FactSheet

ncirs NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

HPV VACCINES

FREQUENTLY ASKED QUESTIONS

This fact sheet provides responses to common patient questions and concerns about human papillomavirus (HPV) and the HPV vaccines and vaccination. There is misleading information about HPV vaccines on the Internet and social media. Immunisation providers and the public should be cautioned to check that they obtain information from reliable and trusted sources. More detailed information about HPV and HPV vaccines can be found in the NCIRS fact sheet Human papillomavirus (HPV) vaccines for Australians: information for immunisation providers.

Questions about new changes to the HPV vaccine and vaccination schedule

- Q1. Why has the vaccine been replaced in Australia? What is different about the new 9vHPV vaccine?
- Q2. Why has the schedule changed for those aged less than 15 years?
- Q3. Why is a three-dose schedule still recommended for those aged 15 years or older and for people with immunocompromising conditions?
- Q4. How will these changes affect people who have started but not finished a HPV vaccination schedule?
- Q5. Will those who received the previous 4vHPV vaccine need to be vaccinated again?

Questions about HPV vaccine safety

- Q6. How do we know HPV vaccines are safe?
- Q7. I've read that the ingredients in the HPV vaccine cause autoimmune diseases. Is that true?
- Q8. I've heard that HPV vaccines trigger a range of rare but serious conditions, such as POF, POTS and CRPS. Is that true?
- Q9. Do HPV vaccines cause fainting?
- Q10. How do we know the vaccines won't cause cancer? Surely if HPV can, a vaccine based on it might too?
- Q11. I've heard HPV vaccines could cause infertility. Is that true?
- Q12. Is it safe to get a vaccine when pregnant?
- Q13. I've heard that it is a genetically modified vaccine. Is that true?

Questions about HPV and HPV vaccines in general

- Q14. Is a vaccine really needed if only a small proportion of HPV infections lead to cancer?
- Q15. I've heard there are many HPV types that can infect people, but the vaccine only protects against nine. Can I still get cancer caused by HPV even if I am vaccinated?
- Q16. Is it true that the risk of cervical cancer in Australia is really low, even without vaccination?
- Q17. I thought HPV vaccine prevents against cervical cancer. Why is it being offered to boys too?
- Q18. Will other HPV types replace those we vaccinate against?

Questions about HPV vaccine efficacy and impact

- Q19. Isn't leading a healthy lifestyle enough to prevent cancer?
- Q20. I've heard the vaccine doesn't work if you're already sexually active. Is that true?
- Q21. How do we know the vaccine will prevent cancers caused by HPV when cancer takes years to develop?
- Q22. Are there reductions in HPV disease in Australia since vaccination was introduced in 2007?

Other issues

- Q23. If all the trials were sponsored by the vaccine manufacturer, can we trust their data?
- Q24. Why is there information on the Internet and social media saying the vaccines are dangerous if it isn't?
- Q25. Could receiving HPV vaccine make my daughter or son promiscuous?

Questions about new changes to the HPV vaccine and vaccination schedule

Q1. Why has the HPV vaccine been replaced in Australia? What is different about the new vaccine?

There are many HPV virus types, some of which are considered to be 'high-risk' because infection with these types is associated with the development of cancer (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68),[1] and some of which are 'low-risk' because they result in less serious disease like genital warts (HPV types 6 and 11).[2] The high-risk HPV types can cause a variety of cancers in both males and females, including cancers of the vagina, cervix, anus, penis and head and neck.[3] In unvaccinated people in Australia, HPV types 16 and 18 account for about 77% of HPV-positive cervical cancers, and HPV types 31, 33, 45, 52 and 58 for another 15%.[4]

There are currently three HPV vaccines registered for use in Australia: bivalent (2vHPV) vaccine Cervarix®; quadrivalent (4vHPV) vaccine Gardasil®; and nonavalent (9vHPV) vaccine Gardasil®9. Each vaccine protects a person against infection from its target HPV types. The new 9vHPV vaccine, available in Australia since early 2018, protects against all the 4vHPV types **plus** an additional five high-risk HPV types, 31, 33, 45, 52 and 58.

Since the National HPV Vaccination Program began in Australia in 2007, the use of the 4vHPV vaccine has resulted in drastic declines in rates of infection, pre-cancerous lesions and genital warts in the vaccinated cohorts.[5-7] Switching to the 9vHPV vaccine will provide protection against additional HPV virus types,[8] and will extend the protection of Australians against HPV infection and HPV-related disease.

Q2. Why has the schedule changed for those aged less than 15 years?

The vaccination schedule for the National HPV Vaccination Program's target age cohort, adolescents aged 12–13 years, has changed from a 3-dose to a 2-dose schedule. Since the commencement of the program in 2007, several studies have demonstrated that the antibody response to a 2-dose HPV vaccination schedule in younger adolescents (with the 2 doses given 6–12 months apart in individuals <15 years of age) is comparable to a 3-dose schedule in women aged 15–26 years (in whom clinical protection in clinical trials has been demonstrated).[9-11]

This new schedule will provide the same protection with the added advantages of a reduced number of injections and reduced demand for resources for school-based vaccination programs.

Q3. Why is a three-dose schedule still recommended for those aged 15 years or older and for people with immunocompromising conditions?

There is currently insufficient evidence to support a change to a 2-dose schedule for people aged 15 years and older and for immunocompromised individuals of any age. People in these groups should still receive a 3-dose HPV vaccination schedule for adequate protection.

Q4. How will these changes affect people who have started but not finished HPV vaccination?

Irrespective of which of the three HPV vaccines (2vHPV, 4vHPV or 9vHPV) a person has started vaccination with, 9vHPV vaccine can be used to complete any ongoing HPV vaccination schedule. A person completing a HPV vaccination schedule with 9vHPV vaccine, who started with either 4vHPV or 2vHPV vaccine, will be considered fully protected against the respective vaccine's shared HPV types. Because 9vHPV vaccine shares protection against HPV types 16 and 18, which are the greatest public health concern, mixed schedules are considered to be adequate, provided appropriate minimum intervals and dose requirements are met. See *The Australian Immunisation Handbook* (AIH).

