GRADE tables: Comparison of 2 doses of human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) administered either intramuscularly (IM) or intradermally (ID) to 3 doses of HDCV or PCECV administered either IM or ID in people indicated to receive rabies pre-exposure prophylaxis (PrEP) vaccination

NCIRS is conducting GRADE assessments in support of the Australian Technical Advisory Group on Immunisation (ATAGI) and making pilot results available on the Centre's website. Please read this material as a supplement to the Australian Immunisation Handbook rabies and other lyssaviruses chapter.

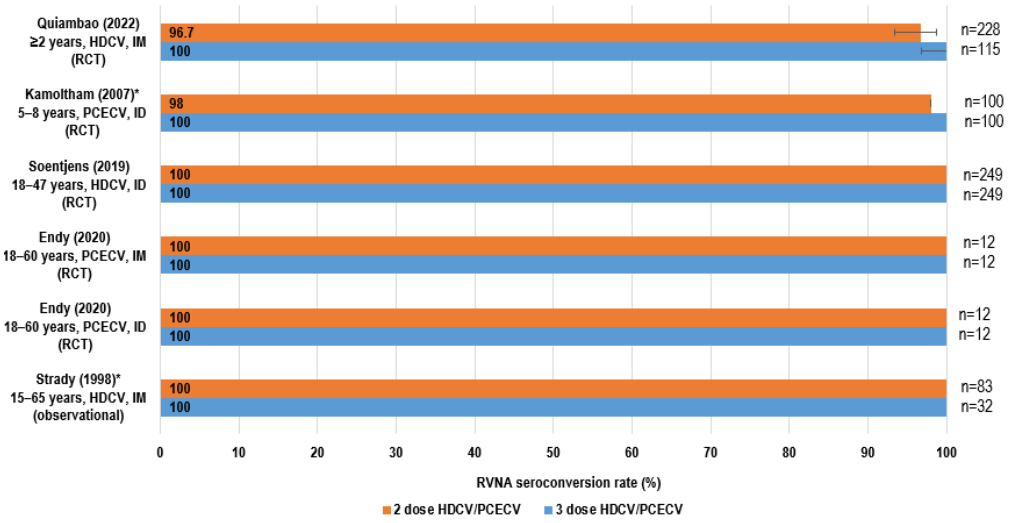
2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP)

Patient or population: People who are indicated to receive rabies PrEP
Intervention: 2 doses of HDCV or PCECV
Comparison: 3 doses of HDCV or PCECV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
CRITIAL OUTCOMES				
Vaccine-related serious adverse events (SAEs) Assessed with: any vaccine-related adverse event/adverse reaction that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability or incapacity Follow-up: range 28 days–372 days	There were no vaccine-related SAEs reported in any of the trials. In the trial that reported numerical results, there were no SAEs in either 2 dose (0.0%; 95% CI: 0.0–1.6) or 3 dose arms (0.0%; 95% CI: 0.0–3.2). In one trial, 1 SAE (reversible diplopia and hemianopsia) occurred during the primary vaccination session 14 days after receiving the 3rd (final) rabies vaccine injection in a 3-dose ID schedule. This was deemed unrelated to the rabies vaccine study, as it occurred some days after receiving a measles- mumps-rubella vaccine in another medical centre (violation of the trial protocol).	1,606 (4 RCTs)[1-4]	⨁⨁⨁◯ Moderate[a]	2 doses IM or ID HDCV/PCECV for PrEP likely results in little to no difference in vaccine-related SAEs compared to 3 doses HDCV/ PCECV PrEP.

