Evidence to Recommendations: CVD 103-HgR among children and adolescents aged 2–17 years

Jennifer P. Collins, MD, MSc

CDC Lead, Cholera Vaccine Work Group

Advisory Committee on Immunization Practices

January 12, 2022

Background of the work group

- **June 2016:** ACIP recommended the cholera vaccine CVD 103-HgR (Vaxchora) for adult travelers aged 18–64 years from the United States to an area with active cholera transmission
- **October 2020:** ACIP cholera vaccine work group formed
- **December 2020:** FDA extended the approved usage to include children and adolescents aged 2–17 years
- **February 2021:** Work group presented background information and the manufacturer presented pediatric clinical trial data

Evidence to Recommendation (EtR) Framework: policy question

- Should ACIP recommend CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission?

PICO components

Population	Children and adolescents aged 2–17 years traveling to an area with active cholera transmission
Intervention	Lyophilized CVD 103-HgR (single-dose, oral, live-attenuated bacterial vaccine*)
Comparison	No cholera vaccine
Outcomes	- Cholera diarrhea, moderate or severe - Cholera diarrhea, any severity - Serious adverse events - Non-serious adverse events

*$4x10^8$–$2x10^9$ colony forming units with buffer (50 ml if 2–5 years; 100 ml if 6–17 years)

Evidence to Recommendations (EtR) Framework

EtR Domain	Question
Public health problem	Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission of public health importance?
Benefits and harms	How substantial are the desirable anticipated effects?
	How substantial are the undesirable anticipated effects?
	Do the desirable anticipated effects outweigh the undesirable effects?
	What is the overall certainty of the evidence for the critical outcomes?
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?
	Is there important variability in how patients value the outcome?
Acceptability	Is CVD 103-HgR acceptable to key stakeholders?
Resource use	Is CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?
Equity	What would be the impact of CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission on health equity?
Feasibility	Is CVD 103-HgR feasible to implement among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?

EtR domain: public health problem

Public health problem questions

- **Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a public health problem?**
  - Are the consequences cholera serious (i.e., severe or important in terms of the potential benefits or savings)?
  - Is cholera urgent?
  - Are many travelers aged 2–17 years from the United States affected by cholera?
  - Is cholera related to emerging diseases, antimicrobial resistance, or epidemic potential?
  - Are disadvantaged groups or populations disproportionately/differentially affected by cholera?

No | Probably no | Probably yes | Yes | Varies | Don't know

- Are the consequences of cholera serious?
- Is cholera urgent?

- Infection with toxigenic *V. cholerae* O1 can cause a range of symptoms

- Cholera gravis is rapidly fatal if untreated
- Fluid management is the primary focus treatment
- Rehydration can reduce the fatality rate to <1%
- Patients with cholera gravis may require up to 350 ml/kg of fluids within the first 24 hours of illness

Are many travelers aged 2–17 years from the United States affected by cholera?

- Most international travelers from the United States do not get cholera[1]
  - do not visit areas with active cholera transmission
  - have good access to safe food and water
- During 2012–2018, 64 cholera cases reported in the United States
  - 5 (8%) aged 2–17 years
  - 2 deaths (adults)
  - 56 (88%) travel associated
- National cholera case counts underestimate the true burden

[1]https://wwwnc.cdc.gov/travel/diseases/cholera#areas

- Is cholera related to emerging diseases, antimicrobial resistance, or epidemic potential?
- Are disadvantaged groups or populations disproportionately/differentially affected by cholera?

- Antibiotic resistance can occur
- Fluids are the mainstay of treatment; antibiotics are adjunctive therapy in moderate to severe illness
- An estimated 1.3–4.0 million cholera cases and 21,000–143,000 deaths occur worldwide each year[1]
- Cholera epidemics are associated with unsafe water and inadequate sanitation
- Secondary cases are rare if sanitation is adequate
- A US outbreak from a returning traveler is unlikely

[1]https://www.who.int/health-topics/cholera#tab=tab_1

Public health problem: work group deliberations

- **Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a public health problem?**
  - Cholera is a public health problem for local populations in endemic settings due to unsafe drinking water and inadequate sanitation
  - For travelers from the United States, the risk varies by
    - travel destination
    - travel activities
    - access to safe water, food, and sanitation
  - Cholera may pose a meaningful **individual risk** for ill travelers with inadequate or delayed access to fluid replacement
  - May become a bigger problem for travelers in the future
  - Having a supply of cholera vaccine for US travelers is important

