

6.01 HUMAN PAPILLOMAVIRUS 9-VALENT VACCINE, Injection 0.5mL, pre-filled syringe Gardasil®9, Seqirus (Australia) Pty Ltd

1 Purpose

- 1.1 The Chief Medical Officer of the Department of Health and Aged Care requested the PBAC consider a variation to the National Immunisation Program (NIP) listing of the human papillomavirus 9-valent vaccine (9vHPV), Gardasil®9, from two doses to one dose for the adolescent vaccination program and to extend the upper age limit for catch up vaccination.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Females and males eligible for HPV vaccination
Intervention	1 dose of HPV vaccine
Comparator	2 or 3 doses of HPV vaccine
Outcomes	Vaccine efficacy against HPV-related infection and disease HPV antibody seropositivity and/or GMCs
Clinical claim	In the immunocompetent population, 1-dose is non-inferior to 2- or 3-dose in terms of efficacy Fewer mild-moderate short term adverse events

Source: Table 2, pp 2-3 of the CMO submission

GMC = geometric mean concentrations; HPV = human papillomavirus

2 Background

- 2.1 In April 2022, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) completed an evaluation of emerging evidence which indicated that a single dose HPV vaccine schedule provided comparable efficacy to two and three dose HPV vaccination schedules.¹ Based on evidence from 55 studies, it was concluded that one dose of HPV vaccine delivers comparable protection to multi-dose schedules in immunocompetent populations. The United Kingdom's Joint Committee on Vaccination and Immunisation (JCVI) in February 2022 recommended shifting to a one dose vaccination schedule for the pre-adolescent school-based program, which they reaffirmed in a statement in August 2022. JCVI anticipates implementing this schedule in the 2023–2024 school year following agreement on a policy decision and have recommended a single dose schedule for all

¹ World Health Organization Strategic Advisory Group of Experts on Immunization. Meeting of the Strategic Advisory Group of Experts on Immunization. One-dose Human Papillomavirus (HPV) vaccine offers solid protection against cervical cancer. Weekly Epidemiological Record April 2022.

immunocompetent people up to their 25th birthday (for whom vaccination is currently funded under their national program).

- 2.2 Aligning with considerations by these immunisation technical advisory committees, the Australian Technical Advisory Group on Immunisation (ATAGI) and the National Centre for Immunisation Research and Surveillance (NCIRS) initiated a review on evidence regarding the use of a single dose HPV vaccination in mid-2022.
- 2.3 At its August 2022 meeting, ATAGI agreed that the evidence currently available supports changing the HPV vaccine schedule from a two dose to a one dose schedule in immunocompetent people aged up until 25 years. ATAGI proposed extending the upper age limit of eligibility for NIP-funded dose to 25 years to allow all individuals who did not receive a funded dose during the routine program to receive funded HPV vaccine (the current age limit for two NIP-funded doses of HPV vaccine is 19 years). This expansion aligns with the original intention of the HPV vaccination program to maximise protection against all HPV-related cancers and would ensure equitable access for all those eligible.

Previous PBAC consideration

- 2.4 The PBAC previously considered the cost-effectiveness of Gardasil 9 in July 2017 as a two-dose schedule. In this assessment, Gardasil 9 was recommended for listing on the NIP for females and males aged 12-13 years as part of a school-based program.
- 2.5 Prior to this, a 4-valent HPV vaccine, Gardasil®, was available on the NIP, using a three-dose schedule. Gardasil was initially included on the NIP in 2007 for females aged 12-13 years. In 2013 this was expanded to include males 12-13 years, with a catch-up program for males aged 14-15 years.

3 Proposed NIP listing

- 3.1 The table below presents ATAGI's proposed updated recommendations to the NIP listing of 9vHPV vaccine.

