



Australian Government
Department of Health

COMMUNICABLE DISEASES INTELLIGENCE

2020 Volume 44
<https://doi.org/10.33321/cdi.2020.44.33>

Scientific evidence supporting recommendations on the use of the 9-valent HPV vaccine in a 2-dose vaccine schedule in Australia

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Communicable Diseases Intelligence

ISSN: 2209-6051 Online

This journal is indexed by Index Medicus and Medline.

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Communicable Diseases Intelligence (CDI) is a peer-reviewed scientific journal published by the Office of Health Protection, Department of Health. The journal aims to disseminate information on the epidemiology, surveillance, prevention and control of communicable diseases of relevance to Australia.

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Abstract: The Australian Technical Advisory Group on Immunisation (ATAGI) updated recommendations on the use of human papillomavirus (HPV) vaccines in the *Australian Immunisation Handbook* in 2018, regarding the use of the recently available 9-valent (9vHPV) vaccine, Gardasil 9, and a 2-dose schedule for young adolescents for HPV vaccines. This report provides an overview of the relevant scientific evidence that underpinned these updated recommendations. The 9vHPV vaccine includes 5 HPV types (HPV 31, 33, 45, 52 and 58) additional to the 4 that are also covered by the 4vHPV (Gardasil) vaccine (HPV 6,11,16,18). Accordingly, the 9vHPV vaccine is expected to prevent an additional 15% of cervical cancers and up to 20% of other HPV-related cancers. Non-inferior antibody responses after two 9vHPV vaccine doses given 6–12 months apart in girls and boys aged 9–14 years compared to women aged 16–26 years after three doses support the 2-dose schedule for adolescents of this age group. In clinical trials 9vHPV vaccine was well-tolerated with a similar safety profile to 4vHPV vaccine. The switch to 9vHPV vaccine and a 2-dose schedule is anticipated to improve public acceptability of the program and reduce HPV-related disease in the long-term.

Keywords: Human papilloma virus, HPV vaccine, Cervical cancer, Vaccine schedule, genital warts

Introduction

Human papillomavirus (HPV) infection is common, with the average lifetime probability of acquiring HPV infection estimated at approximately 85% for females and 91% for males.¹ The prevalence of HPV infection varies geographically, demographically and by anatomical site. The most consistent data on prevalence of HPV infection are obtained from cervical screening in females. In Australia, the prevalence of any HPV infection in the cervix of females undergoing routine cervical screening in 2007, prior to commencement of HPV vaccination through the National Immunisation Program (NIP), was

estimated to peak at 64% in the 15–20 year age group and to then decline gradually to 12% in the 41–45 year age group.² Men who have sex with men (MSM) and immunocompromised individuals have higher rates of certain HPV infections and related cancers.³

HPV associated cancers in Australia

HPV infection is a cause of cervical and several other anogenital cancers, such as anal, penile, vulval and vaginal cancers. Some cancers of the oropharynx and oral cavity are also caused by HPV infection. In an Australian study, HPV was detectable in approximately 93% of cervi-

ⁱ The Australian Technical Advisory Group on Immunisation (ATAGI) provides evidence-based advice on immunisation policies, programs and research priorities to the Minister for Health and other key policy makers on the Immunise Australia Program and other related issues. ATAGI recommendations, approved by the National Health and Medical Research Council, are published in the Australian Immunisation Handbook.

cal cancers diagnosed between 2005 and 2015.⁴ HPV types 16 and 18 are the most prevalent types associated with cancer, and were detected in 77% of samples. An additional 14.8% (or 15.9% of HPV-positive cervical cancers) contained HPV types 31, 33, 45, 52 and 58. These HPV types were found in 8.2% of cervical adenocarcinomas, which are not well detected by cytology-based screening.

