FactSheet

NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

Human papillomavirus (HPV)

HUMAN PAPILLOMAVIRUS (HPV) VACCINES FOR AUSTRALIANS: INFORMATION FOR IMMUNISATION PROVIDERS

This fact sheet provides information on HPV disease and vaccines to assist immunisation providers in the delivery of HPV vaccination. It can be used in conjunction with the NCIRS resource: HPV vaccines – frequently asked questions, which provides responses to common questions and concerns. There is misleading information about HPV vaccines on the internet and social media; readers should check they obtain information from reliable and trusted expert sources.

Disease and epidemiology

- Genital human papillomavirus (HPV) is a common sexually transmitted infection in both males and females. Most people will acquire an HPV infection within a few years of becoming sexually active. Around 90% of the population will be infected with HPV in their life.
- The majority of genital HPV infections are asymptomatic and are cleared within a year. A small proportion of HPV infections persist in the genital epithelium where they can lead to abnormalities in the cells. In rare cases, these abnormalities progress, usually over many years, to cancer.
- Cancers caused by HPV infection include cancer of the cervix, vagina, vulva, penis and anus. HPV infection is also associated with some cancers of the head and neck.
- There are many types of HPV. Of the 40 known mucosal HPV types, HPV types 16 and 18 are the most common causes of HPV-associated cancers. A further 11 types are classified as carcinogenic (types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) or probably carcinogenic (type 68). Some HPV types are not associated with cancer; for example, HPV types 6 and 11 are the types that commonly cause genital warts.

Who should be vaccinated?

- HPV vaccine is included in the Australian National Immunisation Program (NIP). As part of the new schedule from 2018, it is provided via school-based programs for girls and boys aged 12–13 years in a 2-dose schedule. The 2nd dose is given 6–12 months after the 1st dose.
- A 3-dose schedule is recommended for individuals who commence vaccination at the age of 15 years or older, or for those with significant immunocompromising conditions, with doses given at 0, 2 and 6 months.
- Those who receive the vaccine prior to commencement of sexual activity will gain the most benefit from HPV vaccination.

Vaccines

- Three HPV vaccines are registered for use in Australia: the 9-valent HPV vaccine (9vHPV; Gardasil®9), which protects against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 and is being provided under the NIP from 2018 onwards; the quadrivalent HPV vaccine (4vHPV; Gardasil®), which protects against HPV types 16, 18, 6 and 11 and was used under the NIP from 2007 to 2017; and the bivalent HPV vaccine (2vHPV; Cervarix®), which protects against HPV types 16 and 18 and is available on the private market.
- All three vaccines are safe and generally well tolerated. The most common side effect is a local reaction at the site of the injection.
- Vaccination does not prevent infection from all HPV types. Therefore, cervical screening remains an important preventive strategy against cervical cancer for women.

The disease

Human papillomaviruses (HPVs) are small, non-enveloped DNA viruses. HPVs infect and replicate within cutaneous and mucosal epithelial tissues. There are 40 known HPV 'types' which infect the mucosal epithelium, classified according to sequence variation in the major genes.

Transmission of genital HPV occurs largely via sexual contact. There is a 50–80% chance of HPV transmission following unprotected sexual intercourse with a person with a current HPV infection.[1-3] The majority of genital HPV infections are subclinical and resolve spontaneously, clearing (i.e. no longer detectable) within 12–24 months of initial infection. Depending on the infecting HPV type, a small proportion of HPV infections can persist (estimated at 3–10%),[4] resulting in cellular abnormalities and, in a subset of cases, precancerous disease; a subset of these progress into cancer. The progression from mucosal HPV infection to cancer can take many years.

