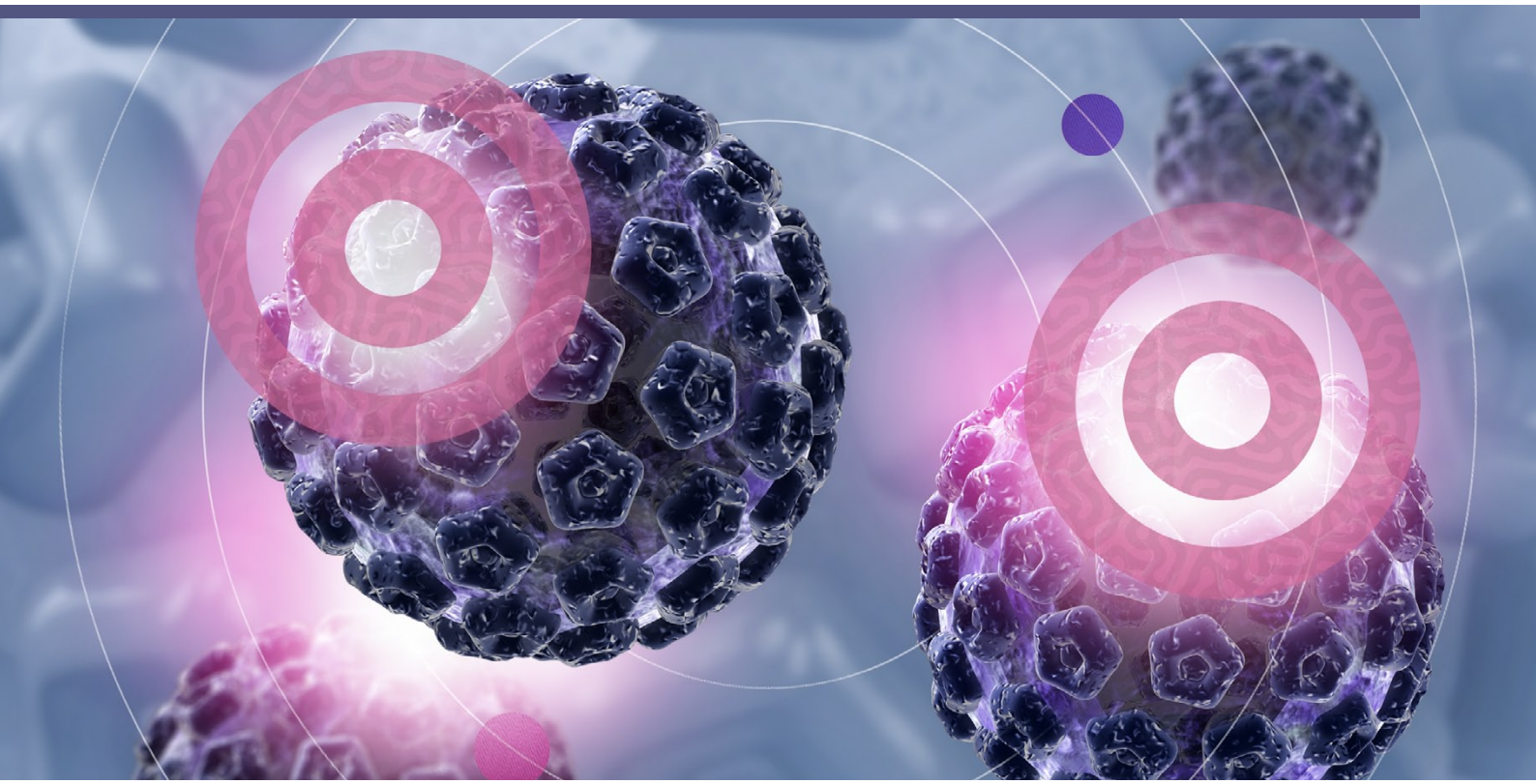


HPV vaccination: getting the programme back on track

Vaccination against human papillomavirus (HPV) infection provides safe and effective protection from genital warts, most cervical cancers and many anogenital and oropharyngeal cancers. However, HPV vaccination rates in New Zealand could be better; higher rates of vaccination will protect more individuals and offer more effective "herd immunity" against these conditions.