Name, Restriction, Manner of administration and form	Nationally Negotiated Price	Proprietary Name and Manufacturer				
HUMAN PAPILLOMAVIRUS (HPV) (9-VALENT) VACCINE 0.5 mL, Injection	\$ [REDACTED] per dose	Gardasil 9 Seqirus (Australia) Pty Ltd				
Clinically recommended dosing schedule	<table border="1"> <thead> <tr> <th data-bbox="424 450 927 488">Current recommendation</th> <th data-bbox="927 450 1396 488">Proposed new ATAGI recommendation</th> </tr> </thead> <tbody> <tr> <td data-bbox="424 488 927 741"> <ul style="list-style-type: none"> Age 9–14 years: 2 doses of 9vHPV vaccine (6–12 months between doses) Age ≥15 years: 3 doses of 9vHPV vaccine (2 months between dose 1 and dose 2; 4 months between dose 2 and dose 3) Immunocompromised people aged ≥9 years: 3 doses of 9vHPV vaccine (as above) </td> <td data-bbox="927 488 1396 741"> <ul style="list-style-type: none"> Age: 9-25 years: 1 dose of 9vHPV Age ≥26 years: at least 2 doses of 9vHPV vaccine (6–12 months between doses)^ Immunocompromised age ≥9 years: 3 doses of 9vHPV vaccine (as above) </td> </tr> </tbody> </table>		Current recommendation	Proposed new ATAGI recommendation	<ul style="list-style-type: none"> Age 9–14 years: 2 doses of 9vHPV vaccine (6–12 months between doses) Age ≥15 years: 3 doses of 9vHPV vaccine (2 months between dose 1 and dose 2; 4 months between dose 2 and dose 3) Immunocompromised people aged ≥9 years: 3 doses of 9vHPV vaccine (as above) 	<ul style="list-style-type: none"> Age: 9-25 years: 1 dose of 9vHPV Age ≥26 years: at least 2 doses of 9vHPV vaccine (6–12 months between doses)^ Immunocompromised age ≥9 years: 3 doses of 9vHPV vaccine (as above)
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Eligibility for NIP-funded schedule	<table border="1"> <tbody> <tr> <td data-bbox="424 741 927 1064"> <ul style="list-style-type: none"> Routine program: 2 doses given at age 12–13 years Catch-up program: 2 funded doses available until age 19 years Immunocompromised: 3 doses for ages 12–<15 years </td> <td data-bbox="927 741 1396 1064"> <ul style="list-style-type: none"> Routine program: 1 dose of 9vHPV given at age 12-13 years Eligibility for missed doses: Individuals who do not receive their 1 dose of 9vHPV at age 12-13 remain eligible for a funded dose of 9vHPV until age 25 years (i.e. 26th birthday date) Immunocompromised people: 3 doses of 9vHPV vaccine until age 25 years (i.e. 26th birthday date) </td> </tr> </tbody> </table>		<ul style="list-style-type: none"> Routine program: 2 doses given at age 12–13 years Catch-up program: 2 funded doses available until age 19 years Immunocompromised: 3 doses for ages 12–<15 years 	<ul style="list-style-type: none"> Routine program: 1 dose of 9vHPV given at age 12-13 years Eligibility for missed doses: Individuals who do not receive their 1 dose of 9vHPV at age 12-13 remain eligible for a funded dose of 9vHPV until age 25 years (i.e. 26th birthday date) Immunocompromised people: 3 doses of 9vHPV vaccine until age 25 years (i.e. 26th birthday date) 		
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Source: Table 1, p1 of the CMO submission

Abbreviations: NIP, National Immunisation Program

*Intervals between doses are recommended as per the Australian Immunisation Handbook. There is no specified upper limit for the interval before the final dose.

^ATAGI are still reviewing and finalising the clinical recommendation

3.2 9vHPV is currently TGA registered as a three dose schedule, or alternatively as a two dose schedule for individuals aged 9 to 14 years. The submission noted that a recommendation of a single dose for those up to 25 years of age would be a variation from the TGA Product Information. However, ATAGI and the NIP currently and previously have recommended vaccine schedules in this context, e.g. for pneumococcal and meningococcal.

Routine HPV vaccination program for adolescents

3.3 The current NIP Schedule provides HPV vaccines for individuals aged 12-13 routinely as part of a school-based program. The NIP adolescent program includes school visits for HPV, meningococcal ACWY and diphtheria, tetanus and pertussis vaccination.

3.4 ATAGI noted dose 2 coverage varies by jurisdiction, gender and sociodemographic factors (socioeconomic status (SES) and geographical remoteness).

3.5 ATAGI recommends revising the current two dose schedule to become a single-dose schedule using the same 9vHPV vaccine, for individuals aged 12-13 years who do not have an immunocompromising condition. A three dose schedule should continue to be provided for individuals who are immunocompromised at the time of schedule initiation.

Eligibility for missed doses

- 3.6 Funding for any missed doses currently extends only to people aged up to 19 years, despite recommendations in the Australian Immunisation Handbook that course completion of missed dose/s, based on clinical benefit provided, should occur at older ages.
- 3.7 ATAGI recommends expanding the upper limit of age eligibility for NIP-funded vaccination to allow people up to age 25 years (inclusive) to receive missed dose/s of funded HPV vaccine (thus removing the current age limit of 19 years for two NIP-funded doses of HPV vaccine). The submission noted the use of a single dose schedule of HPV vaccine for those commencing vaccination aged 15 years and older, rather than three doses in this age group, which is currently recommended if commencing vaccination at or after 15 years of age, will simplify efforts to provide missed doses and potentially enable protection of a greater number of individuals at a reduced out-of-pocket expense.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of the evidence

Clinical effectiveness

- 4.1 The submission presented the following key studies supporting the use of a single dose of HPV vaccine.

