 16/18 is almost identical for both Maori and non-Maori populations in New Zealand.⁷³

The most common HPV types in women with CIN-2/3 were HPV 16 (51%), 18 (21%), 31 (4%), 45 (3%) and 52 (3%).⁷² Although cervical screening has reduced the incidence of cervical cancer by 70% or more where screening has been effectively implemented, cervical cancer remains a leading cause of death in countries without effective screening programmes. The incidence of cervical cancer in New Zealand is among the lowest in the world. In 2014 there were 144 new cervical cancer registrations.⁷⁴ The age-standardised registration rate was 5.5 per 100,000 population. The registration rate for Maori women was 10.8 per 100,000, 2.5 times greater than for non-Maori women.

Classification of abnormalities

Abnormalities are classified by whether it is a cytologic or histologic specimen and by its severity. For example, exposure to HPV results in productive viral infections that may cause mild abnormalities which are referred to as low-grade squamous intraepithelial lesions (LSILs) by cytologists or cervical intraepithelial neoplasia 1 (CIN-1) by pathologists. These can be caused by either LrHPV or hrHPV which indicate the presence of HPV infection. Most HPV infections, including high-risk genotypes, typically become undetectable within 6–12 months. Persistent (detectable) infection is associated with the development of CIN-2+.^{75,76}

Risk of progression to cancer

CIN-3 (histologically confirmed) must be regarded as the precursor for cervical cancer. Many high-grade precursors will not progress to cancer even after protracted periods of follow-up of up to 30 years. It is important to stress to the patient that HPV infection does not equal cancer (indicator of risk). The median age of women with CIN-3 is 27–30 years. The median age for women with a cervical screen-detected invasive cancer is 10 years or more older than the median age of women presenting with CIN-3.⁷⁷

New Zealand data have demonstrated that, in women with CIN-3 managed only with small diagnostic biopsy and who have persistent abnormal smears, the cumulative incidence of invasive cancer of the cervix was 50%.⁷⁸ Previously it was thought it took many years to progress from incident HPV infection to high-grade precursor lesion; however, intensive prospective follow-up of women in their early 20s has demonstrated that rapid development of CIN-2 and 3 can occur, often within a few months of incident infection.⁷⁹ It does however, take many years in most cases to progress from a high-grade precursor to invasive cervical cancer.

Some CIN-2 lesions, particularly in young women, will regress, while others persist with risk of progression. The risk of progression is considerably higher with a HPV 16 or 18 infection than with other high-risk genotypes. HPV 16 persists longer than other types, with an absolute risk of CIN-3 approaching 40% after 5 years' persistence.⁸⁰

Risk factors

Cigarette smoking,^{81,82} and coinfection with HIV have been consistently demonstrated as co-factors for cervical cancer.⁸³ Long-term use of hormonal contraceptives,⁸⁴ high parity⁸⁵ are less important cofactors

Anal cancer

Although a relatively uncommon cancer, the incidence of anal cancer in the United States has increased substantially in the last three decades. The incidence in the general population is approximately 2/100,000 and is more common in women than men. In contrast, the rate of anal cancer is estimated to be 35/100,000 among MSM and 137/100,000 among HIV-positive MSM.⁸⁶ The attributable fraction due to HPV is 88%.⁶⁵ HPV 16 and 18 cause 70% of AIN and anal cancers.

Vulval and vaginal cancers

Vulval and vaginal cancers are rare cancers globally. In Oceania, 40% of vulval cancers is estimated to be due to HPV (86% for warty/basaloid squamous cell carcinoma [SCC] and 14% for keratinising SCC).⁸⁷ 70% of vaginal cancer is estimated to be due to HPV.⁶⁵ New Zealand studies have demonstrated usual-type HSIL to have a significant invasive potential in women age 30 years and over with a mean transit time to invasion of 4 years.⁸⁸ Investigation of the role of co-factors for persistence and progression is difficult because of the ubiquitous and transient nature of HPV infection.

Penile cancer

Penile cancer is also rare, with an attributable fraction due to HPV at 50%.⁶⁵

MOLECULAR (DNA) DIAGNOSIS OF ANOGENITAL HPV INFECTION

KEY POINTS

- Primary HPV screening will be introduced within the next two years. When the screening programme changes, women 25 years and older will be screened with hrHPV every 5 years. hrHPV detected will have partial genotyping and reflex cytology.
- Currently, High-risk HPV (hrHPV) testing is used in conjunction with cervical screening in four situations:
 1. Triage women aged 30 or older who have a low grade (LSIL) or atypical squamous cells of undetermined significance [ASC-US] cytology result and no abnormal cytology sample in the previous 5 years, to either referral to colposcopy (hrHPV Detected) or repeat cytology (hrHPV Not Detected).
 2. Follow-up of women who have been treated for a histologically confirmed high-grade squamous lesion (CIN2/3) (Test of Cure).
 3. Follow-up of women with previous high-grade squamous abnormality more than 3 years previously (historical testing) (Test of Cure – historical testing). The previous abnormality can include abnormal cytology (ASC-H/HSIL) or histology (CIN2/3) results and women may or may not have been treated.
 4. Discordant cervical cytology/histology/colposcopy results (Specialist testing).

hrHPV testing is currently only used in the management and follow-up of women with squamous lesions because glandular lesions have a lower hrHPV positivity rate than squamous lesions.

hrHPV test ordering:

1. Triage with low grade cytology: is determined by the laboratory based on the current LBC result and the NCSP screening history.
- 2-3. Test of Cure: The sample taker needs to order the hrHPV test in conjunction with the Liquid Based Cytology (LBC) sample for women who are being followed-up after treatment for HSIL or for historical testing based on the National Cervical Screening Programme (NCSP) screening history.
4. Specialists order hrHPV tests when appropriate for women with discordant results.

Introduction

Molecular diagnosis of HPV relies on detection of viral DNA. A variety of DNA detection methods are available.

Polymerase chain reaction amplification (PCR) of a short region of specific HPV DNA is probably the most sensitive method.⁸⁸

hrHPV testing was introduced in New Zealand to the NCSP management pathway in October 2009 as an adjunct to cervical cytology in specific clinical situations (key points above). Two internationally validated PCR-based commercial tests are currently being used by National Cervical Screening Programme (NCSP) approved laboratories.

hrHPV testing has been repeatedly found to have a high negative predictive value (~99%). This means that women with a negative hrHPV test are most unlikely to have any of previously listed 14 hrHPV types and are most unlikely to progress to a pre-cancerous abnormality. It is the strong negative predictive value of hrHPV testing that has the most effective clinical use in conjunction with cervical cytology.

hrHPV testing is more sensitive for detecting high-grade cervical abnormalities than LBC cytology. Cytology is more specific because it identifies actual cell abnormalities whereas HPV testing identifies the presence of infection, not cell changes. A positive hrHPV test indicates increased risk of developing an abnormality. hrHPV testing is performed in conjunction with cytology using liquid-based cytology (LBC). This allows testing for both cytology and hrHPV on one cervical sample.

HPV testing in the National Cervical Screening Programme (NCSP)

(The full NCSP Guidelines can be accessed at www.nsu.govt.nz/health-professionals/national-cervical-screening-programme/cervical-screening-guidelines).

The testing laboratory relies on the sample taker discussing and gaining consent from the woman for possible hrHPV testing.