KEY PRACTICE POINTS:

- Without vaccination, approximately 80% of sexually active adults will be infected by at least one strain of HPV during their lifetime
- The HPV vaccine (Gardasil 9) protects against nine strains of HPV:
  - Two low-risk strains that cause approximately 90% of genital warts
  - Seven high-risk strains that cause the majority of cervical cancers and many anogenital and oropharyngeal cancers
- To achieve more effective "herd immunity", vaccination rates need to be 75–80%; latest figures show 67% coverage in New Zealand
- Females and males aged nine to 26 years are eligible for a subsidised course of vaccination
- Vaccination against HPV before the age of 14 years is associated with a stronger immune response therefore only two doses are required in this age group; three doses are otherwise required
- The school-based HPV immunisation programme aims to vaccinate children in Year 7 or 8 (aged 11–12 years)
- It is recommended that practices place an active recall for patients aged 14 years to offer HPV vaccination to those who have not received it; this is also an opportunity to check vaccination status in general
- Ensure that all young adults, i.e. those aged 26 years and under, are aware that they are eligible for subsidised HPV vaccination; some may have missed out on the vaccine through the school-based programme and are unaware that it is available to them

The HPV vaccination schedule in New Zealand

The human papillomavirus (HPV) vaccine reduces the incidence of diseases associated with HPV infection, including genital warts, most cervical cancers and many anogenital and oropharyngeal cancers. Since January, 2017, all females and males aged nine to 26 years have been eligible to receive subsidised vaccination; previously it was only subsidised for females until age 20 years. At the same time as subsidised access to the vaccine was widened, protection was extended from four strains of HPV to nine strains, by changing from Gardasil to Gardasil 9.

Further information on the nonavalent HPV vaccine is available from: **www.bpac.org.nz/2016/hpv.aspx**

The number of doses varies by age

Table 1 describes the groups of people eligible for subsidised vaccination and the number of doses recommended. School-based immunisation normally begins at age 11 or 12 years (Year 7 or 8), however, the vaccine can be given early to patients who are immunocompromised or prior to organ transplant.[1] People aged 27 years and older who received at least one dose of HPV vaccine before turning 27 years can complete the schedule fully subsidised. The vaccine can be administered unsubsidised to people aged 27 years and over if they are likely to benefit (Table 1).[1]

Immunocompromised patients can receive the HPV vaccination

HPV vaccination can be safely administered to people who are immunocompromised, e.g. those who have received chemotherapy or with HIV infection, because the vaccine contains non-replicating, non-infectious viral subunits.[1, 3]

HPV vaccine can be given during pregnancy or while breast feeding

While it is recommended to wait until after pregnancy to administer the HPV vaccine, there is no evidence that it causes adverse effects such as congenital abnormalities or spontaneous abortion.[4] The HPV vaccine is safe to receive while breastfeeding.[4]

How effective has HPV vaccination been in New Zealand?

The number of diagnoses of genital warts has significantly decreased since the introduction of the vaccine; the latest surveillance data reported a 17% decline in diagnoses in primary care in all ages from 2014 to 2015.[5] Data collected from the Auckland Sexual Health Service showed an 83% reduction in genital wart diagnoses in young females in 2013 compared with 2008, before the HPV vaccination programme was introduced.[6] It is too early to detect any effects of HPV vaccination on cancer rates in New Zealand as this requires lengthy follow-up periods.

Table 1. HPV vaccine schedules adapted from the Ministry of Health (2017)[1]

	Number of doses	Schedule	Subsidy
Children aged 9–14 years	2	0 and 6–12 months	Yes
People aged 15–26 years	3	0, 2 and 6 months	Yes
People aged 9–26 years with: ■ Confirmed HIV infection OR ■ Organ or tissue transplant (including stem cells)	3	0, 2 and 6 months	Yes
People aged 9–26 years who are post-chemotherapy	One additional dose	≥ 1 month after the last dose	Yes
People aged 27 and older† who may benefit, e.g.: ■ Those with little previous exposure to HPV ■ Men who have sex with men ■ Those with HIV infection	3	0, 2 and 6 months	No

† The HPV vaccine is registered for use in females aged 9–45 years and in males aged 9–26 years, however, there are no concerns that the efficacy or safety in males up to the age of 45 years will differ significantly from females of the same age or younger males.[1] The unsubsidised cost of three doses varies but is approximately $500 as of February 2019.[2]

Vaccination rates against HPV in New Zealand are too low

The target for HPV vaccination is 75% coverage across all DHBs, which the Ministry of Health hoped to achieve by December, 2017. This level of coverage is considered to provide more effective "herd immunity" where those unwilling or unable to receive the vaccine are also protected.[7] This target was not met, with latest figures showing only 67% coverage for females born in 2003.*[8] The lowest rate of vaccination was in European/Others (65%), with higher rates in Māori (67%), Asian (71%) and Pacific peoples (73%).[8]

