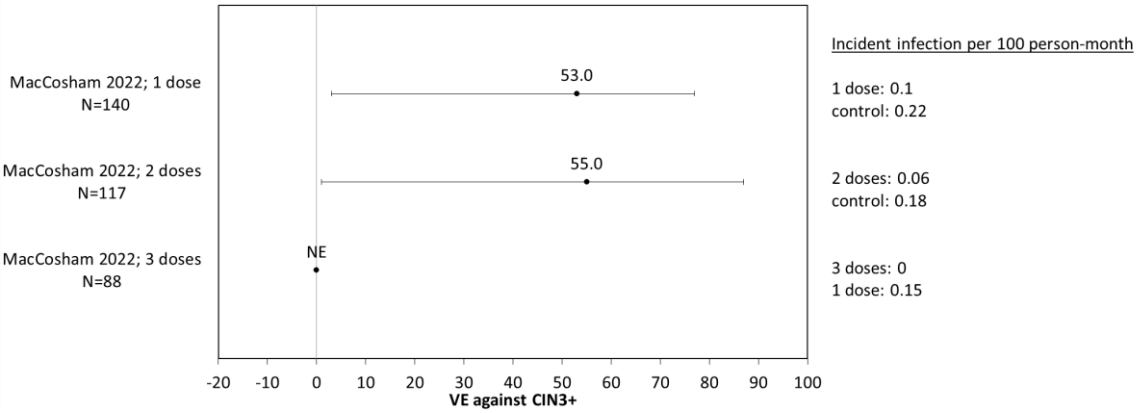
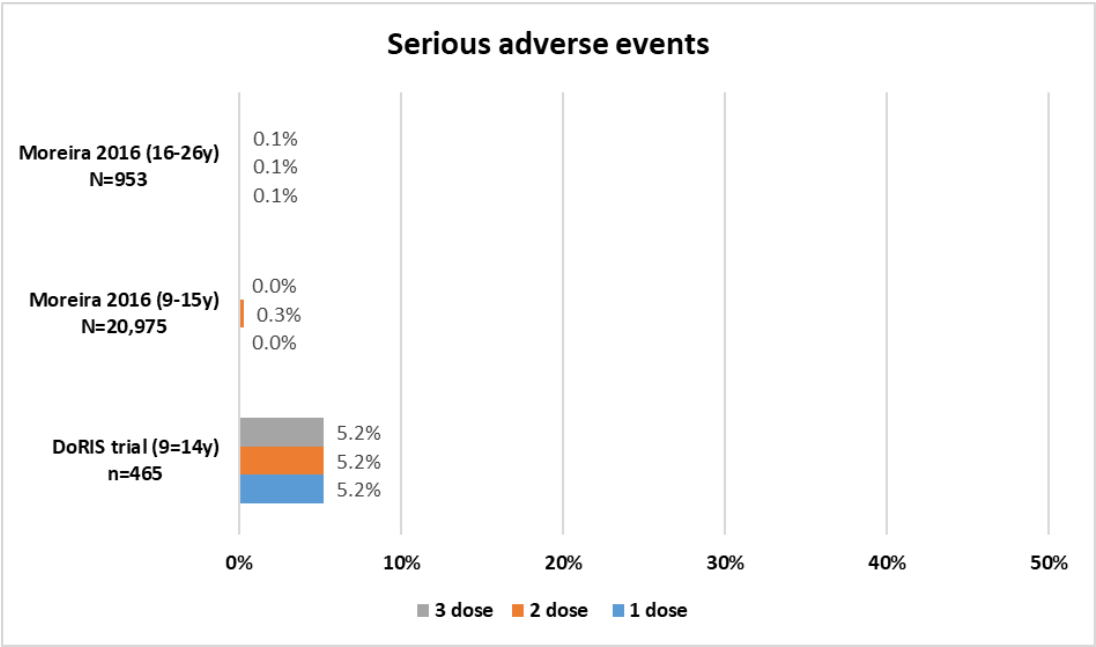
NCIRS is conducting GRADE in support of ATAGI and making pilot results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook Human Papillomavirus Chapter.