Table 2: Summary of key studies presented in the submission

Trial and Study ID	Study type	Intervention vs comparator	Follow up period	Study population	Findings
Efficacy					
KEN SHE trial Barnabas RV, Brown ER, Onono MA, et al. Efficacy of single-dose HPV vaccination among young African women. <i>NEJM Evid</i> 2022;1:EVIDoa2100056.	RCT, efficacy	1 dose 9vHPV and 1 dose 2vHPV vs control	18 months	Females 15-20 years 2vHPV n=760 9vHPV n=758 Unvaccinated n=757	VE against incident persistent HPV infection at month 18: HPV16/18*: 97.5% (95% CI: 81.7–99.7) 9vHPV-types (9vHPV): 88.9% (95%CI: 68.5–96.1) *HPV16/18 VE was the same for 2vHPV & 9vHPV
IARC trial (India) Basu P, Malvi SG, Joshi S, et al. Vaccine efficacy against persistent human papillomavirus (HPV) 16/18 infection at 10 years after one, two, and three doses of quadrivalent HPV vaccine in girls in India: a multicentre, prospective, cohort study. <i>The Lancet Oncology</i> 2021;22:1518-29.	Prospective cohort	1, 2, 3 doses of 4vHPV vs. unvaccinated	10 years	Females 10-18 years 1 dose=2135 2 dose=1452 3 dose=1460 Unvaccinated = 1260	VE against persistent HPV16/18 infection at year 10: 1 dose: 95.4% (95% CI: 85.0–99.9) 2 dose: 93.1% (95% CI: 77.3–99.8) 3 dose: 93.3% (95% CI: 77.5–99.7)
Brotherton JM, Budd A, Rompotis C, et al. Is one dose of human papillomavirus vaccine as effective as three?: A national cohort analysis. <i>Papillomavirus Res</i> 2019;8:100177	Retrospective cohort	1, 2, 3 doses of 4vHPV vs. unvaccinated	2.5 years	Females ≤15 years 1 dose n=8,618 2 dose n=18,190 3 dose n=174,995 Unvaccinated=48,845	aHR of CIN2/AIS+, compared to unvaccinated: 1 dose: 0.65 (95%CI: 0.52–0.81) 2 dose: 0.61 (95%CI: 0.52–0.72) 3 dose: 0.59 (95%CI: 0.54–0.65) HR of 1 vs 3 dose: 1.01 (95%CI: 0.81–1.26)
CVT trial Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. <i>JNCI: Journal of the National</i>	Prospective cohort	1, 2, 3 doses of 2vHPV vs. unvaccinated	11 years	Females 18–25 years 1 dose n=112 2 dose n=62 3 dose n=1365 Unvaccinated n=1783	VE against HPV16/18 9 or 11 years post vaccination (prevalent infections) 1 dose: 82% (95%CI: 40.2–97.0) 2 dose: 83.8% (95%CI: 19.5–99.2) 3 dose: 80.2% (95%CI: 70.7–87.0)

Public Summary Document – December 2022 PBAC Meeting

Trial and Study ID	Study type	Intervention vs comparator	Follow up period	Study population	Findings
<i>Cancer Institute 2020</i> ;112:1038-46					VE against HPV16/18 11 years post vaccination (incident infections) 1 dose: 53.9% (95%CI: -57.1 to 92.4) 2 dose: 58.4% (95%CI: -110.9 to 97.9) 3 dose: 84.9% (95%CI: 69.8–93.2)
Kreimer AR, Struyf F, Del Rosario-Raymundo MR, et al. Efficacy of fewer than three doses of an HPV-16/18 AS04-adjuvanted vaccine: combined analysis of data from the Costa Rica Vaccine and PATRICIA Trials. <i>Lancet Oncol</i> 2015;16:775-86	Pooled results with CVT trial	1, 2, 3 doses of 2vHPV vs. Hep A control	12 months	Females 15–25 years 1 dose n=292 2 dose n=611 3 dose n=11,104 Unvaccinated n=11,203	VE against incident HPV16/18 infection at 12 months: 1 dose: 95% (95%CI: 73–100) 2 dose: 90% (95%CI: 69–98) 3 dose: 87% (95%CI: 84–90)
Immunogenicity					
DoRIS trial Watson-Jones D, Chungalucha J, Whitworth H, et al. Immunogenicity and safety results comparing single dose human papillomavirus vaccine with two or three doses in Tanzanian girls - the DoRIS randomised trial. <i>Pre-print available at SSRN: https://ssrn.com/abstract=4055429</i> 2022	RCT	1, 2, 3 doses of 9vHPV and 2vHPV	24 months	Females 9-14 years 310 for 9vHPV, 2vHPV and unvaccinated each	>99% seropositive for HPV16 and >98% seropositive for HPV18 at 24 months for both vaccines. GMs lower for 1 dose group compared to 2 or 3 at all timepoints for both vaccines. No difference in antibody avidity index.
Glica V, Sauvageau C, Panicker G, et al. Long intervals between two doses of HPV vaccines and magnitude of the immune	Post-hoc analysis of 2 cohort studies	1 dose 9vHPV vs 4vHPV (with extended interval 2 nd dose)	1-6 months (study A); 3-8 years (study B)	Study A (9vHPV 1-6m interval): 85 boys, 88 girls aged 9–10 years Study B (4vHPV 3-8y interval): 31 girls aged 9–14 years	GMT post dose 1, 3-8y post 4vHPV vs 1-6m post 9vHPV HPV6: 6.1 (3.0, 10.6) vs 5.3 (4.6, 6.1) HPV11: 7.7 (4.5, 13.1) vs 5.8 (5.1, 6.6) HPV16: 20.1 (12, 33.7) vs 29.7 (26.2, 33.7)