Of the mucosal HPV types, 13 are designated as 'high-risk' types due to their causal association with the development of cervical cancer (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68).[5] These HPV types are also associated with the development of other cancers in females and males, including vaginal, anal and penile cancers, and head and neck cancers. An infection with HPV is necessary for the development of the associated cancers; however, an HPV infection on its own is not enough for cancer development as not all HPV infections progress to cancer.[6-8]

Of the genital HPV types considered to be 'low risk', types 6 and 11 are major causes of genital warts (causing approximately 95% of genital warts) and recurrent respiratory papillomatosis.[9]

Epidemiology of HPV infection and associated disease

HPV infection rates vary greatly between geographic regions and population groups, but it is estimated that around 90% of the general population will be infected with HPV at some point in their lives.[10] HPV infection rates are highest among young women, usually peaking soon after the age when most young women become sexually active.[11] However, in men, HPV infection is evident at all ages and the risk of acquiring new HPV infection seems to remain stable over time.[12] A person's lifetime number of sex partners is a significant predictor of HPV acquisition, although HPV is frequently acquired from a first and only sexual partner.[13]

The largest burden of HPV-associated cancers in Australia is attributable to cervical cancer. Prior to the introduction of HPV vaccination of females, every year in Australia, Pap testing would detect low-grade cervical abnormalities in about 90,000 women and high-grade cervical abnormalities in a further 15,000 women. However, since the HPV vaccination program began in 2007, the incidence of high-grade cervical abnormalities has decreased, including in women up to 30 years of age, suggesting the ongoing impact of the vaccination program.[14-16]

Prior to vaccine introduction, due to the success of the National Cervical Screening Program, Australia had relatively low rates of incidence and mortality from cervical cancer, particularly compared with less developed countries in the world.[17] In 2007, the age-standardised incidence rate of cervical cancer in Australia was 6.8 per 100,000, and the mortality rate was 1.8 deaths per 100,000 women. Cervical cancer in Australia now occurs predominantly in unscreened or under-screened women. Indigenous women have more than twice the risk of developing cervical cancer and a mortality rate 4 times that of non-Indigenous women, an indication of both lower participation rates in cervical screening programs and greater prevalence of cofactors for cervical cancer.[15,18] The incidence and mortality rates of other HPV-associated cancers in women (vaginal, vulvar and anal) are lower than those for cervical cancer.

The burden of HPV-associated cancers in males in Australia is less than that in women; however, HPV-associated cancer incidence in males, particularly for anal and tonsillar cancers, has been increasing in recent decades while remaining relatively stable in females. Men who have sex with men are at particularly high risk of HPV-associated disease. The estimated incidence of anal cancer among men who have sex with men in Australia is greater than that of cervical cancer in women prior to the introduction of cervical screening program.[19] There are no systematic screening programs in place for HPV-associated disease in males because there is currently limited evidence to support secondary prevention for these conditions.[20]

Who should be vaccinated

Routine vaccination under the National Immunisation Program

HPV vaccination is recommended for females and males aged 12–13 years in a 2-dose schedule (0, 6–12 months) using 9-valent HPV (9vHPV) vaccine. From February 2018 the 9vHPV vaccine replaced the quadrivalent HPV (4vHPV) vaccine on the National Immunisation Program (NIP). Vaccination is mainly delivered through school-based programs. Individuals aged 15–18 years (i.e. past their 15th birthday) at the time of their 1st HPV vaccine dose require a 3-dose schedule (0, 2, 6 months) for adequate protection. Because of this, older adolescents may need to pay to complete the indicated vaccine schedule. Every effort should be made to ensure vaccination is given at 12–13 years of age.

Other recommendations for vaccination

Persons who are immunocompromised
A 3-dose schedule of 9vHPV vaccine is recommended for immunocompromised individuals, regardless of their age at the commencement of vaccination. These individuals have a higher risk of persistent HPV infection and related disease. The conditions where the 3-dose schedule is required include primary or secondary immunodeficiencies (B lymphocyte antibody and T lymphocyte complete or partial deficiencies), HIV infection, malignancy, organ transplantation or significant immunosuppressive therapy.

