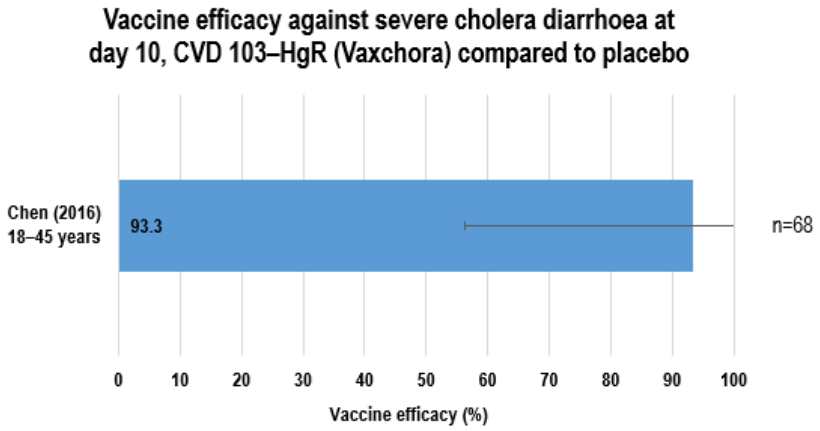
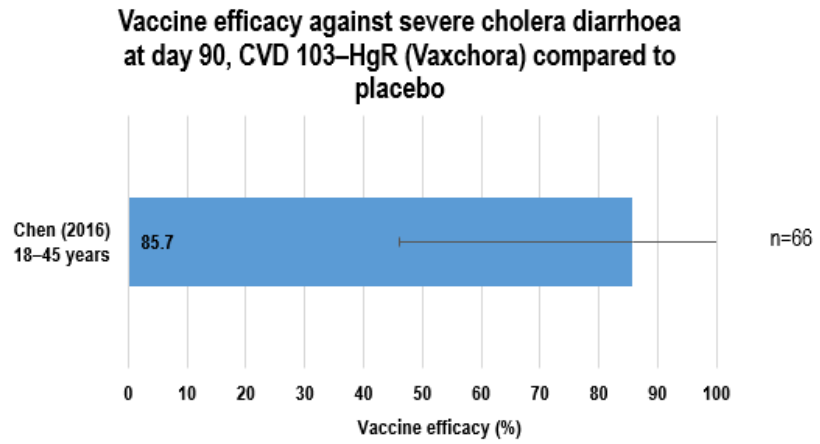
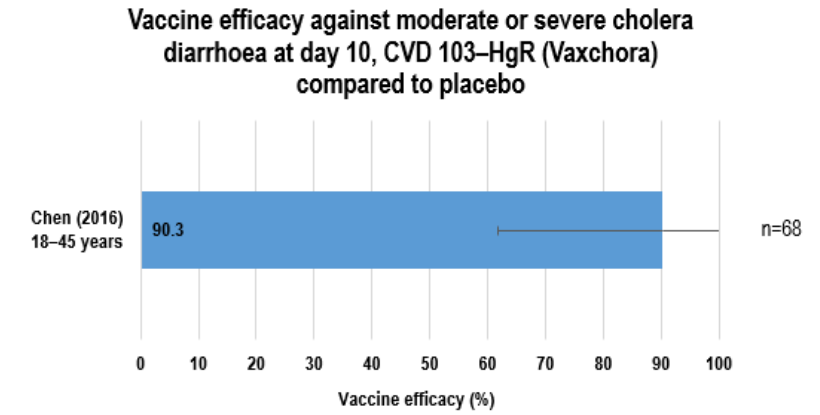
GRADE tables: Comparison of CVD 103–HgR (Vaxchora) to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera

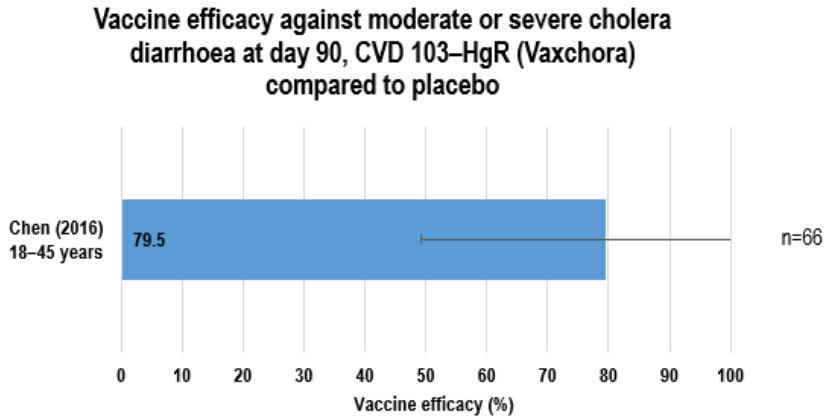
NCIRS is conducting GRADE assessments in support of the Australian Technical Advisory Group on Immunisation (ATAGI) and making pilot results available on the Centre's website. Please read this material as a supplement to the Australian Immunisation Handbook cholera chapter.