Public health problem: work group determination

- **Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a public health problem?**
  - Most members felt probably yes
  - Some felt probably no or varies

EtR domain: benefits and harms

Benefits and harms questions

- **How substantial are the desirable anticipated effects overall and for each main outcome for which there is a desirable effect?**

Minimal | Small | Moderate | Large | Varies | Don't know

- **How substantial are the undesirable anticipated effects overall and for each main outcome for which there is an undesirable effect?**

Minimal | Small | Moderate | Large | Varies | Don't know

Benefits and harms questions

- **Do the desirable effects outweigh the undesirable effects?**

- Favors intervention (CVD 103-HgR)
- Favors comparison (placebo)
- Favors both
- Favors neither
- Unclear

- **What is the overall certainty of this evidence for the critical outcomes?**

- High
- Moderate
- Low
- Very low

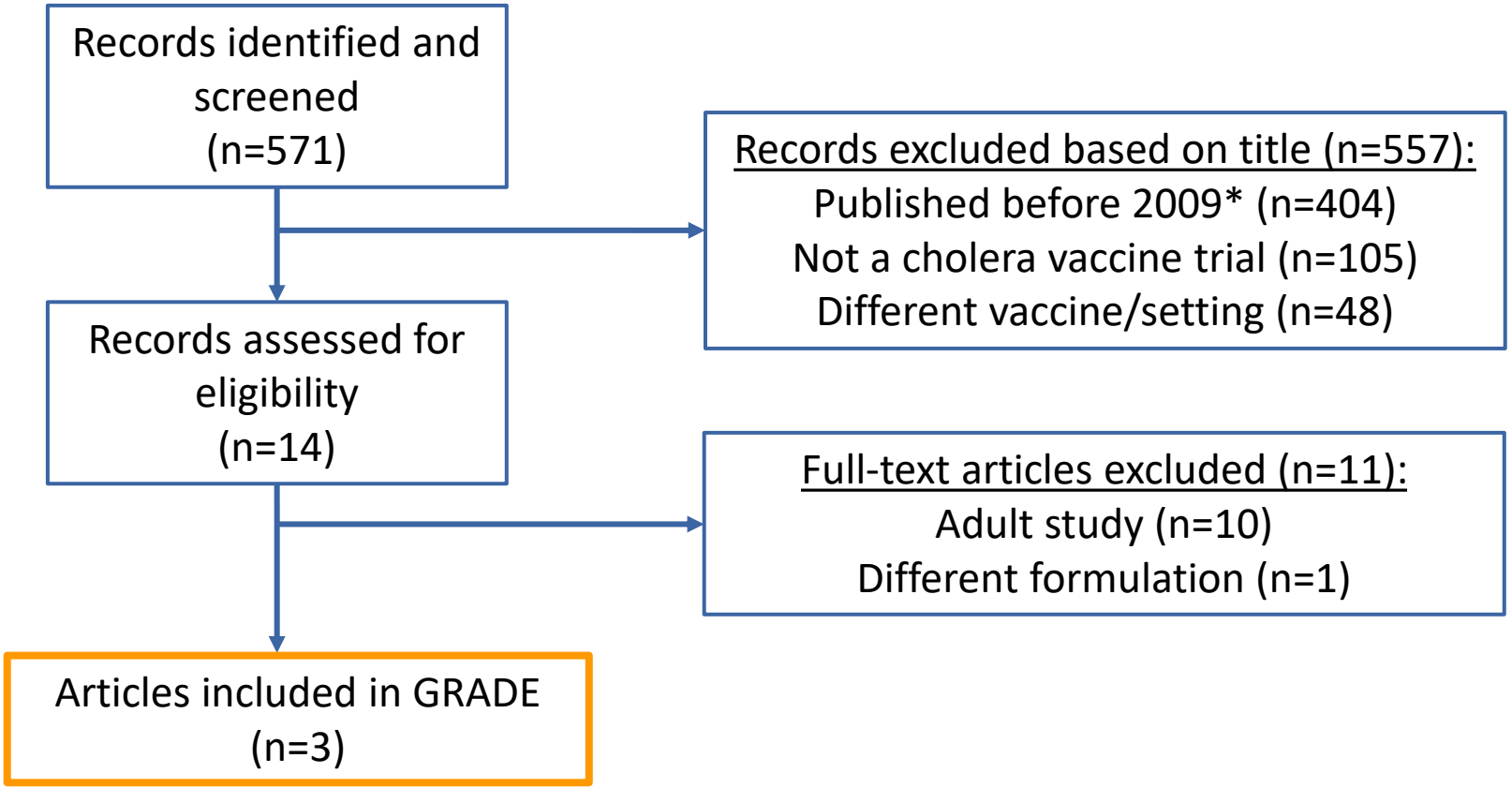
PICO outcomes

Outcome	Importance
Benefits	
Cholera diarrhea, moderate or severe	Critical
Cholera diarrhea, any severity	Critical
Harms	
Serious adverse events	Critical
Non-serious adverse events	Important

GRADE evidence retrieval

- **Databases:** PubMed, Embase, and Cochrane Library, written in English
- **Search terms:** cholera, *Vibrio cholerae,* CVD 103-HgR, cholera vaccine
- **Inclusion:** provided data on the current formulation and dose of CVD 103-HgR and 1) involved human subjects aged 2–17 years, 2) reported primary data relevant to the efficacy and safety outcomes, and 3) conducted in cholera non-endemic settings
- Titles and abstracts screened by 2 reviewers

GRADE evidence retrieval



*The current formulation of CVD 103-HgR was not available before 2009

3 articles summarized a phase 4, randomized, double-blind placebo-controlled trial

(manufacturer presented to ACIP in February 2021)

Setting	• Seven U.S. sites • July 2017 – September 2019
Inclusion	Healthy children and adolescents aged 2–17 years* • Cohort 1: 12–17 years • Cohort 2: 6–11 years • Cohort 3: 2–5 years
Randomization (6:1 ratio)	CVD 103-HgR 1x10^9 CFU vs. 0.9% saline placebo (6:1 ratio)
Optional sweetener	PureVia Stevia**