Public Summary Document – December 2022 PBAC Meeting

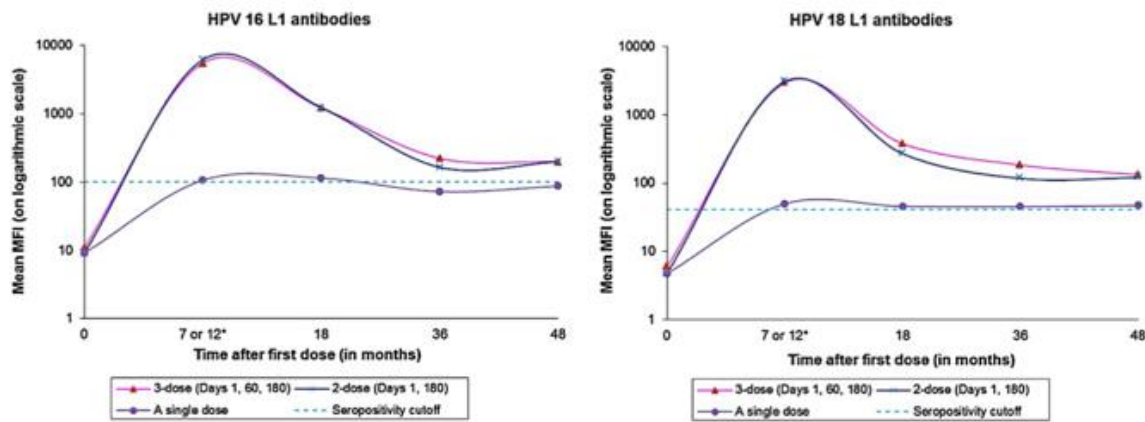
Trial and Study ID	Study type	Intervention vs comparator	Follow up period	Study population	Findings
response: a post hoc analysis of two clinical trials. <i>Hum Vaccin Immunother</i> 2019;15:1980-5					HPV18: 6.3 (3.8, 10.2) vs 11 (9.5, 12.7)
IARC trial Sankaranarayanan R, Joshi S, Muwonge R, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. <i>Vaccine</i> 2018;36:4783-91 (India)	Prospective cohort	1, 2, 3 doses of 4vHPV vs. unvaccinated	48 months	Females 10-18 years Approx 1000 per dose group at day 1 Ns at month 36 – 1 dose: 510 2 dose: 278 3 dose: 271	GMTs were substantially lower for the 1-dose group relative to the 3-dose group at all timepoints up to 48 months. GMR 1 vs 3 dose at month 36: HPV16 0.33 (0.28–0.37), HPV18 0.25 (0.21–0.29), HPV6 0.21 (0.18–0.24), HPV11 0.18 (0.16–0.21) Geometric avidity indices at 7 and 18 months were similar and non-inferior across groups.
CVT trial Safaeian M, Sampson JN, Pan Y, et al. Durability of Protection Afforded by Fewer Doses of the HPV16/18 Vaccine: The CVT Trial. <i>Journal of the National Cancer Institute</i> 2018;110 Safaeian M, Porras C, Pan Y, et al. Durable antibody responses following one dose of the bivalent human papillomavirus L1 virus-like particle vaccine in the Costa Rica Vaccine Trial. <i>Cancer prevention research (Philadelphia, Pa)</i> 2013;6:1242-50.	Prospective cohort	1, 2, 3 doses of 2vHPV vs. unvaccinated	11 years	Females 18-25 years 1 dose n=112 2 dose n=62 3 dose n=1365	GMTs were lower for the 1-dose group relative to the 3-dose group at all timepoints up to 11 years. GMTs for 2-dose group also lower than 3-dose.

Source: Table 3, pp 4-7 of the CMO submission

CVT: Costa Rica HPV Vaccine Trial; GMR: Geometric Mean titre Ratio; GMT: Geometric Mean Titre; PATRICIA: Papilloma Trial against Cancer In young Adults; RCT: Randomised Controlled Trial; VE: Vaccine Effectiveness