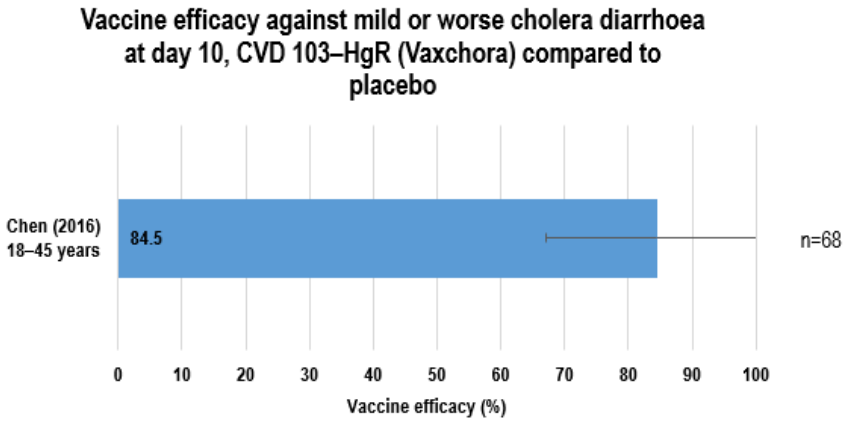
CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera

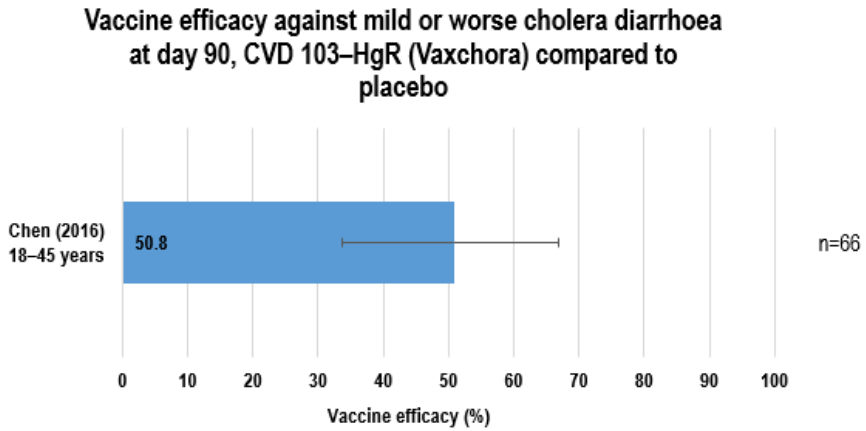
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera
Intervention: CVD 103–HgR (Vaxchora)
Comparison: Placebo

Outcomes	Impact	№ of participants [assessed/total, n/N] (studies)	Certainty of the evidence (GRADE)	Interpretation
CRITICAL OUTCOMES				
Efficacy against severe cholera diarrhoea Assessed with: ≥5.0 L of cumulative diarrhoeal stool Follow-up: 10 days		68/197 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a,b]	CVD 103–HgR (Vaxchora) likely results in a large reduction in severe cholera diarrhoea at 10 days compared with placebo.