Summary of findings: PICO 2: 1 dose of 9vHPV compared to 2 or 3 doses of 9vHPV

Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: 2 or 3 doses of 9vHPV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
VE against incident genital vaccine-type (4vHPV or 9vHPV) infection (FU 12 months)		271 (1 RCT)	⨁⨁⨁⨁ High	1 dose of 9vHPV results in little to no difference in incident genital vaccine-type (4vHPV or 9vHPV) compared to 2 doses

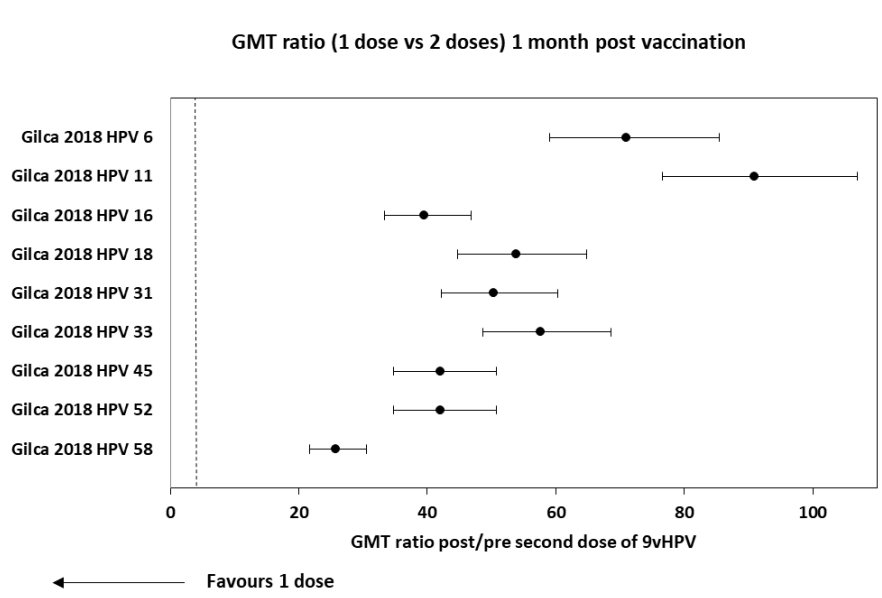
Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: 2 or 3 doses of 9vHPV

<table>
<tr>
<td>Serious adverse events (SAE)</td>
<td> 
</td>
<td>22,393 (3 RCT)</td>
<td>⨁⨁⨁◯ Moderate[a]</td>
<td>1 dose of 9vHPV likely results in little to no difference in serious adverse events compared to 2 or 3 doses.
Note: in a 1 dose schedule, the adverse events after doses 2 and 3 would be avoided.</td>
</tr>
<tr>
<td>Seropositive (FU 1 months)</td>
<td>
<table>
<tr><th colspan="5">Gilca 2018</th></tr>
<tr><th>HPV type</th><th>N</th><th>1 dose</th><th>N</th><th>2 doses</th></tr>
<tr><td>6</td><td>88</td><td>100.0 (95.9–100.0)</td><td>172</td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>11</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>16</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>18</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>31</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>33</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>45</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>52</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
<tr><td>58</td><td>88</td><td>100.0 (95.9–100.0)</td><td></td><td>100.0 (97.9–100.0)</td></tr>
</table>
</td>
<td>260 (1 RCT)</td>
<td>⨁⨁⨁◯ Moderate[a,c]</td>
<td>1 dose of 9vHPV likely results in little to no difference in seropositivity compared to 2 doses at 1 month post vaccination</td>
</tr>
</table>

Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: 2 or 3 doses of 9vHPV

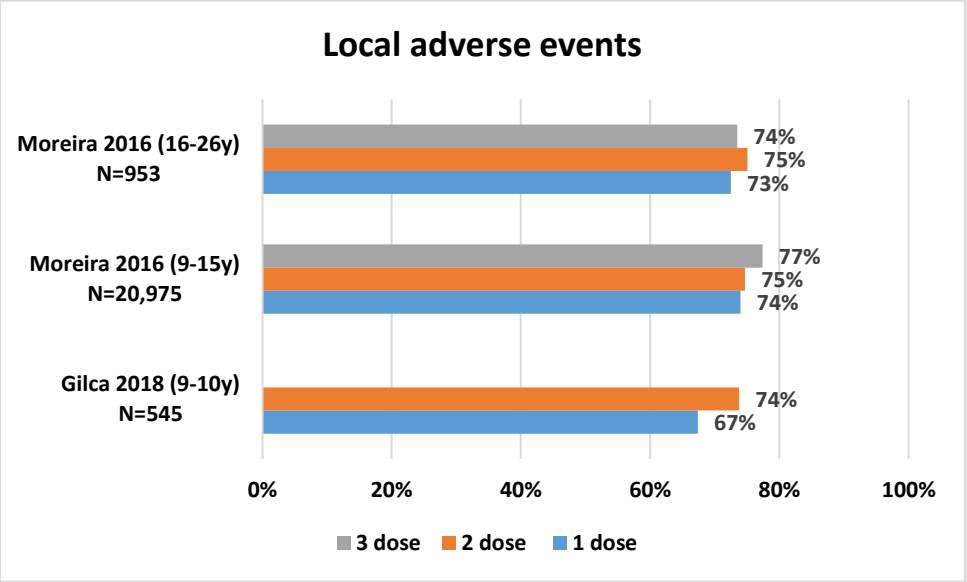
<table>
<tr>
<td>Seropositive (FU 7 months)</td>
<td>
DoRIS trial
<table>
<tr><th>HPV type</th><th>N</th><th>1 dose</th><th>N</th><th>2 doses</th><th>N</th><th>3 doses</th></tr>
<tr><td>16</td><td>144</td><td>100.0%</td><td>142</td><td>100.0%</td><td>140</td><td>100.0%</td></tr>
<tr><td>18</td><td>135</td><td>98.5%</td><td>137</td><td>100.0%</td><td>142</td><td>100.0%</td></tr>
</table>
Difference (95% CI)
1 dose vs. 2 doses:
- HPV 16: -0.7% (-3.8, 2.0)
- HPV18: -1.4% (-5.1, 1.3)
1 dose vs. 3 doses:
- HPV16: 0.0% (-3.1, 3.4)
- HPV18: -0.7% (-4.5, 2.8)
Non-inferiority (concluded if lower limit of 95% CI >-5%) between 1 dose and 2 doses or 3 doses was met for HPV 16 and HPV 18.
</td>
<td>429 (1 RCT)</td>
<td>⊕⊕⊕◯ Moderate[a,c]</td>
<td>1 dose of 9vHPV likely results in little to no difference in seropositivity compared to 2 or 3 doses at 6 months post vaccination</td>
</tr>
<tr>
<td>Seropositive (FU 12 months)</td>
<td>
DoRIS trial
<table>
<tr><th>HPV type</th><th>N</th><th>1 dose</th><th>N</th><th>2 dose</th><th>N</th><th>3 doses</th></tr>
<tr><td>16</td><td>145</td><td>100.0%</td><td>142</td><td>100.0%</td><td>140</td><td>100.0%</td></tr>
<tr><td>18</td><td>136</td><td>96.3%</td><td>137</td><td>100.0%</td><td>142</td><td>100.0%</td></tr>
</table>
Difference (95% CI)
1 dose vs. 2 doses:
- HPV 16: -0.7% (-3.8, 2.0)
- HPV18: -0.7% (-4.0, 2.1)
1 dose vs. 3 doses:
- HPV16: -0.7% (-3.8, 2.0)
- HPV18: -0.7% (-4.0, 2.1)
Non-inferiority (concluded if lower limit of 95% CI >-5%) between 1 dose and 2 doses or 3 doses was met for HPV 16 and HPV 18.
</td>
<td>429 (1 RCT)</td>
<td>⊕⊕⊕◯ Moderate[a,c]</td>
<td>1 dose of 9vHPV likely results in little to no difference in seropositivity compared to 2 or 3 doses at 12 months post vaccination</td>
</tr>
</table>

Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: 2 or 3 doses of 9vHPV

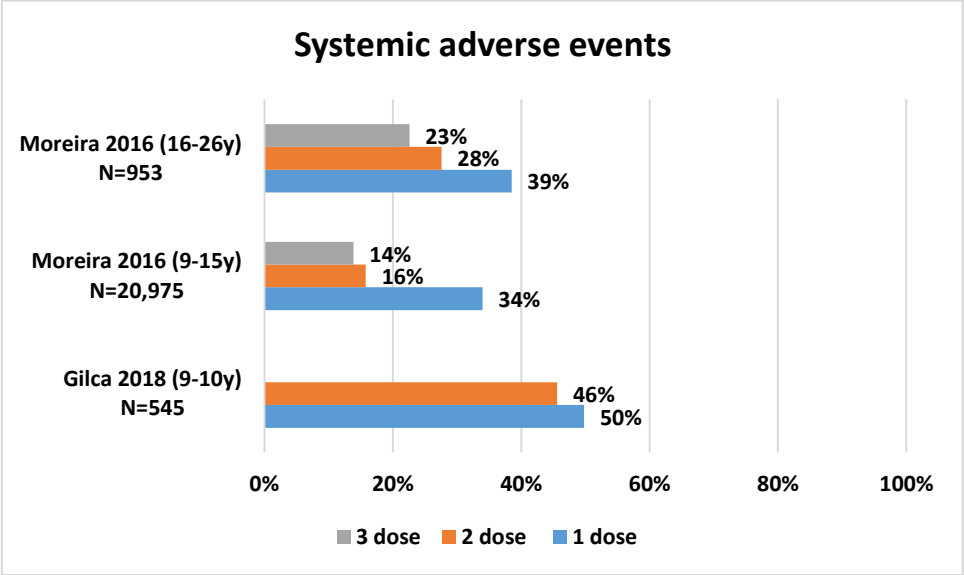
<table>
<tr>
<td>Seropositive (FU 24 months)</td>
<td>
<table>
<tr><th colspan="7">DoRIS trial</th></tr>
<tr><th>HPV type</th><th>N</th><th>1 dose</th><th>N</th><th>2 dose</th><th>N</th><th>3 doses</th></tr>
<tr><td>16</td><td>145</td><td>99.3%</td><td>141</td><td>100.0%</td><td>140</td><td>100.0%</td></tr>
<tr><td>18</td><td>136</td><td>97.8%</td><td>136</td><td>100.0%</td><td>142</td><td>99.3%</td></tr>
</table>
Difference (95% CI)
1 dose vs. 2 doses:
- HPV 16: -0.7% (-3.8, 2.0)
- HPV18: -1.4% (-5.1, 1.3)
1 dose vs. 3 doses:
- HPV16: -0.7% (-3.8, 2.1)
- HPV18: -1.4% (-5.1, 1.3)
Non-inferiority (concluded if lower limit of 95% CI >-5%) between 1 dose and 2 doses or 3 doses was met for HPV 16 and not met for HPV18.
</td>
<td>429 (1 RCT)</td>
<td>⊕⊕⊕◯
Moderate[a,c]</td>
<td>1 dose of 9vHPV likely results in little to no difference in seropositivity compared to 2 or 3 doses at 24 months post vaccination</td>
</tr>
<tr>
<td>GMT ratio (FU 1 month)</td>
<td>


</td>
<td>260 (1 RCT)</td>
<td>⊕⊕⊕◯
Moderate[a,c]</td>
<td>1 dose of 9vHPV likely results in lower GMTs compared with 2 doses at 1 months post vaccination</td>
</tr>
</table>

Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: 2 or 3 doses of 9vHPV

Local adverse events		22,473 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	Dose 1 of 9vHPV likely results in little to no difference in local adverse events compared to dose 2 and 3. Note: in a 1 dose schedule, the adverse events after doses 2 and 3 would be avoided.

Patient or population: Immunocompetent females and males aged ≥9 years
Intervention: 1 dose of 9vHPV
Comparison: 2 or 3 doses of 9vHPV

Systemic adverse events		22,473 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	Dose 1 of 9vHPV likely results in little to no difference in systemic adverse events compared to dose 2and 3. Note: in a 1 dose schedule, the adverse events after doses 2 and 3 would be avoided.

