GRADE Review and Work Group Plans

Karen K. Wong, MD MPH
For the Cholera Vaccine Work Group

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National Center for Emerging and Zoonotic Infectious Diseases
Division of Foodborne, Waterborne, and Environmental Diseases

Acknowledgments

ACIP Cholera Vaccine Work Group

Kashmira Date
Sandra Fryhofer
Mark Gershman
Barbara Mahon
Eric Mintz
Kathy Neuzil
Walt Orenstein
Art Reingold
Laura Riley
Ed Ryan
John Su
Mary Wilson
COL Margaret Yacovone

CDC

Erin Burdette
Sam Crowe
Caroline Jackman
Jessica Korona
Amanda Cohn
Wendy Carr

CVD 103-HgR is live attenuated single-dose oral cholera vaccine

- No cholera vaccine currently available in United States
- Vaccines available outside United States require two doses
- CVD 103-HgR previously licensed in other industrialized countries, marketed as Orochol/Mutacol
  - Manufacture ceased for business reasons
- PaxVax acquired license to re-develop vaccine as Vaxchora™ (newer formulation)
  - BLA filed October 2015, adults ≥18 years old
  - FDA action date expected in mid-June

Policy question for GRADE review

- **Should live attenuated oral cholera vaccine CVD 103-HgR be recommended for use in adults ≥18 years of age at risk of travel-related exposure to toxigenic *Vibrio cholerae* O1?**
  - Population: Adults who live in the United States and are traveling to cholera-affected areas.
  - Intervention: CVD 103-HgR administered as a single oral dose.
  - Current Option: No oral cholera vaccine is currently recommended or available to adults in the U.S.

Outcome measures included in evidence profile

OUTCOME	IMPORTANCE
Benefits	
Prevent cholera death	Critical
Prevent life-threatening (>5L*) cholera diarrhea	Critical
Prevent severe (>3L*) cholera diarrhea	Critical
Prevent cholera diarrhea of any severity	Important
Induce vibriocidal antibody response	Important
Harms	
Serious adverse events	Critical
Systemic adverse events	Critical
Decrease effectiveness of co-administered vaccines or medications	Critical

* Volume over course of illness

Evidence retrieval

- Systematic review of PubMed and Embase papers in any language published between 1988, when CVD 103-HgR was first developed, and January 2016
- Efforts made to obtain available unpublished literature
- References of relevant papers reviewed
- Articles included if they presented data on CVD 103-HgR and
  - Involved human subjects
  - Reported primary data
  - Included data relevant to the outcome measures being assessed
  - Included data for a relevant dose (~4×10^8–2×10^9 CFU)

Evidence retrieval

- 77 studies identified in initial review
  - 49 excluded
    - 41 either did not include CVD 103-HgR data or any primary data
    - 8 pediatric studies
    - 1 cost-benefit analysis
  - 28 studies in GRADE evaluation

Studies of CVD 103-HgR included in evidence review (n=28)

- **Of the 28 studies**
  - 3 of newer formulation (Vaxchora™)
    - All randomized controlled trials (RCTs)
  - 25 of older formulation
    - 18 RCTs
    - 7 observational studies
- **5 were challenge studies**
  - 3 RCTs (1 new formulation)
  - 2 observational studies

Evidence related to GRADE outcomes

OUTCOME	No. RCTs	No. observational	Data available
Benefits			
Prevent cholera death	4*	1	Yes, limited
Prevent life-threatening (>5L) cholera diarrhea	1*	0	Yes, limited
Prevent severe (>3L) cholera diarrhea	3*	0	Yes
Prevent cholera diarrhea of any severity	4*	3	Yes
Induce vibriocidal antibody response	19*	3	Yes
Harms			
Serious adverse events	20*	4	Yes
Systemic adverse events	20*	4	Yes
Decrease effectiveness of co-administered vaccines or medications	3	1	Yes, limited