The prevalence of HPV among anal cancer specimens in an Australian study was 96%, with HPV type 16 the most common (75%).⁵ The estimated HPV-attributable proportions of other cancers, that are rarer in incidence, are 50% in penile, 40% in vulval, 70% in vaginal, 40% in oropharyngeal and 7% in oral cavity cancers.^{6–8}

In Australia, the incidence rate of cervical cancer has more than halved since 1982 but has remained stable and low at approximately 7 per 100,000 since 2002.⁹ Mortality rates from cervical cancer have also reduced, from 5.2 per 100,000 in 1982 to 1.7 per 100,000 in 2013.⁹ In 2014 there were 223 deaths due to cervical cancer. The incidence rate of anal cancer has doubled among Australians from 1982 (0.8 per 100,000) to 2013 (1.6 per 100,000).¹⁰ The incidence rates of other HPV-associated anogenital cancers have remained stable, and ranged from 0.7 per 100,000 for penile to 2.3 per 100,000 for vulval cancer.⁸ HPV-related oropharyngeal cancers were found to increase steadily at an estimated 1% per year from 1982–2005 and are now estimated to stand at about 2.4 per 100,000.^{8,11}

Genital warts and HPV

HPV infection, primarily with the low-risk HPV types 6 and 11, causes genital warts. In Australia, before the implementation of HPV vaccination, around 4% each of both males and females, aged 16–59 years, self-reported ever having been diagnosed with genital warts, and the estimated annual incidence rate of genital warts between 2000 and 2006 was 219 per 100,000.^{12,13}

Impact of HPV vaccination in Australia

HPV vaccination through the NIP commenced in 2007 using the quadrivalent (4vHPV) vaccine, Gardasil, which protects against HPV types 6, 11, 16 and 18. The program initially targeted females aged 12–13 years and included catch-up vaccination for females aged up to 26 years until the end of 2009. It was extended to male adolescents in 2013. The program has led to dramatic declines in HPV infection and disease.

Among sexually active women aged 18–24 years fully vaccinated with 4vHPV vaccine, the prevalence of HPV cervical infection declined from 60% to 49% for all HPV types and from 29% to 2% for the 4vHPV types.¹⁴ Among women less than 20 years of age, incidence rates of high-grade cervical abnormalities (HGAs, precursors of cervical cancer), declined between 2007 and 2015 from 11.6 to 4.1 per 1,000 screened.⁹ Corresponding reductions in HGA incidence in women up to 29 years of age, undergoing cervical screening, have also been observed.^{15–17} Large declines of over 90% and over 70% in genital warts incidence, among Australian females aged <21 years and aged 21–30 years respectively, have been reported from sexual health centres.¹⁸ Among heterosexual men, incidence of genital wart diagnoses declined from the pre-vaccination period by over 80% in those aged <20 years and by over 50% in the 21–30 year age group as a result of a herd effect of the female-only HPV vaccination program.¹⁸

Steps to improve prevention of cervical and other HPV-related cancers

In Australia, there are three HPV vaccines registered for use: the 4vHPV vaccine (Gardasil); bivalent (2vHPV) vaccine Cervarix; and non-valent (9vHPV) vaccine Gardasil 9. The 9vHPV vaccine includes the HPV types (HPV 6, 11, 16 and 18) covered by the 4vHPV vaccine plus five additional oncogenic HPV types (31, 33, 45, 52 and 58). From February 2018, 9vHPV vaccine replaced 4vHPV vaccine on the NIP.

By expanding the HPV types covered, the 9vHPV vaccine is expected to provide young females protection against approximately 90% of cervical-cancer-causing HPV types.⁴ For other HPV-associated cancers, data from the USA suggest that 9vHPV use would potentially further reduce incidence beyond that prevented by 4vHPV vaccine by 18% for vaginal, 14% for vulval, 11% for anal and 9% for penile cancers.⁸ In December 2017 the Australian National Cervical Screening Program (NCSP) transitioned to the use of HPV-based testing as the primary screening test, which is more sensitive than previous cytology-based screening. It is estimated that this will potentially reduce new cervical cancer cases and deaths by up to 36% in unvaccinated cohorts and up to 29% in 4vHPV-vaccinated cohorts.¹⁹

HPV vaccination schedule change for young adolescents

The vaccination schedule for the routine adolescent target cohort for HPV vaccine has changed from three to two doses (Box 1). The 3-dose schedule recommended and used from 2007 to 2017 was based on primary studies that established the efficacy and immunogenicity of HPV vaccines in 3-dose schedules, and on the initial registration of 4vHPV vaccine with Therapeutic Goods Administration of Australia.

