



# Evidence to recommendations summary, considerations for use, and proposed policy option: CVD 103-HgR among children and adolescents aged 2–17 years

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# Outline

- Summary of January 12<sup>th</sup> ACIP meeting presentation
  - Policy question
  - EtR Summary
- Considerations for prevention of cholera and use of CVD 103-HgR
- Proposed policy option for discussion

# Evidence to Recommendation (EtR) Framework: policy question and PICO components

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

|                     |   |
|---------------------|---|
| <b>Population</b>   | Children and adolescents aged 2–17 years traveling to an area with active cholera transmission  |
| <b>Intervention</b> | Lyophilized CVD 103-HgR (single-dose, oral, live-attenuated bacterial vaccine*)   |
| <b>Comparison</b>   | No cholera vaccine  |
| <b>Outcomes</b>     | <ul style="list-style-type: none"><li>- Cholera diarrhea, moderate or severe</li><li>- Cholera diarrhea, any severity</li><li>- Serious adverse events</li><li>- Non-serious adverse events</li></ul> |

\* $4 \times 10^8$ – $2 \times 10^9$  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  | Work group determination |
|------------------------------|---|--------------------------|
| <b>Public health problem</b> | Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission of public health importance?                            | Probably yes             |
| <b>Benefits and harms</b>    | 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                      |
| <b>Acceptability</b>         | Is CVD 103-HgR acceptable to key stakeholders?  | Yes                      |
| <b>Equity</b>                | 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                   |
| <b>Feasibility</b>           | 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             |
| <b>Values</b>                | 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               |
| <b>Resource use</b><br>4     | 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               |

# 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

|                                |  |   |  |   |  |  |
|--------------------------------|--|---|--|---|--|--|
| <b>Balance of consequences</b> | Undesirable consequences <b>clearly outweigh</b> desirable consequences in most settings | Undesirable consequences <b>probably outweigh</b> desirable consequences in most settings | The balance between desirable and undesirable consequences <b>is closely balanced or uncertain</b> | <b>Desirable consequences probably outweigh</b> undesirable consequences in most settings | Desirable consequences <b>clearly outweigh</b> undesirable consequences in most settings | Evidence to determine the balance of consequences is <b>insufficient</b> |
|--------------------------------|--|---|--|---|--|--|

# 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

| <b>Type of recommendation</b> | We do not recommend the intervention* | We recommend the intervention* for individuals based on shared clinical decision-making | We recommend the intervention* |
|-------------------------------|---------------------------------------|---|--------------------------------|
|-------------------------------|---------------------------------------|---|--------------------------------|

# Considerations for prevention of cholera and use of CVD 103-HgR

# CDC's Travelers Health Branch updates the list of countries with active cholera transmission monthly

## Travelers' Health

Travelers Health > Disease Directory (47) > Cholera



### Travelers Health

Destinations

Travel Notices +

Find a Clinic +

Travel Advice and Resources +

Disease Directory (47) -

**Cholera**

Zika Travel Information +

CDC Yellow Book +

Frequently Asked Questions +

## Cholera

Please note: As of December 2020, the maker of the cholera vaccine will temporarily stop making and selling this vaccine. The cholera vaccine may be in limited supply or unavailable.

### What is cholera?

Cholera is a disease caused by bacteria called *Vibrio cholerae*. Cholera bacteria spread from one person to another in places where sanitation is poor and there is limited access to safe drinking water.

You can get sick with cholera by drinking water or eating food contaminated with cholera bacteria. Cholera symptoms include diarrhea, nausea, dizziness, and vomiting. People with severe cholera have large amounts of watery diarrhea. Often described as "rice-water stool," cholera diarrhea can have a pale, milky appearance. Cholera can lead to death if a person becomes dehydrated from loss of fluids and electrolytes.

### Who is at risk?

Most international travelers do not get cholera because they do not visit areas with active cholera transmission and usually have good access to safe food and water.

Cholera is found in countries around the world but is extremely rare in the United States and other industrialized nations.

