# Coversheet on evidence assessment by ATAGI using the GRADE framework for oral live attenuated cholera vaccine CVD 103–HgR (Vaxchora) in children and adults

A summary of the use of the GRADE approach in the development of ATAGI and Australian Immunisation Handbook recommendations for CVD 103–HgR (Vaxchora) use in children and adults

## Background

- In September 2023, CVD 103–HgR (Vaxchora) was TGA approved and registered on the Australian Register of Therapeutic Goods for children and adults aged 2 years and over.
- CVD 103–HgR (Vaxchora) is a new formulation of an older cholera vaccine.
- Currently, Dukoral (oral inactivated cholera vaccine) is the only cholera vaccine option available for people in Australia.
- In March 2023, in anticipation of the availability of CVD 103–HgR (Vaxchora) in Australia, ATAGI undertook GRADE assessment of CVD 103–HgR (Vaxchora) to allow for informed recommendations on its use.
- The Australian Immunisation Handbook has been updated to reflect ATAGI recommendations on the use of CVD 103–HgR (Vaxchora) as a new cholera vaccine option for Australian people aged 2 years over who have a high risk of exposure to cholera while travelling.

## Research questions

1. Should children and adults aged ≥2 years who have a high risk of exposure to cholera use CVD 103–HgR (Vaxchora) oral, live attenuated cholera vaccine?

**Table 1: Population, Intervention, Comparator, Outcomes (PICO) – CVD 103–HgR (Vaxchora) vs. placebo, 2 years of age and over**

| | |
|---|---|
| Population | Children and adults aged ≥2 years |
| Intervention | CVD 103–HgR (Vaxchora) [current formulation only] |
| Comparator | Placebo |
| Outcomes | *Critical*<br>• Efficacy against severe (≥5.0 L)* cholera diarrhoea (day 10 and day 90)<br>• Efficacy against moderate (≥3.0 L) or severe (≥5.0 L) cholera diarrhoea (day 10 and day 90)<br>• Efficacy against mild** or worse severity cholera diarrhoea (day 10 and day 90)<br><br>*Important*<br>• Serious adverse events (SAE) (up to day 180)<br>• Serum vibriocidal antibody (SVA) seroconversion response (≥4-fold vibriocidal titre rise against classical Inaba compared to baseline; day 10 and day 180 post-vaccination)<br>• Solicited systemic adverse events (up to day 7) |

*Volume of cumulative diarrhoeal stool

**Defined as the passage of ≥2 unformed stools (grade 3–5) over a 48-hour period that equals or exceeds 200 mL, or a single unformed stool of ≥300 mL and <3 L total diarrhoea

## Literature search

A literature search was completed on 21/12/2022 to identify all studies on CVD 103–HgR (Vaxchora). Details of the search methods used are presented in Appendix A. Citations were included for review if they met the following criteria:

- *Study design:* Randomised controlled trial (RCT), observational study, meta-analysis
- *Population:* 2 years of age and over
- *Intervention:* CVD 103–HgR (Vaxchora)
- *Comparator:* Placebo
- *Outcomes:* Efficacy, immunogenicity, safety

The published literature search retrieved a total of 918 unique citations, of which seven citations met the pre-defined inclusion criteria for the comparison of CVD 103–HgR (Vaxchora) vs. placebo. Three RCTs in children and adolescents under 18 years of age investigated immunogenicity outcomes; two of these investigated both immunogenicity and safety outcomes. The other four RCTs were in adults aged 18 years and over and investigated both immunogenicity and safety outcomes; one also assessed efficacy. None of the studies investigated use of CVD 103–HgR (Vaxchora) in adults aged 65 years or older.

## Inclusion criteria and rationale

**Table 2: Rationale for PICO and inclusion criteria**

| PICO | Rationale |
|---|---|
| Study type<br><br>RCT, observational study, meta-analysis | Vaccine effectiveness studies are not widely available for the PICO question. There are also limited efficacy studies; therefore, studies investigating immunogenicity outcomes that correspond to correlates of protection against cholera diarrhoea were included. |
| Population<br><br>2 years of age and over | • Population of interest for this vaccine<br>• Population for which this vaccine is registered for use |
| Intervention<br><br>CVD 103–HgR (Vaxchora) [current formulation only] | Note that CVD 103–HgR was previously licensed under a different formulation that contained ~5 × $10^8$ colony-forming units (CFUs). (This was subsequently commercialised as Orochol and Mutacol [Swiss Serum and Vaccine Institute, Switzerland].) Additionally, a formulation containing ~5 × $10^9$ CFU (Orochol E) was prepared for use in developing countries.<br><br>CVD 103–HgR was reformulated in 2009. Following discussions with portfolio leads, early studies investigating the previous formulation were excluded. |
| Comparator<br>placebo | RCTs using non-placebo comparators were not included, as these do not fit the PICO research question. |

| PICO | Rationale |
|---|---|
| Outcomes | • Included outcomes as stated above in Table 1; included iteratively according to outcomes found in the studies<br>• Ranking of importance discussed in many iterations with portfolio leads and ATAGI full panel<br><br>General framework (depending on outcomes measured in studies available):<br><br>*Critical*<br>• Efficacy against severe (≥5.0 L) cholera diarrhoea (day 10 and day 90)<br>• Efficacy against moderate (≥3.0 L) or severe (≥5.0 L) cholera diarrhoea (day 10 and day 90)<br>• Efficacy against mild or worse severity cholera diarrhoea (day 10 and day 90)<br>• SAE (up to day 180)<br><br>*Important*<br>• SVA seroconversion rates (≥4-fold vibriocidal titre rise against classical Inaba compared to baseline; day 10 and day 180 post-vaccination)<br>• Solicited systemic AE [up to day 7]<br><br>*Note:* Excluded immunogenicity studies that investigated a very specific immune response based on serology rather than protection from cholera |

*Abbreviations:* AE=adverse events; RCT=randomised controlled trial; SAE=serious adverse events; SCR=seroconversion rate; SVA=serum vibriocidal antibody

## Risk of bias assessment

Risk of bias (RoB) assessment was carried out on all included studies by one assessor using the RoB 2.0 tool for RCTs (see Appendix B).