Since the commencement of the program, several studies have demonstrated that immunogenicity of HPV vaccination using 2 doses given at least 6 months apart, in younger adolescent cohorts, is comparable with 3-dose schedules in older vaccine recipients. In 2014, the World Health Organization (WHO) amended its HPV vaccination recommendations to endorse a 2-dose schedule for those individuals less than 15 years of age when commencing vaccination.^{20,21} A review of evidence by the WHO's Strategic Advisory Group of Experts on Immunisation concluded that immunogenicity of a 2-dose HPV vaccination schedule in girls was non-inferior to a 3-dose HPV vaccination schedule in women in whom clinical efficacy had been demonstrated.²² These immunogenicity findings

have also been demonstrated in males. The key advantages of a 2-dose schedule for adolescent HPV vaccination, identified by WHO, include cost-effectiveness and programmatic benefits potentiating higher vaccination coverage. The National Immunisation Technical Advisory Groups of many countries have adopted these recommendations and have moved to 2-dose schedules for adolescent HPV vaccination.

Methodology

The ATAGI HPV Working Party, supported by the National Centre for Immunisation Research and Surveillance (NCIRS), has undertaken a comprehensive review of the evidence relating to the immunogenicity, efficacy, effectiveness and safety of *a*) the 9vHPV vaccine and *b*) 2-dose HPV vaccination schedules. An extensive literature review has been conducted to identify all relevant studies on 9vHPV vaccine and 2-dose HPV vaccination schedules up to November 2017; unpublished data made available by vaccine manufacturers as well as relevant citations of data published since November 2017 have also been included in the review. This evidence forms the basis of the ATAGI updated HPV vaccination recommendations.

Results and Discussion

The following subsections summarise the key evidence underpinning the ATAGI updated recommendations on HPV vaccinations. As outlined below, there is evidence from pivotal randomised controlled trials (RCTs) on the additional benefit of 9vHPV vaccine and the comparable protective effect of 2-dose HPV vaccination schedules to 3-dose schedules in adolescents 9–14 years of age.

Comparative benefits of 9vHPV and 4vHPV vaccines

The comparative benefits of 9vHPV vaccine relative to 4vHPV vaccine were assessed in a pivotal trial with clinical endpoints (persistent infection and combined high-grade cervical, vulvar and vaginal disease associated with vaccine-type

Box 1: New ATAGI recommendations on HPV vaccination for Australians

- Young adolescents (females and males) who commence vaccination before their 15th birthday are recommended to receive 2 doses of HPV vaccine, ideally at the age of approximately 12–13 years. The second vaccine dose should be administered 6–12 months after the first dose. This schedule is recommended regardless of which of the three currently registered HPV vaccines is (or has been) used: 9vHPV vaccine (Gardasil9), 4vHPV vaccine (Gardasil), or 2vHPV vaccine (Cervarix).
- Individuals who commence HPV vaccination on or after their 15th birthday are recommended to receive 3 doses of HPV vaccine. The 3-dose schedule is recommended at times 0 (first dose), 2 and 6 months.
- A 3-dose HPV vaccine schedule is also recommended for certain immunocompromised individuals, regardless of age at commencement of HPV vaccination. The relevant immunocompromising conditions include: primary or secondary immunodeficiencies (B lymphocyte antibody and T lymphocyte complete or partial deficiencies), HIV infection, malignancy, organ transplantation, or significant immunosuppressive therapy.