Men who have sex with men
Men who have sex with men, who have not previously been vaccinated, are also recommended to receive HPV vaccination, independent of their HIV status or the presence of other immunocompromising conditions. Men who have sex with men are at increased risk of HPV infection and associated disease, notably genital warts and anal cancer. They are also less likely to benefit from herd protection attained from HPV vaccination of females. Patterns of male HPV infection are markedly different from those of women, with stable incidence and prevalence throughout life, rather than early generation of effective immunity in the majority in the years following sexual debut, as occurs in women. HPV vaccination can prevent reinfection or spread of existing infection through the anogenital tract.

Women treated for high-grade cervical disease
HPV vaccination should also be considered for women who have received treatment for cervical intraepithelial neoplasia (CIN) 2+ (i.e. high-grade cervical disease). The vaccine will have no impact on current infection or disease but can prevent reinfection (e.g. from a partner), spread of infection through the genital tract and new infection with other HPV types covered by the vaccine.[21] Women with CIN have demonstrated an inability to effectively clear the virus and constitute a group at increased risk of future susceptibility to HPV-related disease.

Adults aged ≥19 years
Vaccination of all adults aged 19 years and older is not routinely recommended, as many are likely to have been exposed to one or more vaccine HPV types through sexual activity.

HPV vaccines have their highest efficacy when given to those who are not already infected with the HPV types targeted by the vaccine. At the individual level, the primary factor which influences the likelihood of previous exposure to HPV, and in turn potential benefit from HPV vaccine, is the number of sexual partners.

A recent study estimated that of all the HPV infections that cause cervical cancer, 50% have been acquired by age 20 and 75% by the age of 30.[22] This is a strong indicator that the capacity to benefit from HPV immunisation decreases with increasing age, and reinforces that cervical cancer prevention in sexually active women (whether vaccinated or not) is best achieved through cervical screening.[23]

In 2017, cervical screening in Australia began using an HPV test as the primary screening test, and this change is predicted to further reduce the incidence of cervical cancer by up to another 30%.[24]

Pre-immunisation screening with HPV tests or by serological testing is not warranted.

Vaccines

All HPV vaccines contain virus-like particles (VLPs) which are made using recombinant vaccine technology. They are not live vaccines. HPV vaccines are prophylactic; that is, they are designed to prevent initial HPV infection. They are not therapeutic vaccines and will not clear an existing HPV infection. When HPV vaccines are given as a 2- or 3-dose schedule, they elicit antibody titres many times higher than those observed in natural infection.[25-29] However, there is no routine diagnostic serological assay for detecting HPV antibodies. A protective antibody threshold has not been established, and serological testing before or after vaccination is not required.

9-valent HPV vaccine

Gardasil®9 (Seqirus/Merck & Co Inc) is a 9-valent HPV vaccine (9vHPV; types 6, 11, 16, 18, 31, 33, 45, 52 and 58) registered in Australia for use in females aged 9–45 years and males aged 9–26 years. From 2018 Gardasil®9 is the HPV vaccine used in Australia's National HPV Vaccination Program.

Quadrivalent HPV vaccine

Gardasil® (Seqirus/Merck & Co Inc) is a quadrivalent VLP HPV vaccine (4vHPV; types 16, 18, 6 and 11) registered in Australia for use in females aged 9–45 years and in males aged 9–26 years. Gardasil® was the HPV vaccine used in the National HPV Vaccination Program from 2007 to 2017.

Bivalent HPV vaccine

Cervarix® (GlaxoSmithKline) is a bivalent VLP HPV vaccine (2vHPV; types 16 and 18) registered in Australia for use in females aged 10–45 years. Cervarix® is not registered for use in males of any age. It is supplied in Australia only on the private market.

Administration

The dose of 9vHPV, 4vHPV and 2vHPV vaccine is 0.5 mL administered intramuscularly.

A 2-dose schedule is recommended for those who receive their 1st HPV vaccine dose before their 15th birthday, administered at 0 (the day the 1st dose is given) and 6–12 months.