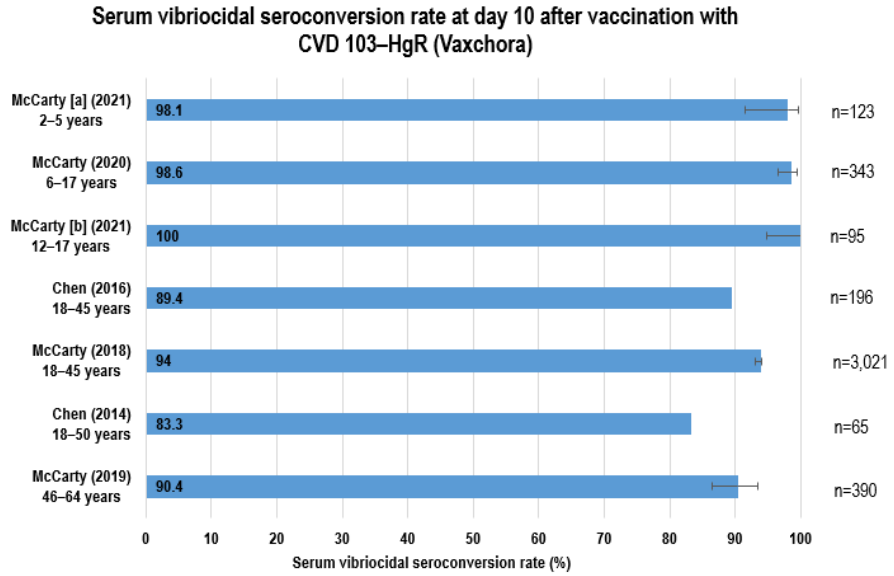
CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera				
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera **Intervention:** CVD 103–HgR (Vaxchora) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants [assessed/total, n/N] (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Efficacy against severe cholera diarrhoea Assessed with: ≥5.0 L of cumulative diarrhoeal stool Follow-up: 90 days		66/197 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a,b]	CVD 103–HgR (Vaxchora) likely results in a large reduction in severe cholera diarrhoea at 90 days compared with placebo.
Efficacy against moderate or severe cholera diarrhoea Assessed with: ≥3.0 L to ≥5.0 L of cumulative diarrhoeal stool Follow-up: 10 days		68/197 (1 RCT)[1]	⊕⊕⊕◯ Moderate[a,b]	CVD 103–HgR (Vaxchora) likely results in a large reduction in moderate or severe cholera diarrhoea at 10 days compared with placebo.

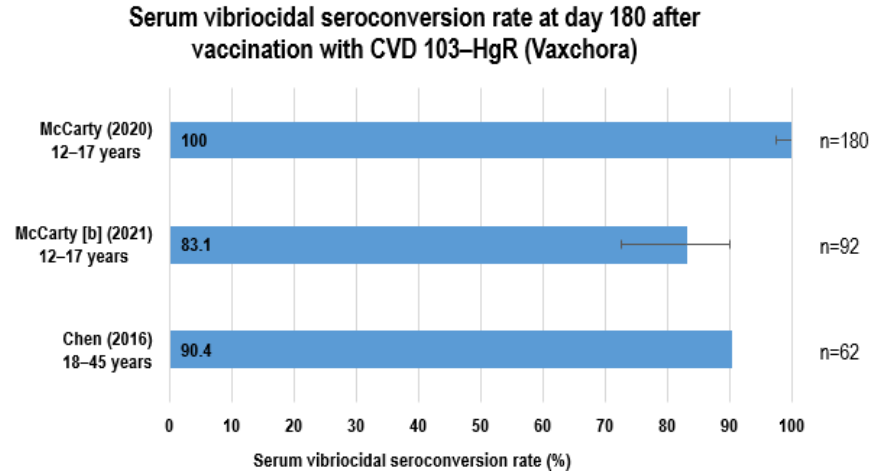
CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera				
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera **Intervention:** CVD 103–HgR (Vaxchora) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants [assessed/total, n/N] (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Efficacy against moderate or severe cholera diarrhoea Assessed with: ≥3.0 L to ≥5.0 L of cumulative diarrhoeal stool Follow-up: 90 days		66/197 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a,b]	CVD 103–HgR (Vaxchora) likely results in a reduction in moderate or severe cholera diarrhoea at 90 days compared with placebo.

CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera				
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera **Intervention:** CVD 103–HgR (Vaxchora) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants [assessed/total, n/N] (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Efficacy against mild or worse severity cholera diarrhoea Assessed with: ≥2 unformed stools (grade 3–5) over a 48-hour period ≥200 mL, or a single unformed stool of ≥300 mL and <3 L total diarrhoea Follow-up: 10 days		68/197 (1 RCT)[1]	⨁⨁⨁⨁ High[a]	CVD 103–HgR (Vaxchora) results in a large reduction in mild or worse severity cholera diarrhoea at 10 days compared with placebo.

CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera				
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera **Intervention:** CVD 103–HgR (Vaxchora) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants [assessed/total, n/N] (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Efficacy against mild or worse severity cholera diarrhoea Assessed with: ≥2 unformed stools (grade 3–5) over a 48-hour period ≥200 mL, or a single unformed stool of ≥300 mL and <3 L total diarrhoea Follow-up: 90 days		66/197 (1 RCT)[1]	⨁⨁⨁⨁ High[a]	CVD 103–HgR (Vaxchora) results in a reduction in mild or worse severity cholera diarrhoea at 90 days compared with placebo.