The 9vHPV vaccine is suitable to be used to complete a schedule that was commenced with 4vHPV or 2vHPV vaccine. The 9vHPV vaccine targets the HPV types covered by 4vHPV vaccine (6, 11, 16 and 18), plus five additional oncogenic HPV types (31, 33, 45, 52 and 58). Individuals who commenced a 4vHPV or 2vHPV vaccine schedule and completed it with 9vHPV vaccine will be adequately protected against the vaccines' shared HPV types.

HPV) and immunogenicity in women aged 16–26 years, where both vaccines were given in a 3-dose schedule.²³ In this trial, 9vHPV vaccine had high comparative efficacy and was clinically superior against disease due to 9v-non-4vHPV types (31, 33, 45, 52 and 58) compared to the 4vHPV vaccine (Table 1). The 9vHPV vaccine also produced non-inferior antibody geometric mean titres (GMTs) and seroconversion rates for the 4vHPV types compared to 4vHPV vaccine.

Comparison of two- and three-dose HPV vaccine schedules

For all three HPV vaccines, data on immunogenicity (comparing seroconversion and antibody titres) show that a 2-dose schedule in adolescents aged 9–14 years is non-inferior to a 3-dose schedule in young adults aged 16 years and over.

Immunogenicity has been used to infer clinical efficacy in younger adolescents through

immunobridging in 2-dose schedule trial data, whereby post-vaccination antibody responses in younger adolescents (who are unlikely to have experienced sexual debut) are compared to those in young adults in whom clinical efficacy has been demonstrated.

A pivotal clinical trial compared immunogenicity of 9vHPV vaccine in 2-dose schedules (at 0 and 6 months or at 0 and 12 months) in adolescent females and males, aged 9–14 years, with a 3-dose schedule (0, 2 and 6 months) in females aged 16–26 years.²⁴ The trial showed high seroconversion irrespective of dose schedule, with more than 99% of the adolescent girls and boys, and 97.9–99.6% of the women, becoming seropositive for all 9vHPV types one month post the last 9vHPV vaccine dose. The GMTs of antibody for all 9vHPV types in girls and boys after either of the alternative 2-dose schedules were also non-inferior to GMTs of women after 3 doses of 9vHPV vaccine. Girls aged 9–14 years were given 9vHPV vaccine in a 3-dose schedule

Table 1: Estimates of efficacy against HPV types 31, 33, 45, 52 and 58-related disease with 3 doses of 9vHPV compared to 3 doses of 4vHPV among women aged 16–26 years.

Clinical Endpoint	9vHPV group			4vHPV group			Comparative efficacy of 9vHPV vaccine against disease due to HPV types unique to 9vHPV vaccine	95% CI
	Number of cases (non-4vHPV types 31, 33, 45, 52, 58-related)	Number of participants	Incidence rate/1,000 person-years	Number of cases (non-4vHPV types 31, 33, 45, 52, 58-related)	Number of participants	Incidence rate/1,000 person-years		
High-grade cervical, vulvar and vaginal disease ^a and cancer	1	6016	0.1	30	6017	1.6	96.7%	80.9–99.8%
High-grade cervical disease and cancer ^b	1	5948	0.1	27	5943	1.5	96.3%	79.5–99.8%
Persistent infection ≥6 months	35	5939	2.1	810	5953	52.4	96.0%	94.4–97.2%

a Includes high-grade cervical epithelial neoplasia, adenocarcinoma in situ, cervical cancer, high-grade vulvar intraepithelial neoplasia, high-grade vaginal intraepithelial neoplasia, vulvar cancer and vaginal cancer

b Includes high-grade cervical intraepithelial neoplasia, adenocarcinoma in situ and cervical cancer
Data source: Jaura et al. 2015²³

in an exploratory third arm of the study; overall, GMTs for all 9vHPV types except HPV 45 were higher and non-inferior in those who received 2 doses of 9vHPV vaccine at 0 and 12 months compared to those who received either 2 doses at 0 and 6 months or the 3-dose schedule.