The following is a list of countries that have areas of active cholera transmission

- **Africa:** Benin, Cameroon, Democratic Republic of the Congo, Ethiopia, Kenya, Mozambique, Niger, Nigeria, Somalia, Uganda
- **Asia:** Afghanistan, Bangladesh, India, Nepal, Yemen
- **Americas:** none
- **Pacific:** none



[Find health recommendations for your destination](#)

# Regardless of cholera vaccination status, travelers to cholera-affected areas should use personal protective measures\*



Consume safe food  
and water



Wash hands often  
with soap and  
safe water



Follow recommended  
sanitation practices

# CVD 103-HgR is the only cholera vaccine licensed for use in the United States

- Single dose, live, attenuated oral vaccine derived from *Vibrio cholerae* O1
- Production temporarily discontinued during COVID-19 pandemic
- Will be available beginning **May 1, 2022**

# 62,179 doses of CVD 103-HgR sold in the United States during 2016–2019\*

| Year         | Doses sold in the United States |
|--------------|---------------------------------|
| 2016         | 1,474                           |
| 2017         | 10,016                          |
| 2018         | 22,625                          |
| 2019         | 28,064                          |
| <b>Total</b> | <b>62,179</b>                   |

\*Data provided by the manufacturer.

Notes about timeline:

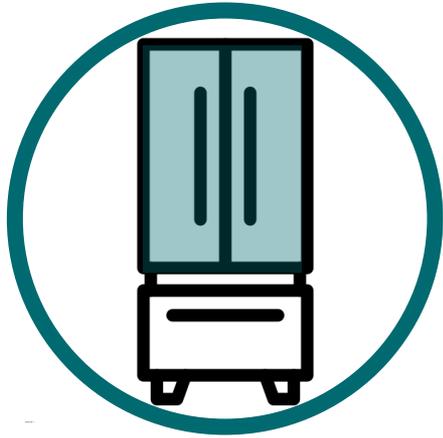
- In June 2016, ACIP approved CVD 103-HgR for adults aged 18–64 years traveling to areas with active cholera transmission.

- At time of initial FDA licensure, the vaccine was required to be stored frozen. In the fall of 2019, FDA approved a change in storage conditions to 36°F–46°F (2°C–8°C).

# Administration setting

- CVD 103-HgR may be optimally administered in a travel clinic given relatively complicated dose preparation and administration
- Many travel clinics have closed
- Administration in non-travel clinics is permissible
- CVD 103-HgR should be **prepared and consumed in a medical office** to minimize potential dosing errors
- Providers should **carefully follow instructions in the package insert**

# Buffer component and active component packets refrigerated at 36°F to 46°F (2°C to 8°C)



- Should not be out of refrigeration for more than 12 hours before reconstitution
- Should not be exposed to temperatures >80°F (27°C)

- Protected from light and moisture



# Administration of CVD 103-HgR



Recipients should **avoid consuming food or drinks for 60 minutes** before and after vaccine administration\*



- Only cold or room temperature **PURIFIED BOTTLED** or **SPRING WATER** should be used to reconstitute the buffer\*



- Tap water contains chlorine that can affect the viability of orally ingested live attenuated bacterial vaccines

# Preparation and reconstitution\*

- For children aged <6 years half of the **reconstituted buffer solution** should be discarded (i.e., after buffer sachet is mixed with water)
- If the packets are reconstituted in the improper order, the vaccine must be discarded
- Must be consumed within 15 minutes