Any person who has previously begun HPV vaccination before the age of 15 years, but not completed their schedule, can complete vaccination with only 2 doses of HPV vaccine, provided the 2nd dose is received at least 5 months after their 1st dose. For persons who commenced HPV vaccination aged 15 years or older, 3 doses of HPV vaccine are required. If any scheduled doses have been missed, earlier doses should not be repeated. While there are no upper limits on the receipt of the 2nd dose for those who commenced vaccination before the age of 15 years, timely completion of vaccination should be prioritised.

Q5. Will people who received the bivalent or quadrivalent vaccine need to be vaccinated again with the new vaccine?

Any person who has previously completed a 3-dose or a 2-dose schedule (provided that the age and dose requirements were met [**see AIH]**) of any registered HPV vaccine in Australia is considered to be adequately protected and will not require any further doses of HPV vaccine. All registered HPV vaccines in Australia protect against the most prevalent cancer-causing HPV types, 16 and 18.

Re-vaccination with the 9vHPV vaccine is neither routinely recommended nor funded under the National Immunisation Program for those who have previously completed a HPV vaccination schedule with either 4vHPV vaccine or 2vHPV vaccine. However, research on the receipt of additional doses of 9vHPV vaccine in those who have completed HPV vaccination has demonstrated that it is safe.[12]

If seeking to re-vaccinate with the 9vHPV vaccine to extend a person's protection against the additional HPV types unique to the 9vHPV vaccine, a number of factors should be considered. The biggest predictor of exposure to HPV viruses is sexual activity and number of sexual partners; therefore, timing of sexual debut following any previous vaccination should be considered.[13] It has been estimated that of the HPV infections that cause cervical cancer in women, 50% have been acquired by age 20 and 75% by age 30.[14] This shows a decreasing potential for benefit from HPV immunisation with increasing age. While very rarely serious and usually minor in nature, any decision to re-vaccinate should also consider the potential for adverse events following immunisation. Overall, the incremental benefits of re-vaccinating to extend protection are likely to be marginal in older people and/or those who are sexually active.

Questions about HPV vaccine safety

Q6. How do we know HPV vaccines are safe?

Overall, the HPV vaccines have an excellent safety profile, similar to that for other vaccines routinely used in the National Immunisation Program. Monitoring done around the world in millions of people across many countries has found no credible evidence that there is any illness that occurs more frequently among people who have had HPV vaccine compared to those who have not.[15,16] The HPV vaccine trials for Gardasil®9, Gardasil® and Cervarix® which provided data for registration of the vaccine involved many tens of thousands of people worldwide. The trials have been evaluated by many expert groups, including the Food and Drug Administration (FDA) in the USA and the Therapeutic Goods Administration (TGA) in Australia, all of which have concluded that the vaccines are safe and effective. According to the World Health Organization (WHO), to date over 270 million doses of the vaccine have been distributed worldwide, with many countries monitoring vaccine safety post-licensure (i.e. after the vaccine is in use).[17]

Clinical trials have shown that the 9vHPV vaccine is safe and there are no significant concerns regarding its safety in Australia. Studies have showed that the 9vHPV vaccine has a similar safety profile to that of the 4vHPV vaccine and that it is generally well tolerated in adolescent girls and boys as well as women and men.[18-23] Across multiple trials of

the 9vHPV vaccine in adolescents involving over 15,000 participants, the most common side effect was minor reactions at the injection site (pain, redness and swelling), which occurred in about 90% of recipients.[15] These injection site reactions occur with a slightly higher frequency with the 9vHPV vaccine compared to that with the 4vHPV vaccine, and this is likely associated with the increased concentration of ingredients present in the 9vHPV vaccine. In some people, fainting, or related symptoms such as dizziness, can be triggered in response to painful stimuli such as vaccination; however, this can be avoided with appropriate care (***see* Q9**).[17] Research shows that the 9vHPV vaccine can be safely administered with other vaccines often given to adolescents, including meningococcal and diphtheria-tetanus-pertussis vaccines.[24,25]

Ongoing, in-depth follow-up in women and men vaccinated in the clinical trials is continuing to monitor the duration of vaccine effectiveness and to confirm safety over longer periods of time. Post-licensure safety monitoring is also ongoing, particularly through passive reporting systems which allow all healthcare professionals and members of the public to report any suspected adverse events following vaccination.[26] (***see also* Q7 *and* Q8**). More detailed information of reported reaction rates are published each year by the National Centre for Immunisation Research and Surveillance (NCIRS) and TGA (www.health.gov.au/internet/main/publishing.nsf/Content/cda-aefi-anrep.htm). The safety of HPV vaccine is monitored through AusVaxSafety, Australia's active vaccine safety surveillance system (www.ausvaxsafety.org.au). Injection site reactions, including pain, are known to occur following administration of HPV vaccines, and the current reported event rates are consistent with what are expected according to the existing data.

The only contraindication to vaccination with Gardasil® and Gardasil®9 is known anaphylaxis (severe allergic reaction) to yeast or severe allergy to any other vaccine ingredient(s). As with any medication, there is always a small risk of an allergic reaction (anaphylaxis) following administration. Although these events are rare, all patients should be observed for 15 minutes after vaccination.

Q7. I've read that the ingredients in the HPV vaccine cause autoimmune diseases. Is that true?

Like many other vaccines, HPV vaccines contain an adjuvant. Adjuvants are substances added to vaccines to improve the immune response to the part of the vaccine that mimics the pathogen. The adjuvant in 9vHPV and 4vHPV vaccines is an aluminium adjuvant. Some people have raised concerns that aluminium adjuvants cause autoimmune disease. However, aluminium-containing adjuvants have been around for more than 50 years and are widely used in human vaccines. Much larger amounts of aluminium are taken into the body through other means, such as food, than through vaccines. There is no evidence that aluminium in vaccines results in any serious or long-term adverse events, including autoimmune diseases.[27,28] Similarly, the adjuvant used in the other HPV vaccine registered in Australia, the 2vHPV vaccine (Cervarix®), has a unique adjuvant, ASO4, which contains aluminium in the form of aluminium hydroxide, combined with another compound called monophosphoryl lipid A. No association has been found between ASO4-containing vaccines (including Cervarix®) and autoimmune conditions.[29,30]

Evidence from clinical trials and post-licensure studies of the 4vHPV vaccine shows no link between the vaccine and autoimmune diseases.[18,22] An analysis of several early and pivotal trials, involving a total of more than 20,000 girls and women aged 9–26 years and about 1,350 boys aged 9–16 years, found that the overall proportion of participants who reported new onset autoimmune conditions was similar among those who got the vaccine and those who got a placebo (2.4% of people in each group). Post-licensure epidemiological studies have not identified any association between HPV vaccination and autoimmune conditions including multiple sclerosis and type 1 diabetes.