Outcomes	Safety and immunogenicity

*without a significant medical history or physical examination findings at screening. In female participants of childbearing potential, a urine pregnancy test was performed at screening and before vaccine administration.

**Sweetener added for 437/471 (93%) CVD 103-HgR and 73/79 (92%) placebo recipients

Outcomes 1 and 2:
- Cholera diarrhea, moderate to severe
- Cholera diarrhea, any severity

NO PEDIATRIC STUDIES DIRECTLY ASSESSED VACCINE EFFECTIVENESS

- Assessment based on immunobridging to adults
  - Oral wild-type *Vibrio cholerae* O1 administered to participants aged 18–45 years following vaccine or placebo
  - Correlation coefficient between cumulative diarrhea (in L) and fold-increase in serum vibriocidal antibody:
    - -0.75 at 10 days
    - -0.69 at 3 months
- In endemic settings, fold-increases in SVA correlated with protection in both adults and children

*Chen WH et al. Clin Infect Dis. 2016: 62. 1329–1335.

GRADE evidence table:

Cholera diarrhea, moderate to severe* OR any severity*

Assessed via SVA seroconversion (≥4-fold rise in titer) on day 11

Certainty assessment							Summary of findings					Importance
# studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	# patients		Effect		Certainty	
							CVD 103-HgR n/N % (95% CI)	Placebo n/N % (95% CI)	Relative risk (95% CI)	Absolute risk (95% CI)		
2	RCT	Not serious [a]	Not serious	Serious[c]	Not serious	None	393/399 (98.5%)	1/67 (1.5%)	65.99 (9.43–461.69)	97,000 more per 100,000 From 12,582 more to 100,000 more	Type 2 (moderate)	Critical

[a]Loss to follow-up for SVA at day 11: 2–5 year cohort (CVD 103 HgR: 47/150 (32%); Placebo: 6/26 (24%)), 6–11 year cohort (CVD 103-HgR 25/321 (8%); Placebo: 6/53 (11%)).

[b]Serious concern for indirectness because efficacy is inferred from immunobridging. SVA seroconversion is an indirect correlate of protection with biologic plausibility. Dichotomous definition of seroconversion (≥4-fold rise in titer) is different than fold-increases in SVA. In an adult challenge study (Chen, 2016), the correlation coefficient between cumulative diarrhea (L) and fold-increase in serum-vibriocidal antibodies was -0.75 at day 10 and -0.69 at 3 months.

