Australian Government

Department of Health

Australian Technical Advisory Group on Immunisation: Public consultation on changes to the recommended use of human papillomavirus (HPV) vaccines

The Australian Technical Advisory Group on Immunisation (ATAGI) is consulting with stakeholders on proposed changes to the HPV vaccination recommendations for inclusion in the Australian Immunisation Handbook, with an intention to submit the recommendation to the National Health and Medical Research Council (NHMRC) for its approval under section 14A of the *National Health and Medical Research Council Act 1992.*

This draft includes new recommendations and the rationale for the proposed changes.

You are invited to make a submission on the draft recommendation by 30 November 2017.

In particular, ATAGI is seeking comments on the following:

- Are there additional potential benefits, risks or unintended consequences which could arise from the proposed changes to the use of HPV vaccines, not already outlined and how likely are they to occur?
- Are there additional clinical or implementation considerations which need to be outlined?

Should you require additional information please contact ATAGI Secretariat on atagi.secretariat@health.gov.au.

Summary

The Australian Technical Advisory Group on Immunisation (ATAGI), which advises the Australian Government on clinical recommendations for vaccinations, is proposing changes to the use of human papillomavirus (HPV) vaccine.

The proposed changes reflect the current best clinical practice for prevention of HPV infection and associated disease and will be published in the Australian Immunisation Handbook online (http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10-updates).

The ATAGI continues to recommend routine HPV vaccination for young females and males aged up to 19 years. HPV vaccine is funded under the National Immunisation Program (NIP) and delivered predominantly by state and territory school-based immunisation programs to children aged approximately 12–14 years (dependent upon the secondary school grade or cohort targeted in each state and territory). Vaccination of groups who have an increased risk of HPV-related disease also continues to be recommended, notably immunocompromised persons and men who have sex with men (MSM).

Two recent developments support changes to HPV vaccine recommendations. Firstly, a new nonavalent HPV ("9vHPV") vaccine has been registered for use in Australia and is now recommended for routine use to provide maximal protection against HPV-related disease. The 9vHPV vaccine covers five additional cancer-causing (oncogenic) HPV types (types 31, 33, 45, 52 and 58) in addition to the types currently included in the quadrivalent HPV ("4vHPV") vaccine (types 6, 11,16 and 18) and the bivalent HPV ("2vHPV") vaccine (types 16 and 18).

Secondly, a wide body of evidence demonstrates that administration of HPV vaccine to persons aged 9–14 years in a 2-dose schedule, where there is a minimum interval of 6–12 months between doses, provides protection that is comparable to the use of a 3-dose HPV vaccination schedule where doses are given at shorter intervals. A 2-dose HPV vaccine schedule in this age group is now widely recommended internationally, including by the World Health Organization (WHO).[1]

Rationale

The Therapeutic Goods Administration registered Gardasil 9 as a 2-dose schedule in June 2017 and the Pharmaceutical Benefits Advisory Committee recommended in July that it be provided through the NIP. The vaccine is expected to be available in Australia from 2018.

These changes have prompted a review of the HPV recommendations in the Australian Immunisation Handbook.

Recommendations

1. ATAGI proposes the following changes to the use of HPV vaccines in Australia (Table 1)

a) All individuals (males and females) who commence vaccination at the age of 9 to 14 years, except immunocompromised individuals (see (b) below), should receive two doses of 9vHPV vaccine given 6–12 months apart (0, 6–12 months).

b) The following population groups should receive three doses of 9vHPV vaccine given at 0, 2 and 6 months:

i) immunocompromised individuals (males and females) at any age;

ii) males and females who receive their first dose of 9vHPV after turning 15 years of age.