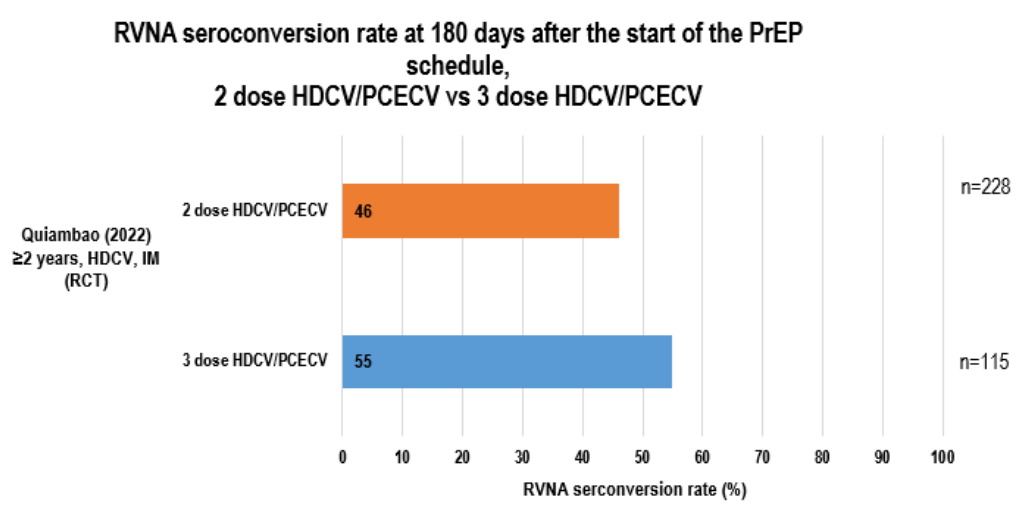
2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP)

Patient or population: People who are indicated to receive rabies PrEP
Intervention: 2 doses of HDCV or PCECV
Comparison: 3 doses of HDCV or PCECV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
IMPORTANT OUTCOMES				
Rabies virus neutralising antibody (RVNA) seroconversion rate (SCR) (%) [RCT] Assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL Follow-up: ≥7 days post-last PrEP dose	RVNA seroconversion rate at ≥7 days post-last PrEP dose, administered either IM or ID, 2 dose HDCV/PCECV vs 3 dose HDCV/PCECV  *Dose 2 is administered on day 28 rather than day 7 as per current recommendations.	1,089 (4 RCTs)[1-4]	⊕⊕◯◯ Low[a,b]	2 doses of IM or ID HDCV/PCECV PrEP may result in little to no difference in RVNA seroconversion rate ≥7 days after the end of the PrEP schedule compared to 3 doses of IM or ID HDCV/PCECV PrEP.
RVNA seroconversion rate (SCR) (%) [observational] Assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL Follow-up: ≥7 days post-last PrEP dose		115 (1 observational study)[5]	⊕◯◯◯ Very low[a,b,c,e]	The evidence is very uncertain about the effect of 2 doses of IM HDCV PrEP on RVNA seroconversion rate ≥7 days after the end of the PrEP schedule compared to 3 doses of IM HDCV PrEP.

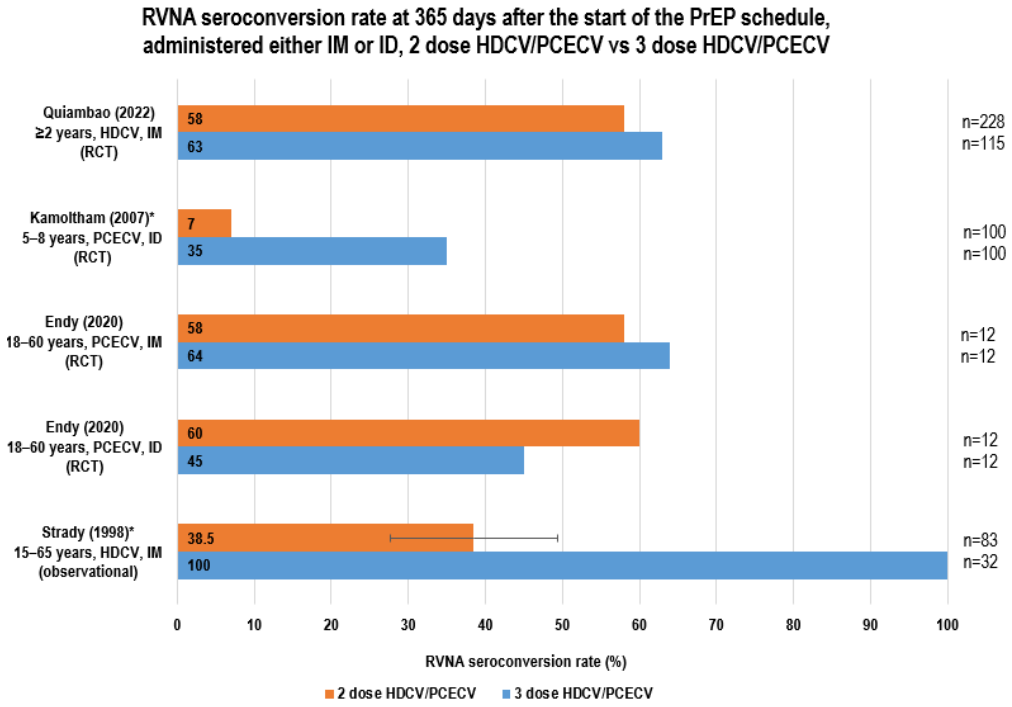
2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP)