[c]The RCTs enrolled healthy children and adolescents aged 2–17 years and my not represent all children and adolescents in this age group, such as those with immunocompromising conditions.

[d]Seroconversion on day 11 occurred among 292/296 (98.6% [98.3% CI: 95.9–99.6%]) of CVD 103-HgR recipients aged 6–17 years and among 101/103 (98.1% [98.3% CI: 91.5–99.6%]) of CVD 103-HgR recipients aged 2–5 years. Seroconversion in each of these age groups met prespecified non-inferiority criteria (lower limit of the 96.7% CIs on the difference between the groups exceeding -10) compared with adults 18–45 years from a phase 3 lot consistency study.

GRADE evidence table: serious adverse events

Assessed via serious adverse events (through day 181)

Certainty assessment							Summary of findings					Importance
# studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	# patients		Effect		Certainty	
							CVD 103-HgR n/N % (95% CI)	Placebo n/N % (95% CI)	Relative risk (95% CI)	Absolute risk (95% CI)		
2	RCT	Not serious [a]	Not serious[b]	Not serious[c]	Very serious[d]	None	1/468 0.2%	1/75 1.3%	0.16 (0.01–2.53)	1,120 fewer per 100,000 (from 1,320 fewer to 2,040 more)	Type 3 (low)	Critical

[a]Loss to follow-up for serious adverse events: CVD 103-HgR: 3/471 (0.6%), placebo: 4/79 (5%).

[b]No SAEs were attributed to the vaccine in either study.

[c]The RCTs enrolled healthy children and adolescents aged 2–17 years and may not represent all children and adolescents in this age group, such as those with immunocompromising conditions.

[d]Very serious concern for imprecision based on the small sample size to assess rare serious adverse events, the small number of events, and the wide 95% confidence interval that crosses the line of no effect.

GRADE evidence table: non-serious adverse events

Assessed via any solicited adverse event, day 1–8

Certainty assessment							Summary of findings					Importance
# studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	# patients		Effect		Certainty	
							CVD 103-HgR n/N % (95% CI)	Placebo n/N % (95% CI)	Relative risk (95% CI)	Absolute risk of (95% CI)		
2	RCT	Not serious[a]	Not serious[b]	Not serious[c]	Very serious[d]	None	258/468 55.1%	38/75 50.7%	1.09 (0.86–1.38)	4,560 more per 100,000 (from 7,093 fewer to 19,253 more)	Type 3 (low)	Important

[a]Loss to follow-up for solicited adverse events CVD 103-HgR: 3/471 (0.6%), placebo: 4/79 (5%).

[b]Solicited adverse events were reported by a lower percentage of study participants aged 2–5 years (CVD 103-HgR: 40.4%, placebo: 34.6%) than aged 6–17 years (CVD 103-HgR: 61.8%, placebo: 59.2%). This may relate to limited language skills in the younger age group and was deemed not serious.

[c]The RCTs enrolled healthy children and adolescents aged 2–17 years and may not represent all children and adolescents in this age group, such as those with immunocompromising conditions.

[d]Serious concern for imprecision because the wide confidence intervals cross the line of no effect.

Benefits and Harms: Summary of GRADE

Outcome	Importance	Design (# studies)	Findings	Evidence type*
Benefits				
Cholera diarrhea, moderate to severe	Critical	RCT (2)	CVD 103-HgR effectively induces SVA seroconversion, **an imperfect correlate of protection** against cholera	Type 2 (moderate)
Cholera diarrhea, any severity	Critical	RCT (2)	CVD 103-HgR effectively induces SVA seroconversion, **an imperfect correlate of protection** against cholera	Type 2 (moderate)
Harms				
Serious adverse events	Critical	RCT (2)	No SAEs were judged to be related to the vaccine.	Type 3 (low)
Non-serious adverse events	Important	RCT (2)	Frequency of non-serious adverse events was not meaningfully different among CVD 103-HgR versus placebo recipients	Type 3 (low)

Benefits and harms: work group determination

- **How substantial are the desirable anticipated effects overall and for each main outcome for which there is a desirable effect?**

- **How substantial are the undesirable anticipated effects overall and for each main outcome for which there is an undesirable effect?**