***Table 1*:** Comparison of the ATAGI current and proposed recommendations for HPV vaccination

Recommendation	Vaccine	Cohort	Number of doses	Schedule of doses
Current*	2vHPV† vaccine (females only) 4vHPV† vaccine (males and females)	Commencing vaccination aged 9–18 years	3 doses	0, 1 and 6 months (2vHPV vaccine) 0, 2 and 6 months (4vHPV vaccine)
Current*	2vHPV† vaccine (females only) 4vHPV† vaccine (males and females)	Immunocompromised any age‡	3 doses	0, 1 and 6 months (2vHPV vaccine) 0, 2 and 6 months (4vHPV vaccine)
Proposed*	9vHPV vaccine (males and females)	Commencing vaccination aged 9–14 years	2 doses	0, 6–12 months§
Proposed*	9vHPV vaccine (males and females)	Immunocompromised any age‡	3 doses	0, 2 and 6 months¶
Proposed*	9vHPV vaccine (males and females)	Commencing vaccination aged ≥15 years	3 doses	0, 2 and 6 months¶

*HPV vaccine may be administered from 9 years of age, however, the optimal time for vaccination is approximately12–14 years, as provided under the school-based National Immunisation Program (NIP).

†Both 2vHPV and 4vHPV vaccines have been registered in Australia. Only 4vHPV vaccine has been provided under the National Immunisation Program (NIP) since HPV vaccination was funded in 2007.

‡Immunocompromised individuals include those with primary or secondary immunodeficiencies (B lymphocyte antibody and T lymphocyte complete or partial deficiencies), HIV infection, malignancy, organ transplantation, autoimmune disease, or significant immunosuppressive therapy (but does not include asplenia or hypopsplenia).

§If an individual has received two doses of HPV vaccine with an interval of less than 5 months between dose 1 and dose 2, a third dose is required at least 12 weeks after the second dose. If the second dose is received at <6 months but ≥5 months after the first dose, a third dose is not required, as clinical trial data support this interval still being sufficiently immunogenic.

¶Minimum intervals recommended for a 3-dose schedule are at least 4 weeks between dose 1 and dose 2 and at least 5 months between dose 1 and dose 3.

2 ATAGI proposes the following recommendations for use of 9vHPV ('catch up') in individuals previously vaccinated with 2vHPV or 4vHPV vaccines

a) 9vHPV vaccine can be used to complete an HPV vaccination schedule commenced with either the 4vHPV or 2vHPVvaccine.

b) No catch up is recommended for individuals who have completed a full schedule (either age and interval appropriate 2- or 3- dose schedules) with either 4vHPV or 2vHPV.

Research evidence

Recommendation 1: Use of 9vHPV in Australia

The ATAGI recommends that 9vHPV vaccine be administered in a 2-dose schedule at 0 and 6–12 months. The newly registered 9vHPV vaccine has been demonstrated to be as protective against the four HPV types included in the 4vHPV vaccine (types 6, 11, 16 and 18) and with a similar safety profile to the 4vHPV vaccine. Moreover, the 9vHPV vaccine provides protection against five additional HPV types than those currently included in the 4vHPV vaccine and is thus anticipated to further decrease HPV incidence and associated disease burden.

A 2-dose schedule of 9vHPV vaccine is anticipated to provide protection equivalent to that obtained from a 3-dose schedule in females and males aged 9–14 years and has several advantages over the 3-dose schedule. Advantages include a reduced number of injections, likely greater acceptance of vaccination, reduced resource demands for the school based programs, and reduced opportunity for adverse events from multiple vaccine doses.

Clinical trial data outlined below support the proposed use of the 9vHPV vaccine (as well as 4vHPV and 2vHPV vaccines) in a 2-dose schedule.

Immunogenicity, efficacy and safety of 9vHPV compared with 4vHPV vaccine

A pivotal clinical trial compared the 9vHPV vaccine to the 4vHPV vaccine in more than 14,000 women aged 16–26 years in a 3-dose schedule.[2] This study showed that the 9vHPV vaccine produced an immune response against the HPV types included in both vaccines (types 6, 11, 16 and 18) which was equal to that produced by the 4vHPV vaccine. The 9vHPV vaccine also prevented more infection and disease associated with the additional five HPV types included (types 31, 33, 45, 52 and 58) than the 4vHPV. Another clinical trial compared three doses in women aged 16–26 years, for whom efficacy had already been demonstrated, with two doses in males and females aged 9–14 years and showed immune responses were similar after the final dose in the course.[3]