* Data are currently unavailable for females born after 2003 and there are currently no statistics for coverage in males

Catch-up vaccinations following the supply shortage

There was a supply shortage of HPV vaccines in New Zealand during late 2017 and through most of 2018. This issue has been resolved and health professionals in primary care are now able to order unrestricted quantities of the vaccine. However, the Ministry of Health indicates that there are a significant number of eligible people, particularly young males, who have not completed the full course of vaccinations due to the shortage. The following guidance is provided for health professionals scheduling "catch-up" vaccinations:

- If a person has started the course of HPV vaccinations they do not need to begin the course again, regardless of the amount of time that has passed; give the next dose as scheduled
- If the second HPV vaccination is given at age 15 years or older a third dose is recommended and subsidised
- People who turned age 27 years after April 1, 2018, who received their first dose of HPV vaccine before 1 April, 2019, and international students who turn age 18 years during this period are eligible to receive a subsidised course of HPV vaccinations*

* A manual claim should be submitted after the first dose. Once this has been accepted the subsequent doses should be processed automatically.

HPV and the benefits of vaccination

HPV infection is spread via close skin-to-skin contact which can occur during penetrative and non-penetrative sexual contact, e.g. oral sex.[9] In very rare cases, HPV can be transmitted from mother to fetus perinatally.[1] Approximately 80% of sexually active adults will be infected by at least one strain of HPV during their lifetime, with the risk of infection increasing in proportion to the number of sexual partners.[9]

The natural history of HPV infection, i.e. without vaccination, is often transient and asymptomatic, with a loss of detectable HPV occurring after 6–12 months.[9] However, in some individuals the repeated division of infected cells will result in the development of anogenital warts, often weeks or months after acquiring the infection.[9] In 10–20% of people the infection will persist latently over years, strongly increasing their risk of developing a neoplasia, which may eventually progress to invasive cancer.[10] The reasons why some people have persistent infections with HPV are not completely understood but may involve genetics and environmental factors such as alcohol consumption and tobacco smoking.[10] Consistent use of condoms only reduces the rate of transmission by 30–60% as they may not cover all areas of infection.[9]

Vaccination protects against nine strains of HPV

The current HPV vaccine prevents infection from nine strains of HPV, including two low-risk strains (6 and 11) that cause approximately 90% of genital warts and seven high-risk strains (16, 18, 31, 33, 45, 52 and 58) that cause the majority of cervical cancers; strains 16 and 18 are associated with approximately 70% of invasive cervical cancers.[9]

HPV vaccination prevents more than 97% of genital intraepithelial neoplasias and anogenital warts among females aged 16–26 years who have tested negative for prior infection with HPV (see: "Routine cervical screening is still required").[1,11] Less data are available regarding the vaccine's efficacy in males, but there is evidence that more than 90% of external genital lesions, including warts and genital intraepithelial neoplasias, are prevented in males aged 16–26 years.[12] N.B. Genital intraepithelial neoplasias are rare among young males and females.

Long-term immune responses occur in almost all people

One month after completing the HPV vaccination schedule, 99.6% – 100% of people aged 9–26 years will have antibodies present against all nine strains covered by the vaccine.[11] It is unclear how long protection lasts as studies are ongoing, however, it is known to persist for at least ten years with no decrease in efficacy, therefore booster vaccinations are not considered necessary if the full schedule has been completed.[11]

Vaccination at an early age is associated with greater protection

Vaccination against HPV is associated with a stronger immune response in younger people.[13] For this reason, only two doses of the vaccine are required for those aged under 14 years, compared with three in older groups. It is important that young people and caregivers understand that the reason why vaccination is recommended at age 11–12 years is to maximise the recipient's immune response and avoid the need for additional doses, rather than it being a predictor of imminent sexual activity.