Benefits and harms: work group determination

- **Do the desirable effects outweigh the undesirable effects?**

- [x] Favors intervention (CVD 103-HgR)
- [ ] Favors comparison (placebo)
- [ ] Favors both
- [ ] Favors neither
- [ ] Unclear

- **What is the overall certainty of this evidence for the critical outcomes?**

- [ ] High
- [ ] Moderate
- [x] Low
- [ ] Very low

EtR domain: values

Values questions

- **1. Does the target population feel the desirable effects are large relative to the undesirable effects?**
- **2. Is there important uncertainty about, or variability in, how patients value the outcomes?**

Values

- No research evidence identified
- Cholera vaccines are optional
- Individuals can decide whether to get it based on their values

Values: work group determination

- **1. Does the target population feel the desirable effects are large relative to the undesirable effects?**
- **2. Is there important uncertainty about, or variability in, how patients value the outcomes?**

EtR domain: acceptability

Acceptability questions

- **Is the intervention acceptable to key stakeholders?**
  - Are there key stakeholders that would not accept the distribution of benefits, harms, and costs?
  - Are there key stakeholders that would not accept the costs or undesirable effects in the short term for the desirable effects in the future?

Acceptability

- No research evidence identified
- Travel medicine providers and medical associations (IDSA, AAP, PIDS) are likely to find it acceptable to administer CVD 103-HgR to children and adolescents aged 2–17 years traveling to an area with active cholera transmission

Acceptability: work group determination

- **Is the intervention acceptable to key stakeholders?**

EtR domain: resource use

Resource use questions

- **Is CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?**
  - What is the cost-effectiveness of the vaccination?
  - How does the cost-effectiveness of the vaccination vary in any sensitivity analyses?
  - How does the cost-effectiveness change in response to changes in context, assumptions, model structure, across different studies, etc.?

No | Probably no | Probably yes | Yes | Varies | Don't know

Resource use: work group determination

- No research evidence identified
- Cost-analysis was not conducted given optional nature of CVD 103-HgR among travelers

Resource use: work group determination

- **Is CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?**

EtR domain: equity

Equity questions

- **What would be the impact on health equity of CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?**
  - Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered?
  - Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?
  - Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings?
  - Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?

Minimal | Small | Moderate | Large | Varies | Don't know

Equity

- No research evidence identified
- Concern for possible inequity
- Underserved populations may have difficulty accessing and paying for the vaccine
  - Travelers visiting friends and relatives (VFR) in cholera endemic areas are likely highest risk for illness but are often uninsured
  - For other travel vaccines, VFR travelers are often less likely than other travelers to come to travel clinics and receive pre-travel vaccines

Equity: work group determination

- **What would be the impact of CVD 103-HgR among children and aged adolescents 2–17 years traveling to an area with active cholera transmission on health equity?**

EtR domain: feasibility

Feasibility questions

- **Is CVD 103-HgR feasible to implement among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?**
  - Is the intervention sustainable?
  - Are there important barriers that are likely to limit the feasibility of implementing the intervention or that require consideration when implementing it?
  - Is access to the vaccine an important concern?
  - Would the vaccine recommendation have any impact on health equity?
  - Are there important considerations when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?

No | Probably no | Probably yes | Yes | Varies | Don't know

Feasibility

- Likely feasible to administer to children and adolescents aged 2–17 years **in a travel clinic**
  - Dose preparation is more complicated than routine childhood vaccines
    - Requires reconstitution in bottled purified/spring water
    - Half of buffer is discarded for children aged <6 years
  - May be optimally ingested with specific sweeteners
    - >92% of trial participants used PureVia Stevia
    - 89% of study participants consumed the complete dose
    - SVA seroconversion with partial dosing
      - 18/26 (69.2%) who consumed <50% of dose
      - 7/7 (100%) who consumed 50 – <80% of dose
- The recommendation may impact health equity

Feasibility questions

- **Is CVD 103-HgR feasible to implement among children and adolescents 2–17 years traveling to an area with active cholera transmission?**

Summary

EtR Domain	Question	Work group determination
Public health problem	Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission of public health importance?	Probably yes
Benefits and harms	How substantial are the desirable anticipated effects?	Moderate
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable anticipated effects outweigh the undesirable effects?	Favors CVD 103-HgR
	What is the overall certainty of the evidence for the critical outcomes?	Low
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Don’t know
	Is there important variability in how patients value the outcome?	Don’t know
Acceptability	Is CVD 103-HgR acceptable to key stakeholders?	Yes
Resource use	Is CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?	Don’t know
Equity	What would be the impact of CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission on health equity?	Varies
Feasibility	Is CVD 103-HgR feasible to implement among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?	Probably yes