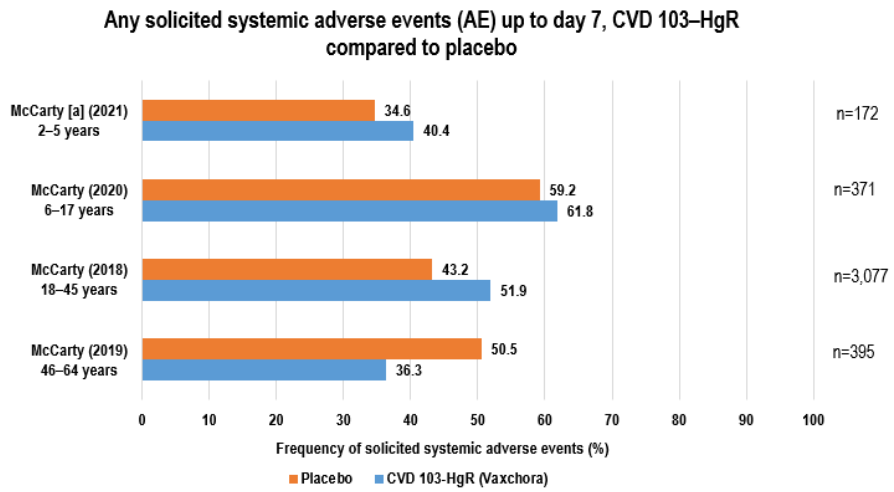
CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera				
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera **Intervention:** CVD 103–HgR (Vaxchora) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants [assessed/total, n/N] (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Serious adverse events (SAEs) Assessed with: frequency of serious adverse events at follow-up Follow-up: mean 180 days	No SAEs were vaccine-related in any of the 6 RCTs. Overall frequencies of SAE were trivial and similar between vaccine and placebo arms.	4,353/4,357 (6 RCTs)[1-6]	⨁⨁⨁◯ Moderate[c]	CVD 103–HgR (Vaxchora) likely results in little to no difference in serious adverse events compared with placebo.
IMPORTANT OUTCOMES				

CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera				
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera **Intervention:** CVD 103–HgR (Vaxchora) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants [assessed/total, n/N] (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Serum vibriocidal antibody seroconversion rate Assessed with: ≥4-fold vibriocidal antibody titre rise against classical Inaba strain over baseline Follow-up: 10 days		4,233/4,453 (7 RCTs)[1-7]	⨁⨁⨁⨁ High	CVD 103–HgR (Vaxchora) results in a large increase in serum vibriocidal antibody seroconversion at 10 days compared with placebo.

CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera				
Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera **Intervention:** CVD 103–HgR (Vaxchora) **Comparison:** Placebo				
Outcomes	**Impact**	**№ of participants [assessed/total, n/N] (studies)**	**Certainty of the evidence (GRADE)**	**Interpretation**
Serum vibriocidal antibody seroconversion rate Assessed with: ≥4-fold vibriocidal antibody titre rise against classical Inaba over baseline Follow-up: 180 days		334/482 (3 RCTs)[1,5,7]	⨁⨁⨁◯ Moderate[b]	CVD 103–HgR (Vaxchora) likely results in a large increase in serum vibriocidal antibody seroconversion at 180 days compared with placebo.

CVD 103–HgR (Vaxchora) compared to placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera

Patient or population: Children and adults aged ≥2 years who have a high risk of exposure to cholera
Intervention: CVD 103–HgR (Vaxchora)
Comparison: Placebo

Outcomes	Impact	№ of participants [assessed/total, n/N] (studies)	Certainty of the evidence (GRADE)	Interpretation
Solicited systemic adverse events Assessed with: frequency of solicited reactogenicity for any event Follow-up: range 1 days to 7 days		4,015/4,094 (4 RCTs)[3-6]	⊕⊕⊕◯ Moderate[d]	CVD 103–HgR (Vaxchora) likely results in little to no difference in solicited systemic adverse events compared with placebo.