Conditions associated with HPV infection

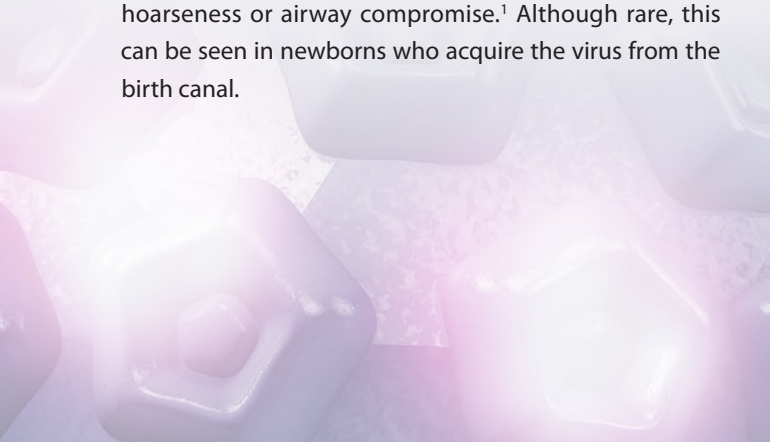
HPV infects human epithelial cells and there are more than 100 subtypes with differing propensities to infect mucosal or cutaneous tissue.[9] There are more than 40 types of HPV that infect the anogenital area and throat, the majority of which are sexually transmitted.[9] It has been reported that high-risk HPV strains cause 5% of all cancers worldwide.[14]

Anogenital warts: Anogenital warts typically occur within weeks or months of infection with HPV.[9] Strains 6 and 11 account for approximately 90% of all cases of anogenital warts.[15] These warts do not lead to cancer but they can cause physical discomfort, anxiety and social stigma.

Cervical cancer: It is well established that persistent infections with HPV cause cervical cancer and the association is present in virtually all cases worldwide.[16] Most females infected with HPV, however, do not develop cervical cancer.[9] The progression from cervical intraepithelial neoplasia to cervical cancer usually occurs over 15–20 years, but a compromised immune system may accelerate this.[9] There were 180 cases of cervical cancer registered in New Zealand in 2016.[17]

Other cancers: Infection with HPV is associated with approximately 75% of oropharyngeal cancers.[18] The incidence of HPV-related oropharyngeal cancer is increasing in New Zealand and is four- to five-times higher in males than females (3.01 and 0.65 cases per 100,000 population, respectively).[18] Infection with high-risk HPV is also associated with over 90% of anal, 70% of vulval and vaginal, and 50% of penile cancers.[9] These cancers are relatively rare but their prevalence in New Zealand is increasing.[9]

Other conditions: Low-risk HPV can also cause benign growths in the respiratory tract which may present as hoarseness or airway compromise.[1] Although rare, this can be seen in newborns who acquire the virus from the birth canal.



Vaccination is also beneficial for people who are sexually active

People who are sexually active, including those who have already been infected with HPV and those who have developed HPV-related conditions, may also benefit from vaccination. Most significantly, the vaccine will provide these people with protection against strains of HPV they have not encountered. It may also prevent reinfection with a strain they have been previously exposed to if they cleared the infection without producing antibodies against that strain. Many people who are infected with HPV do not develop immunity as seroconversion is poor.[9] Immunity from vaccination is more effective than immunity post-exposure to the wild virus. There are no safety concerns associated with vaccination in people who are already infected with HPV or who have developed an HPV-related condition.[1]

Strategies for increasing vaccine uptake in primary care

Some people in New Zealand are unaware they are entitled to fully subsidised HPV vaccinations or were not eligible at the time and have therefore not participated in the school-based programme. General practices should identify any eligible enrolled patients who have not received HPV vaccination.

A routine recall at age 14 years is recommended. For example:

1. Schedule an automatic reminder to occur when a patient turns 14 years and send a recall letter if appropriate
2. Establish a monthly recall for all people who have turned 14 in the previous month

People aged 15–26 years who have not received the full schedule of HPV vaccines (or any at all) can be flagged in the patient management system to be offered the vaccine at their next consultation. Patients who do not regularly attend primary care may require a recall offering them subsidised vaccination.

Best practice tip: use the recall as an opportunity to also check for completion of two measles, mumps and rubella (MMR) vaccines, tetanus-diptheria-pertussis (Tdap) vaccination (usually given in a school-based programme at age 11 years), and a history of varicella or varicella vaccination.

The ASK approach to vaccination discussions

Health professionals sometimes meet resistance when discussing vaccination. The ASK approach is one option clinicians can use when discussing potentially emotive issues:

- **A**cknowledging the person's concerns

- **S**teering the conversation
- **K**nowing the facts

Not every person will express the same concerns, so acknowledging differing viewpoints and being non-judgemental is important when discussing vaccination.