If an individual has received 2 doses of HPV vaccine with an interval of <5 months between dose 1 and dose 2, then a 3rd dose is needed at least 12 weeks after the 2nd dose. If the 2nd dose is received at <6 months but ≥5 months after the 1st dose, a 3rd dose is not needed.

A 3-dose schedule is recommended for those who receive their 1st HPV vaccine dose on or after their 15th birthday, administered at 0, 1 and 6 months for 2vHPV vaccine, and at 0, 2 and 6 months for 9vHPV and 4vHPV vaccines.

The minimum acceptable interval for HPV vaccines in a 3-dose schedule is 4 weeks between doses 1 and 2, and 12 weeks between doses 2 and 3.

Contact your local state or territory health department for guidance if HPV vaccine has been given at less than the recommended minimum interval. See also *The Australian Immunisation Handbook* (www.immunise.health.gov.au).

If scheduled doses have been missed, earlier doses should not be repeated. The missed dose(s) should be given as soon as practicable.

Re-vaccination with the 9vHPV vaccine is not routinely recommended, nor funded under the NIP, for those who have previously completed an HPV vaccination schedule with either 4vHPV or 2vHPV vaccine. While provision of additional doses of 9vHPV vaccine appears safe,[30] both 4vHPV and 2vHPV vaccines provide effective protection against HPV types 16 and 18. These are the most common high-risk HPV types found in HPV-positive cervical cancers in Australia[23] and globally, and are the overwhelming cause of all other HPV-related cancers.

Vaccine efficacy/effectiveness

The efficacy of HPV vaccines has been extensively assessed in clinical trials enrolling females. In women who are naïve to (i.e. have never been infected with) the vaccine HPV types, a 3-dose schedule of 9vHPV vaccine is highly effective (>96%) at preventing persistent type-specific infection and combined high-grade cervical, vulvar and vaginal disease associated with HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58.[29,31] Younger adolescents respond better to the vaccine in a 2- or 3-dose schedule: those who receive their 1st HPV vaccine dose when aged 9–14 years develop higher levels of HPV antibodies than older adolescents and young women in whom clinical efficacy has been demonstrated.[28,29,32] Similarly, 4vHPV and 2vHPV vaccines are highly efficacious and/or immunogenic against their respective HPV types in 2- and 3-dose schedules.[25,27,29,33-37]

9vHPV vaccine has been shown to be immunogenic in males aged 9–26 years.[28,38] Vaccination with 4vHPV vaccine, whose four HPV types are included in the 9vHPV vaccine, has been demonstrated to prevent more than 85% of persistent anogenital infections and external genital lesions due to 4vHPV types among HPV-naïve participants.[39] In a subset of these participants, who were men who have sex with men, vaccine efficacy was 95% against intra-anal HPV infection and 75% against high-grade anal intraepithelial neoplasia from vaccine HPV types.

When vaccine efficacy is assessed in all clinical trial participants, regardless of baseline HPV status, the overall impact of the vaccine is lower, indicating reduced vaccine effectiveness in persons who are sexually active. For example, in a pooled analysis of the efficacy of 4vHPV vaccine in women aged 16–26 years, vaccination prevented 98.2% (93.3–99.8%) of high-grade cervical lesions (CIN2 or worse) associated with vaccine HPV types in women who were naïve to vaccine HPV types prior to vaccination. However, for all women enrolled in the trials (including those who were already infected with the vaccine HPV types), the overall efficacy of the

vaccine against high-grade cervical lesions associated with vaccine HPV types was lower at 51.5% (40.6–60%). This highlights that vaccination will not clear an existing HPV infection or prevent disease that may be caused by an existing HPV vaccine-type infection, emphasising the importance of vaccinating prior to HPV exposure.[27,40,41]

Duration of immunity through vaccination is not yet known although it is likely to be long term, with stable antibody titres demonstrated for over 10 years after immunisation with 2vHPV and 4vHPV vaccines.[31,42,43] Pre-adolescent males and females have a good immune response to vaccination, producing higher antibody levels than young women.[28,44] Antibody persistence and efficacy for at least 5 years has been demonstrated in young women who were vaccinated with 9vHPV vaccine.[31,45]

Vaccine safety

HPV vaccines are currently included in national immunisation schedules in 82 countries,[46] with more than 270 million doses distributed worldwide.[47] Extensive clinical trial and post-marketing safety surveillance data indicate that the 9vHPV, 4vHPV and 2vHPV vaccines are well tolerated and safe.