Patient or population: People who are indicated to receive rabies PrEP
Intervention: 2 doses of HDCV or PCECV
Comparison: 3 doses of HDCV or PCECV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
RVNA seroconversion rate (SCR) (%) [RCT] Assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL Follow-up: 180 days		343 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a,e]	2 doses of IM HDCV PrEP likely results in a small reduction in RVNA seroconversion rate 180 days after the start of PrEP schedule compared to 3 doses of IM HDCV PrEP.

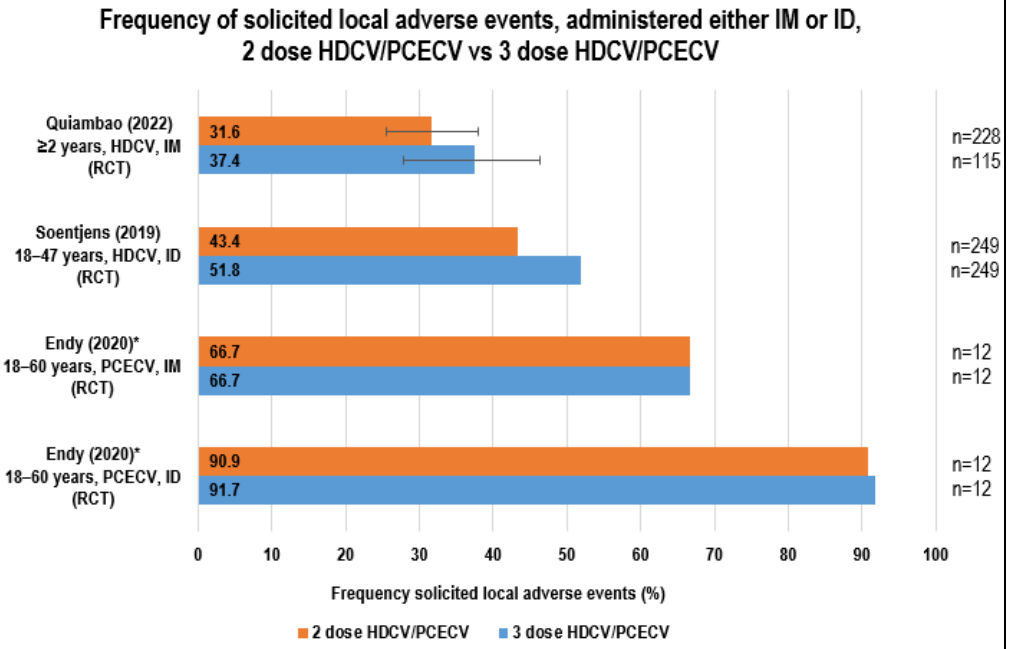
2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP)

Patient or population: People who are indicated to receive rabies PrEP
Intervention: 2 doses of HDCV or PCECV
Comparison: 3 doses of HDCV or PCECV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
RVNA seroconversion rate (SCR) (%) [RCT] Assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL Follow-up: 365 days	 *Rather than being administered on day 7, as per current recommendations, dose 2 was administered on day 28.	591 (3 RCTs)[1,2,4]	⊕◯◯◯ Very low[a,b,d]	The evidence is very uncertain about the effect of 2 doses of IM or ID HDCV/PCECV PrEP on RVNA seroconversion rate 365 days after the start of PrEP schedule compared to 3 doses of IM or ID HDCV/PCECV PrEP.
RVNA seroconversion rate (SCR) (%) [observational] Assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL Follow-up: 365 days		115 (1 observational study)[5]	⊕◯◯◯ Very low[a,b,c,e]	The evidence is very uncertain about the effect of 2 doses of IM HDCV PrEP on RVNA seroconversion rate 365 days after the start of PrEP schedule compared to 3 doses of IM HDCV PrEP.

