Coversheet on evidence assessment by ATAGI using the GRADE framework

Summary of key methods and decisions on evidence assessment using GRADE (Grading of Recommendations Assessment, Development and Evaluation) for developing ATAGI recommendations on the use of a single dose of human papillomavirus (HPV) vaccine for the Australian Immunisation Handbook

Background

- In April 2022, the World Health Organization (WHO) completed a comprehensive GRADE assessment of the evidence supporting use of a single dose of HPV vaccine and recommended a single dose schedule of the HPV vaccine to females aged 9 to 20 years.[1]
- Throughout 2022 ATAGI provided advice to the Department of Health regarding potential changes to the HPV schedule in Australia.
- In February 2023, the routine 2-dose HPV schedule in Australia provided to adolescents aged 12 to 13 years under the National Immunisation Program, changed to a single dose schedule.
- ATAGI undertook GRADE assessment in 2022 to underpin the relevant recommendation on the use of a single HPV dose in Australia.
- This GRADE assessment utilises and builds on the WHO assessment. The PICO questions used by WHO are tailored to the Australian context and the literature search has been updated.

Research questions

1. Should adolescents and young adults receive a single dose of 9vHPV compared to no vaccine/control vaccine/placebo?

Table 1 PICO 1: 1 dose vs. no vaccine/control vaccine/placebo

Population	Immunocompetent females and males aged ≥9 years
Intervention	1 dose of 9vHPV
Comparator	no vaccine/control vaccine/placebo
Outcomes	HPV infection Genital infection CIN3+ Serious adverse events

2. Should adolescents and young adults receive a single dose of 9vHPV compared to two or three doses?

Table 2 PICO 2: 1 dose vs. 2 or 3 doses

Population	Immunocompetent females and males aged ≥9 years
Intervention	1 dose of 9vHPV
Comparator	2 or 3 doses of 9vHPV
Outcomes	Genital infection Serious adverse events Seropositivity GMT ratio Local adverse events Systemic adverse events

The PICOs were created based on WHO Strategic Advisory Group of Experts (SAGE) Working Group's GRADE assessments. The intervention in the PICOs were adjusted to 9vHPV as it is the vaccine currently (as of 2022) recommended in Australia. The GRADE project sought to expand upon the findings of the WHO GRADE, identifying additional studies that has been published since its completion in March 2022.

PICO 1 with a comparator of "no vaccine or control vaccine" was included to ensure all available evidence on a single dose schedule was identified (there are large pivotal studies that did not include a 2 or 3 dose treatment arm). PICO 2 comparator was a multi-dose schedule. The HPV vaccine recommendation in the target population in Australia prior to the HPV schedule change was 2 doses.

Literature search

A literature search was performed on 8 March 2023 to identify studies assessing immunogenicity, efficacy, effectiveness and/or safety outcomes of a single dose of the 9vHPV vaccine. Details of the search methods are presented in Appendix A. The citations were selected for review if they met the following criteria:

- Study type: randomized controlled trial (RCT), observational study
- Population: Males and females aged ≥9 years
- Intervention: 1 dose 9vHPV
- Comparator: 2 or 3 doses 9vHPV
- Outcomes: Effectiveness, efficacy, immunogenicity, safety

A total of six citations[2-7] met the above pre-defined inclusion criteria. Among those there were four RCTs and two observational studies. Three of the studies were included in PICO 1 and four of the studies were included in PICO 2.