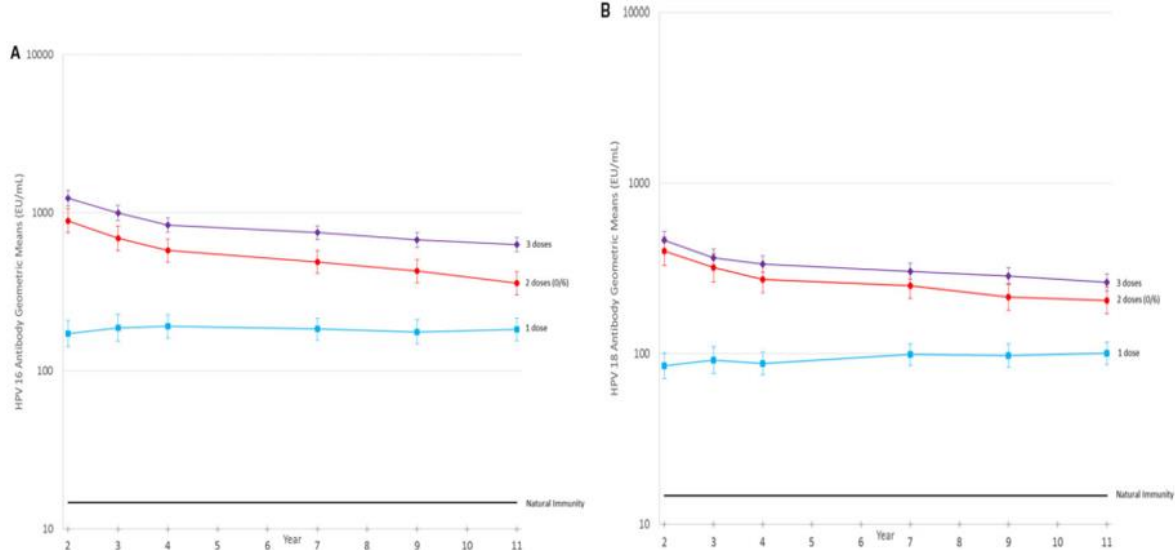
- 4.2 A single dose of HPV vaccine was examined in the submission for immunogenicity and efficacy/effectiveness in healthy girls and women aged 9 to 25 years, extending to 11 years post vaccination.
- 4.3 In the review of the evidence for HPV vaccine (and other vaccines), ATAGI prioritises findings with clinical disease endpoints over immunogenicity endpoints. Immunogenicity outcomes are used as a surrogate endpoint when clinical data is unavailable. Immunogenicity endpoints were primarily used for HPV vaccine in the past given the long latency period between acquisition of HPV infection and development of disease. However, data on clinical disease endpoints are now available. ATAGI noted that it specifically examined evidence on immunogenicity from randomised controlled trials (RCTs) examining vaccine use in the target NIP population and long-term immunogenicity data up to 11 years post-vaccination to fill the gaps in current evidence on clinical endpoints.
- 4.4 Evidence for a single dose of 9vHPV was based on two RCTs and one post hoc analysis of two small clinical trials. The current evidence supports the efficacy of a single dose of 9vHPV vaccine against persistent HPV16/18 infection, which is a pre-requisite for developing HPV-related cervical cancer; findings for other endpoints (including cervical disease or other site specific HPV-related cancers) have not been reported yet due to the typically long latency period between infection acquisition and clinical disease.
- 4.5 Data from observational cohort studies of 4vHPV and 2vHPV vaccines demonstrate clinical effectiveness of a single dose of HPV vaccine over 11 years post vaccination. In most studies, the comparator is a three dose schedule of HPV vaccine. This includes evidence of effectiveness against cervical pre-cancerous lesions among Australian women who received only one dose of the 4vHPV vaccine. These studies report that the effectiveness of a single dose of vaccine is equivalent to a multi-dose (two or three doses) schedule of HPV vaccine and persists over time.
- 4.6 A single dose of 9vHPV vaccine generates an immune response (seroconversion) in more than 98% of vaccine recipients up to two years post vaccination, although the geometric mean concentrations (GMCs) are noted to be lower than those who receive a two or three dose schedule. There was no difference in the antibody avidity indices between dose groups. GMCs following a single dose stabilise from 12 months to 24 months. A threshold level of HPV antibodies that correlates with clinical protection has not been established. As current evidence supports clinical protection even with lower GMCs, the lower but stable GMCs from post year 1 onwards do not appear to indicate reduced protection. Long-term immunogenicity studies of 4vHPV and 2vHPV vaccine show similar findings to the study of 9vHPV vaccine. GMCs following a single dose of 4vHPV or 2vHPV stabilise from 12 months out to 11 years post vaccination (refer to Figures 1 and 2 below).

Figure 1: Mean median fluorescent intensity (MFI) values for HPV16 and 18 L1 antibodies at different time points among girls who received 1, 2 or 3 doses of 4vHPV vaccine



Source: Sankaranarayanan R, Joshi S, Muwonge R, et al. Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. *Vaccine* 2018;36:4783-91; Figure 2 of the CMO submission.

Figure 2: HPV16 and HPV18 antibody levels (GMTs) over time by number of doses received from the CVT trial



A: HPV16 antibodies; B: HPV18 antibodies.

Sample size as follows:

- Year 2: 1 dose (n=78), 2 dose (n=52), 3 dose (n=120)
- Year 4: 1 dose (n=134), 2 dose (n=79), 3 dose (n=2034)
- Year 11: 1 dose (n=112), 2 dose (n=62), 3 dose (n=1365)

Source: Kreimer AR, Sampson JN, Porras C, et al. Evaluation of Durability of a Single Dose of the Bivalent HPV Vaccine: The CVT Trial. *JNCI: Journal of the National Cancer Institute* 2020;112:1038-46; Figure 3 of the CMO submission

4.7 The pre-PBAC response from the sponsor raised concerns of potential waning from a single HPV vaccine dose over time. ATAGI was satisfied that there is currently clinical and immunogenicity data with follow-up out to 11 years post vaccination that show ongoing clinical protection that does not wane. ATAGI noted that trials are ongoing and there are plans to present longer term data soon but ATAGI did not agree that it was necessary to wait for the results of these additional studies before recommending a change in the current schedule. The JCVI explored scenarios of potential waning in modelling studies that were designed to assess the implication of adopting a one dose

schedule, unlike the Simms et al.² model which was designed to compare 4vHPV and 9vHPV vaccines. A one dose schedule was not predicted to substantially increase cervical cancers if duration of protection extended beyond 20 years. Even if the duration of protection did not extend beyond 20 years, the impact would not be immediate and clinical trials with long term follow-up would be available.