EtR framework summary: work group interpretations

*CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission

Balance of consequences	Undesirable consequences ***clearly outweigh*** desirable consequences in most settings	Undesirable consequences ***probably outweigh*** desirable consequences in most settings	The balance between desirable and undesirable consequences ***is closely balanced or uncertain***	Desirable consequences ***probably outweigh*** undesirable consequences in most settings	Desirable consequences ***clearly outweigh*** undesirable consequences in most settings	Evidence to determine the balance of consequences is ***insufficient***

EtR framework summary: work group interpretations

*CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission

Balance of consequences	Undesirable consequences ***clearly outweigh*** desirable consequences in most settings	Undesirable consequences ***probably outweigh*** desirable consequences in most settings	The balance between desirable and undesirable consequences ***is closely balanced or uncertain***	Desirable consequences ***probably outweigh*** undesirable consequences in most settings	Desirable consequences ***clearly outweigh*** undesirable consequences in most settings	Evidence to determine the balance of consequences is ***insufficient***

EtR framework summary: work group interpretations

*CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission

Type of recommendation	We do not recommend the intervention*	We recommend the intervention* for individuals based on shared clinical decision-making	We recommend the intervention*

EtR framework summary: work group interpretations

*CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission

Type of recommendation	We do not recommend the intervention*	We recommend the intervention* for individuals based on shared clinical decision-making	We recommend the intervention*

Acknowledgements

ACIP members
- Pablo Sanchez (chair)
- Matt Daley (member)

***Ex officio* members**
- Bill Alexander (NIH)
- Tina Mongeau (FDA)

ACIP liaisons
- Carol Baker (IDSA)
- Elizabeth Barnett (ISTM)
- Adam Ratner (AAP)

Technical advisors
- Mike Brady
- Ed Ryan (Harvard)
- Mary Wilson (UCSF/Harvard)

CDC work group contributors
- Grace Appiah (NCEZID/DGMQ)
- Bruce Gutelius (NCEZID/DFWED)
- Eric Mintz (NCEZID/DFWED)
- Talia Pindyck (NCEZID/DFWED)
- John Su (NCEZID/DHQP)
- Farrell Tobolowsky (NCEZID/DFWED)

ACIP secretariat
- Jessica MacNeil
- Stephanie Thomas

CDC GRADE consultants
- Douglas Campos-Outcalt
- Rebecca Morgan

Thank you!
Questions?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Extra slides: GRADE assessment

GRADE certainty of evidence

Reflects the extent to which confidence in an estimate of the effect is adequate to support a particular recommendation

Grade	Definition
Type 1 (high)	Further research is **unlikely** to change our confidence in the estimate or effect
Type 2 (moderate)	Further research is **likely to have an important impact** on our confidence in the estimate of effect and may change the estimate
Type 3 (low)	Further research is **very likely to have an important impact** on our confidence in the estimate of effect and is likely to change the estimate
Type 4 (very low)	Any estimate of effect is **very uncertain**

Certainty of evidence. GRADEpro GDT. https://gradepro.org/

GRADE certainty of evidence

- **Initial type determined by study design**
  - Type 1 (high) – randomized control trials
  - Type 3 (low) – observational studies
- Factors that can downgrade evidence profile
  - **Risk of bias** – failure to conceal allocation, failure to blind, loss to follow-up. Risk of bias may vary across outcomes.
  - **Inconsistency** – criteria for evaluating include similarity of point estimates, extent of overlap of confidence intervals, statistical tests of heterogeneity including chi-square and I^2.
  - **Indirectness –** Considers the generalizability of the evidence to the original PICO components (i.e, do study patients, intervention, comparison, or outcomes differ from those of interest?)
  - **Imprecision** – Considers the fragility of the relative and absolute effect measures based on the interpretation of the 95% CIs and the optimal information size
- Other factors can downgrade or upgrade evidence: publication bias, dose-response gradient, large magnitude of effect, opposing residual confounding

Articles included in GRADE evidence review

Am. J. Trop. Med. Hyg., 00(0), 2020, pp. 1–5
doi:10.4269/ajtmh.20-0917

Safety and Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Children Aged 2–5 Years in the United States