The non-inferior immunogenicity in adolescents receiving alternative 2-dose schedules of 9vHPV vaccine, compared to women receiving 3-dose schedules, provides evidence for recommending a 9vHPV vaccine 2-dose schedule (at 0 and 6–12 months) for those commencing HPV vaccination before their 15th birthday.

Two-dose schedules of 4vHPV and 2vHPV vaccines have also demonstrated non-inferior immunogenicity, effectiveness and efficacy against vaccine type HPV infection and disease. Non-inferior antibody responses to 4vHPV vaccine in girls aged 9–13 years post 2-dose schedule, compared to women aged 16–26 years post 3-dose schedule, were demonstrated in a RCT.²⁵ In follow-up data from this trial, girls receiving 2-dose schedule had higher levels of antibody persistence up to 60 months after dose 2, compared to women receiving 3 doses of 4vHPV vaccine.²⁶ In a large study in India, unmarried females aged 10–18 years, had very low and similar incidence of HPV 6, 11, 16 or 18 infection ($\leq 1\%$), following 4vHPV vaccine in a 2-dose schedule at 0 and 6 months, to that following 3 doses.²⁷ No persistent HPV 16 or 18 infections were seen after a median follow-up of about 5 years.

Further support for a 2-dose schedule with a minimum 6 month interval comes from a post-licensure study where a 2-dose interval of ≥ 4 months had a non-inferior protective effect against genital warts compared to a completed 3-dose schedule.²⁸ In this study young women aged < 23 years who had received only 2 doses of 4vHPV vaccine had a statistically significant trend towards greater protection against genital warts as the time interval between the 2 doses increased beyond 4 months.

The 2vHPV vaccine in a 2-dose schedule has been shown to elicit non-inferior antibody responses against both HPV 16 and 18 in girls aged 9–14 years for up to 60 months after first vaccine dose, compared to 3-dose schedules in young women aged 15–25 years.^{29–33} Post-hoc analysis of data from two RCTs also found that 2vHPV vaccine 2-dose schedules only produced non-inferior efficacy compared to 3-dose schedules when doses were separated by an interval of 6 months rather than by shorter intervals.³⁴

Use of a three-dose HPV vaccine schedule

The immunogenicity and efficacy of 2-dose HPV vaccine schedules have not been adequately evaluated in those aged ≥ 15 years. Clinical trials have not directly assessed 2-dose HPV vaccination in those aged 16–26 years. Therefore, continuation of the 3-dose schedule is recommended if HPV vaccination was started after the 15th birthday.

There are no data available on 2-dose HPV vaccination schedules in young adolescents with compromised immunity. It is unclear whether a reduced dose schedule would provide sufficient protection in people with conditions in which the antibody response to vaccination may be diminished. As such, it is recommended that immunocompromised individuals, regardless of age at commencement of HPV vaccination, are given a 3-dose HPV vaccination schedule for adequate protection. The specific conditions where the 3-dose schedule is applicable, based on expert evidence-based guidelines and the immune mechanisms of protection against HPV infection, include primary or secondary immunodeficiencies (B lymphocyte antibody and T lymphocyte complete or partial deficiencies), HIV infection, malignancy, organ transplantation, or significant immunosuppressive therapy.³⁵

Use of 9vHPV vaccine in those vaccinated with 2vHPV or 4vHPV

The 9vHPV vaccine is suitable, safe and effective to use to complete a schedule started with

either 2vHPV or 4vHPV vaccine. Depending on age at first dose, a total of either 2 or 3 doses are required for schedule completion. In clinical trials, 9vHPV vaccine had good efficacy against disease due to 9v-non-4v types and sufficient immunogenicity against 4vHPV types.²³ The 9vHPV vaccine in a 2-dose schedule had non-inferior immunogenicity to 9vHPV vaccine in a 3-dose schedule in adolescent girls and boys.²⁴ Therefore it is reasonable to infer that completion of 2-dose or 3-dose 4vHPV (or 2vHPV) vaccination schedules with 9vHPV vaccine will provide adequate protection against their shared vaccine HPV types.