A 2015 French study in over 2 million girls also showed no link with many of these conditions, but suggested a possible very small risk (approximately 1 in 100,000 girls vaccinated) of Guillain-Barré syndrome (GBS), a disease that causes inflammation of nerves and results in generalised muscle weakness, and for which the cause is usually unknown. However, a relationship between HPV vaccination and GBS has not been observed in any other well-conducted studies.[17] There is ongoing research to monitor if there is any increased risk of GBS after HPV vaccine. Providers and the public should remember that the benefits of vaccination far outweigh any small theoretical risk.

Q8. I've heard that the HPV vaccine triggers a range of rare but serious conditions, such as POF, POTS and CRPS. Is that true?

There have been case reports hypothesising that a range of rare and poorly understood conditions, such as premature ovarian failure (POF), postural orthostatic tachycardia syndrome (POTS) and complex regional pain syndrome (CRPS), could be induced by HPV vaccines. These reports lack scientific and epidemiological credibility and do not provide sufficient evidence to suggest a causal link between the vaccine and these illnesses. One country, Japan, has suspended promotion of the use of HPV vaccine, despite an expert Japanese committee and all respected scientific groups worldwide finding no evidence that the vaccine is responsible for causing these conditions.

POF, also known as premature menopause, occurs when the menstruation cycle ceases before the age of 40, and in up to 90% of cases, the cause is unknown. It has recently been suggested that the HPV vaccine may be a cause, based on some reports of teenage girls in Australia and America presenting with POF-like symptoms after receiving the HPV vaccine. However, because many girls have received HPV vaccine and POF has long been known to occur in females who have not been vaccinated, these few cases do not show an increase in POF or prove a link to the vaccine. Complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) are conditions which have been detailed in multiple case reports regarding HPV vaccination. CRPS involves chronic pain typically following often minor trauma or injury,[31] and POTS involves substantial, sustained increase in heart rate when moving from lying to sitting.[16] Both conditions are thought to be caused by a variety of known and unknown factors and are diagnostically challenging with onset difficult to determine and symptoms often overlapping with other conditions. There is no evidence to support HPV vaccine being a particular trigger of CRPS over and above that rarely seen for any other painful stimuli. Similarly, POTS occurs irrespective of vaccination, and pre-clinical and clinical studies have found no evidence or basis to suggest a causative relationship between POTS and HPV vaccination.[32]

Overall, there is no strong scientific or epidemiological evidence to suggest that the HPV vaccines can induce POF, POTS or CRPS. These diseases of unclear aetiology, unfortunately, do occur in adolescents and young people, whether they are vaccinated or unvaccinated, and there is no evidence that they occur more frequently in HPV vaccinated populations.[15,21,32-35]

Over 270 million HPV vaccine doses have been administered worldwide and the vaccine has been shown to have an excellent safety profile.[17] Evidence from surveillance systems and follow-up studies have not indicated that these illnesses are occurring more frequently in vaccinated people than in unvaccinated people. The Global Advisory Committee on Vaccine Safety of the WHO has reviewed HPV vaccines seven times – most recently in 2017 – and continues to endorse their safety.[17] In addition, the Centers for Disease Control and Prevention (CDC) in the USA, the Australian Technical Advisory Group on Immunisation (ATAGI) and many other experts continue to recommend that HPV vaccine be administered and promoted to prevent HPV-related disease and deaths.

Q9. Does the vaccine cause fainting?

Some people who receive an injection of any kind do faint or have other symptoms associated with fainting, such as headache or feeling weak, nauseous and/or dizzy. Others may become very anxious due to fear of needles and/or the responses of others around them who are being vaccinated (e.g. in school-based clinics). These reactions are more common in adolescents and young people, independent of whether a vaccine is being given. Although sometimes distressing, these symptoms usually resolve with simple treatment such as lying down, adequate food and drink intake, and reassurance. When administering the vaccine, it is important to make sure patients have eaten properly before vaccination and are observed for 15 minutes afterwards.[36]

In May 2007, media reports publicised that a group of school girls in Melbourne became unwell after being vaccinated.[37] These girls all recovered. Their symptoms were attributed by treating medical staff to fainting and anxiety/stress reactions.

Q10. How do we know the vaccine won't cause cancer? Surely if HPV can, a vaccine based on it might too?

None of the HPV vaccines registered in Australia can cause cancer. The viral proteins which can disrupt normal cell growth and repair mechanisms and ultimately result in cancer are well described in the scientific literature.[38-40] They are not contained in the HPV vaccines.

HPV vaccines are made using recombinant DNA technology and contain only 'virus-like particles' (***see*** **Q13**). The vaccines contain only proteins from the outer coat of the virus, with no viral DNA. It is not a live virus, and is not infectious.

Q11. I've heard the vaccine could cause infertility. Is that true?

No. There is no biologically plausible way in which the vaccine could cause infertility in either women or men. HPV infection, unlike some other sexually transmitted infections such as chlamydia, is not a cause of infertility. Studies of high doses of the vaccine in female and male rats showed no effect on fertility.[41,42]

Some Internet sites report disturbing claims that one ingredient of the vaccine, polysorbate 80, causes infertility in rats. This is based on one study of newborn rats (weighing 10–17 grams) given extremely large doses (20–200 times the amount in Gardasil®) injected into the abdomen.[43] However, the TGA has reviewed available data regarding polysorbate 80 and fertility and concluded that there is no evidence that polysorbate 80 at a level of 50 µg per 0.5 mL dose of Gardasil® poses a hazard to human reproduction or fertility. Polysorbate 80 is used as an emulsifier and is found in numerous medications, including other vaccines, and is used as a food additive and in cosmetics.