The main side effects of the vaccines are local reactions at the injection site (pain, redness and swelling). These reactions occur in about 80–90% of vaccine recipients but are less frequent in younger girls and in boys than in adult women.[44,48,49] The 9vHPV vaccine has demonstrated a similar safety profile to that of the 4vHPV vaccine (which it has replaced in the National HPV Vaccination Program), but with a slightly increased frequency in injection site reactions, likely due to the increased concentration of adjuvant.[50,51] Meta-analyses on pooled data from multiple clinical trials on both the 4vHPV and 2vHPV vaccines have shown no increase in the risk of serious adverse events (SAEs) among vaccine recipients compared with control/placebo recipients.[49,52,53] A meta-analysis comparing groups that received 9vHPV and 4vHPV vaccines has shown the two vaccines have a similarly low rate of SAEs.[51] No deaths, reported in safety surveillance systems data in Australia or overseas, have been determined to be causally related to HPV vaccines.

There is no strong scientific or epidemiological evidence to suggest that HPV vaccines can induce syndromes such as premature ovarian failure (POF), postural tachycardia syndrome (POTS) or complex regional pain syndrome (CRPS).[54] These diseases of unclear aetiology unfortunately occur in adolescents and young people, whether they are vaccinated or unvaccinated, and there is no evidence that these conditions occur more frequently in HPV-vaccinated populations. The Global Advisory Committee on Vaccine Safety of the World Health Organization has reviewed HPV vaccines seven times – most recently in 2017 – and continues to endorse their safety and use in young adolescents.[47]

Health professionals should report any adverse events following HPV immunisation via the method in place in their relevant state or territory. More information on reporting adverse events following immunisation, including contact information, can be found in *The Australian Immunisation Handbook* (www.immunise.health.gov.au)

Adverse event reports for HPV vaccines can be found on the TGA website (www.tga.gov.au/all-alerts) and HPV adverse events are included in annual national adverse events reports published in *Communicable Diseases Intelligence* (most recent report available at http://www.health.gov.au/internet/main/publishing.nsf/Content/cdi4103-l; previous reports available at www.health.gov.au/internet/main/publishing.nsf/Content/cda-aefi-anrep.htm).

Australia conducts active vaccine safety surveillance for 9vHPV vaccine in vaccinated people across all states and territories using AusVaxSafety. For more information, visit www.ausvaxsafety.org.au.

Concomitant administration with other vaccines

9vHPV vaccine has been assessed in clinical trials when delivered concomitantly (at the same visit but at a separate injection site with a separate syringe) with: reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (dTpa) and quadrivalent meningococcal (A, C, W_{135}, Y) conjugate vaccine (4vMenCV).[55,56] Co-administration was well tolerated and induced a robust immune response to all vaccines.

Interchangeability

9vHPV vaccine can be used to complete an HPV vaccination schedule commenced with either 4vHPV vaccine or 2vHPV vaccine, providing the appropriate minimum intervals are adhered to and recommended dose numbers are given.

Previously administered doses do not need to be repeated, regardless of the time since those doses were administered.

A person who receives 9vHPV vaccine to complete a schedule initiated with either 4vHPV or 2vHPV vaccine should be considered fully protected against the respective vaccine's shared HPV types (i.e. types 6, 11, 16 and 18 for schedules initiated with 4vHPV vaccine;

and types 16 and 18 for schedules initiated with 2vHPV vaccine). However, protection against other vaccine types may be lower than that in those who receive a full schedule using 9vHPV vaccine.

