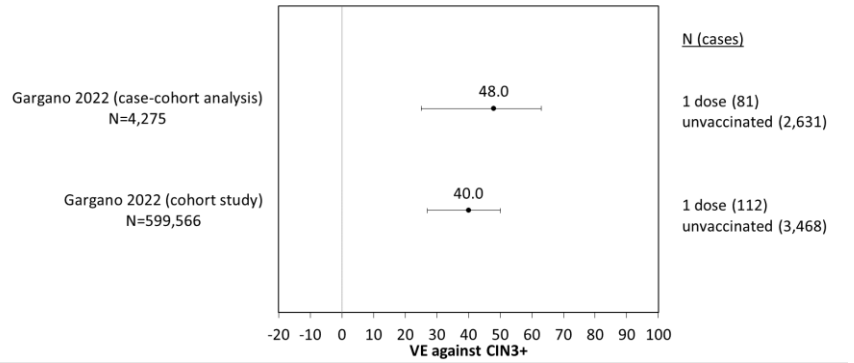
NCIRS is conducting GRADE in support of ATAGI and making pilot results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook Human Papillomavirus Chapter.

Summary of findings: PICO 1: 1 dose of 9vHPV compared to no vaccine/control vaccine

Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: no vaccine / control vaccine

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
VE against incident HPV16/18 infection (FU 18 months)	VE 9vHPV = 97.5% (95% CI 81.6, 99.7); p<0.0001 N (incident infection) = 1 dose (1) vs. control (36)	1,720 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]	9vHPV likely results in a large decrease in incident HPV16/18 infections at 18 months post vaccination compared to control vaccine
VE against incident HPV16/18 infection (FU >18 months)	VE = 100% N (incident infection) = 1 dose (0) vs. control (16)	833 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]	9vHPV likely results in a large decrease in incident HPV16/18 infections at greater than 18 months post vaccination compared to control vaccine
VE against incident 9vHPV type infection (FU 18 months)	VE = 88.9% (95% CI 68.5, 96.1); p<0.0001 N (incident infection) = 1 dose (4) vs. control (29)	1,515 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]	9vHPV likely results in a large decrease in incident 9vHPV type infections at 18 months post vaccination compared to control vaccine
VE against incident 9vHPV type infection (FU >18 months)	VE = 95.02% (95% CI 62.14, 99.35) N (incident infection) = 1 dose (1) vs. control (14)	474 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]	9vHPV likely results in a large decrease in incident 9vHPV type infections at greater than 18 months post vaccination compared to control vaccine
VE against incident genital vaccine-type (4v or 9v) infection (FU 12 months)	VE = 53% (95% CI 3, 77) Rate (incident infection) = 1 dose 4vHPV or 9vHPV (0.10 per 100 person-months) vs control (0.22 per 100 person-months)	271 (1 RCT)	⊕⊕⊕◯ Moderate[b,c]	9vHPV may result in a decrease in incident genital 9vHPV or 4vHPV type infections at 12 months post vaccination compared to control vaccine

Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: no vaccine / control vaccine

VE against CIN3+(FU ≥24 months)		599,566 (1 observational)	⊕⊕⊕◯ Moderate[b,c]	9vHPV may result in a decrease in incident CIN3+at 24 months and over post vaccination compared to no vaccination
Serious adverse events	1 dose: 34 (3.5%) Control: 39 (5.2%)	1,720 (1 RCT)	⊕⊕⊕◯ Moderate[a,b]	1 dose of 9vHPV likely results in little to no difference in serious adverse events compared to control vaccine

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: 9vHPV: 9-valent human papillomavirus vaccine; CI: confidence interval; CIN: Cervical intra-epithelial neoplasia; FU: follow-up; HPV: human papillomavirus; VE: vaccine effectiveness

Explanations

a. Risk of bias downgraded to some concerns due to missing outcome data.
b. Inconsistency cannot be assessed as only 1 study included.
c. Risk of bias downgraded to some concerns due to selection of the reported results (protocol could not be identified)

Evidence Profile: PICO 1: 1 dose of 9vHPV compared to no vaccine / control vaccine

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VE against incident HPV16/18 infection (FU 18 months)									
1	RCT	Serious[a]	NA[b]	Not serious	Not serious	None	The vaccine effectiveness of 1 dose of 9vHPV compared to control vaccine against incident HPV16/18 infection 18 months post vaccination was 97.5%	⊕⊕⊕◯ Moderate	Critical
VE against incident HPV16/18 infection (FU >18 months)									
1	RCT	Serious[a]	NA[b]	Not serious	Not serious	None	The vaccine effectiveness of 1 dose of 9vHPV compared to control vaccine against incident HPV16/18 infection over 18 months post vaccination was 100%	⊕⊕⊕◯ Moderate	Critical
VE against incident 9vHPV type infection (FU 18 months)									
1	RCT	Serious[a]	NA[b]	Not serious	Not serious	None	The vaccine effectiveness of 1 dose of 9vHPV compared to control vaccine against incident the 9vHPV type infections 18 months post vaccination was 88.9%	⊕⊕⊕◯ Moderate	Critical
VE against incident 9vHPV type infection (FU >18 months)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	RCT	Serious[a]	NA[b]	Not serious	Not serious	None	The vaccine effectiveness of 1 dose of 9vHPV compared to control vaccine against incident the 9vHPV type infections over 18 months post vaccination was 88.9%	⊕⊕⊕◯ Moderate	Critical
VE against incident genital vaccine-type (4v or 9v) infection (FU 12 months)									
1	RCT	Serious[c]	NA[b]	Not serious	Not serious	None	The vaccine effectiveness of 1 dose of a HPV vaccine (4vHPV or 9vHPV) against incident genital (4v or 9v type) infection was 53% at 12 months post vaccination	⊕⊕⊕◯ Moderate	Critical
VE against CIN3+ (FU ≥24 months)									
1	Observational study	Serious[c]	NA[b]	Not serious	Not serious	None	The vaccine effectiveness of 1 dose of a HPV vaccine (2vHPV, 4vHPV or 9vHPV) against CIN3+ ranged from 40-48% at ≥24 months post vaccination	⊕⊕⊕◯ Moderate	Critical
Serious adverse events									
1	RCT	Serious[a]	NA[b]	Not serious	Not serious	None	The rate of serious adverse events was 3.5% for 1 dose of 9vHPV and 5.2% for the control vaccine	⊕⊕⊕◯ Moderate	Critical