Providers and the public should be aware that false scares about vaccines leading to infertility are sometimes used to disrupt immunisation campaigns. For example, scare campaigns in Nigeria in 2003 about the polio vaccine leading to infertility resulted in reduced vaccine uptake and consequent polio outbreaks.[44]

Q12. Is it safe to get the vaccine when pregnant?

Although it is recommended that HPV vaccination be avoided during pregnancy, there is no indication that inadvertent administration of the vaccine to a pregnant woman will result in an increased risk of adverse pregnancy outcomes. The rate of adverse pregnancy outcomes has been shown to be similar in 4vHPV vaccine and placebo recipients. In particular, there was no evidence of an impact on spontaneous abortion rates, foetal deaths or number of live births. Congenital anomalies were rare and the types of anomalies that occurred in both groups were consistent with those generally observed in pregnancies in women in the 16–26 years age group.[45]

Post-licensure surveillance of HPV vaccination during pregnancy has also been reviewed using pregnancy registries established by the vaccine manufacturers. Data from the Gardasil® registry are published and do not indicate any issues or new safety signals.[46]

Women who wish to conceive following a course of Gardasil® are able to commence trying to fall pregnant immediately following the third dose, as the vaccine is not a live virus.

For women who fall pregnant before completing the 3-dose vaccine schedule, the schedule can safely be resumed following pregnancy. As with other vaccines, there is no need to recommence the vaccine schedule from the 1st dose.

Q13. I've heard that it is a genetically modified vaccine. Is that true?

No, none of the HPV vaccines contain viral DNA and they cannot 'interact' with your DNA. HPV vaccines are made using recombinant DNA technology which means they contain very pure protein rather than killed or live viruses. Hepatitis B vaccine is made using similar technology.

The technique of producing the protein found in the coat of the virus, which then naturally self-assembles into 'virus-like particles' (VLPs), was first discovered by Professor Ian Frazer and colleagues in Brisbane.[47] Prior to this discovery, all attempts to create a vaccine against HPV had proven unsuccessful. The genetic code (or instructions) to make the protein of the viral coat is inserted into either a yeast (for Gardasil®9 and Gardasil®) or an insect cell (for Cervarix®). The yeast or insect cell then makes the protein which assembles itself into VLPs which have the same shape (a sphere) as HPV but contain no viral DNA.

Questions about HPV and HPV vaccines in general

Q14. Is the vaccine really needed if only a small proportion of HPV infections lead to cancer?

It is estimated that 3–10% of HPV infections persist for long periods which can lead to the development of pre-cancerous abnormalities. In most cases, the pre-cancerous lesions disappear on their own over time; however, in some cases they progress to cause cancer. Although only a small *proportion* of HPV infections result in disease, many people still develop cellular abnormalities and cancers because HPV infections are so common in the population.

Prior to HPV vaccination, every year Pap screening in Australia detected low-grade cervical abnormalities in about 90,000 women and high-grade cervical abnormalities in a further 15,000 women. Although screening is in place to detect these pre-cancerous lesions, it was estimated that in 2017 there would still be 912 cases (which translates to a rate of 7.3 per 100,000 women) and 254 deaths due to cervical cancer.[48]

Apart from the cervix, HPV is also associated with cancers of several other body sites in both women and men.[49-51] In 2013, 225 Australian women and 160 Australian men were diagnosed with anal cancer,[48] of which approximately 85% of cases are caused by HPV.[50] In addition, about 600 new cases of cancer of the mouth and throat are detected every year in Australia, of which HPV causes about 60%. It is important to note that most of these cancers would have arisen from HPV infections that were acquired prior to the availability of vaccination.

The advantage of vaccination is that it *prevents* infections with the HPV types that are included in the vaccine and, therefore, also prevents the development of the pre-cancerous lesions and cancer that these infections may cause. While screening is effective, it will only detect HPV infection once it has already developed. When HPV vaccine is given prior to HPV exposure, vaccination is highly effective (in males and females) in preventing persistent infection with the HPV types included in the vaccine. In the years since the HPV vaccination program was introduced in Australia in 2007, reductions in lesions caused by HPV are already being recorded (***see* Q20 and Q21**).[52]

Q15. I've heard there are many HPV types that can infect people, but the vaccine used in Australia only protects against nine. Can I still get cancer caused by HPV even if I am vaccinated?

There are 40 known HPV types which can infect the mucosal surfaces of humans and potentially cause disease. The HPV types included in the 9vHPV vaccine (Gardasil®9) were specifically chosen because they are the types which are most commonly associated with cancers (HPV types 16, 18, 31, 33, 45, 52 and 58) or non-cancerous lesions such as genital warts (HPV types 6 and 11).[8,53] For example, an Australian study looking at HPV types found that in cases of HPV-positive cervical cancers, HPV types 16 and 18 were detected in 77% of cases and around another 15% were types 31, 33, 45, 52 and 58.[4] In other cancers caused by HPV that occur in males and females, such as anal cancer, HPV types 16 and 18 are found in approximately 85%. HPV types 6 and 11 are not commonly detected in cancers; however, they are responsible for nearly all cases of genital warts in males and females.[50]

Although the 9vHPV vaccine protects against the HPV types which most commonly cause serious disease, some of the HPV types not included in the vaccine can still cause cancer. It is for this reason that it is still important that women over the age of 18 years undergo regular cervical screening, as per national guidelines under the renewed National Cervical Screening Program. Screening for women aged 25–74 years is recommended every 5 years (or 2 years after the last Pap test).

More information about the changes to the National Cervical Screening Program can be found at www.cancerscreening.gov.au.

Q16. Is it true that the risk of cervical cancer in Australia is really low, even without vaccination?