Inclusion criteria and rationale

Table 3 Rationale for PICO and inclusion criteria

Inclusion criteria	Rationale
Study type: RCT, observational study	All study types comparing 9vHPV to 2 or 3 doses of a HPV vaccine, control vaccine, no vaccine or placebo vaccines were included. Only studies with full publications were included (i.e. abstracts or studies with results on clinical trials.gov only were excluded)
Population Immunocompetent females and males aged ≥9 years	Females and males aged ≥9 years are eligible and recommended to receive 9vHPV in Australia (in 2022). Although adults are not routinely recommended to receive HPV vaccination, the upper age limit was not defined to ensure all evidence was identified. It was assumed that majority of evidence would include populations vaccinated between ages 9-18 years. Immunocompetent population was selected as no data was known to be available on single HPV dose in immunocompromised. No change to the recommendation for immunocompromised populations were made. Evidence was not separated out by males and females given the limited studies in males.
Intervention 1 dose 9vHPV	The intervention was restricted to 9vHPV as it is the vaccine currently (as of 2022) recommended in Australia. A detailed and comprehensive GRADE assessment including all HPV vaccines (2vHPV, 4vHPV and 9vHPV) was performed by SAGE in January 2022. The findings from this assessment were referred to when making the Australian recommendations
Comparator No vaccine/control vaccine 2 or 3 doses	PICO 1 comparator was no vaccine or control vaccine. This was included to ensure all available evidence on a single dose schedule was identified as there are large pivotal studies that did not include a 2 or 3 dose treatment arm. The results from this comparison can still be used to inform the effectiveness and protection from a single HPV dose. PICO 2 comparator was a multi-dose schedule – either 2 or 3 doses. The HPV vaccine recommendation in the target population in Australia prior to the HPV schedule change was 2 doses.
Outcomes	Included outcomes as stated above in Table 1 and Table 2
	Ranking of importance of each critical or important outcomes discussed iteratively reaching consensus with the ATAGI full panel.
	General framework (depending on outcomes measured in studies available): Critical - Mortality due to cervical, vaginal vulval, anal, penile, or head and neck cancer - Cervical intraepithelial neoplasia (CIN) grade 3+; CIN2+ - Histological and cytological abnormalities - Anogenital wart - HPV infection Important - Seroconversion or seropositivity

	- GMT of HPV antibodies - Local adverse events - Systemic adverse events Note: some outcomes may be missing in GRADE projects due to absence of data from available studies. Additional outcomes specifically reported in studies were included due to relevance.

Abbreviations: 9vHPV, 9-valent human papillomavirus vaccine; CIN, cervical intraepithelial neoplasia; GMT, geometric mean titre; HPV, human papillomavirus; RCT, randomised controlled trial

Risk of bias assessment

Risk of bias (RoB) was assessed for all selected studies, not included in the WHO SAGE review, using the standard GRADE criteria. One assessor independently undertook this using the ROB 2.0 tool for randomised controlled trials and ROBINS-I for observational studies (Appendix B). For studies already included in the SAGE GRADE assessment, the results from the RoB assessment performed by SAGE were sourced.

References

1. Cochrane Response. Efficacy, effectiveness and immunogenicity of one dose of HPV vaccine compared with no vaccination, two doses, or three doses World Health Organization; March 2022. Available from: https://cdn-auth-cms.who.int/media/docs/default-source/immunization/position_paper_documents/human-papillomavirus-(hpv)/systematic-review-of-1-dose-of-hpv-vaccinec14d7ee3-e409-4a1a-afd9-c3e7e0dd2bd9.pdf (Accessed 24 April 2023).
2. Barnabas RV, Brown ER, Onono MA, et al. Efficacy of single-dose HPV vaccination among young African women. NEJM Evidence 2022;1:EVIDoa2100056.
3. Gargano JW, You M, Potter R, et al. An Evaluation of Dose-Related HPV Vaccine Effectiveness Using Central Registries in Michigan. Cancer Epidemiol Biomarkers Prev 2022;31:183-91.
4. MacCosham A, El-Zein M, Burchell AN, et al. Protection to Self and to One's Sexual Partner After Human Papillomavirus Vaccination: Preliminary Analysis From the Transmission Reduction And Prevention with HPV Vaccination Study. Sex Transm Dis 2022;49:414-22.
5. Watson-Jones D, Changalucha J, Whitworth H, et al. Immunogenicity and safety of one-dose human papillomavirus vaccine compared with two or three doses in Tanzanian girls (DoRIS): an open-label, randomised, non-inferiority trial. The Lancet Global Health 2022;10(10):e1473-e84.
6. Gilca V, Sauvageau C, Panicker G, et al. Immunogenicity and safety of a mixed vaccination schedule with one dose of nonavalent and one dose of bivalent HPV vaccine versus two doses of nonavalent vaccine - A randomized clinical trial. Vaccine 2018;36(46):7017-24.
7. Moreira ED, 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(2) (no pagination).