- 4.8 In immunocompromised individuals there is currently limited evidence on the effectiveness of two dose schedules, and no studies that examined a one dose schedule in this population have been identified. A single study examining a two dose schedule of HPV vaccine in individuals living with HIV infection found that a two dose schedule was as immunogenic in younger adolescents with immune reconstitution as a three dose schedule in older adolescents without immune reconstitution. The submission noted the interpretations of this study's findings are limited due to bias arising from the imbalance in participant characteristics between those receiving two compared with three doses, and the relatively small sample size. Findings may also not be generalisable to individuals with other immunocompromising conditions particularly those without immune reconstitution.

Comparative harms

- 4.9 Safety of a single dose HPV schedule was not reviewed in detail in the submission. However, it is anticipated that a single injection compared with two injections will reduce the number of mild-moderate short term adverse events expected after any vaccine dose. In 2020, 91% of adolescents aged 12 to 13 years who received HPV first dose, concomitantly with the diphtheria, tetanus and whooping cough vaccine did not report any adverse event. As reported by AusVaxSafety, injection site pain, swelling or redness was the most commonly reported adverse event followed by tiredness, headache and fever. The submission noted that given that evidence shows a single dose provides equivalent clinical protection to two doses, subjecting adolescents to the potential risk of adverse events after a second dose is not justifiable.

Clinical claim

- 4.10 The submission described that in the immunocompetent population, one dose of HPV vaccine is non-inferior to two or three dose of vaccine in terms of efficacy, with fewer mild-moderate short term adverse events.
- 4.11 The PBAC considered that based on the clinical and immunogenicity evidence available, it is likely that a single dose of 9vHPV vaccine is non-inferior in terms of efficacy as compared with a two dose schedule in non-immunocompromised individuals, and at least as comparable if not more so, in terms of safety (a single

² Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. *Lancet Public Heal.* 2016;1(2):e66–75.

compared with two injections will reduce the number of mild-moderate short term adverse events expected after any vaccine dose).

Economic analysis

4.12 The PBAC recalled in July 2017 that the cost effectiveness of 9vHPV was acceptable on the basis of the range of ICERs calculated by the evaluation (of \$35,000 to < \$45,000 per QALY gained, assuming the same price per dose for 4vHPV as for the 3-dose schedule (of \$/dose)) and the sponsor (of \$0 to < \$5,000 per QALY gained (which assumed \$/dose)) (paragraph 7.15, human papillomavirus 9-valent vaccine (Gardasil 9) Public Summary Document, July 2017 PBAC meeting). Once standard adolescent vaccines are accounted for, there are currently no additional subsidies for HPV vaccines for individuals 20 years of age and older under the NIP.

4.13 No new economic evaluation was provided with this submission.

Estimated PBS usage & financial implications

4.14 The tables and figures below were presented in the submission to provide an estimate of the population who has been vaccinated with Gardasil 9 over the last 4 years based on the Department of Health and Aged Care’s Australian Immunisation Register (AIR) data.

Table 3: HPV vaccination coverage (%) at 15 years of age, by gender and Indigenous status in Australia 2020 and 2021

Population**	2020		2021	
	Dose 1	Dose 2	Dose 1	Dose 2
All adolescents				
Girls	86.6	80.5	86.2	80.3
Boys	84.9	77.6	84.4	77.2
Indigenous adolescents				
Girls	87.8	75.0	86.1	73.3
Boys	83.0	68.0	80.6	66.2

Source: Annual immunisation coverage report 2021 Table 5, Table 6; Table 6 of the CMO submission

** Population derived from the AIR population (includes Medicare card holders and vaccinated non-Medicare card holders).

Table 4: Number of first and second dose HPV vaccinations among 11–<15 year olds, by year and indigenous status