Due to the very successful cervical screening program in Australia, mortality due to cervical cancer is one of the lowest in the world (1.9 deaths per 100,000 women in 2014).[48] However, the likelihood of a woman who lives up to 85 years of age dying of cervical cancer is 1 in 496. The highest mortality rate due to cervical cancer in Australia is among women who are unscreened or under-screened. Although screening prevents a large majority of cervical cancers, prior to the introduction of the HPV vaccination program it was estimated that nearly 560 cervical cancers per year were preventable by HPV vaccines that covered HPV types 16 and 18.[50] In addition, Pap screening identified pre-cancerous

lesions due to vaccine HPV types in tens of thousands of women each year. These women then had to undergo further tests and sometimes treatment (such as surgery) to remove the lesions to prevent development of cancer. It is predicted that the renewed National Cervical Screening Program, which began in December 2017, will reduce the incidence of cervical cancer by up to another 30%.[54]

HPV vaccination is a preventive healthcare measure to be used in conjunction with the current cervical screening program. As vaccination prevents infection with the most common HPV types associated with cancer, it means that, for these types, the initial persistent infection, and the subsequent progression to pre-cancerous lesions and then cancer, doesn't occur at all (***see*** **Q14**). Due to the lead time of several years from HPV infection to development of cervical cancer, the impact of HPV vaccine on cancer incidence is not expected to be observed for decades after program introduction. However, studies have demonstrated a substantial reduction in the incidence of cervical pre-cancerous lesions in young vaccine-eligible women.[48,55,56] Although vaccination reduces the risk of pre-cancerous lesions being detected and requiring invasive treatment, vaccination does not protect against all HPV types, so screening is still required for vaccinated women.

In addition to reducing the risk of cervical cancer, HPV vaccination protects against HPV infections and associated disease in other sites, such as the anus, vulva, vagina, penis, and head and neck (***see*** **Q17**). There are no screening programs in place to detect cancers at these sites.

Q17. I thought HPV vaccine prevents against cervical cancer. Why is it offered to boys too?

Cervical cancer is the most common HPV-associated cancer worldwide, so the majority of HPV research has been focused on understanding the role of HPV in causing that cancer type specifically. Because HPV vaccine development was initially focused on preventing cervical cancer, the first clinical trials involved only girls and women. However, as research has continued, much more is now known about the role of HPV in causing other cancers that affect men (such as penile cancer) and both men and women (such as head, neck and anal cancers).[50] (***see*** **Q14**)

A major clinical trial of the 4vHPV vaccine in males 16–26 years of age showed the vaccine prevented more than 85% of persistent anogenital infections and external genital lesions (primarily genital warts) due to vaccine HPV types among participants not already infected by those types.[57] Immunogenicity of the 9vHPV vaccine in adolescent boys aged 9–14 years and men aged 16–26 years has been shown to be non-inferior to that in women aged 16–26 years, in whom vaccine efficacy has been demonstrated.[9,23]

Not only will HPV vaccination help prevent HPV infection and associated diseases in individual males, but research suggests vaccinating boys will contribute to increasing protection against HPV in girls due to 'community (herd) immunity'.[58]

Q18. Will other HPV types replace those we vaccinate against?

Virological studies of HPV indicate that there is very little, if any, interaction between virus types, that is, they don't compete with each other.[59] HPV16 appears to be unique in terms of its propensity to cause disease. Therefore, it is unlikely that other HPV types will replace the cancer-causing types 16, 18, 31, 33, 45, 52 and 58 if infection with these types is prevented through vaccination. The types of HPV infection occurring over time in Australia are being closely monitored.

Although it is unlikely that there will be 'replacement disease' following the prevention of HPV type 16, 18, 31, 33, 45, 52 and 58 infection, we will still see disease from the remainder of the 40 or so HPV types that cause disease. This is why continuing to have cervical screening is important (***see*** **Q15**).

Questions about HPV vaccine efficacy and impact

Q19. Isn't leading a healthy lifestyle enough to prevent cancer?

Although there is evidence that a healthy diet and exercise can help protect against certain other cancers, such as bowel cancer, there is no definitive evidence that these factors will protect against cancers associated with HPV. The only way to ensure protection from infection with HPV (which is the necessary first step in the cancer development process) is to

remain completely sexually abstinent. Although the risk of acquiring HPV infection increases with the number of sexual contacts, even having only one partner who is infected can result in getting an HPV infection and HPV-related cancer.[13,60] Most people with a current HPV infection do not display any symptoms or signs – that is, you can't tell if you or your partner has the virus. Similarly, if infected, there is no way to ensure or know if the body's immune system will be able to clear the virus on its own or if that infection is silently progressing to cancerous changes.

Factors which have been shown to increase a person's risk of persistent HPV infection, and thus of developing related cancers, include:

- genetic factors[61,62]
- smoking[63,64]
- the presence of a co-infection with other sexually transmitted infections, such as herpes or chlamydia
- whether there is severe immune suppression, such as HIV infection.[65]

Other factors that increase the risk for cervical cancer in particular include having had a very large number of births (seven or more) and long-term oral contraceptive use.[66]

A person may be able to reduce their risk of HPV infection somewhat by consistent condom use, but it should be emphasised that HPV can be transferred via contact between genital and mucosal surfaces that are not covered by the condom.

Q20. I've heard the vaccine doesn't work if you get it after you've already become sexually active. Is that true?

For HPV vaccine to work, it *must* be given before a person comes in contact with HPV viruses. As HPV infection is commonly transmitted during sexual activity, HPV infection rates are highest in young people[14,67] (***see*** **Q5**). Because of this, the best time to vaccinate is in early adolescence before exposure to HPV. In addition, younger adolescents respond better to the vaccine: those who receive their first HPV vaccine dose when aged 9–14 years develop higher levels of HPV antibodies than older adolescents.[9]

If the vaccine is given to people who are already sexually active, there is a higher chance they would have already been exposed to one or more of the vaccine HPV types and, in turn, the benefit of the vaccine will be reduced. This has been demonstrated in clinical trials of HPV vaccines. In women aged 16–26 years who had not yet been infected with any vaccine HPV types, vaccination prevented more than 98% of high-grade cervical lesions (CIN2 or worse) associated with those types. However, when all women enrolled in these trials were considered (including those who were already infected with any HPV type), protection for the whole group was lower at only 52%.[68]

Q21. How do we know the vaccine will prevent cancers caused by HPV when cancer takes years to develop?

Although most HPV infections are cleared by the body naturally and never result in cancer, if an HPV infection persists the virus can eventually integrate into cells and prevent them from repairing themselves normally, causing pre-cancerous lesions. Over time, a proportion of these pre-cancerous lesions can progress into cancer.[69] So, while not all HPV infections cause cancer, infection is the necessary first step for the development of cervical and other HPV-related cancers. Although other factors may be important in determining progression to cancer (***see*** **Q22**), cancer does not occur without HPV infection.