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: 4vHPV: 4-valent human papillomavirus vaccine; 9vHPV: 9-valent human papillomavirus vaccine; GMT: geometric mean titres; HPV: human papillomavirus; RCT: randomised controlled trial

Explanations

a. Inconsistency cannot be assessed as only 1 study included.
b. Risk of bias downgraded to some concerns due to selection of the reported results (protocol could not be identified)
c. Risk of bias downgraded to some concerns due to no information on allocation concealment.

Evidence Profile: PICO 2: 1 dose of 9vHPV compared to 2 or 3 doses of HPV vaccine

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
VE against incident genital vaccine-type (4v or 9v) infection (FU 12 months)									
1	RCT	Not serious	NA[a]	Not serious	Not serious	None	The vaccine effectiveness of 1 dose of a HPV vaccine (4vHPV or 9vHPV) against incident genital vaccine type (4vHPV or 9vHPV) was 53% for 1 dose and 65% for 2 doses at 12 months post vaccination	⊕⊕⊕⊕ High	Critical
Serious adverse events									
4	RCT	Serious[b]	Not serious	Not serious	Not serious	None	The rate of serious adverse events ranged from 0.1% to 5.2% for 1 dose, 0.1% to 5.2% for 2 doses and 0.1% to 5.2% for 3 doses	⊕⊕⊕◯ Moderate	Critical
Seropositive (FU 1 month)									
1	RCT	Serious[c]	NA[a]	Not serious	Not serious	None	The proportion of participants who were seropositive for HPV6, 11, 16, 18, 31, 33, 45, 52, 58 was 100% for 1 dose and 2 doses at 1 month post vaccination	⊕⊕⊕◯ Moderate	Important
Seropositive (FU 7 months)									
1	RCT	Serious[b]	NA[a]	Not serious	Not serious	None	The proportion of participants who were seropositive for HPV6, 11, 16, 18, 31, 33, 45, 52, 58 ranged from 98.5% to 100% for 1 dose and 100% for 2 or 3 doses at 6-7 months post vaccination	⊕⊕⊕◯ Moderate	Important
Seropositive (FU 12 months)									
1	RCT	Serious[b]	NA[a]	Not serious	Not serious	None	The proportion of participants who were seropositive for HPV16 and 18 was 100% and 96.5% for 1 dose and 100% for dose 2 and 3 at 12 months post vaccination	⊕⊕⊕◯ Moderate	Important
Seropositive (FU 24 months)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1	RCT	Serious[b]	NA[a]	Not serious	Not serious	None	The proportion of participants who were seropositive for HPV16 and 18 was 99.3% and 97.8% for 1 dose and ranged from 99.3% to 100% for dose 2 and 3 at 24 months post vaccination	⊕⊕⊕◯ Moderate	Important
GMT ratio (FU 1 month)									
1	RCT	Serious[c]	NA[a]	Not serious	Not serious	None	The GMT ratios for HPV 6, 11, 16, 18, 31, 33, 45, 52, 58 at 1 month post vaccination favoured 2 doses over 1 dose	⊕⊕⊕◯ Moderate	Important
Local adverse events									
3	RCT	Serious[c]	Not serious	Not serious	Not serious	None	The rate of local adverse events after each dose ranged from 67.4% to 74% for 1 dose, 73.8% to 75.1% for 2 doses and 73.5% to 77.4% for 3 doses. Note that with a 1-dose schedule, the adverse events occurring after 2 or 3 doses would not occur.	⊕⊕⊕◯ Moderate	Important
Systemic adverse events									
3	RCT	Serious[c]	Not serious	Not serious	Not serious	None	The rate of systemic adverse events after each dose ranged from 34.0% to 49.8% for 1 dose, 15.8% to 45.6% for 2 doses and 13.9% to 22.6% for 3 doses. Note that with a 1-dose schedule, the adverse events occurring after 2 or 3 doses would not occur.	⊕⊕⊕◯ Moderate	Important

Abbreviations: 4vHPV: 4-valent human papillomavirus vaccine; 9vHPV: 9-valent human papillomavirus vaccine; GMT: geometric mean titres; HPV: human papillomavirus; RCT: randomised controlled trial

Explanations

a. Inconsistency cannot be assessed as only 1 study included.
b. Risk of bias downgraded to some concerns due to selection of the reported results (protocol could not be identified).
c. Risk of bias downgraded to some concerns due to no information on allocation concealment.