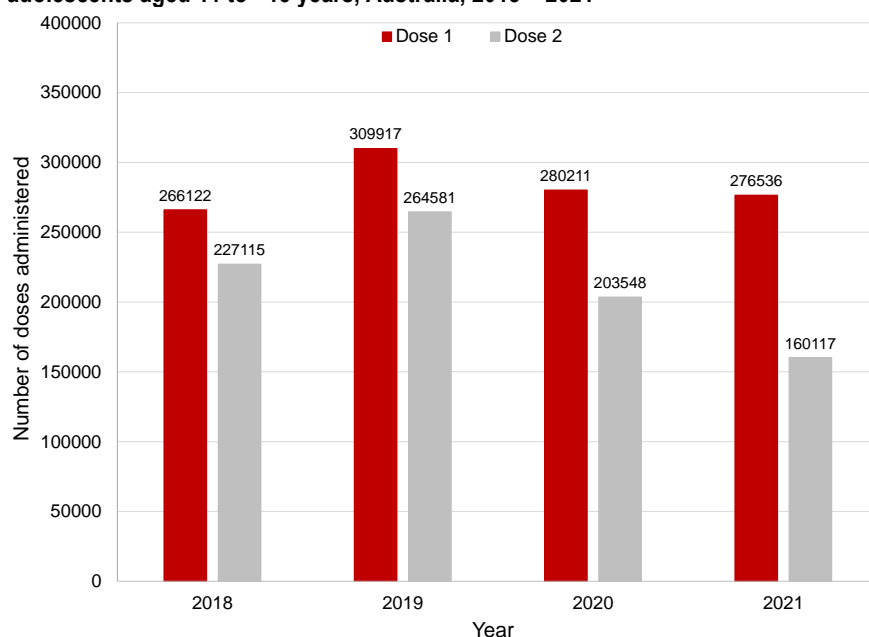
Population*	Dose	2018	2019	2020	2021
All adolescents	1	255,122	309,917	280,211	276,536
Indigenous adolescents	1	13,206	15,481	14,078	13,531
'catch-up'***	1	N/A	N/A	N/A	N/A
	2	See figure	21,435	23,678	48,681

* Population derived from the AIR population (includes Medicare card holders and vaccinated non-Medicare card holders).

** Reflects receipt of 2nd dose among adolescents aged 11–14 years who received their first dose in the previous year

Source: Impact of COVID-19 on School-based Vaccination Programs July 2022 Figure 1, Figure 2 and Figure 5 (plus text); Table 7 of the CMO submission

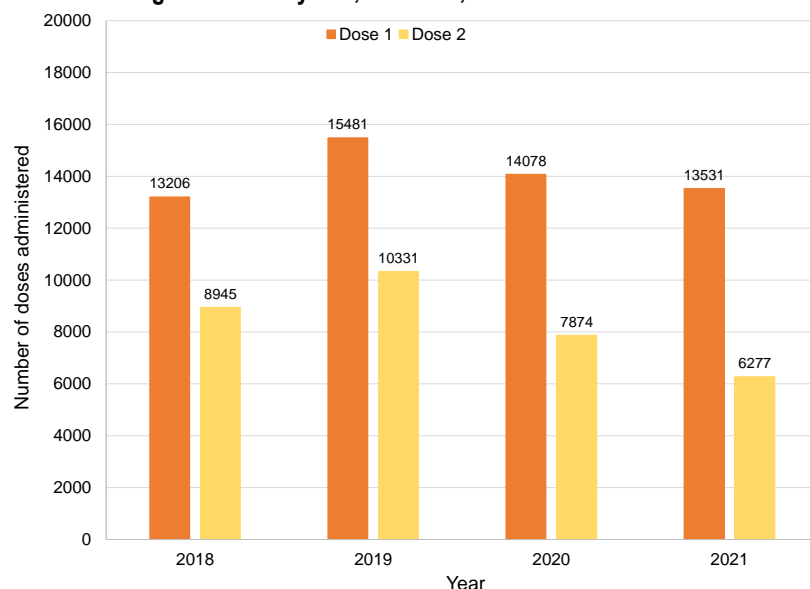
Figure 3: Number of first and second (administered in same calendar year as first) dose HPV vaccinations, adolescents aged 11 to <15 years, Australia, 2018 – 2021*



Source: Impact of COVID-19 on School-based Vaccination Programs July 2022; Figure 1 of the CMO submission

*Increased numbers in 2019 are an artefact as WA vaccinated 2 school cohorts (year 7 and year 8) while switching over to a year 7 vaccination program

Figure 4: Number of first and second (administered in same calendar year) dose HPV vaccinations, Indigenous adolescents aged 11 to <15 years, Australia, 2018 – 2021*



Source: Impact of COVID-19 on School-based Vaccination Programs July 2022; Figure 2 of the CMO submission

*Increased numbers in 2019 are an artefact as WA vaccinated 2 school cohorts (year 7 and year 8) while switching over to a year 7 vaccination program

4.15 The PBAC noted that there is currently approximately 85% coverage for first dose across those at 15 years of age, by gender and Indigenous status in Australia 2020 and 2021. However, coverage reduces amongst all groups for the second dose.

- 4.16 The sponsor noted the Department’s request to provide updated estimates of utilisation and financial implications for the NIP based on the ATAGI recommendation for the proposed revised one dose HPV vaccine schedule in its pre-PBAC response. However, no estimates were provided given the sponsor’s argument that the one dose schedule has not been demonstrated to provide non-inferior efficacy based on the clinical evidence currently available and that there is currently no agreed price for a one dose program.