The areas where the management of women with abnormal cervical samples within the NCSP may benefit from hrHPV testing include the following:

1. **The triage of women 30 years and over with ASC-US or LSIL cytology** (without an abnormal cytology sample in the last 5 years). (See Chart 1 on page 19.)
 - 'Reflex' testing is ordered by the laboratory for women with ASC-US/LSIL and eliminates the need for repeat cytology testing for those women who are hrHPV detected.
 - A negative hrHPV test can reassure a woman that she is very unlikely to have a significant lesion and can be safely followed by a repeat cytology test in 12 months. If the repeat cytology result at 12 months is normal, she can return to regular 3-yearly screening.
 - Women with ASC-US/LSIL smears who test positive for hrHPV should be referred for colposcopy.
2. **The follow-up of women who have been treated for a histologically confirmed high-grade squamous lesion (CIN2/3) – Test of Cure.** (See Chart 2 on page 20.)
 - Women who have been previously treated for histologically confirmed CIN-2/3 are at a small increased risk of further disease and cervical cancer. Recurrence may be due to limitations of colposcopy, inadequate treatment/persistent disease or new infection.

Cotesting using cytology and hrHPV testing as a combined test allows better identification of women at risk of persistent or recurrent lesions, while enabling many women to return to regular 3-yearly screening.
 - Women treated for CIN-2/3 currently undergo follow-up colposcopy and cytology within 6-12 months after treatment. It should be noted that hrHPV testing should not be carried out sooner than 12 months after treatment of high-grade lesions, as viral clearance may take more than 12 months to occur.
 - hrHPV testing and cytology should be carried out 12 months after treatment and annually thereafter until a woman has tested negative by both tests on two consecutive occasions, 12 months apart. A woman can then return to regular three-yearly screening.
 - Women who test hrHPV positive, despite having cytology assessed as negative post-colposcopy, should be referred back to colposcopy. The reason for this is the risk of residual disease requiring assessment and further treatment, despite the apparently negative cytology.
 - It is the sample taker's responsibility to order hrHPV testing in this situation.

As indicated in flowchart HPV Testing Guidance 2 (pages 51 and 52 of Guidelines for Cervical Screening in New Zealand). (See Chart 2 on page 20.)

3. **Women with high-grade lesions (cytology HSIL/ASC-H; histology CIN2/3) more than 3 years previously, treated or untreated and currently managed by cytology alone (Test of Cure – historical testing).** (See Chart 3 on page 20.)

It is the smear taker's responsibility to order hrHPV testing in this situation.

 - This group of women, currently managed by annual cytology for more than 3 years with all tests assessed as negative, can be managed with cotesting (cytology and hrHPV) to ascertain if they can safely return to regular 3-yearly screening.
 - hrHPV testing and cytology should be carried out and annually thereafter until a woman has tested negative by both tests on two consecutive occasions, 12 months apart. A woman can then return to regular 3-yearly screening.
 - It is the sample taker's responsibility to gain consent and order hrHPV testing in this situation.
 - Those women who test positive for hrHPV despite repeated negative cytology are likely to have a low risk of CIN-2/3 and can be retested with cytology and hrHPV annually thereafter, until a woman has tested negative by both tests on two consecutive occasions, 12 months apart. Persistent hrHPV test positivity can be discussed with a colposcopist and referral can occur if deemed appropriate.
 - Refer to colposcopy for any clinical concern or an abnormal cytology result.
4. **Post-colposcopy management of women with discordant results e.g. high-grade cytology and negative, satisfactory colposcopy.**

It is the colposcopist/specialist responsibility to order hrHPV testing in this situation.

 - A single colposcopic examination can miss significant lesions.
 - Where findings on colposcopy/histology are negative or show low-grade changes only and the discordance persists following case review, hrHPV testing can be a useful adjunct to further management.
 - The NCSP recommends a woman return to 3-yearly screening only after two negative sets of hrHPV plus cytology tests 12 months apart.

- Failure to detect CIN-2/3 lesions in a woman with high-grade cytology (following review of the smear) should lead to consideration of a diagnostic excisional procedure, or observation for 1 year with colposcopy, cytology and HPV testing.
- Specialist colposcopists are responsible for ordering hrHPV testing in this situation.

Note:

- Women with a history of genital warts do not need to begin screening at an earlier age or have screening more frequently.
- hrHPV testing should be used for squamous lesions (as indicated in the HPV flowcharts) but is not currently recommended for the follow-up of glandular abnormalities. For historical testing situations, it is therefore very important that the sample taker identifies whether a previous abnormality was squamous or glandular. This is particularly important for women who were investigated or treated overseas, as their results may not be held on the New Zealand NCSP Register.

Samples required for hrHPV DNA detection and typing

1. Specimens are collected using a broom-type collection device and either:
 - vigorously rinsed in the sample vial fluid if using ThinPrep (do not leave the broom head in ThinPrep vial), or
 - the head of the device must be detached and placed into the vial fluid if using SurePath.
2. Liquid-based cytology sample (ThinPrep or SurePath) are sent directly to the laboratory by the sample taker. The sample needs to be taken and sent in accordance with your local laboratory protocol.
3. If lubrication is necessary, NCSP recommends use of warm water where possible or lubricant sparingly away from the opening end/tip of the speculum (use waterbased gel) because lubricant can mask cells limiting or making LBC sample unsatisfactory for testing. This is particularly important when using ThinPrep LBC.

NB: The following charts are taken from NCSP Guidelines, see www.nsu.govt.nz/health-professionals/national-cervical-screening-programme/cervical-screening-guidelines.

Chart 1: Triage of women 30 years and over with ASC-US or LSIL (who have not had an abnormal smear within the last 5 years)

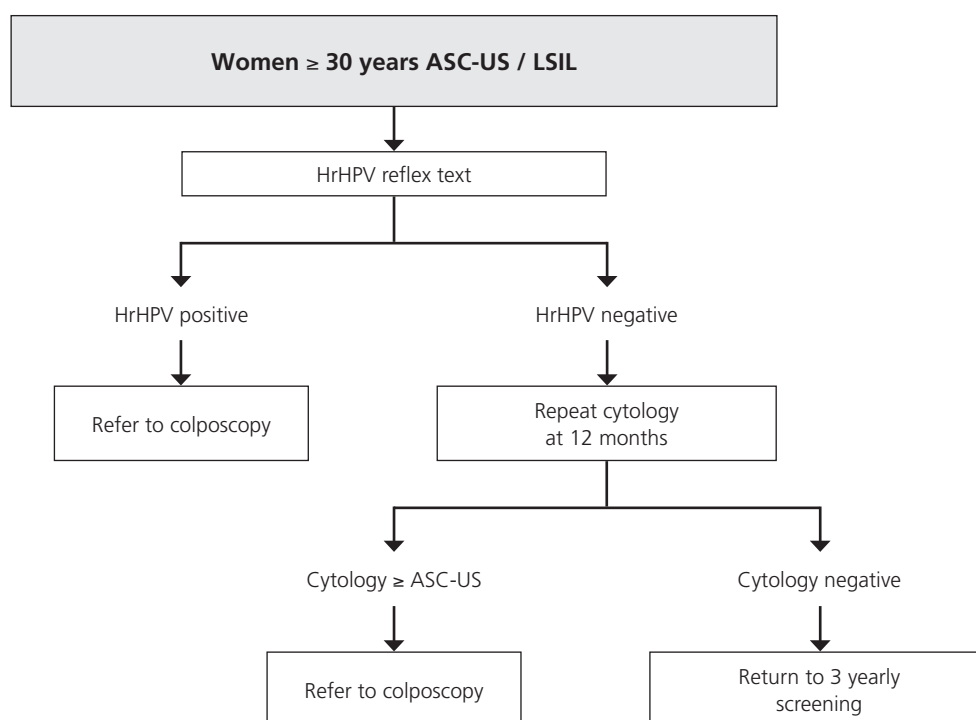


Chart 2: HPV Testing Guidance – Follow-up of women treated for high grade lesions