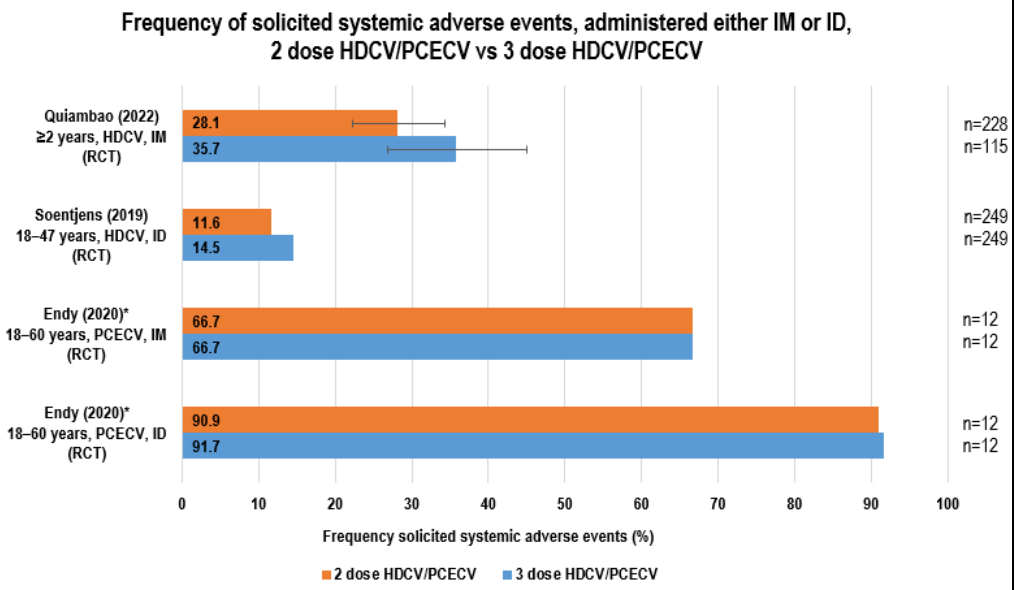
2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP)

Patient or population: People who are indicated to receive rabies PrEP
Intervention: 2 doses of HDCV or PCECV
Comparison: 3 doses of HDCV or PCECV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited local adverse events (AEs) Assessed with: frequency of solicited reactogenicity for any injection site and/or local event Follow-up: range 1 day to 7 days	 * Endy (2020) results include frequency of both solicited local and systemic adverse events.	889 (3 RCT)[1-3]	⊕⊕⊕◯ Moderate[a,e]	2-dose IM or ID HDCV/PCECV PrEP likely results in a small reduction in solicited local adverse events compared to 3-dose IM or ID HDCV/PCECV PrEP.

2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP)

Patient or population: People who are indicated to receive rabies PrEP
Intervention: 2 doses of HDCV or PCECV
Comparison: 3 doses of HDCV or PCECV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited systemic adverse events (AEs) Assessed with: frequency of solicited reactogenicity for any systemic event Follow-up: range 1 day to 7 days	 *Endy (2020) results include frequency of both solicited local and systemic adverse events.	889 (3 RCT)[1-3]	⊕⊕⊕◯ Moderate[a,e]	2-dose IM or ID HDCV/PCECV PrEP likely results in a small reduction in solicited systemic adverse events compared to 3-dose IM or ID HDCV/PCECV PrEP.

2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP)

Patient or population: People who are indicated to receive rabies PrEP
Intervention: 2 doses of HDCV or PCECV
Comparison: 3 doses of HDCV or PCECV

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation

Explanations
a. Small sample size (<400); study may not be powered to detect a difference between groups and/or clinical trials are not powered to detect rare serious adverse events
b. Interval between dose 1 and 2 varies from the currently recommended interval. Rather than being administered on day 7, as per current recommendations, dose 2 was administered on day 28. (Kamoltham [2007] and Strady [1988])
c. Serious risk of bias in the domain of confounding
d. Inconsistent results, with one study reporting results in opposition to other studies (higher proportion post-dose 2 compared to post-dose 3) and wide range of values for post-dose 2 results
e. Inconsistency is N/A, as only one study of this design in the outcome

Abbreviations: AE=adverse events; HDCV=human diploid cell vaccine; ID=intradermal; IM=intramuscular; PCECV=purified chick embryo cell vaccine; PrEP=pre-exposure prophylaxis; PVCV=purified Vero cell vaccine; PVRV=purified Vero cell rabies vaccine (Verorab); RCT=randomised controlled trial; RVNA=rabies virus neutralising antibody; SAE=serious adverse events; SCR=seroconversion rate

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: 7ur 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 the effect.