Contraindications/precautions

HPV vaccine should not be given to anyone who has experienced an anaphylactic reaction after a previous dose of the vaccine or to any component of the respective vaccine (including yeast for 9vHPV and 4vHPV vaccines).

HPV vaccine should not be administered during pregnancy. If an HPV vaccine is inadvertently administered during pregnancy, the rest of the vaccination schedule should be deferred until after pregnancy. Females who inadvertently receive a dose of HPV vaccine around the time of conception or during pregnancy should be informed that the scientific evidence suggests there is no harm to the pregnant woman or her fetus. For more information on vaccine safety during pregnancy, see *The Australian Immunisation Handbook* (see www.immunise.health.gov.au).

Other considerations

Cervical screening in women who have been vaccinated

Regular cervical screening tests are still recommended, as per national guidelines under the renewed National Cervical Screening Program, for women who have received HPV vaccine. Screening for women aged 25–74 years is recommended every 5 years (or 2 years after the last Pap test). In sexually active women, the most important preventive intervention against cervical disease remains regular cervical screening. Vaccination is *not* an 'alternative' to cervical screening; together these two approaches provide optimal protection against disease.

The renewed National Cervical Screening Program was implemented on 1 December 2017, and uses the Cervical Screening Test – replacing the former Pap smear-based program. The Cervical Screening Test involves highly accurate HPV testing that has greater sensitivity for the detection of high-grade CIN. The renewed program is predicted to further reduce the incidence and mortality of cervical cancer in Australia. More information about the renewed National Cervical Screening Program, and associated changes, can be found at: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-screening-1.

National HPV Vaccination Program Register (the 'HPV Register')

The HPV Register was established to monitor and evaluate the HPV Vaccination Program. The HPV Register collects data about HPV vaccine doses administered, select demographic data and data on the person who administers the vaccine.

General practitioners and other immunisation providers are strongly encouraged to notify all HPV vaccine doses administered to the HPV Register. This ensures patient records of vaccination are up to date and provides a resource which immunisation providers can check to confirm a patient's vaccination history. The register also sends reminder notices and completion statements to vaccinated persons (or their parents/guardians) and will facilitate notification to the patient if it is ever identified in the future that a booster dose is required. It also ensures accurate coverage statistics are available for program evaluation and monitoring.

Detailed information about the HPV Register can be found at www.hpvregister.org.au.

Responding to questions about HPV vaccine

Please see the NCIRS fact sheet HPV vaccines – frequently asked questions for information to assist providers in answering patient concerns about the vaccine.

Additional resources for primary medical care/vaccination providers

- *The Australian Immunisation Handbook*, 10th edition – the most up-to-date clinical recommendations are contained in the online version of the *Handbook* www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home
- Immunise Australia website www.immunise.health.gov.au