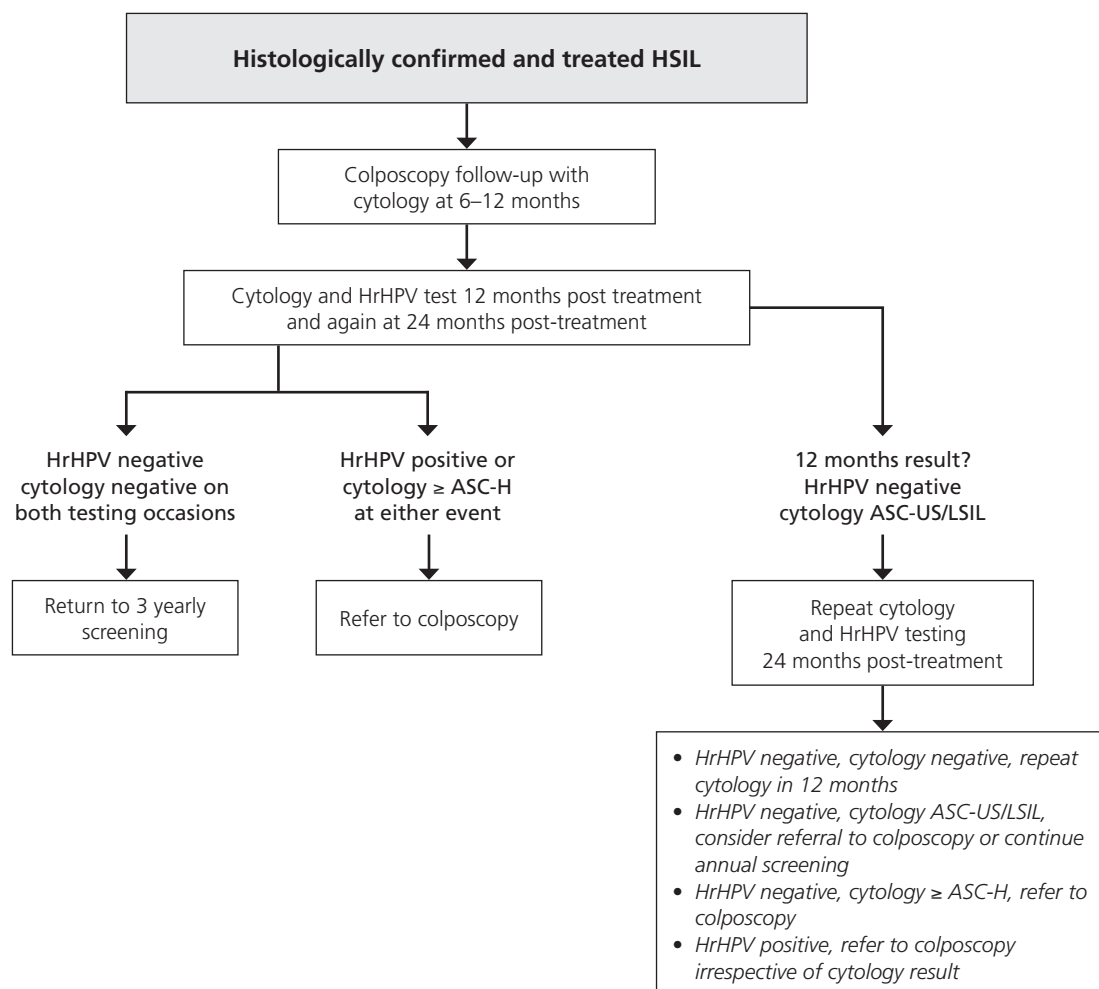
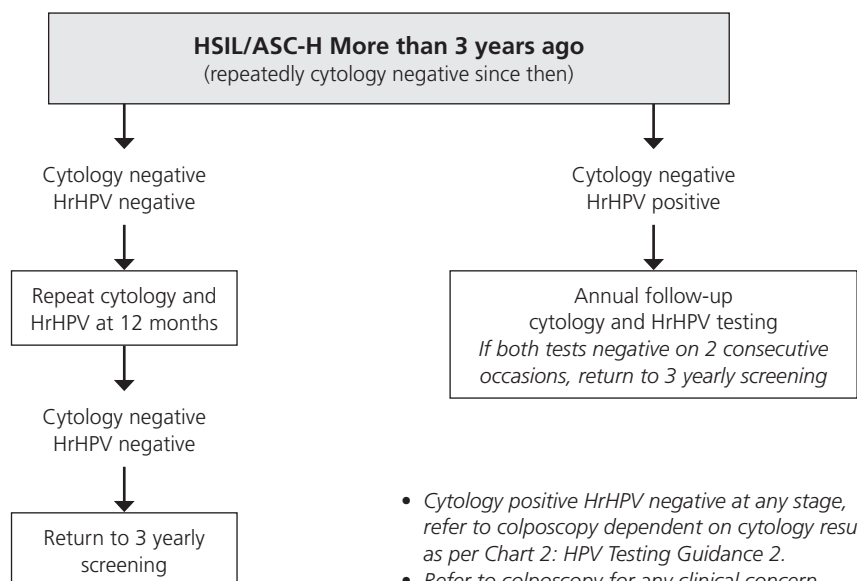


Chart 3: HrHPV testing of women with a high grade lesion more than 3 years previously, with subsequent repeated negative cytology tests (historical testing)



PREGNANCY AND BREASTFEEDING

Pregnancy

KEY POINTS

- It is common to develop external genital warts in pregnancy. This is probably the consequence of altered immunity and increased blood supply
- It is extremely rare for babies to develop clinical anogenital HPV.
- Recurrent respiratory papillomatosis (RRP) is the most common benign laryngeal tumour in children and is thought to be caused by HPV acquired during passage through the birth canal of an infected mother. Types 6 and 11 are most commonly involved. The incidence is ~4–5 per 100,000 children.⁸⁹
- Transient HPV colonisation in the neonate is common, but persistent infection is unusual.
- Smaller genital warts in pregnancy may not require treatment as spontaneous resolution after delivery often occurs. If treatment is being considered, ablative methods, e.g. cryotherapy or diathermy, should be used.
- Genital warts can proliferate and become friable. Monitoring is recommended.
- Caesarean section has not been shown to significantly reduce maternal-fetal transmission.

Removal during pregnancy is often requested by the patient and can be performed with ablative methods.⁹⁰ HPV types 6 and 11 can, rarely, cause laryngeal papillomatosis in infants and children. A Danish study reported an incidence of seven per 1000 where there was a documented history of external genital warts.⁹¹ Tasca and Clarke report an overall incidence of 3.5 per million person-years and a prevalence of four cases per 100,000 children.⁹² In babies born to mothers with genital warts, HPV DNA can be isolated from aerodigestive swabs in a third to a half of cases; however, the risk of development of RRP is approximately 1 in 400. Presentation can be at any age, but typically it is at 3–4 years with progressive hoarseness.