Evidence to Decision Framework: individual perspective

Should 1 dose of 9vHPV be recommended over 2 or 3 doses 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	2 or 3 doses of dose of 9 valent human papillomavirus vaccine (9vHPV)
Main outcomes	Serious adverse events Seropositive 1-24 months post vaccination GMT ratios Local adverse events Systemic adverse events
Setting	Tanzania, Canada
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Prior to 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 9vHPV vaccine has comparable, high seroprotection to two or three doses. Immunogenicity data of shows that one dose provides lower GMTs to two or three doses based on one study.[4] In this same study, there were no differences in the antibody avidity indices between dose groups.
- It is noted that for HPV immunogenicity there is no known correlate of protection, though HPV vaccines have been found to generate antibody titres that are 100-fold greater than natural infection.[5,6]
- 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.[7,8] This was based on 59 studies reviewed in 2022. The findings are supportive of the desirable effects identified in this GRADE assessment.

- 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.[9-11]

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 after 1 dose of HPV vaccine and comparable to those occurring after 2 or 3 doses. In a 1 dose schedule, the adverse events after doses 2 and 3 would be avoided.
- 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.[12]
- As reported by AusVaxSafety, injection site pain, swelling or redness was the most commonly reported adverse event followed by tiredness, headache and fever.[12]
- Reducing the number of required doses to 1 dose means that adverse events occurring after later doses (i.e. dose 2 and 3) would not occur; therefore the undesirable effects of vaccination would be reduced with a 1 dose schedule.

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
Is *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
- 1 dose provides equivalent protection to 2 or 3 doses, while the adverse events occurring after 2 or 3 doses would be avoided with a 1 dose schedule

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 had received 1 dose of HPV vaccine.[13]

- A reduced dose schedule is more likely to be acceptable to recipients, and simpler to implement by program staff.

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.

References

1. Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sex Transm Dis* 2014;41:660-4.
2. Australian Institute of Health and Welfare (AIHW). Australian Institute of Health and Welfare. Cancer data in Australia: Cancer summary data visualisation. Canberra: AIHW; 2021. Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation (Accessed 24 April 2023).
3. Patel C, Brotherton JM, Pillsbury A, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent? *Euro Surveill* 2018;23.
4. 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.
5. Dillner J, Kjaer SK, Wheeler CM, et al. Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: randomised controlled trial. *Bmj* 2010;341:c3493.
6. Kaufmann AM, Nitschmann S. [Vaccine against human papillomavirus : PATRICIA Study (PApilloma TRIal against Cancer In young Adults)]. *Internist (Berl)* 2010;51:410, 2-3.
7. 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).
8. Strategic Advisory Group of Experts (SAGE). Strategic Advisory Group of Experts (SAGE) Working Group on potential contribution of HPV vaccines and immunization towards cervical cancer elimination. SAGE meeting April 2022; March 2022. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://cdn.who.int/media/docs/default-source/immunization/position_paper_documents/human-papillomavirus-(hpv)/hpv-background-document--report-march-2022.pdf?sfvrsn=b600e252_1
9. Abel MK, Mann AK, Sonawane K, et al. Prevalence of Oral Human Papillomavirus Infection by Number of Vaccine Doses Among US Adults. *JNCI Cancer Spectr* 2021;5.
10. Gheit T, Muwonge R, Lucas E, et al. Impact of HPV vaccination on HPV-related oral infections. *Oral Oncol* 2023;136:106244.
11. Joshi S, Anantharaman D, Muwonge R, et al. Evaluation of immune response to single dose of quadrivalent HPV vaccine at 10-year post-vaccination. *Vaccine* 2023;41:236-45.
12. Australian Government Department of Health. Vaccine safety in Australia 2020. Canberra: 2020. Available from: https://www.health.gov.au/sites/default/files/documents/2021/10/ausvaxsafety-summary-report-2020-12-13-year-infographic.pdf (Accessed 24 April 2023).
13. National Centre for Immunisation Research and Surveillance (NCIRS). Annual Immunisation Coverage Report 2021. Sydney: November 2022. Available from: https://ncirs.org.au/annual-immunisation-coverage-report-2021-available-now (Accessed 24 April 2023).