Because of the long time it takes for cancer to develop, HPV vaccine trials needed to assess the efficacy of the HPV vaccine against the early stages of the disease process (i.e. 'surrogate' outcomes), rather than cancer as the end result.[70] These surrogate outcomes included the vaccine's ability to prevent an initial HPV infection, as well as pre-cancerous lesions. In coming decades studies will be able to show how the vaccine reduces actual cancers.

In clinical trials, HPV vaccination has been shown to prevent cervical, penile and anal infections due to the vaccine HPV types.[23,57,71] More importantly, the vaccines were also highly effective (90 to 100%) in preventing the step closer to cancer: pre-cancerous lesions caused by HPV.[72] This outcome is taken as the most practical measure of the success of vaccination over time. This is accepted in much the same way that detection and removal of such lesions in the cervix,

through cervical screening programs, is accepted as a means to reduce cervical cancer. Surveillance data have shown substantial reductions in high-grade pre-cancerous cervical lesions in women eligible to receive HPV vaccination in Australia (***see*** **Q21**).[6,56]

Q22. Are there reductions in HPV disease in Australia since vaccination was introduced in 2007?

Data are already showing that since the Australian HPV vaccination program commenced in April 2007, there has been an overall decline in HPV disease in females and males.[7,56,73] For example, the number of high-grade pre-cancerous lesions detected in 20–24-year-old women has dropped from 18.1 per 1,000 women screened in 2007 to 13.5 per 1,000 women in 2013.[52] This decline will be reflected in declines in cervical cancer in the coming decades.

In addition, reductions in HPV infection and HPV genital warts are being recorded in Australian females and males. One study has demonstrated a near disappearance of genital warts among young women <21 years of age (eligible for vaccine) since the introduction of the vaccine.[7]

There has been a significant decline in new genital wart diagnoses observed in heterosexual males of the same age as the girls targeted by the HPV vaccination program. However, there has been no significant reduction in new cases of genital warts reported by men who have sex with men which suggests they get limited benefit from the female program.[74]

As cancer can take many decades to develop after an initial HPV infection, definitive evidence of a reduction in the incidence of cervical cancer resulting from the HPV vaccination program is expected in years to come (***see*** **Q20**).

Other issues

Q23. If all the trials were sponsored by the vaccine manufacturer, can we trust their data?

There are many processes in place to ensure the integrity of the data presented by manufacturers of vaccines.[75] The regulatory requirements for vaccines are very stringent. Prior to undertaking vaccine trials, manufacturers consult large regulatory agencies, such as the Food and Drug Administration (FDA) in the USA, to ensure that all required information is collected and presented.

Trials are conducted by academic research organisations, rather than by the sponsor company themselves, requiring approval from independent ethics committees. To reduce bias, all key trials of Gardasil®9 were conducted in a blinded, randomised fashion which means that neither the participant nor the doctor/study personnel knew who had received the active vaccine. In addition, trials are overseen by independent safety panels that are also blinded.

Results from clinical trials submitted to scientific journals for publication are subject to ‘peer review’. This means that the results are independently scrutinised by experts in the field prior to publication.

Before vaccines are licensed for use, regulatory authorities request specific data from the manufacturers and conduct their own analyses of the trial data. In Australia, the TGA evaluates the safety and efficacy of the vaccine in detail before recommending that it be registered for use.

Once a vaccine is registered, the Australian Technical Advisory Group on Immunisation (ATAGI) provides independent expert advice to government regarding the potential use of the vaccine in Australia, after considering the data on the vaccine as well as information on the disease in the Australian setting. Recommendations on vaccine use in Australia are published in AIH endorsed by the National Health and Medical Research Council.[76]

Q24. Why is there information on the Internet and social media saying the vaccine is dangerous if it isn’t?

There are many competing interests and a wide range of views available on the Internet and it is often difficult to determine whose opinion it is that you are reading.

Some people who choose alternative lifestyles may reject mainstream medicine, including vaccinations. While this position should be respected as their choice, it is important for others who are considering vaccination to be aware that

some information provided on the Internet comes from organisations or people who are philosophically opposed to vaccination.[77-79]

Anti-vaccination groups voice concern about most vaccines, including HPV vaccines. Their perceptions can be found on websites such as those of the Australian Vaccination Skeptics Network (AVN) and the National Vaccination Information Center (NVIC). Press releases from such organisations may often be alarming and controversial and thus generate considerable media interest.

The American College of Pediatricians, a highly conservative small group of approximately 200 members, distinct from the highly respected American Academy of Pediatrics (that represents over 64,000 paediatricians in the USA) released a statement in January 2016 raising concerns around the HPV vaccine. They point to reports that 'hypothesise' that the vaccine may induce premature ovarian failure (POF). However, it is important to realise that these concerns are ideologically, and not scientifically, based. Due to its non-medical agenda, this organisation does not represent the views and recommendations of the main medical or scientific bodies in the USA, Australia or many other countries. It is very important to be assured that information on HPV vaccines is balanced and obtained from credible and trusted sources (***see* Q8**).

Q25. Could receiving HPV vaccine make my daughter or son promiscuous?

No, there is no evidence that receiving HPV vaccine could lead to promiscuity. The assumption that underlies this is that adolescents will not engage in 'risky' sexual behaviour if they fear HPV infection and thus vaccination against HPV removes the motivation for abstinence/safe sex. However, this is not supported by evidence. A US study found that only 7% of women cited fear of sexually transmitted diseases as a main reason for not having sex.[80]

Among the participants in the HPV vaccine trials, there was no increase in the number of sexual partners in those who were vaccinated compared with those who were not. In addition, surveys of young women who had received HPV vaccination have found that there is no association with HPV vaccination and risky sexual behaviours such as number of sexual partners. Furthermore, adolescent women who were sexually active and received HPV vaccine were more likely to always wear a condom.[81] This has been supported by data comparing sexual activity–related healthcare outcomes among girls who had received HPV vaccine at 11–12 years of age with those who hadn't.[82] In this study, the risk of any pregnancy, testing for or diagnosis of sexually transmitted infections or contraceptive counselling was not increased in girls who had received HPV vaccine.