Although there appears to be an association between maternal genital warts during vaginal delivery and laryngeal papillomatosis, the route of transmission (transplacental, perinatal, or postnatal) is not completely understood. HPV DNA has been detected in amniotic fluid, raising the possibility of ascending infection, and HPV DNA has been detected in the peripheral blood mononuclear cells of mothers and in cord blood samples.⁹³ Although this may suggest transmission via a haematogenous route, transmission via microscopic tears in the placental membranes, as occurs with other organisms, is a more likely explanation.⁹⁴

There has been a wide variation in reported neonatal transmission rates for HPV, although larger studies using more recent HPV DNA technology indicate that transmission rates are low.^{95,96} In a study of 574 women, 47.1% were identified as being HPV DNA positive (mainly in the third trimester) at age ≤ 24 and 24.4% at age > 24 years. However, 1.6% of newborns were HPV DNA positive at a mean of 65 hours after birth.⁹⁷ Non-concordance between parental and neonatal HPV types suggests the possibility of maternal infection acquired antenatally at untested intervals during pregnancy or, in the case of oral infection, from other contacts after birth.⁹⁸

Follow-up studies of infants from whom HPV DNA was isolated at birth indicate that the virus becomes undetectable in many infants, indicating that contamination rather than true infection has occurred.⁹⁹ It has also been demonstrated that HPV 16 antibodies detected at birth will clear from the infant within 10 months, but not from the mother.⁹⁹

In summary, although HPV infection is frequently detected in pregnant women, detection of HPV in newborns is uncommon and is likely to be due to contamination.

Although caesarean section reduces the risk of HPV isolation from the neonate, it has not been shown to significantly reduce neonatal transmission of HPV, nor of laryngeal papillomatosis.⁹¹ Many studies have been limited by lack of long-term follow-up and assessment of only HPV positivity rates after birth.¹⁰⁰ Caesarean delivery should not be performed solely to prevent transmission of HPV infection to the newborn. In rare instances, caesarean section delivery may be indicated for women with very large genital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding.

Treatment during pregnancy requires some special considerations. Podophyllin and podophyllotoxin should not be used in pregnancy. Maternal and fetal deaths have been reported following the use of podophyllin for large vascular warts. Imiquimod is not recommended as there is insufficient data to recommend its use in pregnant women. Individual case reports and a small case series have been published.

HPV in pregnancy has no link with miscarriage, premature labour or other types of pregnancy complications.

Treatment recommendations

- Appropriate treatments of external genital warts during pregnancy include cryotherapy, surgical removal and laser ablation.
- Podophyllin and podophyllotoxin should not be used in pregnancy. **GRADE C**
- Imiquimod is not recommended.
- Caesarean section does not significantly reduce vertical transmission and is only indicated when genital warts are likely to cause obstruction of the pelvic outlet or excessive bleeding. **GRADE B**

Breastfeeding

The use of podophyllin and podophyllotoxin are not recommended in women who are breastfeeding because of systemic absorption. The New Zealand Formulary states imiquimod can be used in breastfeeding. No quantifiable levels of imiquimod are detected in breast milk. The manufacturers give no specific instructions on the use of imiquimod in lactation. Ablative methods can be used during lactation.

HPV-RELATED DISEASE IN THE HEAD AND NECK: Oropharyngeal squamous cell carcinoma and recurrent respiratory papillomatosis

KEY POINTS

- HPV-associated oropharyngeal cancer is increasingly common, especially in men.
- Increasing number of lifetime oral sex partners is associated with increased risk.
- Patients often present with lymph node metastases.
- Patients with HPV-positive oropharyngeal cancers have a better prognosis than those with HPV-negative cancers.
- In contrast to cervical cancer, no clinically apparent premalignant condition exists in the vast majority of patients. Similarly, there is no reliable laboratory screening test. Therefore, there is currently no indication for population screening for HPV-related head and neck disease.
- Incidence can be expected to decline with vaccination of boys and girls.
- Recurrent respiratory papillomatosis is a benign HPV-related disease of the upper airway which typically presents in young children or young adults and can have a variable course.

Oropharyngeal cancer

Epidemiology

In common with other head and neck cancers, SCC of the oropharynx has traditionally been associated with smoking and alcohol consumption. However, in the last 30 years the incidence of smoking-related head and neck cancer has declined in most countries. In contrast, the incidence of oropharyngeal cancer has been steadily increasing in many countries, including New Zealand. This has coincided with an increasing incidence of HPV as the aetiological factor in these cancers.^{101,102} HPV, along with other viruses and bacteria, preferentially accumulates in the lymphoid tissue of the palatine and lingual tonsils. Because of this, hrHPV is more likely to cause SCC in these locations than at other sites in the upper aerodigestive tract. In the tonsils and base of the tongue, up to 93% of SCC is now attributable to HPV, with significant international geographic variation.¹⁰³⁻¹⁰⁶ A recent New Zealand study found that 75% of oropharyngeal cancers were attributable to HPV.¹⁰⁷ HPV remains an uncommon factor in cancers of the oral cavity, hypopharynx and larynx.

Risk factors

It has been noted that HPV-related oropharyngeal cancers are approximately four times more common in men than in women.^{101,104} In the United States, the rate of oropharyngeal cancer in men is now higher than the rate of cervical cancer in women.¹⁰¹ The exact reason for this gender predilection is not clear; putative reasons are a greater viral load in the female genital tract and a greater immune response in females than in males.¹⁰⁸ The average age at diagnosis is lower in HPV-associated oropharyngeal cancer than in smoking-related cancer, although the latency after HPV infection is typically at least 10 years, and can be several decades.

The HPV subtypes implicated in oropharyngeal SCC are similar to those involved in cervical cancer. HPV 16 fulfils epidemiological criteria for being high-risk in the oropharynx, and is implicated in up to 90% of HPV cases. HPV types 18, 31, 33, 35 and 52 have not been studied as thoroughly, and are classified as potentially high-risk.^{106,109} A strong correlation is seen between higher numbers of oral sexual partners and the development of oropharyngeal SCC, particularly with six or more lifetime sexual partners.^{110,111} Other features of sexual behaviour which are less strongly associated with head and neck cancer include younger age at sexual debut, history of genital warts or sexually transmitted infections, rare or non-use of condoms and oral-anal sex.¹¹⁰ Similarly, the prevalence of HPV positivity in oral samples is greater in individuals with a higher number of lifetime sexual partners.¹⁰⁴ As a result of these observations, oral sex is believed to be the mode of transmission of HPV to the oropharynx in most cases.

Clinical presentation

Oropharyngeal SCC can present with throat symptoms and an ulcerated or non-ulcerated mass visible on oral examination. However, many patients have lateral cervical lymph node metastases at the time of diagnosis, and not infrequently a neck mass is the only clinical finding at diagnosis. Therefore, HPV-related oropharyngeal SCC should be considered in any patient, particularly a man, presenting with a painless lateral neck mass.

Treatment and prognosis

In recent decades, in most centres the preferred treatment for oropharyngeal SCC has been concurrent chemoradiation therapy. It has been noted that the prognosis for patients with HPV-related oropharyngeal cancer is much better than for those with HPV negative, smoking-related oropharyngeal cancers. Tumours which are HPV positive occurring in smokers have an intermediate prognosis.^{112,113} As a result of the observed better outcome in patients with HPV-related disease, many oncologists have felt that it may be possible to reduce the treatment intensity in some way, thereby reducing the not insignificant side effects of treatment while still maintaining a good prognosis. Such de-intensification may include omitting chemotherapy from the treatment, reducing the radiation therapy dose, and reintroducing surgery as the primary treatment modality. The latter has become more attractive with the development of trans-oral robotic surgery. However, it is generally accepted that, for the present, de-intensification of treatment should only be adopted in the context of a formal clinical trial. Many such trials are currently underway, with results expected in the next few years.¹¹⁴

Counselling patients

In common with anogenital HPV-related disease, a viral aetiology for oropharyngeal cancer raises questions for the patient, their partner and health practitioners. 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.¹¹⁵ At the time of writing there is no clear evidence for transmission of HPV through kissing.

Prevention

In contrast to cervical cancer, no clinically apparent premalignant condition exists in the vast majority of patients. Similarly, there is no reliable laboratory screening test. Therefore, there is currently no indication for population screening for HPV-related head and neck disease.¹¹⁶ However, this is an increasingly prevalent disease, and increased awareness of the disease among health professionals and the general population is to be encouraged. Limiting the number of sexual partners, delaying the onset of sexual activity and using barriers such as condoms and latex dams while performing oral sex, may be expected to minimise the risk of developing HPV-related oropharyngeal cancer.