|   |  |  |
|---|--|--|
| <p>1</p>  <p>Remove the carton from the refrigerator [see <i>Storage and Handling (16.2)</i>]. Locate the 2 packets: the buffer component (Packet 1) and the active component (Packet 2).</p> | <p>2</p>  <p>Pour 100 mL of cold or room temperature (41°F-72°F; 5°C-22°C) purified bottled or spring bottled water into a clean, disposable cup. Do not use tap water, sparkling (carbonated) water, non-purified or non-spring bottled water, other beverages, or other liquids.</p> | <p>3</p>  <p>Use scissors to cut the top off the buffer component packet.</p>  |
| <p>4</p>  <p>Empty buffer component packet contents into cup. Effervescence will occur.</p>  | <p>5</p>  <p>Using a disposable stirrer, stir until the buffer component completely dissolves. <b>For children less than 6 years of age, discard half of the buffer solution.</b></p>   | <p>6</p>  <p>Use scissors to cut the top off the active component packet.</p>   |
| <p>7</p>  <p>Empty the active component packet contents (lyophilized <i>V. cholerae</i> CVD 103-HgR) into the cup containing the buffer solution.</p>  | <p>8</p>  <p>Stir for at least 30 seconds and until the active component disperses to form a slightly cloudy suspension that may contain some white particulates.</p>   | <p>9</p>  <p>VAXCHORA must be consumed within 15 minutes of reconstitution. The recipient should drink the full contents of the cup at once. Some residue may remain in the cup and should be discarded with the cup.</p> |

# Administration of CVD 103-HgR with sweeteners is not currently covered in the package insert

Unpublished data\* demonstrate reconstituted CVD 103-HgR

- **IS NOT COMPATIBLE WHEN MIXED WITH**

- Medicine flavorings that contain propylene glycol
- Foods and drinks (e.g., rice cereal, applesauce, juice, milk)

- **IS COMPATIBLE WHEN MIXED WITH**

- 1–4 grams sucrose\*\*
- 1 gram Stevia sweetener\*\*\*
  - 93% of vaccine recipients aged 2–17 years in the clinical trial used PureVia Stevia

\*Presented by the manufacturer during January 12, 2022 ACIP meeting

\*\* 1/4–1 tsp; a typical sucrose packet contains 4 grams.

\*\*\*A typical Stevia packet contains 1 g. Stevia brands differ regarding the fillers used.

# Advise recipients about most common side effects within 7 days of CVD 103-HgR

- Fatigue
- Headache
- Abdominal pain
- Nausea/vomiting
- Lack of appetite
- Diarrhea

# No clinical trials have evaluated safety or efficacy of **booster doses** of CVD 103-HgR in preventing cholera\*

- Duration of protection beyond the 3-month period evaluated in adults aged 18–45 years is unknown
- Serum vibriocidal antibody assay is likely a surrogate for protection mediated by intestinal mucosa

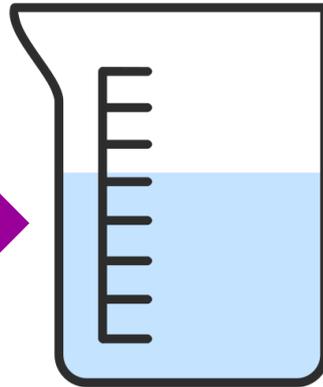
# Coadministration of other medications or vaccines

# Antibiotics might have activity against the vaccine strain

- CVD 103-HgR should be administered **≥14 days** after completion of antibiotics (oral or IV)
- A shorter duration may be acceptable if travel cannot be avoided but may diminish effectiveness