Initiation of sexual activity is influenced by many other factors such as individual psychological factors, drug and alcohol use, family communication and support, community relationships, school factors, and perceptions of peer sexual activity. There is good evidence that receiving information about sexually transmitted infections, providing condoms or discussing sex *does not* result in earlier or more sexual activity.

References

1. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. *The Lancet Oncology* 2009;10:321-2.
2. 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.
3. 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.
4. 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.
5. Tabrizi SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *The Lancet Infectious Diseases* 2014;14:958-66.
6. Australian Institute of Health and Welfare. Cervical screening in Australia 2014–2015. Cat. no. CAN 104. Canberra: AIHW; 2017.

7. Ali H, Donovan B, Wand H, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. [erratum appears in BMJ 2013 May 7;346:f2942]. *BMJ* 2013;346:f2032.

8. 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.

9. 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.

10. 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.

11. Romanowski B, Schwarz TF, Ferguson L, et al. Sustained immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine administered as a two-dose schedule in adolescent girls: five-year clinical data and modeling predictions from a randomized study. *Human vaccines & immunotherapeutics* 2016;12:20-9.

12. 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.

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. 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.

15. Phillips A, Patel C, Pillsbury A, Brotherton J, Macartney K. Safety of human papillomavirus vaccines: an updated review. *Drug Safety* 2018;41:329-46.

16. World Health Organization. Global Advisory Committee on Vaccine Safety statement on safety of HPV vaccines. 17 December 2015. Available from: http://www.who.int/vaccine_safety/committee/GACVS_HPV_statement_17Dec2015.pdf?ua=1 (Accessed 4 April 2017).

17. World Health Organization (WHO). Meeting of the Global Advisory Committee on Vaccine Safety, 7–8 June 2017. *Weekly Epidemiological Record* 2017;92:393-402.

18. Block SL, Brown DR, Chatterjee A, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine. *Pediatric Infectious Disease Journal* 2010;29:95-101.

19. Ferris D, Samakoses R, Block SL, et al. Long-term study of a quadrivalent human papillomavirus vaccine. *Pediatrics* 2014;134:e657-65.

20. Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. *Vaccine* 2011;29:8279-84.

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

22. 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.

23. Castellsague X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine* 2015;33:6892-901.

24. 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.

25. 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.

26. Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA* 2009;302:750-7.

27. Jefferson T, Rudin M, Di Pietrantonj C. Adverse events after immunisation with aluminium-containing DTP vaccines: systematic review of the evidence. *The Lancet Infectious Diseases* 2004;4:84-90.

28. Chao C, Klein NP, Velicer CM, et al. Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine. *Journal of Internal Medicine* 2012;271:193-203.

29. Angelo MG, David MP, Zima J, et al. Pooled analysis of large and long-term safety data from the human papillomavirus-16/18-AS04-adjuvanted vaccine clinical trial programme. *Pharmacoepidemiology and Drug Safety* 2014;23:466-79.

30. Descamps D, Hardt K, Spiessens B, et al. Safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine for cervical cancer prevention: a pooled analysis of 11 clinical trials. *Human Vaccines* 2009;5:332-40.

31. Weinbaum CM, Cano M. HPV vaccination and complex regional pain syndrome: lack of evidence. *EBioMedicine* 2015;2:1014-5.

32. European Medicines Agency. Review concludes evidence does not support that HPV vaccines cause CRPS or POTS [press release]. 5 November 2015. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/11/WC500196352.pdf (Accessed 4 April 2018).

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

34. Vichnin M, Bonanni P, Klein NP, et al. An overview of quadrivalent human papillomavirus vaccine safety: 2006 to 2015. *Pediatric Infectious Disease Journal* 2015;34:983-91.

35. Hawkes D, Buttery JP. Human papillomavirus vaccination and primary ovarian insufficiency: an association based on ideology rather than evidence [editorial]. *Current Opinion in Obstetrics and Gynecology* 2016;28:70-2.

36. Centers for Disease Control and Prevention (CDC), Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. General recommendations on immunization – recommendations of the Advisory Committee on Immunization Practices (ACIP). [erratum appears in MMWR Recomm Rep. 2011 Jul 29;60:993]. *MMWR Recommendations and Reports* 2011;60(RR-2):1-61.

37. Buttery JP, Madin S, Crawford NW, et al. Mass psychogenic response to human papillomavirus vaccination. *Medical Journal of Australia* 2008;189:261-2.

38. Burd EM. Human papillomavirus and cervical cancer. *Clinical Microbiology Reviews* 2003;16:1-17.

39. Greenblatt RJ. Human papillomaviruses:diseases, diagnosis, and a possible vaccine. *Clinical Microbiology Newsletter* 2005;27:139-45.

40. Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. *Virus Research* 2002;89:213-28.

41. Wise LD, Pauley CJ, Michael B, Wolf JJ. Lack of effects on male fertility from a quadrivalent HPV vaccine in Sprague-Dawley rats. *Birth Defects Research Part B Developmental and Reproductive Toxicology* 2010;89:376-81.

42. Wise LD, Wolf JJ, Kaplanski CV, Pauley CJ, Ledwith BJ. Lack of effects on fertility and developmental toxicity of a quadrivalent HPV vaccine in Sprague-Dawley rats. *Birth Defects Research Part B Developmental and Reproductive Toxicology* 2008;83:561-72.

43. Gajdova M, Jakubovsky J, Valky J. Delayed effects of neonatal exposure to Tween 80 on female reproductive organs in rats. *Food and Chemical Toxicology* 1993;31:183-90.

44. Centers for Disease Control and Prevention (CDC). Resurgence of wild poliovirus type 1 transmission and consequences of importation – 21 countries, 2002–2005. *MMWR Morbidity and Mortality Weekly Report* 2006;55:145-50.

45. Dana A, Buchanan KM, Goss MA, et al. Pregnancy outcomes from the pregnancy registry of a human papillomavirus type 6/11/16/18 vaccine. *Obstetrics and Gynecology* 2009;114:1170-8.