GRADE evidence profile

Evidence profile: 2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP) vaccination

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Vaccine-related SAEs (follow-up: range 28 days to 372 days; assessed with: any vaccine-related adverse event/adverse reaction that resulted in death, was life-threatening, required hospitalisation or prolongation of existing hospitalisation, or resulted in persistent or significant disability or incapacity)									
4	Randomised trials	Not serious	Not serious	Not serious	Serious[a]	None	There were no vaccine-related SAEs reported in any of the trials.[1-4] In the trial that reported numerical results, there were no SAEs in either 2-dose (0.0%; 95%CI: 0.0–1.6) or 3-dose arms (0.0%: 95% CI: 0.0–3.2).[1] In one trial, 1 SAE (reversible diplopia and hemianopsia) occurred during the primary vaccination session 14 days after receiving the third (final) rabies vaccine injection in a 3-dose ID schedule.[3] This was deemed unrelated to the rabies study vaccine, as it occurred some days after receiving a measles-mumps-rubella vaccine in another medical centre (violation of the trial protocol).	⊕⊕⊕◯ Moderate	CRITICAL
RVNA seroconversion rate (SCR) (%) [RCT] (follow-up: ≥7 days; assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL)									
4	Randomised trials	Not serious	Not serious	Serious[b]	Serious[a]	None	The RVNA seroconversion rate (SCR) ≥7 days following the second PrEP dose of HDCV or PCECV, administered either IM or ID, ranged from 96.7–100% compared to RVNA SCR of 100% for 3 PrEP doses of IM or ID HDCV or PCECV rabies vaccine.[1-4]	⊕⊕◯◯ Low	IMPORTANT
RVNA seroconversion rate (SCR) (%) [observational] (follow-up: ≥7 days; assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL)									
1	Observational studies	Serious[c]	N/A[e]	Serious[b]	Serious[a]	None	The RVNA SCR ≥7 days following vaccination was 100% (95% CI: NR) after both 2 and 3 doses of PrEP IM HDCV rabies vaccine.[5]	⊕◯◯◯ Very low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
RVNA seroconversion rate (SCR) (%) [RCT] (follow-up: 180 days; assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL)									
1	Randomised trials	Not serious	N/A[e]	Not serious	Serious[a]	None	The RVNA SCR 180 days after the start of the PrEP schedule was 46% (95% CI: NR) for 2 doses of IM HDCV PrEP compared to 55% (95% CI: NR) for 3 doses of IM HDCV rabies vaccine.[1]	⊕⊕⊕◯ Moderate	IMPORTANT
RVNA seroconversion rate (SCR) (%) [RCT] (follow-up: 365 days; assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL)									
3	Randomised trials	Not serious	Very serious[d]	Serious[b]	Serious[a]	None	The RVNA SCR 365 days after the start of the PrEP schedule ranged from 7–60% for 2 doses of IM or ID HDCV or PCECV PrEP compared to 35–64% for 3 doses of IM or ID HDCV or PCECV.[1,2,4]	⊕◯◯◯ Very low	IMPORTANT
RVNA seroconversion rate (SCR) (%) [observational] (follow-up: 365 days; assessed with: WHO-recommended RVNA titre of ≥0.5 IU/mL)									
1	Observational studies	Serious[c]	N/A[e]	Serious[b]	Serious[a]	None	The RVNA SCR 365 days after the start of the PrEP schedule was 38.5% (95% CI: 37.7–38.5) for 2 doses of IM HDCV PrEP compared to 100% (95% CI: NR) for 3 doses of IM HDCV.[5]	⊕◯◯◯ Very low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Solicited local adverse events (Aes) (follow-up: range 1 day to 7 days; assessed with: frequency of solicited reactogenicity for any injection site and/or local event)									
3	Randomised trials	Not serious	N/A[e]	Not serious	Serious[a]	None	The frequency of solicited local Aes ranged from 31.6–90.9%* for 2 dose IM or ID HDCV or PCECV PrEP compared to 37.4–91.7%* for 3 doses of IM or ID HDCV or PCECV PrEP.[1-3] A 2-dose schedule would avoid the adverse events of a 3rd dose. **Note:* Endy (2020) results include frequency of both solicited local and systemic adverse events.[2]	⨁⨁⨁◯ Moderate	IMPORTANT
Solicited systemic Aes (follow-up: range 1 day to 7 days; assessed with: frequency of solicited reactogenicity for any systemic event)									
3	Randomised trials	Not serious	N/A[e]	Not serious	Serious[a]	None	The frequency of solicited systemic Aes ranged from 11.6–90.9%* for 2 doses of IM or ID HDCV or PCECV PrEP compared to 14.5–91.7%* for 3 doses of IM or ID HDCV or PCECV PrEP.[1-3] A 2-dose schedule would avoid the adverse events of a 3rd dose. **Note:* Endy (2020) results include frequency of both solicited local and systemic adverse events.[2]	⨁⨁⨁◯ Moderate	IMPORTANT