As with anogenital HPV-related disease, HPV vaccination holds great promise as a mechanism for preventing the development of benign and malignant head and neck HPV-related disease. Vaccination of both boys and girls prior to the onset of sexual activity is strongly recommended.¹¹⁶

Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis (RRP) is a benign condition characterised by papillomatous growths in the respiratory tract. The larynx is the most commonly affected site, and patients can present with hoarseness or airway symptoms. This condition has a bimodal incidence, occurring in young children and in adults. It is an uncommon condition, affecting approximately four per 100,000 children and four per 100,000 adults.¹¹⁷ It is related to HPV subtypes 6 and 11 in particular.

In children, transmission is thought to be vertical via an infected birth canal in the majority of cases, although intrauterine infection appears to occur in some cases. Vaginal delivery, prolonged labour and being the first-born child of a young mother (<20 years) are associated with an increased risk of developing RRP.⁹¹ Juvenile onset RRP is estimated to be over 200 times more common in mothers with a history of genital warts during pregnancy than in mothers without clinical warts. Despite this, only one in a few hundred children of mothers with a history of genital warts will develop RRP.^{118,119}

Caesarean section has been considered as an option for preventing RRP, however it is not completely protective against RRP and is associated with higher maternal morbidity and mortality and a greater economic cost than vaginal delivery. As a result, caesarean section is not recommended for all pregnant women with genital warts. There may be some benefit in managing genital warts during pregnancy, as long as it does not result in an increased risk of miscarriage.¹²⁰

In adult patients, development of RRP is associated with male gender, increased numbers of lifetime sexual partners and frequency of performing oral sex.^{91,121} In patients with adult onset RRP the virus may have been acquired later in life than patients with juvenile onset RRP, or the development of disease may represent reactivation of a latent infection acquired at birth.¹²⁰

The mainstay of treatment in both adults and children is surgical debridement of the papillomas. This requires specialist referral. Immunisation with a vaccine including HPV types 6 and 11 has the potential to significantly reduce the incidence of RRP. There is some evidence from Australia that this may already be occurring.¹²²

GUIDELINES ON THE MANAGEMENT OF ANOGENITAL HPV IN CHILDHOOD

KEY POINTS

- The prevalence of asymptomatic HPV infection in children is unknown.
- In children anogenital warts may be acquired via sexual transmission requiring specialist referral and multidisciplinary assessment.
- Other routes of transmission include vertical transmission from the mother, particularly in younger children under 4 years or via self-inoculation.
- Diagnosis is clinical and biopsy is rarely required. Virological typing and serology are of no value for forensic purposes.
- Anogenital warts need to be distinguished from other raised lesions including molluscum contagiosum or condyloma lata (syphilis).
- Spontaneous clearance is common and treatment should be reserved for those with significant symptoms.
- Juvenile onset recurrent laryngeal papillomatosis can result from vertical transmission and present with respiratory symptoms. There is a small malignant potential.

Epidemiology

As already described, HPV is the most common viral infection of the adult and adolescent female genital tract.¹²³⁻¹²⁶ Although there was an increase in case reports of anogenital warts in children in the 1980s and 1990s,¹²⁷⁻¹²⁹ serological studies suggest the population prevalence in children remains low.¹³⁰

Clinical presentation

The prevalence of asymptomatic HPV infection of the anogenital region in children is unknown. Children usually present because a caregiver has noted the lesions, although some present with pain or bleeding on defaecation, or secondary infection. Classical cauliflower-like condyloma acuminata do occur in children, but anogenital warts have multiple appearances.^{131,132} There is very little data on the prevalence of infection of the cervix or vagina in children who present with peri-anal or vulval warts.¹³³

The incubation period in children is unknown. There is a high likelihood of spontaneous regression over time.¹³⁴ HPV may be particularly troublesome in children on immuno-suppressive therapy, and the possibility of immune deficiency (including HIV) should be considered in any child who has particularly refractory lesions.^{135,136}

Molecular diagnosis

In determining the source of infection, the virology adds little to the history and clinical examination.¹³⁷ There is little, if any, value in typing for forensic purposes.

Molecular diagnosis relies on the detection of HPV DNA (see **page 17**). The use of PCR is highly sensitive, but there is always a risk of contamination. Many HPV types have been described, but no specific type is invariably associated with a particular clinical appearance.¹³⁸ Infection with multiple types is common¹³⁹ and it is technically impossible to be sure that all types from a given patient have been isolated. HPV DNA can be found in apparently normal tissue surrounding clinical lesions¹³⁴ and in vaginal washings from patients with no detectable lesions.^{140,141} In adolescents and adults, types 1–4 and 7 are found almost exclusively in skin warts.¹³⁸ In children, however, there is a significant prevalence of types 1–3 in anogenital warts.^{142,143} Laryngeal papillomas are usually, but not always, associated with HPV types 6 or 11.^{91,144}

Neoplasia

Malignancy has been reported in children with laryngeal papillomatosis.¹⁴⁵ The risk of late malignancy in children with anogenital infection is not known. There are case reports of vulval dysplasia and carcinoma in young adolescents who had vulval warts from infancy^{146,147} and of Bowenoid papulosis (intraepithelial neoplasia) in childhood.^{148,149} There is no data that early screening in this group improves outcome. Cervical screening in girls who have had a history of sexual contact/abuse or exposure to HPV in childhood should commence at the age recommended by the National Cervical Screening Programme (i.e. not earlier).

Methods of transmission in childhood

In adults, anogenital HPV is a sexually transmitted infection. Sexual transmission clearly occurs in children, but other forms of transmission also occur.

Sexual transmission: It was not recognised until 1971 that anogenital warts in children might be sexually transmitted. From 1971 to 1993, 300 cases were published, of which 29% were sexually transmitted. The percentage of sexual abuse in various studies varied from 0–100%, which may have reflected differences either in the populations studied or in the methodology.¹³¹ A recent multi-centre study found a prevalence of HPV of 13.7% in children referred for possible sexual abuse, compared with 1.3% in a control group.¹⁵⁰

Sexual abuse has been documented in infants whose warts presented as early as the first year of life,¹⁵¹ and suggested in some cases of oral or laryngeal papilloma. However, accumulating evidence suggests that (in young children at least) the presence of warts in the anogenital region or oropharynx and/or the detection of HPV DNA in the anogenital region is not, in isolation, a reliable indicator of childhood sexual abuse.^{94,152–159} The American Academy of Pediatrics (AAP) guidelines conclude that “genital warts (human papillomavirus) can be sexually transmitted in children, but these infections are not diagnostic of abuse by themselves”.¹⁶⁰

Vertical transmission: HPV can be transferred from mothers to their offspring, probably from an infected birth canal.⁹⁶ It is difficult to quantify the risk to these babies, but it appears low.^{97,161} There is no correlation between the presence of HPV DNA in the baby and the presence or absence of known clinical or virologic infection in the mother. The duration of viral shedding and/or persistence of HPV DNA on the skin of infected babies remains unclear. Some authors have reported persistence of HPV DNA to 2 years of age,^{129,162} but other longitudinal studies have found almost no evidence of persistent perinatally acquired infection.^{161,163}

Vertical transmission may also cause juvenile onset respiratory papillomatosis (laryngeal papillomas) that may present as hoarseness, or rarely as recurrent pneumonia or breathing difficulties due to lower respiratory tract involvement.^{91,164} The upper limits of the incubation period from birth to clinical infection have not been established, but in laryngeal disease may be as long as 5 years.^{157,165}