Explanations

a. Only one study assessed vaccine efficacy
b. Small sample size (<400); study may not be powered to detect a difference between groups
c. 3 out of 6 studies had high risk of bias overall due to high risk of bias in domain 5 (risk of bias in selection of the reported result) for the outcome of SAE
d. Some variability of results and few (or no) confidence intervals provided to assess overlap

Abbreviations: AE=adverse event; CI=confidence interval; RCT=randomised controlled trial; SAE=serious adverse event; SCR=seroconversion rate; SVA=serum vibriocidal antibody

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 the effect.

GRADE evidence profile

Evidence profile: CVD 103–HgR (Vaxchora) compared with placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera

Certainty assessment							№ of patients[e]		Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CVD 103–HgR (Vaxchora)	Placebo			
Efficacy against severe cholera diarrhoea (follow-up: 10 days; assessed with: ≥5.0 L of cumulative diarrhoeal stool)											
1	Randomised trials	Not serious	N/A[a]	Not serious	Serious[b]	None	1/35 (2.9%)	13/33 (39.4%)	Vaccine efficacy against severe cholera diarrhoea in healthy adults aged 18–45 years was observed to be 93.3% (95% CI: 56.2–100%) at 10 days post-challenge.[1]	⊕⊕⊕◯ Moderate	CRITICAL
Efficacy against severe cholera diarrhoea (follow-up: 90 days; assessed with: ≥5.0 L of cumulative diarrhoeal stool)											
1	Randomised trials	Not serious	N/A[a]	Not serious	Serious[b]	None	2/33 (6.1%)	15/33 (45.5%)	Vaccine efficacy against severe cholera diarrhoea in healthy adults aged 18–45 years was observed to be 85.7% (95% CI: 46.2–100%) at 90 days post-challenge.[1]	⊕⊕⊕◯ Moderate	CRITICAL
Efficacy against moderate or severe cholera diarrhoea (follow-up: 10 days; assessed with: ≥3.0 L to ≥5.0 L of cumulative diarrhoeal stool)											
1	Randomised trials	Not serious	N/A[a]	Not serious	Serious[b]	None	2/35 (5.7%)	20/33 (60.6%)	Vaccine efficacy against moderate or severe cholera diarrhoea in healthy adults aged 18–45 years was observed to be 90.3% (95% CI: 61.7–100%) at 10 days post-challenge.[1]	⊕⊕⊕◯ Moderate	CRITICAL

Certainty assessment							№ of patients[e]		Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CVD 103–HgR (Vaxchora)	Placebo			
Efficacy against moderate or severe cholera diarrhoea (follow-up: 90 days; assessed with: ≥3.0 L to ≥5.0 L of cumulative diarrhoeal stool)											
1	Randomised trials	Not serious	N/A[a]	Not serious	Serious[b]	None	4/33 (12.1%)	19/33 (57.6%)	Vaccine efficacy against moderate or severe cholera diarrhoea in healthy adults aged 18–45 years was observed to be 79.5% (95% CI: 49.1–100%) at 90 days post-challenge.[1]	⊕⊕⊕◯ Moderate	CRITICAL
Efficacy against mild or worse severity cholera diarrhoea (follow-up: 10 days; assessed with: ≥2 unformed stools (grade 3–5) over a 48-hour period ≥200 mL, or a single unformed stool of ≥300 mL and <3 L total diarrhoea)											
1	Randomised trials	Not serious	N/A[a]	Not serious	Not serious	None	5/35 (14.3%)	30/33 (90.9%)	Vaccine efficacy against mild or worse severity cholera diarrhoea in healthy adults aged 18–45 years was observed to be 84.5% (95% CI: 67.0–100%) at 10 days post-challenge.[1]	⊕⊕⊕⊕ High	CRITICAL
Efficacy against mild or worse severity cholera diarrhoea (follow-up: 90 days; assessed with: ≥2 unformed stools (grade 3–5) over a 48-hour period ≥200 mL, or a single unformed stool of ≥300 mL and <3 L total diarrhoea)											
1	Randomised trials	Not serious	N/A[a]	Not serious	Not serious	None	15/33 (45.5%)	31/33 (93.9%)	Vaccine efficacy against mild or worse severity cholera diarrhoea in healthy adults aged 18–45 years was observed to be 50.8% (95% CI: 33.6%–66.8%) at 90 days post-challenge.[1]	⊕⊕⊕⊕ High	CRITICAL