# Appendix A: Literature search strategy

| **MEDLINE: Cholera vaccines – Vaxchora (as at 21.12.22)** | **EMBASE: Cholera vaccines – Vaxchora (as at 21.12.22)** |
|---|---|
| Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> | Database: Embase <1974 to 2022 December 19> |
| Search strategy: | Search strategy: |
| ---------- | ---------- |
| 1 exp Immunization/ (204000) | 1 exp immunization/ (347604) |
| 2 exp Vaccines/ (269618) | 2 exp vaccine/ (387414) |
| 3 (vaccin$ or immunis$ or immuniz$).tw. (472519) | 3 (vaccin$ or immunis$ or immuniz$).tw. (540913) |
| 4 1 or 2 or 3 (578301) | 4 1 or 2 or 3 (688039) |
| 5 exp Vibrio cholerae/ (9774) | 5 exp Vibrio cholerae/ (14815) |
| 6 exp Cholera/ (9203) | 6 exp cholera/ (10676) |
| 7 exp Cholera Toxin/ (9217) | 7 exp cholera toxin/ (10813) |
| 8 cholera$.tw. (32729) | 8 cholera$.tw. (31987) |
| 9 5 or 6 or 7 or 8 (36465) | 9 5 or 6 or 7 or 8 (40066) |
| 10 4 and 9 (5649) | 10 4 and 9 (7262) |
| 11 exp Cholera Vaccines/ (1758) | 11 exp cholera vaccine/ (3240) |
| 12 10 or 11 (5771) | 12 10 or 11 (8013) |
| 13 exp Vaccines, Attenuated/ (13006) | 13 exp live vaccine/ (16334) |
| 14 (live adj4 attenuate$).tw. (10362) | 14 (live adj4 attenuate$).tw. (11761) |
| 15 13 or 14 (18725) | 15 13 or 14 (23429) |
| 16 12 and 15 (409) | 16 12 and 15 (675) |
| 17 vaxchora$.tw. (14) | 17 vaxchora$.tw. (50) |
| 18 ("CVD 103-HgR$.tw or CVD-103-HgR$" or "CVD103-HgR$" or "CVD 103 HgR$.tw or CVD-103HgR$" or "CVD103HgR$").tw. (18) | 18 ("CVD 103-HgR$.tw or CVD-103-HgR$" or "CVD103-HgR$" or "CVD 103 HgR$.tw or CVD-103HgR$" or "CVD103HgR$").tw. (19) |
| 19 PXVX0200$.tw. (9) | 19 PXVX0200$.tw. (10) |
| 20 PaxVax$.tw. (5) | 20 PaxVax$.tw. (33) |
| 21 Orochol$.tw. (2) | 21 Orochol$.tw. (89) |
| 22 Mutachol$.tw. (1) | 22 Mutachol$.tw. (12) |
| 23 17 or 18 or 19 or 20 or 21 or 22 (43) | 23 17 or 18 or 19 or 20 or 21 or 22 (177) |
| 24 16 or 23 (430) | 24 16 or 23 (790) |

## Appendix B: Risk of bias: RoB 2.0

| Study | Outcome | Domain 1: Risk of bias arising from the randomisation process | Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention) | Domain 3: Missing outcome data | Domain 4: Risk of bias in measurement of the outcome | Domain 5: Risk of bias in selection of the reported result | Overall risk of bias |
|---|---|---|---|---|---|---|---|
| Chen (2016)[1] | Efficacy | Low | Low | Low | Low | Low | Low |
| | Immunogenicity – SVA SCR | Low | Low | Low | Low | Low | Low |
| | SAE | Low | Low | Low | Low | High | High |
| | Safety – other AE | Low | Low | Low | Low | High | High |
| Chen (2014)[2] | Immunogenicity – SVA SCR | Low | Low | Low | Low | Low | Low |
| | SAE | Low | Low | Low | Low | High | High |
| | Safety – other AE | Low | Low | Low | Low | Low | Low |
| McCarty (2018)[3] | Immunogenicity – SVA SCR | Low | Low | Low | Low | Low | Low |
| | SAE | Low | Low | Low | Low | Low | Low |
| | Safety – other AE | Low | Low | Low | Low | Low | Low |
| McCarty (2019)[4] | Immunogenicity – SVA SCR | Low | Low | Low | Low | Low | Low |
| | SAE | Low | Low | Low | Low | High | High |
| | Safety – other AE | Low | Low | Low | Low | Low | Low |
| McCarty (2020)[5] | Immunogenicity – SVA SCR | Low | Low | Low | Low | Low | Low |
| | SAE | Low | Low | Low | Low | Low | Low |
| | Safety – other AE | Low | Low | Low | Low | Low | Low |
| McCarty [a] (2021)[6] | Immunogenicity – SVA SCR | Low | Low | Low | Low | Low | Low |
| | SAE | Low | Low | Low | Low | Low | Low |
| | Safety – other AE | Low | Low | Low | Low | Low | Low |
| McCarty [b] (2021)[7] | Immunogenicity – SVA SCR | Low | Low | Low | Low | Low | Low |

*Abbreviations:* AE=adverse events; SCR=seroconversion rate; SVA=serum vibriocidal antibody

## 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