Given that symptom-free infection is common in pregnancy (see above), one cannot completely exclude the possibility of vertical transmission in any child. However, one should remember that maternal infection does not prove vertical transmission. Several cases have been described in which the mother’s sexual partner was abusing the child.^{165,166} On the basis of the evidence to date, it is reasonable to conclude that most vertical transmission will manifest itself in young children and that child sexual abuse is not the most likely cause of HPV in the majority of cases involving children under the age of 4 years.^{148,157,167}

Other means of transmission: Dermatological literature suggests that children may acquire anogenital warts by infection from cutaneous warts on their own hands (auto-inoculation), or on the hands of adults (hetero-inoculation). Arguments for this hypothesis are the prevalence of HPV 2 in anogenital warts in childhood, and a number of suggestive case reports and case series.^{39,127,142} A Spanish longitudinal study of women enrolled during pregnancy found that the mother’s HPV status at the 6 week post-partum visit was a stronger determinant of HPV infection in the child than maternal HPV status in pregnancy, and suggested that horizontal mother-to-child transmission during the first few months of life might be more important than vertical transmission.¹⁶³ Similarly, other authors have also raised the possibility of fomite transmission.¹⁵⁶

In conclusion, it must be recognised that methods of transmission other than sexual transmission do occur in children, particularly in those under the age of 4 years. However, sexual contact must always be considered in the differential diagnosis, and even in young children a comprehensive multi-disciplinary assessment may be required if there are any other factors which cause concern.

Assessment

Establish the age at which the lesions first appeared, and what symptoms they cause. Consider all means of transmission: vertical (maternal infection including cervical smears; symptoms of respiratory infection); innocent inoculation (other warts in the child or young person; warts in other relatives or caregivers); sexual transmission (adolescent sexual activity; disclosure of sexual abuse; behaviour changes; risk factors for sexual abuse, such as contact with a known sexual offender or a family history of sexual abuse).

Do not forget to examine the whole body (including the conjunctivae, mouth and throat) for warts. Examine the genitalia and anus with a light source and some kind of magnification, such as an auroscope. In females, part the labia and inspect the vulva carefully. In males, do not forget to examine the corona and frenum of the penis (if the foreskin is readily retractile). Not everything that presents as a wart is HPV. The most common alternative diagnosis is molluscum contagiosum, but condyloma lata (syphilis) has been mistaken for genital warts in a child,¹⁶⁸ and almost any kind of papular rash may present in the anogenital region. The diagnosis can usually be made clinically if the child is seen by an experienced clinician, and biopsy is seldom indicated.

If a child under 4 years old presents with anogenital warts, further assessment for sexual abuse is probably not indicated in most cases, unless there are factors in addition to the warts themselves which raise concern. In older children, or if there are other factors which cause concern, consider referral for a multidisciplinary assessment for possible sexual abuse. If in doubt, consult with a paediatrician with expertise in this area. If you do refer, leave other investigations for sexual abuse to the doctor to whom you are referring. A full assessment for possible sexual abuse will include an examination by a doctor trained in the medical assessment of sexual abuse, screening for other STI, and consideration of referral to the statutory authorities for further investigation. Even then, the result may be inconclusive.¹⁶⁹

More extensive medical investigations (such as laryngoscopy, proctoscopy, cystoscopy or vaginoscopy) might rarely be indicated if there were oral lesions or respiratory symptoms in a young child, or if lesions appeared to extend into the anus, urethra or vagina.

Treatment

Anogenital warts will usually regress spontaneously. Infection may be multi-focal, and HPV DNA is almost certainly present in adjacent 'normal' tissue. At present, there is no evidence that treatment in childhood will reduce the (unproven) risk of later neoplasia. Treatment "can be difficult, prolonged and only marginally efficacious"¹²³ and recurrence is common. For all these reasons, active treatment is not usually recommended. Treatment should be reserved for those with significant symptoms. There are many forms of treatment,^{156,170,171} but in young children with extensive lesions, laser or diathermy under general anaesthetic is probably the best option. Several case reports attest to the safety and efficacy of Podofilox gel (podophyllotoxin) or imiquimod cream in children.¹⁷² However, there are no randomised controlled trials of therapy in childhood. The most common therapy for juvenile onset respiratory papillomatosis is laryngoscopy and surgical debulking with laser, sometimes in conjunction with adjuvant antiviral agents.¹⁷³

Follow-up

Follow the patient to ensure that the lesions regress, and see them again after 3–6 months to ensure that they have not recurred. In the case of vertical transmission, it is important to ensure that the mother receives appropriate follow-up of her own infection. If the patient is a sexually active adolescent, you should screen for other STIs and provide sexual health advice. In the case of sexual abuse, the patient should be followed to ensure that appropriate steps have been taken to ensure his or her ongoing safety and to provide support and counselling.

There is no evidence available to guide recommendations for long-term follow-up. It is reasonable to be concerned that children and adolescents with anogenital HPV infection may be at increased long-term risk of malignancy. Therefore, it would be reasonable to recommend early consultation by patients of either sex for anogenital or urethral symptoms. Routine cervical screening should follow the National Cervical Screening Guidelines.

HPV VACCINES

KEY POINTS

- Currently, two HPV vaccines are approved for use (registered) and are available in New Zealand: HPV9 (Gardasil 9, Serirus/MSD) and HPV4 (Gardasil, Seqirus/MSD).

Both vaccines are registered for use in females aged 9-45 years and in males aged 9-26 years.

- HPV vaccines have excellent safety profiles.
- Ideally vaccination should be given prior to the commencement of sexual activity but should still be given after sexual activity commences.
- Observations to date do not indicate any loss of protection and it is expected to be long-term. The vaccine shows effectiveness even with a previous history of CIN or genital warts through its ability to prevent infection with other HPV subtypes.
- HPV9 is free for both males and females from 9 years up to their 27th birthday. Immunisation is part of the National Immunisation Schedule as a school-based programme in Year 8. Those who are not vaccinated at school can receive the vaccine from their local medical clinic.
- HPV9 is free for persons with confirmed HIV infection and for transplant patients up to 27th birthday (see the Immunisation Handbook for details www.health.govt.nz/publication/immunisation-handbook-2017).
- HPV9 is recommended for persons with HIV infections and for transplant patients over age 27 and up to age 45, but is not funded.
- HPV9 is also indicated for females aged up to 45 years, but is not funded beyond age 26.

Human papillomavirus vaccines

Both vaccines contain viral-like particles (VLPs) which are composed of the L1 protein (component of the virus outer layer). The vaccines do not contain viral DNA and cannot cause infection. HPV4 contains VLPs for HPV types 6, 11, 16 and 18, and HPV9 contains VLPs for 6, 11, 16, 18, 31, 33, 45, 52 and 58.

HPV9 has similar high efficacy against genotypes 6, 11, 16 and 18 and it is 97% efficacious against the five additional genotypes included in the formulation.

Schedules and dosing

The number of doses depends on age. The vaccine is more effective at a younger age. Those aged 9-14 inclusively require two doses and those older, or in a high risk group (see later), require three doses.

The **routine** NZ HPV immunisation schedule from 2017 consists of two doses of HPV9 given at 0, and 6-12 months by injection (a minimum of 6 months between the first and second dose). A missed dose does not require the schedule to be restarted.^{174,175}

Persons over the age of 14 years should receive a three-dose schedule.^{176,177} There is flexibility in the three-dose schedule, provided the **minimum interval between the first and last dose** is four months.