Appendix A: Literature Search Strategy

Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> Search Strategy: --- 1 (HPV or (human adj (papilloma virus* or papillomavirus*))).tw,kf. (62030) 2 exp Papillomaviridae/ (37692) 3 exp Papillomavirus Infections/ (41724) 4 or/1-3 (75576) 5 (vaccin* or immuni* or inoculat* or innoculat*).tw,kf. (795461) 6 4 and 5 (18086) 7 (cervarix or gardasil).tw,kf. (705) 8 exp Papillomavirus Vaccines/ (9955) 9 or/6-8 (18938) 10 exp animals/ not humans/ (5099921) 11 9 not 10 (18068) 12 (comment or editorial).pt. (1437485) 13 11 not 12 (17071)	**EMBASE: Update of SAGE search strategy for single dose HPV vaccines combined with 9 valent terms (as at 08.03.23)** **Notes: This search uses the search strategy from the SAGE systematic review. The strategy below has removed the original date limit terms and added new 9 valent terms and 1 dose terms.** **Please note inherent flaws in the original strategy from SAGE remain, including lack of controlled vocabulary terms for Immunization, lack of truncation for vaccine terms and the potential for inadvertent removal of recently added items with the Animal/Humans limits.** Database: Embase <1974 to 2023 March 06> Search Strategy: --- 1 papillomavirus infection/ or papilloma virus infections.mp. or Papilloma virus/ (30861) 2 "human papillomavirus infection*".mp. (4910) 3 1 or 2 (32879) 4 (vaccin* or immuni*).ti. or (vaccin* or immuni*).ab. (781587) 5 3 and 4 (8922) 6 HPV vaccin*.ti. or HPV vaccin*.ab. (13446)

14 (nine valen$ or nine-valen$ or ninevalen$).tw. (96) 15 (9 valen$ or 9-valen$ or 9valen$).tw. (372) 16 (9vHPV or 9xHPV).tw. (127) 17 (nonavalen$ adj5 HPV$).tw. (183) 18 v503.tw. (24) 19 (second generat$ or second-generat$).tw. (31731) 20 14 or 15 or 16 or 17 or 18 or 19 (32390) 21 13 and 20 (603) 22 (single dose$ or single-dose$ or singledose$ or one dose$ or one-dose$ or onedose$ or 1 dose$ or 1-dose$ or 1dose$).tw. (86422) 23 21 and 22 (27)	7 (Gardasil or cervarix).ti. or (Gardasil or cervarix).ab. (998) 8 5 or 6 or 7 (17495) 9 exp animal/ not exp human/ (5141661) 10 8 not 9 (17047) 11 (nine valen$ or nine-valen$ or ninevalen$).tw. (134) 12 (9 valen$ or 9-valen$ or 9valen$).tw. (483) 13 (9vHPV or 9xHPV).tw. (178) 14 (nonavalen$ adj5 HPV$).tw. (231) 15 v503.tw. (33) 16 (second generat$ or second-generat$).tw. (46459) 17 11 or 12 or 13 or 14 or 15 or 16 (47322) 18 10 and 17 (740) 19 (single dose$ or single-dose$ or singledose$ or one dose$ or one-dose$ or onedose$ or 1 dose$ or 1-dose$ or 1dose$).tw. (130834) 20 18 and 19 (37)

Appendix B: Risk of Bias

ROB 2.0

Study	Randomisation process	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
KEN-SHE trial	Low	Low	Some concerns	Low	Low	Some concerns
Gilca 2018	Some concerns	Low	Low	Low	Low	Some concerns
DoRIS trial	Low	Low	Low	Low	Some concerns	Some concerns
MacCosham 2022	Low	Low	Low	Low	Some concerns	Some concerns

ROBINS-I

Study ID	Confounding	Selection of participants	Classification of intervention	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported result	Overall

Gargano 2022	Low	Moderate	Low	Low	Low	Low	Low	Some concerns