Certainty assessment							№ of patients[e]		Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CVD 103–HgR (Vaxchora)	Placebo			
Serious adverse events (follow-up: mean 180 days; assessed with: frequency of serious adverse events at follow-up)											
6	Randomised trials	Serious[c]	Not serious	Not serious	Not serious	None	n/3715 (No numerator available for 3 studies, 18 events reported in other studies)	n/642 (No numerator available for 3 studies, 4 events reported in other studies)	All six studies reported no study or vaccine-related SAEs in either arm.[1-6] In the three RCTs that reported numerical results, rates of SAE ranged between 0%–0.6% in the vaccine arm compared with range 0%–3.8% in placebo.[3,5,6] Two of these studies reported a slightly higher rate of SAE in the placebo arm.[3,6] The other study reported a slightly higher rate of SAE in the vaccine arm compared with placebo.[5]	⊕⊕⊕◯ Moderate	CRITICAL
Serum vibriocidal antibody seroconversion rate (follow-up: 10 days; assessed with: ≥4-fold vibriocidal antibody titre rise against classical Inaba over baseline)											
7	Randomised trials	Not serious	Not serious	Not serious	Not serious	None	3370/3597 (93.7%)	17/636 (2.7%)	Significantly higher serum vibriocidal antibody (SVA) seroconversion rate was observed in the vaccine arm compared with placebo at the day 10 time point (range of vaccine response rate 83.3%–100% in the vaccine arm compared with 0%–4% in the placebo arm).[1-7] SVA seroconversion rates were non-inferior at day 10 in the age-related immune-bridging studies when compared to the 18–45-year age group.[1,3-6]	⊕⊕⊕⊕ High	IMPORTANT

Certainty assessment							№ of patients[e]		Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CVD 103–HgR (Vaxchora)	Placebo			
Serum vibriocidal antibody seroconversion rate (follow-up: 180 days; assessed with: ≥4-fold vibriocidal antibody titre rise against classical Inaba over baseline)											
3	Randomised trials	Not serious	Not serious	Not serious	Serious[b]	None	233/254 (91.7%)	2/80 (2.5%)	Significantly higher SVA seroconversion rate was observed in the vaccine arm compared with placebo at the day 180 time point (range of vaccine response rate 83.1–100% in the vaccine arm compared with 0%–2% in the placebo arm).[1,5,7] There was some variability between the two studies in adolescents aged 12–17 years, with one study reporting a SVA seroconversion rate of 100% and the other reporting a SVA seroconversion rate of 83.1% at the day 180 time point.[5,7]	⊕⊕⊕◯ Moderate	IMPORTANT

Certainty assessment							№ of patients[e]		Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CVD 103–HgR (Vaxchora)	Placebo			
Solicited systemic adverse events (follow-up: range 1 days to 7 days; assessed with frequency of solicited reactogenicity for any event)											
4	Randomised trials	Not serious	Serious[d]	Not serious	Not serious	None	1784/3498 (51.0%)	236/517 (45.6%)	Most studies (3/4) reported higher systemic reactogenicity in the vaccine arm compared with placebo (range 36.3–61.8% in vaccine arm; 34.6–59.2% in placebo; no 95% CI reported, unable to assess overlapping).[3-6] There was variability between the 2 studies that reported p-values, with one finding significantly higher solicited systemic AE in the vaccine group, and the other finding significantly higher solicited systemic AE in placebo.[3,4]	⊕⊕⊕◯ Moderate	IMPORTANT

Explanations

a. Only one study assessed vaccine efficacy
b. Small sample size (<400); study may not be powered to detect a difference between groups
c. Three out of six studies had high risk of bias overall due to high risk of bias in domain 5 (risk of bias in selection of the reported result) for the outcome of SAE
d. Some variability of results and few (or no) confidence intervals provided to assess overlap
e. Manually calculated pooling data from all included studies; denominator is participants assessed, not total randomised participants

Abbreviations: AE=adverse event; CI=confidence interval; RCT=randomised controlled trial; SAE=serious adverse event; SCR=seroconversion rate; SVA=serum vibriocidal antibody

Evidence to Decision (EtD) Framework: CVD 103–HgR (Vaxchora) compared with placebo in children and adults aged ≥2 years who have a high risk of exposure to cholera