References

1. National Health and Medical Research Council (NHMRC). Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities. Canberra: NHMRC; 2005. Available from: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/wh39.pdf (Accessed 7 March 2018).
2. Barnabas RV, Laukkanen P, Koskela P, et al. Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. *PLoS Medicine* 2006;3:e138.
3. Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology* 2002;13:631-9.
4. Monsonego J, Bosch FX, Coursaget P, et al. Cervical cancer control, priorities and new directions. *International Journal of Cancer* 2004;108:329-33.
5. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. *The Lancet Oncology* 2009;10:321-2.
6. World Health Organization, International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks to humans. Volume 90. Human papillomaviruses. Lyon, France: IARC; 2007. Available from: http://monographs.iarc.fr/ENG/Monographs/vol90/mono90.pdf (Accessed 7 March 2018).
7. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. *Journal of Adolescent Health* 2010;46(4 Suppl):S20-6.
8. de Martel C, Ferlay J, Franceschi S, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *The Lancet Oncology* 2012;13:607-15.
9. Garland SM, Steben M, Sings HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. *Journal of Infectious Diseases* 2009;199:805-14.
10. Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sexually Transmitted Diseases* 2014;41:660-4.
11. Smith JS, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of infection with human papillomavirus in females: a global review. *Journal of Adolescent Health* 2008;43:S5-25.
12. Smith JS, Gilbert PA, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of human papillomavirus infection in males: a global review. *Journal of Adolescent Health* 2011;48:540-52.
13. Winer RL, Feng Q, Hughes JP, et al. Risk of female human papillomavirus acquisition associated with first male sex partner. *Journal of Infectious Diseases* 2008;197:279-82.
14. Brotherton JM, Gertig DM, May C, Chappell G, Saville M. HPV vaccine impact in Australian women: ready for an HPV-based screening program. *Medical Journal of Australia* 2016;204:184-e1.
15. Australian Institute of Health and Welfare. Cervical screening in Australia 2014–2015. Cat. no. CAN 104. Canberra: AIHW; 2017.
16. Brotherton JM, Fridman M, May CL, et al. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *The Lancet* 2011;377:2085-92.
17. Australian Institute of Health and Welfare (AIHW), Australasian Association of Cancer Registries (AACR). Cancer in Australia: an overview, 2008. Cancer series no. 46. Cat. no. CAN 42. Canberra: AIHW; 2008.
18. Whop LJ, Garvey G, Baade P, et al. The first comprehensive report on Indigenous Australian women's inequalities in cervical screening: A retrospective registry cohort study in Queensland, Australia (2000-2011). *Cancer* 2016;122:1560-9.
19. Georgousakis M, Jayasinghe S, Brotherton J, et al. Population-wide vaccination against human papillomavirus in adolescent boys: Australia as a case study. *The Lancet Infectious Diseases* 2012;12:627-34.
20. Grulich AE, Hillman R, Brotherton JM, Fairley CK. Time for a strategic research response to anal cancer. *Sexual Health* 2012;9:628-31.
21. Brotherton JM, Wrede CD. Offering HPV vaccination to women treated for high-grade cervical intra-epithelial neoplasia: what do you need to know? *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2014;54:393-4.
22. Burger EA, Kim JJ, Sy S, Castle PE. Age of Acquiring Causal Human Papillomavirus (HPV) Infections: Leveraging Simulation Models to Explore the Natural History of HPV-induced Cervical Cancer. *Clinical Infectious Diseases* 2017;65:893-9.
23. Brotherton JML, Tabrizi SN, Phillips S, et al. Looking beyond human papillomavirus (HPV) genotype 16 and 18: Defining HPV genotype distribution in cervical cancers in Australia prior to vaccination. *International Journal of Cancer* 2017;141:1576-84.
24. Australian Government Department of Health and Ageing. National Cervical Screening Program. 2018. Available from: http://www.cancerscreening.gov.au/internet/screenin

g/publishing.nsf/Content/cervical-screening-1 (Accessed 20/2/2018).

25. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *The Lancet Oncology* 2005;6:271-8.
26. Harper DM, Franco EL, Wheeler CM, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *The Lancet* 2006;367:1247-55.
27. US Food and Drug Administration (FDA). Vaccines and Related Biological Products Advisory Committee meeting, May 18, 2006. Briefing information. 2006. Available from: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm (Accessed 7 March 2018).
28. Iversen OE, Miranda MJ, Ulied A, et al. Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. *JAMA* 2016;316:2411-21.
29. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *New England Journal of Medicine* 2015;372:711-23.
30. Garland SM, Cheung TH, McNeill S, et al. Safety and immunogenicity of a 9-valent HPV vaccine in females 12-26 years of age who previously received the quadrivalent HPV vaccine. *Vaccine* 2015;33:6855-64.
31. Huh WK, Joura EA, Giuliano AR, et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *The Lancet* 2017;390:2143-59.
32. Petersen LK, Restrepo J, Moreira ED, Jr., et al. Impact of baseline covariates on the immunogenicity of the 9-valent HPV vaccine - A combined analysis of five phase III clinical trials. *Papillomavirus Res* 2017;3:105-15.
33. Dobson SR, McNeil S, Dionne M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. *JAMA* 2013;309:1793-802.
34. Romanowski B, de Borba PC, Naud PS, et al. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine: analysis of a randomised placebo-controlled trial up to 6.4 years. *The Lancet* 2009;374:1975-85.
35. Puthanakit T, Huang LM, Chiu CH, et al. Randomized Open Trial Comparing 2-Dose Regimens of the Human Papillomavirus 16/18 AS04-Adjuvanted Vaccine in Girls Aged 9-14 Years Versus a 3-Dose Regimen in Women Aged 15-25 Years. *Journal of Infectious Diseases* 2016;214:525-36.
36. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New England Journal of Medicine* 2007;356:1928-43.
37. FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *The Lancet* 2007;369:1861-8.
38. Castellsague X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine* 2015;33:6892-901.
39. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males. [erratum appears in N Engl J Med 2011 Apr 14;364(15):1481]. *New England Journal of Medicine* 2011;364:401-11.
40. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New England Journal of Medicine* 2007;356:1915-27.
41. Hildesheim A, Herrero R, Wacholder S, et al. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: a randomized trial. *JAMA* 2007;298:743-53.
42. Das R, Saah A, Iversen OE. Effectiveness, immunogenicity, and safety of Gardasil™ in pre-adolescents and adolescents – 10 years of follow-up [abstract 13-03]. Eurogin 2016; June 2016; Salzburg, Austria.
43. Lehtinen M, Lagheden C, Luostarinen T, et al. Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point–registry-based follow-up of three cohorts from randomized trials. *BMJ Open* 2017;7:e015867.
44. Van Damme P, Olsson SE, Block S, et al. Immunogenicity and safety of a 9-valent HPV vaccine. *Pediatrics* 2015;136:e28-39.
45. Guevara A, Cabello R, Woelber L, et al. Antibody persistence and evidence of immune memory at 5years following administration of the 9-valent HPV vaccine. *Vaccine* 2017;35:5050-7.
46. Brotherton JML, Bloem PN. Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage. *Best Pract Res Clin Obstet Gynaecol* 2018;47:42-58.
47. World Health Organization (WHO). Meeting of the Global Advisory Committee on Vaccine Safety, 7–8 June 2017. *Weekly Epidemiological Record* 2017;92:393-402.

48. Macartney KK, Chiu C, Georgousakis M, Brotherton JM. Safety of human papillomavirus vaccines: a review. *Drug Safety* 2013;36:393-412.

49. Moreira ED, Jr., Block SL, Ferris D, et al. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. *Pediatrics* 2016;138.

50. Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of Human Papillomavirus Vaccines: An Updated Review. *Drug Safety* 2017.

51. Costa APF, Cobucci RNO, da Silva JM, et al. Safety of Human Papillomavirus 9-Valent Vaccine: A Meta-Analysis of Randomized Trials. *J Immunol Res* 2017;2017:3736201.

52. Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. *BMC Infectious Diseases* 2011;11:13.

53. Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. *CMAJ Canadian Medical Association Journal* 2007;177:469-79.

54. World Health Organization (WHO). Global Advisory Committee on Vaccine Safety, 2–3 December 2015. *Weekly Epidemiological Record* 2016;91:21-31.

55. Kosalaraksa P, Mehlsen J, Vesikari T, et al. An open-label, randomized study of a 9-valent human papillomavirus vaccine given concomitantly with diphtheria, tetanus, pertussis and poliomyelitis vaccines to healthy adolescents 11-15 years of age. *Pediatric Infectious Disease Journal* 2015;34:627-34.

56. Schilling A, Parra MM, Gutierrez M, et al. Coadministration of a 9-valent human papillomavirus vaccine with meningococcal and Tdap vaccines. *Pediatrics* 2015;136:e563-72.