In the pivotal clinical trial described above, and in other studies, those who received 9vHPV vaccine were more likely to report a reaction at the injection site than those receiving 4vHPV vaccine (90.7% compared with 84.9%).[2] A safety review of seven phase III clinical trials evaluated reactions to 9vHPV vaccine against 4vHPV or placebo in males and females aged 9–26 who received three doses and concluded that serious adverse reactions were reported in <0.1% of the more than 15,000 total participants.[4] This review concluded that safety profiles of the 4vHPV and 9vHPV given in three-dose schedules were similar, with the exception of injection site reactions being slightly more common with 9vHPV vaccine.[4]

Disease potentially preventable by inclusion of additional five HPV types in the 9vHPV vaccine

Use of the 9vHPV vaccine in place of the 4vHPV vaccine has the potential to further reduce the HPV disease burden in Australia. A recent review reported that approximately 15% of all HPV-associated cancers in women and 4% of cancers in men are attributable to the five HPV types unique to the 9vHPV vaccine.[5] A recent cancer-typing study suggested that use of the 9vHPV vaccine in the target age group will likely extend prevention to approximately 93% of the total cervical cancer causing HPV types in Australia.[6]

Immunogenicity and safety of 2-dose versus 3-dose schedule of 9vHPV vaccine

Efficacy trials were not feasible in the primary target age group for HPV vaccines (older children and young adolescents) because collection of genital samples to assess clinical endpoints was considered unethical. All HPV vaccines have been registered for use based on their clinical efficacy in females 15 to 45 years of age and males 16 to 26 years of age. Clinical efficacy has then been inferred in younger individuals, using pre-licensure immunobridging studies that have demonstrated that the immune responses in the various different age groups are similar. When immune responses are similar, it is accepted that the vaccines will work equally well against infection and disease among the different age groups.

Specifically, a clinical trial demonstrated that the HPV vaccine type immune responses in females and males aged 9–14 years who received two doses of 9vHPV vaccine at least six months apart were equal to the immune responses in women aged 15–26 years who received three doses on a schedule where vaccine was given at times 0, 2 and then 6 months.[3] It is thus anticipated that in the younger age group this 2-dose 9vHPV vaccine schedule is as equally effective as a 3-dose 9vHPV vaccine schedule.

The immunogenicity of a 2-dose schedule in this age group was also supported by data using the other HPV vaccines (4vHPV and 2vHPV vaccines). For example, among girls aged 9–13 years who received two doses of 4vHPV vaccine six months apart, immune responses to HPV types 16 and 18 one month after the second dose were similar to responses in women aged 16–26 years (in whom clinical efficacy had been demonstrated) who received three doses within six months.[7] Another clinical trial demonstrated that two doses of 2vHPV vaccine administered to girls aged 9–14 years elicited the same immune response against HPV types 16 and 18 as a 3-dose schedule of 2vHPV vaccine given to women aged 15–25 years.[8] The 2vHPV vaccine in a 3-dose schedule had previously been proven effective in this older age group.[9]

HPV vaccines used in either 3- or 2-dose schedules have also been shown to be safe. There are no significant safety concerns regarding any of the available HPV vaccines. This statement is supported by an ATAGI review of the evidence supporting the use of a 2-dose HPV vaccine schedule as well as by extensive evidence reviews conducted by the World Health Organization Global Advisory Committee on Vaccine Safety and a number of other key national and international peak bodies.[1,10-13]

Recommendation 2: Use of 9vHPV in individuals previously vaccinated with 2vHPV or 4vHPV vaccines

The 9vHPV vaccine can be used to complete a schedule started with either 4vHPV or 2vHPV vaccines.

There have been no studies directly examining the use of 9vHPV vaccine to complete a series commenced with 4vHPV or 2vHPV vaccines. However, because 9vHPV vaccine in a 2-dose schedule has been demonstrated to produce an equivalent immune response to 9vHPV vaccine in a 3-dose schedule in girls and boys aged 9–14 years,[3] and the immune responses to the common HPV types in both the 9vHPV and 4vHPV vaccines (types 6, 11, 16 and 18) were demonstrated equivalent when either was given in a 3-dose schedule,[2] it is reasonable to assume that completion of a 2-dose or a 3-dose 4vHPV or 2vHPV vaccination schedule with 9vHPV vaccine will provide adequate protection against the common HPV types (6, 11, 16 and 18).

The 9vHPV vaccine is not recommended for those who have already completed a full (age appropriate) schedule with either 4vHPV or 2vHPV vaccines.