Abbreviations: 4vHPV: human papilloma virus vaccine; 9vHPV: 9-valent human papilloma virus vaccine**;** NA: not applicable; RCT: randomised controlled trial; VE: vaccine effectiveness

Explanations

a. Risk of bias downgraded to some concerns due to missing outcome data.
b. Inconsistency cannot be assessed as only 1 study included.
c. Risk of bias downgraded to some concerns due to selection of the reported results (protocol could not be identified)

Evidence to Decision Framework: individual perspective

Should 1 dose of 9vHPV be recommended over no vaccine/control vaccine of 9vHPV use in females and males aged ≥9 years for the prevention of human papillomavirus?	
Population	Immunocompetent females and males aged ≥9 years
Intervention	1 dose of 9 valent human papillomavirus vaccine (9vHPV)
Comparison	No vaccine/control vaccine
Main outcomes	Serious adverse events VE against incident HPV infections VE against incident genital vaccine-type infections VE against CIN3+
Setting	Kenya, USA, Canada
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Prior to the introduction of HPV vaccination, HPV infection was very common with up to 90% of the general population being infected at some point.[1] HPV infection can lead to cervical, anal, penile, vulvar and oropharyngeal cancers. It can also cause other lesions such as cutaneous warts, genital warts and respiratory papillomatosis.
- In Australia 2018, the incidence rate of cervical cancer was 7.3 per 100,000 and the mortality rate was 1.6 per 100,000 women.[2] All cervical cancers are attributable to HPV
- The proportion of other cancers attributable to HPV ranges from 40% for vulval cancers to approximately 90% for anal cancers.[3] In Australia in 2018 the incidence of vulval cancer, vaginal cancer, penile cancer and anal cancer was 2.3, 0.6, 1.1 and 2.1 per 100,000, respectively.[2]

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- The evidence shows that one dose of an HPV vaccine is effective. High vaccine efficacy against HPV 16 and 18 infection (97.5%) was found in one RCT.[4]
- Evidence from the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE) systematic review on the efficacy, effectiveness and immunogenicity of one dose of HPV vaccine found that there was high certainty of evidence in favour of one dose of HPV vaccine.[5,6] This was based on 59 studies reviewed in 2022. The findings of the desirable effects identified in this GRADE assessment are consistent with those of the WHO SAGE.
- In support of this GRADE assessment the WHO SAGE search was updated in 2023 to identify additional 2vHPV and 4vHPV single dose evidence. The search identified 4 additional studies that were all consistent with the WHO SAGE findings and the findings of this GRADE assessment.[7-9]

Undesirable Effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- The rates of serious adverse events were low in vaccine recipients and comparable to a control vaccine.
- In 2020, 91% of adolescents aged 12 to 13 years who received HPV 1st dose, concomitantly with the diphtheria, tetanus and whooping cough vaccine in Australia did not report any adverse event.[10]
- As reported by AusVaxSafety, injection site pain, swelling or redness was the most commonly reported adverse event followed by tiredness, headache and fever.[10]

Certainty of evidence
What is the overall certainty of the evidence of effects?

No Included Studies	Very Low	Low	Moderate	High

- The overall certainty of the evidence is moderate, downgraded due to some concerns in the risk of bias of studies.

Values
I*s there important uncertainty about or variability in how much people value the main outcomes?*

Important uncertainty	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

- Unlikely to be important uncertainty in how people value protection against cervical cancer and HPV causing cancers.

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Don't Know	Varies	Favours comparison	Probably favours comparison	Does not favour either comparison or intervention	Probably favours intervention	Favours intervention

- The benefits of protection against HPV disease outweigh any adverse effect of vaccination

Acceptability
Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Vaccination against HPV appears to be acceptable in Australia. In 2021, 86% of girls and 84% of boys by 15 years of age received 1 dose of HPV vaccine.[11]

Feasibility
Is the intervention feasible to implement?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- School based vaccine delivery system already exists for two doses of HPV vaccine. Implementing a one dose schedule is feasible and will potentially simplify program implementation. More resources can be used to monitor and increase vaccine coverage, address and reduce inequities in coverage, and monitor HPV disease and related cancers.

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