Should CVD 103-HgR (Vaxchora) be used in children and adults aged ≥2 years who have a high risk of exposure to cholera?	
Population	Children and adults aged ≥2 years who have a high risk of exposure to cholera
Intervention	CVD 103–HgR (Vaxchora)
Comparison	Placebo
Main outcomes	• Efficacy against severe (≥5.0 L) cholera diarrhoea (day 10 and day 90) • Efficacy against moderate (≥3.0 L) or severe (≥5.0 L) cholera diarrhoea (day 10 and day 90) • Efficacy against mild or worse severity cholera diarrhoea (day 10 and day 90) • Serious adverse events (SAE) (to day 180) • Serum vibriocidal antibody (SVA) seroconversion rate (≥4-fold vibriocidal titre rise over baseline) against classical Inaba (day 10 and day 180) • Any solicited systemic adverse events (to day 7)
Setting	Global high-income settings (US and Australia)
Perspective	Individual

ASSESSMENT					
Problem *Is the problem a priority?*					
Don't know	Varies	No	Probably no	Probably yes	Yes

- There is no risk of cholera in Australia, but cholera can be brought back to Australia by children and adults travelling to cholera-endemic areas.[8]
- Routine cholera vaccination of travellers is not recommended, as risk to travellers is very low, despite cholera being endemic in some countries that Australians visit. Other measures, such as ensuring access to safe food and water, are more important than vaccination to prevent cholera.[8,9] Cholera vaccination is recommended for travellers who have a high risk of exposure to cholera.
- There is a currently available cholera vaccine (Dukoral [inactivated vaccine]) option in Australia.

Desirable effects

How substantial are the desirable anticipated effects?

Don't know	Varies	Trivial	Small	Moderate	Large

- Overall, there is evidence for efficacy against different severities of cholera diarrhoea up to day 90 post-vaccination.[1]
- Most evidence of antibody persistence is based on immunogenicity data to 180 days (6 months) post-vaccination in people aged 12–45 years. There appears to be little to no difference in serum vibriocidal antibody seroconversion rates at 180 days after vaccination with CVD 103–HgR.[1,5,7]
- A long-term immunogenicity sub-study in adolescents aged 12–17 years (n=73) assessed SVA seroconversion rates in vaccinees (no placebo comparator) for 2 years.[7,9] Long-term SVA seroconversion rates: 68.6% (95% CI: 57–78.2%) on day 364; 73.1% (95% CI: 61.5–82.3%) on day 546; and 64.5% (95% CI: 52.1–75.3) on day 729.
- There is no evidence available for long-term immunogenicity or efficacy in young children or older adults.

Undesirable effects

How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- There were no vaccine-related SAE reported in the included studies.
- Undesirable effects include systemic adverse events overall. In comparison, some studies show rates are slightly higher than those seen after placebo, but there is variability in these results and CVD 103–HgR (Vaxchora) likely results in little to no difference in undesirable effects compared with placebo.
- As CVD 103–HgR (Vaxchora) is a live, attenuated oral vaccine, stool shedding and household transmission for up to 7 days were investigated in a phase 1 RCT.[2] The study found that over 7 days, 11.1% (6/54) vaccinees had positive stool shedding (4 of these occurred on day 7). No instances of transmission of the vaccine strain to household contacts were detected in the stool culture up to day 7.[2]

Certainty of evidence

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High

- Certainty of evidence is moderate due to imprecision as some studies had small (<400) sample sizes and may not be powered to detect a difference between vaccine and placebo groups
- No immunogenicity or safety data in infants (<2 years) or older adults (≥65 years) for the current formulation of CVD 103–HgR (Vaxchora)
- No immunogenicity or safety data in immunocompromised populations for the current formulation of live, attenuated CVD 103–HgR (Vaxchora) cholera vaccine. There is limited evidence in HIV-positive participants using the previous formulation[10]
- No immunogenicity or safety data of current formulation of CVD 103–HgR (Vaxchora) in cholera-endemic populations
- No evidence on co-administration of current formulation CVD 103–HgR (Vaxchora) live, attenuated cholera vaccine with other vaccines or medications

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 cholera disease
- No research identified in search that addresses this; additionally, cholera vaccination is optional and not routinely recommended

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

- The overall benefits of efficacy against mild or worse severity cholera diarrhoea probably outweigh the trivial (or small) frequency of systemic adverse events.
- There is evidence of persistence of protection to 180 days post-vaccination in some age groups.
- Undesirable effects are minor and CVD 103–HgR (Vaxchora) likely results in little to no difference in undesirable effects compared with placebo.