Vaccine effectiveness

A 2016 systematic review of literature published from 1 January 2007 to 29 February 2016 summarised the global experiences with HPV4. The global effect of HPV4 vaccine on HPV infection, genital warts and cervical abnormalities based on 57 publications across nine countries were reviewed. The greatest impact was seen in countries with high vaccine uptake and among girls vaccinated prior to HPV exposure. Reductions of up to 90% were reported for vaccine-type HPV infections (HPV 6/11/16/18) and genital warts.¹⁷⁸

HPV4 vaccine is highly efficacious. In the pivotal efficacy trials HPV4 demonstrated high levels of efficacy against persistent disease and other endpoints in both males and females.¹⁷⁹⁻¹⁸²

Since HPV vaccine has been both widely recommended and introduced in many countries it is no longer ethical to conduct placebo-controlled trials with these vaccines.

HPV9 efficacy is non-inferior to HPV4 and extends protection against five additional genotypes. It was assessed alongside the HPV4 comparator in 14,215 women aged 16 to 26 years in a double-blind, phase 2b-3 trial. Participants received either three doses of HPV4 or three-doses of HPV9 at 0, 2 and 6 months. In the per-protocol efficacy population, the incidence rate of high-grade disease related to HPV-31, 33, 45, 52, and 58 (the five additional HPV9 genotypes) was 0.1 per 1000 person-years in the HPV9 group and 1.6 per 1000 person-years in the HPV4 group (1 case vs. 30 cases). HPV9 efficacy was 96.7% (80.9 to 99.8).¹⁸³

There is a range of variables that affect the effectiveness of a vaccine programme and therefore the reported effectiveness in different countries varies. However the positive association between vaccine coverage and effectiveness is clear and consistent.

Vaccine effectiveness, and its impact on disease become evident over time as they can only be measured after a vaccination programme has been implemented. Cancer endpoints cannot be measured for years after the vaccine has been introduced whereas changes in genital warts epidemiology are evident almost immediately.

Among the cohorts eligible for vaccination and where coverage is highest HPV vaccination programmes are associated with significant reductions in the prevalence of vaccine-type HPV. In countries with high HPV vaccine coverage, such as Australia and Denmark, there has been a profound reduction in the number of genital wart cases. Data from Australia suggest elimination is possible. However countries with more moderate coverage, such as New Zealand, have also observed significant reductions.

The impact of HPV immunisation programmes on the incidence of cervical dysplasia is now evident across multiple countries. Early evidence of declines in cervical dysplasia is associated with the vaccine eligible cohorts. Younger women have the strongest evidence of protection after partial doses.¹⁷⁸

Herd immunity has been observed and is evident for persistent infection, incidence of genital warts and cervical dysplasia.

In pivotal efficacy trials among males that included 4,065 boys and men aged 16-26 years, HPV4 also demonstrated high efficacy against all endpoints, as well as effectiveness in reducing the risk for subsequent HPV related disease.¹⁸⁴ Endpoints measured were external genital lesions and persistent infection. Among MSM enrolled in the study there was 94.9% (95% CI 80.4–99.4) per-protocol efficacy against anal infection and associated anal intraepithelial neoplasia (AIN).

Duration of protection

The vaccines are highly immunogenic.¹⁸⁵ HPV vaccines induce robust immunological memory and mathematical modelling suggests that protection from vaccination is likely to be sustained long-term.^{186,187} To date, stable protective efficacy from the HPV vaccines has been demonstrated to 10 years and long-term follow-up studies support this.¹⁸⁸⁻¹⁹⁰ We turn to postlicensure effectiveness studies to monitor the ongoing performance of vaccines.

Effectiveness against genital warts

Evidence shows that high HPV4 vaccination coverage has been associated with dramatic reductions in the diagnosis of genital warts. Australia has published 11 studies on the impact of HPV vaccination on genital warts.¹⁹¹⁻¹⁹⁵ Reductions in inequities are also evidence with reductions similar in Indigenous females, and the relative reduction across different levels of disadvantage similar.¹⁹⁶ Australian data also suggest elimination is possible. There have been no cases of genital warts diagnosed in women under 21 years reported as being vaccinated.¹⁹⁷

Other countries to have reported significant declines in genital warts include Denmark and Sweden.¹⁹⁷⁻¹⁹⁹

New Zealand introduced HPV4 (Gardasil) in 2008. Data from Auckland in 2010 and again in 2013 shows a steady decline, 63% and 83% respectively, in the rate of genital warts.²⁰⁰ Nationally the rates of reported new cases of genital warts have declined from 4,299 in 2008 to 1,659 in 2015, a 61% reduction.²⁰¹

Human papillomavirus immunisation in special groups

Immunosuppressed patients

Immunosuppressive conditions are associated with a higher risk for HPV-associated disease.

Immunogenicity of HPV vaccine in adult solid organ transplant patients is suboptimal when the vaccine is administered early after transplant, and depends upon the type of transplant and immunosuppression.²⁰² However, limited data suggest seroconversion among adolescent kidney and liver transplant patients indicating good immune response.²⁰³

HPV vaccine has been demonstrated to be immunogenic in HIV-infected men²⁰⁴ and women.²⁰⁵

Females aged 9–26 years on immunosuppressive therapy for inflammatory bowel disease developed antibody responses similar to healthy females.²⁰⁶

When vaccinating immunosuppressed patients a three-dose schedule should be used regardless of age.

Frequently Asked Questions

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

- Yes. HPV vaccine can be offered to people who have HPV and would like to use the vaccine to reduce the risk of further acquisition of new HPV or further disease.
- The decision to vaccinate older age groups or those already sexually active should be based on the individuals' assessment of potential benefit and future risk.
- Vaccine protects against the HPV genotypes which a person has not previously encountered.

Limited data in women shows that vaccination may help to prevent recurrence or reactivation of HPV infection. The therapeutic benefit of vaccine in the context of existing external warts or other HPV disease is anecdotal only.^{207,208}

Can people be tested for infection before getting vaccinated?

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

Does natural infection induce protective immunity?

Not always. Current evidence suggests that overall naturally acquired immunity is unlikely to be effective because of the ability of the virus to evade the immune system, but this does not appear to be the case with vaccine derived immunity.

Naturally acquired immunity to reinfection: 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 against other types (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 has commonly been observed in women who become immunosuppressed.

Naturally acquired immunity to tumorigenesis: As natural immunity is very slow to develop, CIN can develop during the period of persistent infection.²⁰⁹⁻²¹³

Will cervical screening still be needed?

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

What if the vaccine is given to a pregnant woman?

These vaccines are not specifically recommended for use in pregnancy at this time. However, enquiry about possible pregnancy is not required before vaccination. Completion of the vaccine course should be deferred if a woman 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 evidence from the clinical trials that administration of HPV vaccine adversely affects fertility, pregnancy, or infant outcomes. Many pregnancies occurred in the trial participants.^{75,214} The key message is "don't do it, but if you do don't worry about it!"

Women may safely breastfeed if they receive the vaccine during that period.

Could less common genotypes replace types 16 and 18?

In theory widespread vaccination may allow less common genotypes to replace the vaccine types, but expert opinion believes this to be unlikely.⁹⁴ Programmes will be monitoring changes in genotyping to ensure prevention continues to be effective. The phenomenon can occur where different strains or types of an agent compete with each other, such as with pneumococcal vaccination. This is not the case with human papillomavirus. A person can be co-infected with several types at one time.

Can people be tested to check immunity after vaccination?

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

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

Yes. The quadrivalent vaccine provided statistically significant levels of protection against type 31 and serum neutralising antibody to types 33 and 52.²¹⁵

Can the HPV vaccine be given with other vaccines?

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

Are the HPV vaccines interchangeable?

Yes. Either vaccine may be used to complete the recommended schedule.