46. Scheller NM, Pasternak B, Molgaard-Nielsen D, Svanstrom H, Hviid A. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. *The New England Journal of Medicine* 2017;376:1223-33.

47. Zhou J, Sun XY, Stenzel DJ, Frazer IH. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology* 1991;185:251-7.

48. Australian Institute of Health and Welfare (AIHW). Cancer in Australia: an overview, 2017. Cancer Series no. 101, Cat. No. CAN 100. Canberra: Australian Institute of Health and Welfare (AIHW); 2017. Available from: https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2017/contents/table-of-contents (Accessed 4 April 2018).

49. 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.

50. Grulich AE, Jin F, Conway EL, Stein AN, Hocking J. Cancers attributable to human papillomavirus infection. *Sexual Health* 2010;7:244-52.

51. Moscicki AB, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine* 2012;30 Suppl 5:F24-33.

52. Brotherton JM, Saville AM, May CL, Chappell G, Gertig DM. Human papillomavirus vaccination is changing the epidemiology of high-grade cervical lesions in Australia [letter]. *Cancer Causes and Control* 2015;26:953-4.

53. Van Damme P, Olsson SE, Block S, et al. Immunogenicity and safety of a 9-valent HPV vaccine. *Pediatrics* 2015;136:e28-39.

54. Australian Government Department of Health and Ageing. National Cervical Screening Program. 2018. Available from: http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/cervical-screening-1 (Accessed 20/2/2018).

55. Crowe E, Pandeya N, Brotherton JM, et al. Effectiveness of quadrivalent human papillomavirus vaccine for the prevention of cervical abnormalities: case-control study nested within a population based screening programme in Australia. *BMJ* 2014;348:g1458.

56. Gertig DM, Brotherton JM, Budd AC, et al. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC Medicine* 2013;11:227.

57. 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.

58. Smith MA, Lew JB, Walker RJ, et al. The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia. *Vaccine* 2011;29:9112-22.

59. Liaw KL, Hildesheim A, Burk RD, et al. A prospective study of human papillomavirus (HPV) type 16 DNA detection by polymerase chain reaction and its association with acquisition and persistence of other HPV types. *Journal of Infectious Diseases* 2001;183:8-15.

60. Koutsky L. Epidemiology of genital human papillomavirus infection. *American Journal of Medicine* 1997;102(5A):3-8.

61. Madeleine MM, Brumback B, Cushing-Haugen KL, et al. Human leukocyte antigen class II and cervical cancer risk: a population-based study. *Journal of Infectious Diseases* 2002;186:1565-74.

62. Hildesheim A, Wang SS. Host and viral genetics and risk of cervical cancer: a review. *Virus Research* 2002;89:229-40.

63. Green J, Berrington de González A, Sweetland S, et al. Risk factors for adenocarcinoma and squamous cell carcinoma of the cervix in women aged 20–44 years: the UK National Case–Control Study of Cervical Cancer. *British Journal of Cancer* 2003;89:2078-86.

64. International Collaboration of Epidemiological Studies of Cervical Cancer. Carcinoma of the cervix and tobacco smoking: collaborative reanalysis of individual data on 13,541 women with carcinoma of the cervix and 23,017 women without carcinoma of the cervix from 23 epidemiological studies. *International Journal of Cancer* 2006;118:1481-95.

65. Vajdic CM, van Leeuwen MT, Jin F, et al. Anal human papillomavirus genotype diversity and co-infection in a community-based sample of homosexual men. *Sexually Transmitted Infections* 2009;85:330-5.

66. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical carcinoma and reproductive factors: collaborative reanalysis of individual data on 16,563 women with cervical carcinoma and 33,542 women without cervical carcinoma from 25 epidemiological studies. *International Journal of Cancer* 2006;119:1108-24.

67. 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.

68. Kjaer SK, Sigurdsson K, Iversen OE, et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (types 6/11/16/18) vaccine against high-grade cervical and external genital lesions. *Cancer Prevention Research* 2009;2:868-78.

69. Wright Jr TC. Natural history of HPV infections. *Journal of Family Practice* 2009;58:S3-S7.

70. Pagliusi SR, Aguado MT. Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine* 2004;23:569-78.

71. 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.

72. 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.

73. Tabrizi SN, Brotherton JM, Kaldor JM, et al. Fall in human papillomavirus prevalence following a national vaccination program. *Journal of Infectious Diseases* 2012;206:1645-51.

74. Chow EP, Read TR, Wigan R, et al. Ongoing decline in genital warts among young heterosexuals 7 years after the Australian human papillomavirus (HPV) vaccination programme. *Sexually Transmitted Infections* 2015;91:214-9.

75. Jüni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. *BMJ* 2001;323:42-6.

76. Nolan TM. The Australian model of immunization advice and vaccine funding. *Vaccine* 2010;28 Suppl 1:A76-83.

77. Australian Academy of Science. The science of immunisation: questions and answers. Canberra: Australian Academy of Science; 2012. Available from: https://www.science.org.au/learning/general-audience/science-booklets/science-immunisation (Accessed 4 April 2018).

78. Offit PA, Jew RK. Addressing parents' concerns: do vaccines contain harmful preservatives, adjuvants, additives, or residuals? *Pediatrics* 2003;112:1394-401.

79. Australian Government Department of Health and Ageing. *Myths and realities: responding to arguments against vaccination. A guide for providers*. 5th ed. Canberra: Australian Government Department of Health and Ageing; 2013. Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/13ACB374291E3532CA257D4D0081E4AA/$File/full-publication-myths-and-realities-5th-ed-2013.pdf (Accessed 4 April 2018).

80. Liddon NC, Leichliter JS, Markowitz LE. Human papillomavirus vaccine and sexual behavior among adolescent and young women. *American Journal of Preventive Medicine* 2012;42:44-52.

81. Monk BJ, Wiley DJ. Will widespread human papillomavirus prophylactic vaccination change sexual practices of adolescent and young adult women in America? *Obstetrics and Gynecology* 2006;108:420-4.

82. Bednarczyk RA, Davis R, Ault K, Orenstein W, Omer SB. Sexual activity-related outcomes after human papillomavirus vaccination of 11- to 12-year-olds. *Pediatrics* 2012;130:798-805.