Explanations

a. Small sample size (<400); study may not be powered to detect a difference between groups, and/or clinical trials are not powered to detect rare serious adverse events
b. Interval between dose 1 and 2 varies from the currently recommended interval. Rather than being administered on day 7, as per current recommendations, dose 2 was administered on day 28. (Kamoltham [2007] and Strady [1988])
c. Serious risk of bias in the domain of confounding
d. Inconsistent results with one study reporting results in opposition to other studies (higher proportion post-dose 2 compared to post-dose 3) and wide range of values for post-dose 2 results
e. Inconsistency is N/A, as only one study of this design in the outcome

Abbreviations: AE=adverse events; HDCV=human diploid cell vaccine; ID=intradermal; IM=intramuscular; NR=not reported; PCECV=purified chick embryo cell vaccine; PrEP=pre-exposure prophylaxis; PVCV=purified Vero cell vaccine; PVRV=purified Vero cell rabies vaccine (Verorab); RCT=randomised controlled trial; RVNA=rabies virus neutralising antibody; SAE=serious adverse events; SCR=seroconversion rate

Evidence to Decision (EtD) framework: 2 doses of IM or ID HDCV or PCECV compared to 3 doses of IM or ID HDCV or PCECV for people who are indicated to receive rabies pre-exposure prophylaxis (PrEP) vaccination

SHOULD PEOPLE WHO ARE INDICATED TO RECEIVE RABIES PrEP VACCINATION RECEIVE 2 DOSES of HDCV or PCECV FOR PrEP AGAINST RABIES?	
Population	People indicated to receive rabies PrEP vaccination
Intervention	2 doses human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) PrEP [IM or ID]*
Comparison	3 doses HDCV or PCECV PrEP (IM or ID)*
Main outcomes	• Vaccine-related serious adverse events (SAE) • Rabies virus neutralising antibody (RVNA) seroconversion rate (SCR)** ≥7 days after final PrEP dose • RVNA SCR (%) persistence of immune response (at day 180 and day 365) • Solicited local adverse events (AE) (up to day 7) • Solicited systemic AE (up to day 7) *Intramuscular (IM), intradermal (ID) **Seroconversion defined as the WHO-recommended antibody titre threshold of ≥0.5 IU/mL
Setting	Philippines, US, Thailand and France
Perspective	Individual

ASSESSMENT

Problem

Is the problem a priority?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Australia is not a rabies-enzootic country.[6] However, bats are a potential source of lyssaviruses and a potential risk for acquiring rabies, and exposure to classical rabies virus can occur from terrestrial animals and other mammals in rabies-enzootic countries. Rabies is nearly always fatal once symptoms begin.[7]
- People who work with bats, laboratory workers who work with live lyssaviruses and some people who travel to rabies-enzootic areas are recommended to receive rabies vaccine as PrEP.
- People with ongoing occupational exposure to lyssaviruses are recommended to receive booster doses of rabies vaccine.
- There are currently two available rabies vaccines (Mèrieux [inactivated, HDCV] and Rabipur [inactivated, PCECV]) as options for rabies PrEP in Australia. Both currently have a 3-dose PrEP schedule.