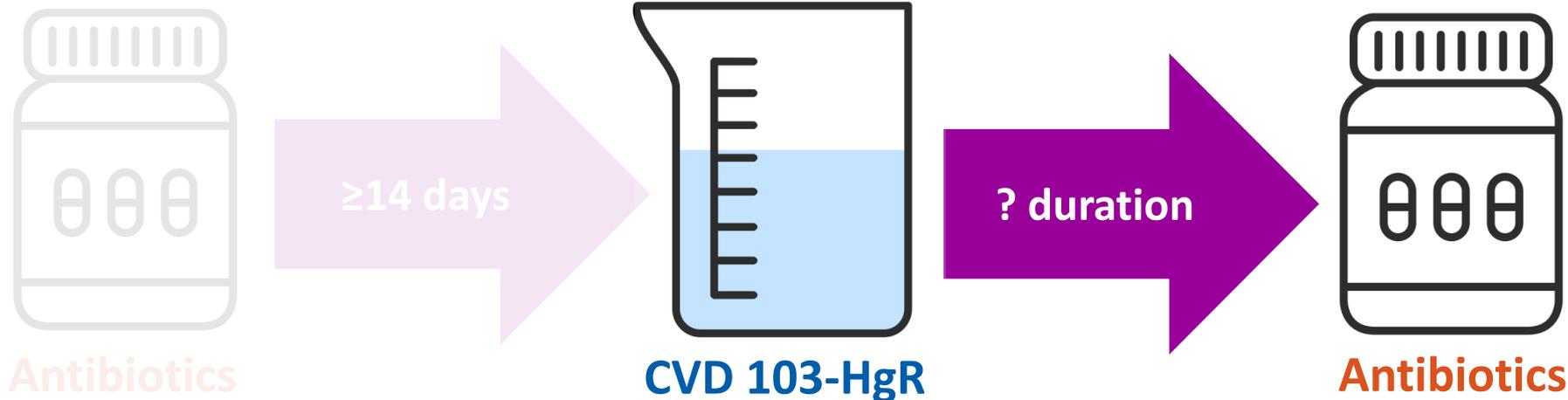
Antibiotics



CVD 103-HgR

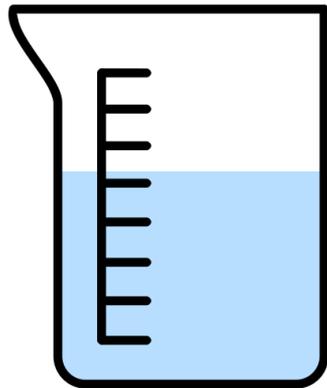
# Optimal minimum duration between completion of CVD 103-HgR and starting **antibiotics** is unknown

- In certain circumstances, antibiotics may be necessary after the vaccine
- Nearly all (>93%) vaccine recipients in clinical trials had seroconversion by 10 days



# Chloroquine may diminish the immune response to CVD 103-HgR

CVD 103-HgR should be administered **≥10 days** before **chloroquine**



CVD 103-HgR



Chloroquine

# Other vaccines

- No data on concomitant administration with other vaccines
- **Enteric-coated live-attenuated typhoid vaccine (Ty21a\*) is another oral travel vaccine**
  - Expert suggests taking the first dose Ty21a  $\geq 8$  hours after CVD 103-HgR
  - Might decrease potential interference of CVD 103-HgR buffer with Ty21a vaccine

# Contraindications and precautions

# CVD 103-HgR is not licensed for children aged <2 years or adults aged $\geq 65$ years



# Allergy

- CVD 103-HgR should not be administered to persons with a history of severe allergic reaction, such as anaphylaxis, to any component of this vaccine or to a prior dose of any cholera vaccine

# No data regarding CVD 103-HgR during pregnancy or breastfeeding



- Pregnant women are at increased risk for poor outcomes from cholera infection
- Pregnant women and their clinicians should consider the risks associated with traveling to areas with active cholera transmission
- The vaccine is not absorbed systemically
- Maternal exposure to the vaccine is not expected to result in exposure to the fetus or breastfed infant
- The vaccine strain might be shed in stool for >7 days after vaccination, and theoretically, the vaccine strain could be transmitted to an infant during vaginal delivery

# No data regarding CVD 103-HgR in persons with altered immunocompetence



- Persons with altered immunocompetence and their clinicians should consider the risks associated with traveling to areas with active cholera transmission
- Consultation with a specialist in immunology or infectious diseases should be considered if travel to an area with active cholera transmission is necessary
- ACIP generally advises against administering live vaccines to persons with most forms of altered immunocompetence\*

# CVD 103-HgR may be shed in the stool of recipients for >7 days

- Patients should be counseled
  - Vaccine strain can potentially be transmitted to non-vaccinated close contacts (e.g., household contacts)
  - Wash hands thoroughly after using the bathroom and before preparing or handling food **for at least 14 days after vaccination**

# Policy option and discussion

# Proposed draft recommendation

Lyophilized CVD 103-HgR is recommended for children and adolescents aged 2–17 years traveling from the United States to an area with active cholera transmission.

# Acknowledgements

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# Thank you! Questions?

For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
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