James M. McCarty,[1]* David Cassie,[2] Lisa Bedell,[2] Michael D. Lock,[2] and Sean Bennett[2]
[1]*Stanford University School of Medicine, Stanford, California;* [2]*Emergent Travel Health, Inc., Redwood City, California*

Am. J. Trop. Med. Hyg., 102(1), 2020, pp. 48–57
doi:10.4269/ajtmh.19-0241

Safety and Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Children and Adolescents Aged 6–17 Years

James M. McCarty,[1]* Emma C. Gierman,[2] Lisa Bedell,[2] Michael D. Lock,[2] and Sean Bennett[2]
[1]*Stanford University School of Medicine, Stanford, California;* [2]*PaxVax, Inc., Redwood City, California*

Am. J. Trop. Med. Hyg., 104(5), 2021, pp. 1758–1760
doi:10.4269/ajtmh.20-1576

Long-Term Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Adolescents Aged 12–17 Years in the United States

James M. McCarty,[1]* David Cassie,[2] Lisa Bedell,[3] Michael D. Lock,[3] and Sean Bennett[3]
[1]*Stanford University School of Medicine, Stanford, California;* [2]*Emergent BioSolutions Canada, Inc., Winnipeg, Canada;* [3]*Emergent Travel Health, Inc., Redwood City, California*

Phase 4, randomized, double-blind placebo-controlled trial: analysis endpoints

Safety	• Adverse events
	  • Solicited (study day 1–8)
	  • Unsolicited (through day 29)
	  • Serious (through day 181)
	• Safety monitoring committee reviewed blinded data on adverse events Q6 months

Immunogenicity	Classic Inaba serum vibriocidal antibodies (SVA)* • All participants: day 1, 11, and 29 (±2) • Cohort 1 (12–17 years): Day 91 (±7) and 181 (±7)
Dosing	% dose consumed
Palatability	5-point hedonic scale 30 minutes after consumption

*Sample size calculated for independent evaluation of 2 objectives in each age cohort: **noninferiority to adults in seroconversion rate** (96.7% CI = 2/3 of alpha), and **minimum seroconversion rate of 70%** (98.3% CI = 1/3 of alpha)

INDIRECT EVIDENCE FOR
- Cholera diarrhea, moderate to severe
- Cholera diarrhea, any severity

Age	Evaluable N	Seroconverted N	% (98.3% CI)	Non-inferior to 18–45 years
Primary endpoint: seroconversion[a] (day 11)				
18–45 years[b,3]	2,687	2513	93.5 (92.3–94.6%)	REF
6–17 years[1]	296	292	98.6 (95.9–99.6%)	YES
2–5 years[2]	103	101	98.1 (91.5–99.6%)	YES

[a]≥4-fold rise in serum vibriocidal antibody titer. Seroconversion among 6–17 year and 2–5 year age groups was non-inferior to adults 18–45 years from a phase 3 lot consistency study based on prespecified 96.7% confidence interval (2/3 of alpha).

[b]In an oral challenge study of adults 18–45 years old: correlation coefficient between cumulative diarrhea (L) and fold-increase in SVA was -0.75 at 10 days and -0.69 at 3 months[3].

[1]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 102(1); 48–57. [2]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 00(0); 1–5. [3]Chen WH et al. Clin Infect Dis. 2016: 62. 1329–1335.

INDIRECT EVIDENCE FOR

- Cholera diarrhea, moderate to severe

- Cholera diarrhea, any severity

Age	Day	CVD 103-HgR N	Placebo N	CVD 103-HgR GMT (95% CI)	Placebo GMT (95% CI)
Secondary endpoint: GMTs					
6–17 years	1	296	47	32 (29–35)	39 (30–53)
	11	296	47	8,531 (7,270–10,009)	41 (29–58)
	29	294	46	2,341 (2,031–2,697)	41 (29–59)
2–5 years	1	103	20	27 (24–30)	26 (19–36)
	11	103	20	4,852 (3,445–6,832)	28 (20–39)
	29	98	18	1,014 (741–1,387)	27 (21–36)

GMT: geometric mean titer

[1]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 102(1); 48–57. [2]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 00(0); 1–5.