Stakeholder meeting for implementation of NIP change

- 4.17 ATAGI recommends that comprehensive consultation with stakeholders involved in delivering HPV vaccination programs be conducted prior to switching to a one dose schedule, to mitigate against unintended consequences of this schedule change. In particular, ensuring equitable access to HPV vaccines through effective and culturally appropriate approaches is critical to reach the goal of cervical cancer elimination and should be a focus of the directed resources. Challenges to achieving high coverage will vary based on the local context, so close consultation is needed to develop tailored strategies accordingly.
- 4.18 ATAGI also recommends clear communication about the shift to a single dose schedule of HPV vaccine with stakeholders, including jurisdictional implementing partners, immunisation providers and the public, in advance of the schedule change. Development and implementation of a comprehensive communication plan should be considered. It is particularly important to emphasise that this change is based on a large volume of evidence that has emerged in recent years, and ATAGI’s recommendations are aligned with those of the WHO SAGE and the UK’s JCVI.

For more detail on PBAC’s view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended a change to the circumstances under which the human papillomavirus 9-valent (9vHPV) vaccine is made available as a designated vaccine for the purposes of the *National Health Act 1953* based on a request for advice that was initiated by the Chief Medical Officer of the Department of Health and Aged Care. The PBAC recommended that the National Immunisation Program (NIP) listing of 9vHPV vaccine be changed from two doses to one dose for the adolescent vaccination program and that the upper age limit for catch up vaccination be updated from 20 years to 25 years.
- 5.2 The PBAC noted the advice of ATAGI regarding the likely non-inferior efficacy of a single dose of 9vHPV vaccine compared to two doses in immunocompetent adolescents aligned with recommendations made by the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) and the United Kingdom’s Joint Committee on Vaccination and Immunisation (JCVI). ATAGI recommended that adolescents and adults aged up to 25 years who did not receive

HPV vaccination during adolescence be eligible to receive a single dose of 9vHPV vaccine (previously up to age 19 years). The clinical impacts of not proceeding with the schedule change would mean people aged 20 to 25 years, who did not receive a funded HPV vaccine during adolescence, will not be eligible for a funded vaccine.

- 5.3 The PBAC noted the dissenting opinion of the sponsor with regards to implementing the proposed change, citing data immaturity and that a hasty move may jeopardise Australia's long-term plans to eliminate HPV. The pre-PBAC response stated the sponsor was supportive of the PBAC commissioning a full clinical and cost-effectiveness review to be conducted as per the PBAC guidelines to ensure any potential change to the HPV vaccine schedule is thoroughly evaluated, given the proposed one dose schedule deviates from the current TGA approved dosage and administration. However, the PBAC noted the ATAGI advice and evidence summarised in section 4 and was reassured by the long-term immunogenicity studies of single versus multiple doses which demonstrated stabilised GMCs out to 11 years. The PBAC advised the plateau in Figures 1 and 2 gives confidence that the protective effect will be persistent over many years.
- 5.4 The PBAC advised that on the basis of presented clinical and immunogenicity data, a single dose schedule of 9vHPV is likely to be non-inferior in terms of effectiveness to two doses in the currently eligible population (12-19 years) and therefore likely to be cost effective (and cost saving) at the existing unit price of the 9vHPV vaccine, including administration costs for the current schedule. Similarly, the PBAC advised a single dose schedule of 9vHPV is likely to be non-inferior in terms of effectiveness to two doses and be cost-effective for immunocompetent individuals from 20-25 years. The PBAC considered that in terms of safety, a single dose of 9vHPV vaccine compared with two doses will likely reduce the number of mild-moderate short term adverse events expected after any vaccine dose.
- 5.5 The PBAC acknowledged the public health value of achieving elimination of cervical cancer, and ATAGI's advice that a move to a one dose schedule will need to be supported by prospective monitoring against elimination goals, noting there is moderate residual risk in unvaccinated young people. The PBAC noted the following considerations would be required for program implementation:
- enhancing HPV vaccine coverage, particularly in those who are currently not receiving one dose
 - enhancing disease surveillance for HPV infection and associated disease
 - evaluation of the HPV vaccination program following this change

Outcome:

Recommended

6 Recommended listing

6.1 Amend current HPV 9-valent vaccine listing in the Determination:

Vaccine and the circumstances in which vaccine may be provided	Brand	Formulation	Number and timing of doses
Human papillomavirus (HPV) (9-valent)	Gardasil 9	Injection (0.5mL)	1 dose
		Each of the following: (a) HPV 6 L1 protein - 30µg; (b) HPV 11 L1 protein - 40µg; (c) HPV 16 L1 protein - 60µg; (d) HPV 18 L1 protein - 40µg; (e) HPV 31 L1 protein - 20µg; (f) HPV 33 L1 protein - 20µg; (g) HPV 45 L1 protein - 20µg; (h) HPV 52 L1 protein - 20µg; (i) HPV 58 L1 protein - 20µg.	

Circumstances

Vaccine may be provided to:

- (a) a person who is at least 12 years of age but less than 14 years of age; or
- (b) a person up to and including 25 years of age who has not received a single dose of HPV vaccine
- (c) Immunocompromised people up to and including 25 years of age – 3 doses

This NIP listing may be subject to further review. Should there be any changes made to the circumstances above the sponsor will be informed.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The PBAC has noted considerations for new recommendations include a focus on ensuring that time is taken to ensure this significant change is implemented well and we are very supportive of this. This includes a clear plan for enhancing vaccination coverage, disease surveillance and evaluation of the ongoing program.