Setting the story straight about safety

More than 100 million doses of the HPV vaccine have been administered worldwide, and it has been well-tolerated in females and males across all age groups.[2] The risks associated with the HPV vaccine are similar to other vaccines. The most common adverse effect is mild-to-moderate injection-site pain which occurs in 83% of people within five days.[11] Other possible adverse effects are generally transient, including swelling, erythema, pruritus and bruising around the injection site, as well as headaches and pyrexia.[2] The risk of anaphylactic reaction after administering the vaccine is approximately three cases per million doses.[1]

There is no evidence linking the HPV vaccine to rare adverse effects

There have been case reports describing an association between administration of the HPV vaccine and the development of some rare conditions, e.g. autoimmune disorders, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS). However, as vaccination is widespread and these conditions are relatively rare it is not possible to analyse the potential relationship between the two without performing large epidemiological studies.

A large Canadian cohort study of more than 290,000 females aged 12–17 years found no increased risk of autoimmune disorders following vaccination with the quadrivalent HPV vaccine.[21] An extensive review of the evidence by the European Medicines Agency (EMA) found no evidence that the HPV vaccine causes CRPS or POTS.[22] The prevalence of both conditions in the general population is approximately 150 cases per million people each year, and the occurrence of CRPS and POTS in young females who had been vaccinated was no higher than would be expected.[22]

Patient information on HPV and the HPV vaccine are available from:

www.hpv.org.nz/resources/information-health-professionals

www.immune.org.nz/diseases/human-papillomavirus-hpv

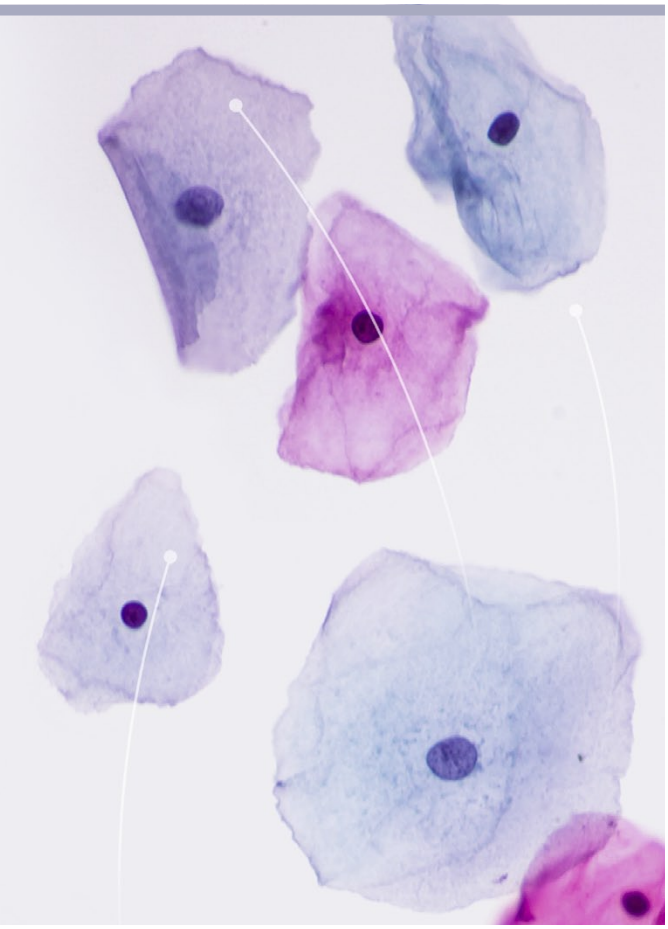
www.cdc.gov/vaccinesafety/vaccines/hpv/hpv-safety-faqs.html

Routine cervical screening is still required

Females who have received the HPV vaccine still need to participate in the National Cervical Screening Programme as the vaccine does not provide protection against every strain of HPV that can cause cervical cancer.[1]

Changes to the screening programme are coming:[19, 20]

- **During 2019** – The frequency of cervical screening will change from every three years to every five years, and the age at which screening begins will be increased to 25 years, from 20 years
- **During 2021** – Instead of initially using liquid-based cytology to identify pre-cancerous or cancerous changes in cells from the cervix, HPV primary screening will instead be the first test; samples containing high-risk HPV strains will subsequently undergo cytology analysis. Cells will be taken from the cervix via the same method used for liquid-based cytology, although in the future self-sampling methods may be available.



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N.B. Expert reviewers do not write the articles and are not responsible for the final content.