INDIRECT EVIDENCE FOR

- Cholera diarrhea, moderate to severe
- Cholera diarrhea, any severity

Age	Day	CVD 103-HgR N	Placebo N	CVD 103-HgR GMT (95% CI)	Placebo GMT (95% CI)
Secondary endpoint: GMT mean fold increase					
6–17 years	11	296	47	268 (229–315)	1 (1–1)
	29	294	46	73 (64–85)	1 (1–1)
2–5 years	11	103	20	182 (131–252)	1 (1–1)
	29	98	18	38 (28–51)	1 (1–1)

GMT: geometric mean titer

[1]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 102(1); 48–57. [2]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 00(0); 1–5.

Outcome 3: serious adverse events[a]

Age	CVD 103-HgR N	Placebo N	CVD 103-HgR SAEs N	Placebo SAEs N
Serious adverse events				
6–17 years	303	48	1[b]	0
2–5 years	123	103	0	1[c]

[a]Serious adverse events (SAEs) were collected through study day 181. SAE definition: an AE that met any of the following criteria: resulted in death, was life-threatening, required hospitalization or the prolongation of an existing hospitalization, resulted in a persistent or significant disability or incapacity, resulted in a congenital anomaly or birth defect, required medical or surgical intervention to prevent impairment or damage, other serious important medical event.
[b]Right leg fracture determined to be unrelated to the vaccine
[c]Pneumonia and asthma requiring hospitalization determined to be unrelated to placebo

[1]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 102(1); 48–57. [2]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 00(0); 1–5.

Outcome 4: non-serious adverse events

Age	CVD 103-HgR N	Placebo N	CVD 103-HgR AEs N (%)	Placebo AEs N (%)
Solicited adverse events[a] (day 1–8)				
6–17 years	322	49	199 (61.8%)	29 (59.2%)
2–5 years	146	26	59 (40.4%)[b]	9 (34.6%)
Unsolicited adverse events[c] (through day 29)				
6–17 years	322	49	79 (24.5%)	16 (32.7%)
2–5 years	146	26	38 (26.0%)	6 (23.1%)

[a]Includes tiredness, headache, abdominal pain, lack of appetite, nausea, vomiting, fever, and diarrhea. Frequencies of individual symptoms did not differ between vaccine and placebo groups, except among 2–5 year cohort: vomiting was significantly more frequent in the placebo group.
[b]Includes one case of potentially life-threatening fever T>40°C
[c]Most considered unrelated to study treatment per manufacturer.

[1]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 102(1); 48–57. [2]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 00(0); 1–5.

Outcome 4: non-serious adverse events

- Solicited events
  - Each participant or parent/guardian recorded on a diary card on study day 1–8
  - On study day 11, blinded study staff reviewed diary cards with them and assigned a grade
- Unsolicited adverse events collected through day 29

SUPPLEMENTAL TABLE 1: TOXICITY GRADING SCALE

Table for Clinical Abnormalities

VACCINE REACTION	MILD (Grade 1)	MODERATE (Grade 2)	SEVERE (Grade 3)	POTENTIALLY LIFE THREATENING (Grade 4)
Abdominal Pain	Mild, no interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization for hypotensive shock
Anorexia (Lack of appetite)	No interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Diarrhea	4 loose stools /24 hours	5 loose stools/24 hours	≥ 6 loose stools/24 hours	ER visit or hospitalization
Fatigue (Tiredness)	Mild, no interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Fever	> 100.4 – 101.1°F (>38.0 – 38.4°C)	≥101.2 – 102°F (≥38.5 –38.9°C)	≥ 102.1°F– 104°F (≥39°C–40°C)	> 104°F (> 40°C)
Headache	Mild, no interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Myalgia	Mild, no interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization
Nausea	Mild, no interference with activity	Some interference with activity	Significant, prevents daily activity	ER visit or hospitalization for hypotensive shock
Vomiting	1–2 episodes/24 hours	> 2 episodes/24 hours	Requires IV hydration	ER visit or hospitalization for hypotensive shock

When developing this Toxicity Grading Scale, PaxVax referred to the recommendations in the FDA's Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Subjects Enrolled in Preventive Vaccine Clinical Trials (US FDA 2007).

Diarrhea 1-3 Stools/24 hours: Record as "loose stools" on the AE CRF.

[1]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 102(1); 48–57. [2]McCarty JM et al. *Am J Trop Med Hyg*. 2020. 00(0); 1–5.