Acceptability

Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably no	Probably yes	Yes

- Acceptability* and palatability assessed in the paediatric and adolescent trials[5,6]
- Found acceptable by 95.3% of vaccinees aged 6–17 years and by 82.7% of vaccinees aged 2–5 years
- *Palatability:*
  - In 6–17 years, was rated as very bad (14.4%), bad (25.1%), neutral (31.7%), good (17.6%) or very good (11.3%) in vaccinees.[5] Sweetener was added by 91.8% of vaccinees. Of participants with unacceptable dosing, palatability was reported as 'very bad' by 80% of vaccinees. Addition of Pure Via® stevia sweetener did not improve participants' opinions regarding treatment palatability
  - In 2–5 years, was rated by caregivers as very good, good, or neutral by 62.3% of vaccinees.[6] Optional PureVia® stevia sweetener was added to all but one of the doses; thus, assessment of its effect on palatability was not possible
- Travel medicine providers and medical associations are likely the other stakeholders impacted; no evidence identified on acceptability of CVD 103–HgR (Vaxchora) to these stakeholders
- Live, attenuated CVD 103–HgR (Vaxchora) is a 1-dose cholera vaccine (Dukoral [inactivated cholera vaccine] is 2 doses for >6 years and 3 doses for 6 years and under). The 1-dose vaccine may be more acceptable to providers and Australians recommended to receive a cholera vaccine

Feasibility *Is the intervention feasible to implement?*					
Don't know	Varies	No	Probably no	Probably yes	Yes

- No direct evidence identified for this issue
- Optional vaccine, not routinely recommended; only recommended for those at high risk of cholera
- The vaccine could be made up at home or in a travel medicine clinic
- Dose preparation may be easier at a travel clinic than at home if instructions are complex or if large quantities of sweetener needs to be added
- Potential for dosing errors in children aged <6 years due to the difference in instructions for CVD 103–HgR (Vaxchora):
    - *For children aged <6 years:* Discard half the reconstituted buffer solution, then add the active component for a total dose of 50 mL
    - *For children and adults ≥6 years:* Make the reconstituted buffer solution, then add the active component for a total dose of 100 mL
- A 1-dose vaccine may be easier to stock

*Acceptability defined as consuming entire volume vaccine within 15 minutes (6–17 years) or consuming ≥80% of vaccine dose (2–5 years)

References

1. Chen WH, Cohen MB, Kirkpatrick BD, et al. Single-dose live oral cholera vaccine CVD 103-HgR protects against human experimental infection with *Vibrio cholerae* O1 El Tor. *Clinical Infectious Diseases* 2016;62:1329-35
2. Chen WH, Greenberg RN, Pasetti MF, et al. Safety and immunogenicity of single-dose live oral cholera vaccine strain CVD 103-HgR, prepared from new master and working cell banks. *Clinical & Vaccine Immunology: CVI* 2014;21:66-73
3. McCarty JM, Lock MD, Hunt KM, et al. Safety and immunogenicity of single-dose live oral cholera vaccine strain CVD 103-HgR in healthy adults age 18–45. *Vaccine* 2018;36:833-40
4. McCarty JM, Lock MD, Bennett S, et al. Age-related immunogenicity and reactogenicity of live oral cholera vaccine CVD 103-HgR in a randomized, controlled clinical trial. *Vaccine* 2019;37:1389-97
5. McCarty JM, Gierman EC, Bedell L, et al. Safety and immunogenicity of live oral cholera vaccine CVD 103-HgR in children and adolescents aged 6-17 Years. *American Journal of Tropical Medicine & Hygiene* 2020;102:48-57
6. McCarty JM, Cassie D, Bedell L, et al. Safety and immunogenicity of live oral cholera vaccine CVD 103-HgR in Children Aged 2-5 Years in the United States. *American Journal of Tropical Medicine & Hygiene* 2020;104:861-5
7. McCarty JM, Cassie D, Bedell L, et al. Long-term immunogenicity of live oral cholera vaccine CVD 103-HgR in Adolescents Aged 12-17 Years in the United States. *American Journal of Tropical Medicine & Hygiene* 2021;104:1758-60
8. Australian Technical Advisory Group on Immunisation. *Australian Immunisation Handbook*. Canberra: Australian Government Department of Health and Aged Care; 2022. Available from: https://immunisationhandbook.health.gov.au/
9. McCarty J, Bedell L, De Lame PA, et al. Update on CVD 103-HgR single-dose, live oral cholera vaccine. *Expert Review of Vaccines* 2022;21:9-23
10. Perry RT, Plowe CV, Koumare B, et al. A single dose of live oral cholera vaccine CVD 103-HgR is safe and immunogenic in HIV-infected and HIV-noninfected adults in Mali. *Bulletin of the World Health Organization* 1998;76(1):63-71