Vaccination against oncogenic types 16 and 18—included in both the 4vHPV and 2vHPV vaccines—will protect against approximately 70% of HPV-related cancers. For an individual to achieve complete protection of the additional five types included in the 9vHPV vaccine (types 31, 33, 45, 52 and 58), which are responsible for an approximate 15% of all HPV-associated cancers,[5] two or three additional doses (depending on age when vaccination was commenced) would be required. This represents additional injections, increased opportunity for adverse events, and additional resources and is thus not recommended.

One trial has examined safety and immune responses to a 3-dose 9vHPV vaccine schedule in females aged 12–26 years who had previously completed 3-dose schedules of 4vHPV vaccine.[14] The study demonstrated that three doses of 9vHPV vaccine were highly immunogenic against the additional five types included in the 9vHPV vaccine (types 31, 33, 45, 52 and 58). The study did not, however, report on immune responses following less than three doses of 9vHPV vaccine.[14] The frequency of injection site adverse events was higher in those receiving 9vHPV compared with those receiving placebo. The rates of vaccine-related systemic adverse events, however, were comparable between the vaccine and placebo group.[14]

Additional information

Following a positive recommendation from the Pharmaceutical Benefits Advisory Committee (PBAC) (http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2017-07/positive-recommendations-2017-07.pdf), from 2018, the 9vHPV vaccine is planned to replace the 4vHPV vaccine for use under the NIP in the 2-dose schedule recommended by the ATAGI in this document.

Benefits/Risks

There are four key benefits from the proposed changes to the use of HPV vaccines:

1. The 9vHPV vaccine provides protection against additional HPV types and an opportunity for a greater reduction in HPV infection and disease.

2. A 2-dose schedule is less resource-intensive to administer, particularly within a school year, compared with a 3-dose schedule.

3. Fewer doses may improve public acceptability and, in the longer term, should result in a greater number of adolescents who have completed a full HPV vaccination series. This is anticipated to result in a greater number of adolescents being fully vaccinated against HPV prior to sexual debut, the time from which the risk of exposure to the virus commences.

4. A reduction in prevalence of vaccine side effects arising from fewer doses being administered is anticipated.

There are three potential risks that may arise from the proposed changes to the use of HPV vaccines:

1. If an adolescent misses out on starting the HPV vaccination series prior to his or her 15th birthday, he or she will require a third dose of vaccine. It will be important to ensure that vaccination is commenced prior to the age of 15 years in order for the child to be fully protected by a 2-dose schedule.
2. The 9vHPV vaccine causes slightly more injection site reactions than the 4vHPV vaccine and may therefore result in a higher proportion of children experiencing pain after each dose.[2,4]
3. As there is no recommendation for additional vaccination with 9vHPV vaccine if an individual has completed vaccination with either 2vHPV or 4vHPV vaccines, there may be concern that these individuals are not protected against the additional five HPV types included in the 9vHPV vaccine.

Preference and values

Implementing these changes to the use of HPV vaccines in line with the best available clinical advice is anticipated to result in additional protection for individuals and the wider community (including those who are not vaccinated) against HPV related diseases, including cancer. This is considered consistent with parental and societal expectations of Australia's NIP.

Resources and other considerations

The Product Information (PI) for 9vHPV vaccine is not publicly available. If you would like to receive a copy of the PI for 9vHPV vaccine, please contact the sponsor of the vaccine directly.

Practical information

Communication to providers will be clearly articulated in the Australian Immunisation Handbook and other guidance to minimise confusion and ensure smooth implementation of these proposed changes in recommendations. In particular, providers require clear guidance regarding those who are suitable to receive the new 2-dose schedule using the appropriate interval between doses, and those who continue to need three doses of HPV vaccine in order to be fully protected. It should also be clear to providers and members of the public that individuals who commenced their HPV vaccination series with either 4vHPV (or less commonly 2vHPV) vaccines may complete the series with the 9vHPV vaccine. However, they will not be eligible to receive additional NIP-funded vaccination with the 9vHPV vaccine should they already have completed the series as they are

considered adequately protected against oncogenic types 16 and 18 that cause approximately 70% of HPV-related cancers. The 9vHPV vaccine could be purchased privately with a prescription.

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