This article is available online at:
www.bpac.org.nz/2019/hpv.aspx

References:

1. Immunisation Handbook 2017. Ministry of Health. 2019. Available from: www.health.govt.nz/publication/immunisation-handbook-2017 (Accessed Feb, 2019).
2. Human Papillomavirus (HPV). The New Zealand HPV Project. 2019. Available from: www.hpv.org.nz (Accessed Mar, 2019) (Accessed Feb, 2019).
3. Garland SM, Brotherton JML, Moscicki AB, et al. HPV vaccination of immunocompromised hosts. Papillomavirus Res 2017;4:35–8. doi:10.1016/j.pvr.2017.06.002
4. Bonde U, Joergensen JS, Lamont RF, et al. Is HPV vaccination in pregnancy safe? Hum Vaccin Immunother 2016;12:1960–4. doi:10.1080/21645515.2016.1160178
5. The Institute of Environemental Science and Research Ltd. Sexually transmitted infections in New Zealand annual surveillnace report 2015. 2018. Available from: https://surv.esr.cri.nz/PDF_surveillance/STISurvRpt/2015/FINAL2015AnnualSTIReport.pdf (Accessed mar, 2019)
6. Oliphant J, Stewart J, Saxton P, et al. Trends in genital warts diagnoses in New Zealand five years following the quadrivalent human papillomavirus vaccine introduction. N Z Med J 2017;130:9–16.
7. Revitalising the National HPV Immunisation Programme with agreed outcomes from the August 2014 workshop. Ministry of Health, 2015. Available from: www.health.govt.nz/publication/revitalising-national-hpv-immunisation-programme (Accessed Feb, 2019).
8. HPV immunisation coverage by ethnicity and eligible birth cohort. Ministry of Health, 2017. Available from: www.health.govt.nz/our-work/preventative-health-wellness/immunisation/hpv-immunisation-programme (Accessed Feb, 2019).
9. Guidelines for the management of genital, anal and throat HPV infection in New Zealand. The New Zealand HPV project. 9th Edition. 2017. Available from: www.nzshs.org/guidelines (Accessed Feb, 2019).
10. Shanmugasundaram S, You J. Targeting persistent Human Papillomavirus infection. Viruses 2017;9. doi:10.3390/v9080229
11. Data sheet. Gardasil 9. Merck Sharp & Dohme (New Zealand) Limited. Available from: www.medsafe.govt.nz/profs/Datasheet/g/gardasil9inj.pdf (Accessed Feb, 2019).
12. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. New England Journal of Medicine 2011;364:401–11. doi:10.1056/NEJMoa0909537
13. Donken R, Ogilvie GS, Bettinger JA, et al. Effect of human papillomavirus vaccination on sexual behaviour among young females. Can Fam Physician 2018;64:509–13.
14. National Cancer Institute. HPV and cancer. 2015. Available from: www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-fact-sheet#r11 (Accessed Mar, 2019)
15. Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol 2012;5:25–36.
16. Bosch FX, Lorincz A, Muñoz N, et al. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244–65.
17. Ministry of Health. Selected cancers 2014, 2015, 2016. 2018. Available from: www.health.govt.nz/publication/selected-cancers-2014-2015-2016 (Accessed Mar, 2019)
18. Chelimo C, Elwood JM. Sociodemographic differences in the incidence of oropharyngeal and oral cavity squamous cell cancers in New Zealand. Australian and New Zealand Journal of Public Health 2015;39:162–7. doi:10.1111/1753-6405.12352
19. Frequently asked questions about proposed changes to the cervical screening test. National Screening Unit. 2018. Available from: www.nsu.govt.nz/health-professionals/national-cervical-screening-programme/hpv-primary-screening/frequently-asked (Accessed Feb, 2019).
20. Change of timing for improvements to the National Cervical Screening Programme. National Screening Unit. 2018. Available from: www.nsu.govt.nz/news/change-timing-improvements-national-cervical-screening-programme (Accessed Feb, 2019).
21. Liu EY, Smith LM, Ellis AK, et al. Quadrivalent human papillomavirus vaccination in girls and the risk of autoimmune disorders: the Ontario Grade 8 HPV Vaccine Cohort Study. CMAJ 2018;190:E648–55. doi:10.1503/cmaj.170871
22. European Medicines Agency. Human, papillomavirus vaccines - Cervarix, Garadasil, Gardasil 9, Silgard. 2016; [Epub ahead of print]. Available from: www.ema.europa.eu/en/medicines/human/referrals/human-papillomavirus-vaccines-cervarix-gardasil-gardasil-9-silgard (Accessed Mar, 2019)