Desirable effects

How substantial are the desirable anticipated effects? (*Note:* Compared to 3 doses HDCV/PCECV)

Don't know	Varies	Trivial	Small	Moderate	Large

- RVNA seroconversion rates (SCR) ≥7 days after the last-PrEP dose were 96.7–100% for 2 PrEP doses HDCV/PCECV compared to 100% for 3 PrEP doses of HDCV/PCECV.[1-5] Quiambao (2022) notes that the non-inferiority criteria for 2 vs 3 doses of HDCV was a lower confidence interval (CI) of the difference in RVNA SCR of ≥–5%, and it did not meet this criterion.[1] The difference in dose 2 and dose 3 was –3.349% points, with 95% CI: –6.751 to 0.464. The evidence from the RCTs suggests there may be little to no difference in seroconversion rates 7 days post-last PrEP dose for 2 doses HDCV/PCECV compared to 3 doses HDCV/PCECV.[1-4] The evidence from the observational study is uncertain.[5]
- There is likely a small difference in RVNA seroconversion at 180 days after the start of the PrEP schedule between 2-dose HDCV/PCECV PrEP (46%) compared to 3-dose HDCV/PCECV PrEP (55%).[1]
- The evidence regarding the RVNA seroconversion rate at ≥365 days after the start of the PrEP schedule is uncertain:
    - *From the RCTs:* There is inconsistency in the results. One study using ID administration found dose 2 had a higher seroconversion than dose 3, with 60% vs 45% of participants having RVNA seroconversion at 365 days after the start of the PrEP schedule with PCECV rabies vaccine.[2] This study also had an arm looking at IM PCECV, which found dose 2 to have lower RVNA seroconversion at 365 days compared to dose 3; this was consistent with the other findings, with RVNA seroconversion post-dose 2 ranging from 7–58% compared to 35–64% for post-dose 3.[1,2,4]
    - *From the observational study:* RVNA seroconversion at 365 days after the start of the PrEP schedule for 2 doses HDCV/PCECV PrEP was 38.5% compared to 100% for 3 doses HDCV/PCECV PrEP, but the evidence is very uncertain.[5]
    - More weighting was put on the evidence from the RCTs.

Undesirable effects

How substantial are the undesirable anticipated effects? (*Note:* Compared to 3 doses HDCV/PCECV)

Don't know	Varies	Large	Moderate	Small	Trivial

- There is likely to be less AE overall with 2 doses of HDCV/PCECV compared to 3 doses HDCV/PCECV, as there are fewer vaccine doses being administered.
- No vaccine-related SAE occurred with either 2-dose HDCV/PCECV or 3-dose HDCV/PCECV.[1-4]
- Undesirable effects of local and systemic adverse events were assessed in three RCTs included in the GRADE:[1-3]
    - Solicited local AE are likely slightly reduced with 2-dose HDCV/PCECV PrEP (31.6–90.9%) compared to 3-dose HDCV/PCECV PrEP (37.4–91.7%).
    - Solicited systemic AE are likely slightly reduced with 2-dose HDCV/PCECV PrEP (11.6–90.9%) compared to 3-dose HDCV/PCECV PrEP (14.5–91.7%).
- The RCT also found no immediate AE (first 30 minutes after vaccination) reported following either 2 doses of HDCV/PCECV PrEP or 3 doses of HDCV/PCECV PrEP.[1]
- One RCT reported that overall AE were higher in the ID arms compared to the IM arms of the study.[2]

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- The certainty of evidence is low. Of the eight outcomes evaluated, the certainty of evidence was moderate for four, low for one and very low for three.
- The outcomes that were rated as moderate were rated as such due to imprecision, as most studies had small (<400) sample sizes and may not be powered to detect a difference between 2 doses HDCV/PCECV and 3 doses HDCV/PCECV.
- The outcomes that had low or very low certainty of evidence were downgraded due to imprecision (with the same rationale as for moderate above), for risk of bias in the confounding domain, indirectness due to variation in dose interval and inconsistency.
- There were no data comparing the vaccine schedules in 'healthy' populations compared with immunocompromised populations.
- RCTs that measure the efficacy of rabies vaccine are not possible, and much of the evidence is therefore reliant on immunogenicity outcomes. There may be an extent to which immunologic 'correlates of protection' may not fully predict protection.