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. HPV vaccine has an excellent safety profile and is well tolerated in all age groups. In the pivotal trials, the majority of adverse events were reported as mild or moderate, with injection site reactions the most common.²¹⁶

No safety signals have been raised since the vaccine was licensed. A summary of the published post-licensure safety data on HPV4 from both active and passive surveillance studies to 2015 included data from more than one million preadolescents, adolescents and adults. The review concluded syncope to be associated with the administration of the vaccine, and possibly skin infections; more detailed analysis of the “infections” suggested some were likely injection site reactions. Serious events were carefully examined with no increase in incidence over background rates.²⁰⁷

A further review has summarised the postlicensure safety studies from many countries to 2016. Some individual studies include over one million participants. With the exception of syncope, which is an injection not a vaccine reaction, no safety signals have been identified.²⁰⁸

ISSUES IN COUNSELLING

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 e.g. www.hpv.org.nz, and referral to a sexual health specialist if required.

KEY INFORMATION FOR PERSONS WITH HPV INFECTION

- Vaccination against HPV has been available for many years and everyone who is eligible should have it.
- 80% of unvaccinated adults will pick up HPV at some point in their life. In most people, it causes no symptoms (you won't know you have it) so is therefore unavoidably shared mainly through sexual (including oral) skin-to-skin contact
- 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, 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 current relationship.
- There are treatments for genital warts and abnormal cells.
- There is no treatment to eliminate HPV itself. HPV is usually dealt with by your body's immune system.
- HPV does not affect fertility.
- HPV does not stop you having a normal sex life.
- There is no single HPV test (such as a blood test) to check for HPV status at multiple body sites. 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?"

KEY INFORMATION FOR PERSONS WITH ANOGENITAL WARTS

- Routine STI screening does not include testing for either HPV or HSV. There is no sure way to know when HPV was acquired.
- If left untreated, genital warts may go away, stay the same, or increase in size or number.
- If warts are in the pubic region avoid shaving or waxing as this may spread the warts.
- Genital warts do not turn into cancer.
- The types of HPV that cause genital warts rarely cause cancer.
- Women with genital warts need to have regular cervical screening and follow the same management pathways as women without visible genital warts.
- Genital warts can develop months or years after acquiring an infection with HPV. Genital warts can be passed on to another person even when there are no visible signs of warts.
- There is no sure way to know when HPV was acquired. Sex partners who have been together tend to share HPV, even when both partners do not show signs of HPV. The presence of genital warts does not mean that a person or his/her partner is having sex outside the current relationship.
- Although genital warts are common and benign, there is considerable psychosocial impact of this diagnosis.
- There are treatments for the conditions caused by HPV, such as genital warts. However, treating genital warts does not treat the virus itself. For this reason, it is common for genital warts to come back after treatment, especially in the first 3 months.
- Inform current sexual partner(s) that genital warts may be transmitted to a partner(s). Partner(s) may benefit from getting tested for other STIs. A current partner may already have HPV, even though she/he may not have visible signs of warts.
- Abstinence from sexual activity with new partners is strongly recommended until the warts are gone or removed. HPV may remain and can still be passed on to partners, even after the warts are gone.
- Condoms may lower the chances of transmitting genital warts if used with every sex act; however, HPV can infect areas that are not covered by a condom and condoms may not fully protect against HPV.
- There is an HPV vaccine available for males and females that prevents genital warts but it will not treat existing HPV or genital warts. This vaccine can prevent most cases of genital warts in persons who have not yet been exposed to wart-causing types of HPV.
- It is not clear if there is any health benefit to informing (future) partners about a past diagnosis of genital warts. This is because it is not known how long the virus remains after warts are gone.

KEY INFORMATION FOR WOMEN REGARDING CERVICAL CANCER SCREENING

- HPV is a common infection and often clears by natural immunity. A positive HPV test does not mean that a person has cancer. Most women who have HPV do not develop abnormal cells or cancer.
- HPV is often shared between partners and can lie dormant for many years; having HPV does not imply other sexual contacts, nor should it necessarily raise concerns about a partner's health.
- Most cervical cancers can be prevented by HPV vaccination and having regular cervical screening. Vaccination, regular screening and following NCSP recommended guidelines if any abnormalities are identified, is the most effective pathway for women to follow to prevent invasive cervical cancer developing.

See **Preventing HPV Cancers By Vaccination: What Everyone Should Know** (www.hpv.org.nz).

KEY INFORMATION ABOUT PREVENTION

HPV vaccination, ideally before ever having sex, is the first line of defence and the most effective way of preventing HPV.

See **Preventing HPV Cancers By Vaccination: What Everyone Should Know** (www.hpv.org.nz).

- Condoms used consistently and correctly may lower the chances of acquiring and transmitting HPV and developing HPV-related diseases, such as genital warts and cervical cancer. However, HPV can infect areas that are not covered by a condom, so condoms do not fully protect against HPV.
- Limiting the number of sex partners can prevent HPV. However, it is important to note, even people with only one lifetime sex partner can get HPV.

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CLINICAL PRESENTATIONS OF ANOGENITAL HPV



Multifocal pigmented HSIL



Penile warts



Multifocal HSIL



Squamous cell carcinoma in situ of glans penis with early invasive carcinoma



Vulval condyloma



Penile pearly papules are a normal variant often mistaken for HPV

MEMBERS OF THE PROFESSIONAL ADVISORY BOARD (PAB) OF THE SEXUALLY TRANSMITTED INFECTIONS EDUCATION FOUNDATION 2017

Sexual Health Physicians

Dr Min Lo (Editor in Chief, HPV Guidelines)

Dr Edward Coughlan

Dr Heather Young

Infectious Disease and Sexual Health Physician

Dr Massimo Giola

NZ Dermatological Society

Dr Darion Rowan

NZ Committee of the Royal Australian and New Zealand College of Obstetrics and Gynaecology

Dr Anne Robertson

Paediatric Society of New Zealand

Dr Lesley Voss

NZ College of General Practitioners

Dr Phil Jacobs

NZ Society of Otolaryngology, Head and Neck Surgery

Dr Julian White

Family Planning

Dr Christine Roke

Immunisation Advisory Centre (IMAC)

Dr Helen Petousis-Harris

Counselling

Claire Hurst

Nursing

Georgina McPherson (NZ HPV Project)

Patient Advocate

Peter

Project Manager

Hayley Samuel, PO Box 2437, Shortland Street, Auckland 1140

Tel: 09 433 6526 Email: info@hpv.org.nz

Additional Contributors:

Principal Scientific Officer, National Screening Unit, Ministry of Health

Harold Neal PhD

Clinical Leader, Pathology, National Cervical Screening Programme

Dr Margaret Sage

Section Leader of Molecular Diagnostics/Virology, LabPlus, ADHB

Fahimeh Rahnama PhD

General Practitioner

Dr Stewart Reid MNZM

Additional Peer Review provided by:*

Sexual Health Physician

Dr Jeannie Oliphant

Clinical Microbiologist

Dr Arlo Upton

General Practitioner

Dr Andrew Miller

Infectious Disease Pharmacist

Eamon Duffy

Midwife

Karen Upton

* Members of the Joint Sexually Transmitted Infections Education Foundation and New Zealand Sexual Health Society Professional Advisory Board (PAB) 2017

Sexually Transmitted Infections Education Foundation

Secretariat:

PO Box 2437, Shortland Street, Auckland 1140, New Zealand

Phone: 09 433 6526

Email: info@stief.org.nz

info@justthefacts.co.nz
www.justthefacts.co.nz



info@hpv.org.nz
www.hpv.org.nz



info@herpes.org.nz
www.herpes.org.nz



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