However, routine vaccination with 9vHPV vaccine is not recommended in those who have already completed a full vaccination schedule with either 2vHPV or 4vHPV vaccine. Both 2vHPV and 4vHPV vaccines protect against HPV 16 and 18, which are the most common oncogenic HPV types found in HPV-associated cancers in Australia and the greatest public health concern.⁴ For complete protection against the additional 5 HPV types included in the 9vHPV, two or three doses (depending on age when vaccination was commenced) would be required in those previously vaccinated with 2vHPV or 4vHPV vaccine. Pragmatic concerns regarding timing of sexual debut and likelihood of exposure to the unique 9vHPV types, the potential of adverse events from additional injections and associated extra costs of vaccination limit the utility of administering 9vHPV vaccine to individuals who have already completed a full course of 2vHPV or 4vHPV.

Duration of protection of HPV vaccination

Data on long-term clinical protection of 9vHPV vaccine in 2-dose schedules are limited. However, the duration of protection offered by a 9vHPV vaccine 2-dose schedule is likely to be similar to 9vHPV and 4vHPV vaccines in 3-dose schedules, as these schedules have comparable immunogenicity in individuals aged 9–14 years.^{23,24} In follow-up trial data 78–100% of young women maintained detectable antibodies

at 60 months after their last dose of 9vHPV vaccine in a 3-dose schedule.³⁶ The 4vHPV vaccine 3-dose schedules have demonstrated ongoing protection for up to 10 years of follow-up against HPV vaccine-type persistent infection and other related clinical outcomes such as genital warts and low-grade and high-grade cervical, vaginal, vulvar cancer precursors and cancers.³⁷

Safety of HPV vaccination

There is robust reassuring data from clinical trials and high quality post-marketing studies, as well as expert reviews indicating that the safety profiles of 2vHPV, 4vHPV and 9vHPV vaccines are very good.^{38,39} In clinical trials, 9vHPV vaccine had a similar safety profile to 4vHPV vaccine and was generally well-tolerated by adolescents and young adults. Minor injection-site reactions (pain, swelling, erythema and pruritus) were the adverse events most common for both these vaccines but are slightly more frequent with 9vHPV vaccine than 4vHPV (e.g. 72.5% vs 61.0% for any injection-site reaction after dose 1).⁴⁰ This is likely to be associated with the higher concentration of adjuvant present in 9vHPV vaccine.³⁹ Reducing the number of doses of HPV vaccine administered from 3 to 2 doses will, however, result in fewer opportunities for adverse events following immunisation. Additionally, there are data to support that concomitant administration of 9vHPV with other vaccines including meningococcal, diphtheria-tetanus-pertussis and poliomyelitis vaccines is safe and does not interfere with immune responses to respective vaccine antigens.^{41,42}

Conclusions

The 9vHPV vaccine offers protection that is non-inferior to that of 4vHPV vaccine against HPV infection and associated disease caused by their shared HPV types and superior against the five oncogenic HPV types unique to 9vHPV. Based on HPV-associated cancer epidemiology, the 9vHPV vaccine is expected to prevent an additional 15% of cervical cancers and up to 20% of other HPV-related cancers among Australians. There is high-level evidence, for all three HPV

vaccines, showing that a 2-dose schedule with a 6–12 month interval between doses in young adolescents provides comparable protection to that of a 3-dose schedule. There is insufficient evidence to extend the use of a 2-dose schedule for those commencing vaccination from 15 years of age and over and for individuals with certain immunocompromising conditions. The advantages of the 2-dose schedule include increased flexibility and the potential to increase cost-effectiveness. Greater public acceptability of a HPV vaccination program protecting against more HPV types and containing fewer doses is anticipated and would lead to improved coverage over time. This, together with complementary changes such as the transition to use HPV-based testing in the NCSP, is expected to further improve HPV related disease prevention in Australia.

Acknowledgements

The preparation of this manuscript and the review of the evidence therein were undertaken at the NCIRS as part of scientific technical support to ATAGI which is funded by the Australian Government Department of Health.

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