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

- There is unlikely to be important uncertainty in how people value protection against rabies.
- No research was identified in the search that addresses this specifically.
- Rabies PrEP vaccination is only routinely recommended for people at high occupational risk or for some travellers to rabies-enzootic regions.
- These populations may appreciate a shorter series of 2 doses HDCV/PCECV that requires fewer vaccines, is less expensive/has fewer out-of-pocket costs, and likely has the same safety profile and provides the same immune response as the currently recommended 3-dose PrEP schedule of HDCV/PCECV.
- There were no data comparing the vaccine schedules in 'healthy' populations with those in immunocompromised populations.

Balance of effects

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

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

- There may be little to no difference in RVNA seroconversion rates ≥7 days post-last PrEP dose for 2 doses HDCV/PCECV (97.6–100%) compared to 3 doses HDCV/PCECV (100%).[1-5]
- There is likely a small difference in RVNA seroconversion at 180 days after the start of the PrEP schedule between 2-dose HDCV/PCECV PrEP (46%) compared to 3-dose HDCV/PCECV PrEP (55%).[1]
- There is differing and uncertain evidence regarding the RVNA seroconversion rate at ≥365 days after the start of the PrEP schedule. One RCT showed RVNA seroconversion at 365 days after the start of the PrEP schedule to be higher for 2-dose ID PCECV PrEP (60%) compared to 3-dose ID PCECV PrEP (45%).[2] This study also had an arm

looking at IM PCECV, which found dose 2 to have lower RVNA seroconversion at 365 days compared to dose 3; this was consistent with the other RCT findings, with 2-dose PrEP RVNA seroconversion ranging from 7–60% compared to 35–64% for 3-dose PrEP at 365 days or more after the start of the PrEP schedule. RVNA seroconversion at 365 days after the start of the PrEP schedule in the observational study for 2-dose HDCV/PCECV PrEP was 38.5% compared to 100% for 3-dose HDCV/PCECV PrEP, but the evidence is very uncertain.[5]

- No vaccine-related SAE occurred with either 2-dose HDCV/PCECV or 3-dose HDCV/PCECV rabies PrEP vaccination.[1-4]
- Other undesirable effects, such as solicited local and systemic AE, are minor and 2 doses HDCV/PCECV likely slightly reduces, or results in little to no difference in, undesirable effects compared to 3 doses HDCV/PCECV.[1-3]
- There is likely to be less AE overall with 2 doses of HDCV/PCECV compared to 3 doses HDCV/PCECV, as there are fewer vaccine doses being administered.

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

- No direct evidence was identified for this issue.
- Employers and employees at workplaces of high occupational risk, some travellers to rabies-enzootic regions, and travel medicine providers and medical associations are likely the main stakeholders impacted. No direct evidence was identified on the acceptability of 2 doses HDCV/PCECV to these stakeholders.
- However, the populations remain the same, and a shorter 2-dose series may be appreciated by the populations, clinical providers and public health officials. There is likely to be minimal impact from changing the current rabies PrEP schedule to 2 doses.
- The simpler and less expensive 2-dose vaccine schedule may be more acceptable to populations recommended for rabies PrEP vaccination and to clinical providers. It is easier to schedule appointments for 2 doses than for 3 doses before travel and before the start of high-risk activities.[7]
- Providers' familiarity with HDCV/PCECV as a rabies PrEP vaccine may make this vaccine acceptable.
- There were no data comparing the vaccine schedules in 'healthy' populations with those in immunocompromised populations.

Feasibility

Is the intervention feasible to implement?

Don't know	Varies	No	Probably no	Probably yes	Yes

- No direct evidence was identified for this issue.
- Rabies PrEP vaccination is only routinely recommended for people at high occupational risk or for some travellers to rabies-enzootic regions.
- No barriers are expected in implementing a 2-dose HDCV/PCECV PrEP schedule compared to the current 3-dose HDCV/PCECV PrEP schedule. In cases where it is difficult to ensure 3 doses are administered before travel or high-risk activities, a shorter 2-dose series will be easier to implement and is feasible.[7]
- A 2-dose PrEP schedule is likely more feasible – it is simpler and less expensive, and less time needed to implement and administer it.[7]
- Vaccination providers may already be familiar with the vaccine and have stock of the vaccine, making it feasible to implement it into the current rabies PrEP schedule.
- Additional guidance will need to be provided for rabies PrEP vaccination in immunocompromised populations, as there were no data comparing these vaccine schedules in 'healthy' populations with those in immunocompromised populations.

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