* Includes ≥1 RCT with the new formulation of CVD 103-HgR vaccine

GRADE evidence type scoring method

- Initial evidence type: RCT (1), Observational (3)
- Criteria for moving down (-1, -2)
  - Risk of bias, inconsistency, indirectness, imprecision, publication bias
- Criteria for moving up (+1, +2)
  - Strength of association, dose response gradient, opposing plausible residual confounding
- Final evidence type
  - 1 = RCTs or overwhelming evidence from observational studies
  - 2 = RCTs with important limitations, or exceptionally strong evidence from observational studies
  - 3 = Observational studies, or RCTs with notable limitations
  - 4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

Strength of association: May be upgraded by one level for risk ratios >2 or <0.5; may be upgraded by two levels if risk ratio >5 or <0.2.

Evidence of benefits: prevention of cholera death

- Challenge studies not designed to assess this outcome
- One large field study showed no difference in deaths from diarrhea of any etiology between vaccinated and comparison populations
  - Cause of death assessed by verbal autopsy

	Study	Site	Type	Population	Time post-vaccination	Deaths, vaccinated persons	Deaths, comparison persons
CHALLENGE	Levine 1988	U.S.	RCT	Adults	1 month	0/6	0/8
	Tacket 1992	U.S	Obs	Adults	4-6 months 8 days	0/14 0/11	0/15 0/11
	Tacket 1999	U.S.	RCT	Adults	3 months	0/28	0/23
	Chen, Cohen 2014*	U.S	RCT	Adults	10 days 3 months	0/35 0/33	0/66
FIELD	Richie 2000	Indonesia	RCT	Adults and children (2–41y)	Up to 4 years surveillance	6/33696 [diarrhea, any etiology]	8/33812 [diarrhea, any etiology]

* New formulation of CVD 103-HgR vaccine

Evidence type: prevention of cholera death (critical outcome)

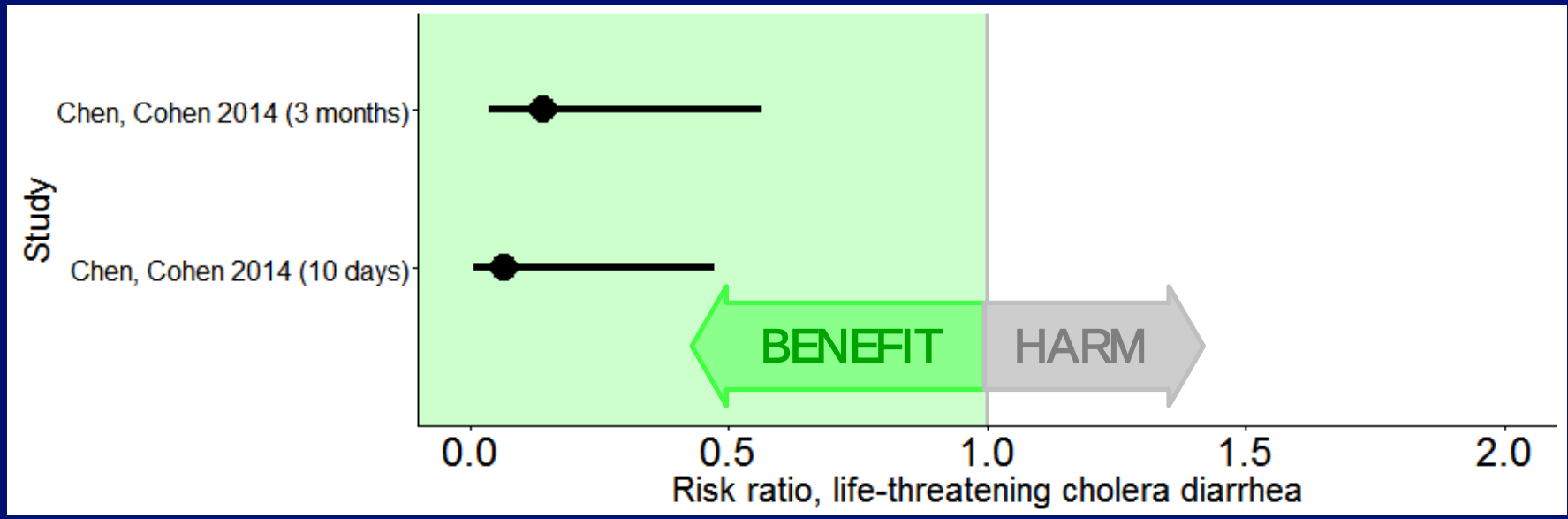
- Insufficient evidence to assess prevention of cholera death

Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Final evidence	Overall evidence type
4 RCTs*	1	N/A	N/A	N/A	Very serious (-2)	N/A	N/A	N/A	N/A
1 Obs	3	N/A	N/A	N/A	Very serious (-2)	N/A	N/A	N/A	

* Includes ≥1 study with new formulation of CVD 103-HgR vaccine

Evidence of benefits: prevention of life-threatening (>5L) cholera diarrhea

- 1 RCT addressed outcome (new formulation of vaccine)
- Challenge with toxigenic *V.cholerae* O1 performed at 10 days or 3 months after vaccination



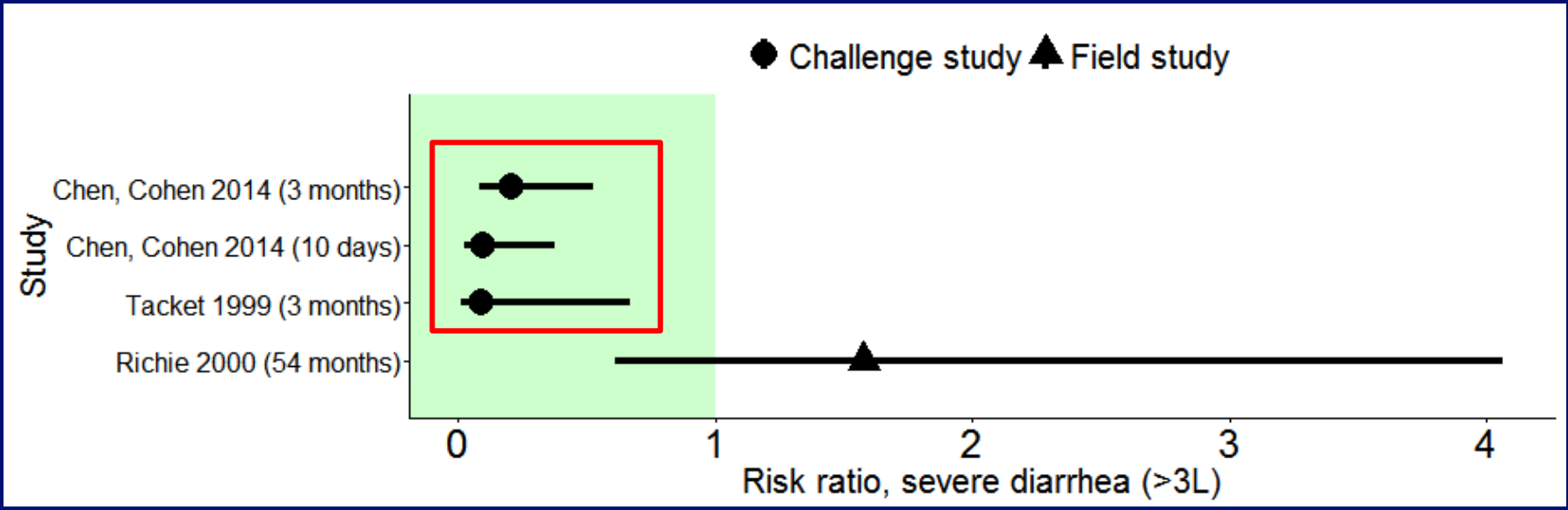
Evidence type: prevention of life-threatening (>5L) cholera diarrhea (critical outcome)

- Strong evidence from 1 RCT with newer formulation of vaccine that CVD 103-HgR prevents life-threatening cholera diarrhea

Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Final evidence	Overall evidence type
1 RCT	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1

Evidence of benefits: prevention of severe (>3L) cholera diarrhea

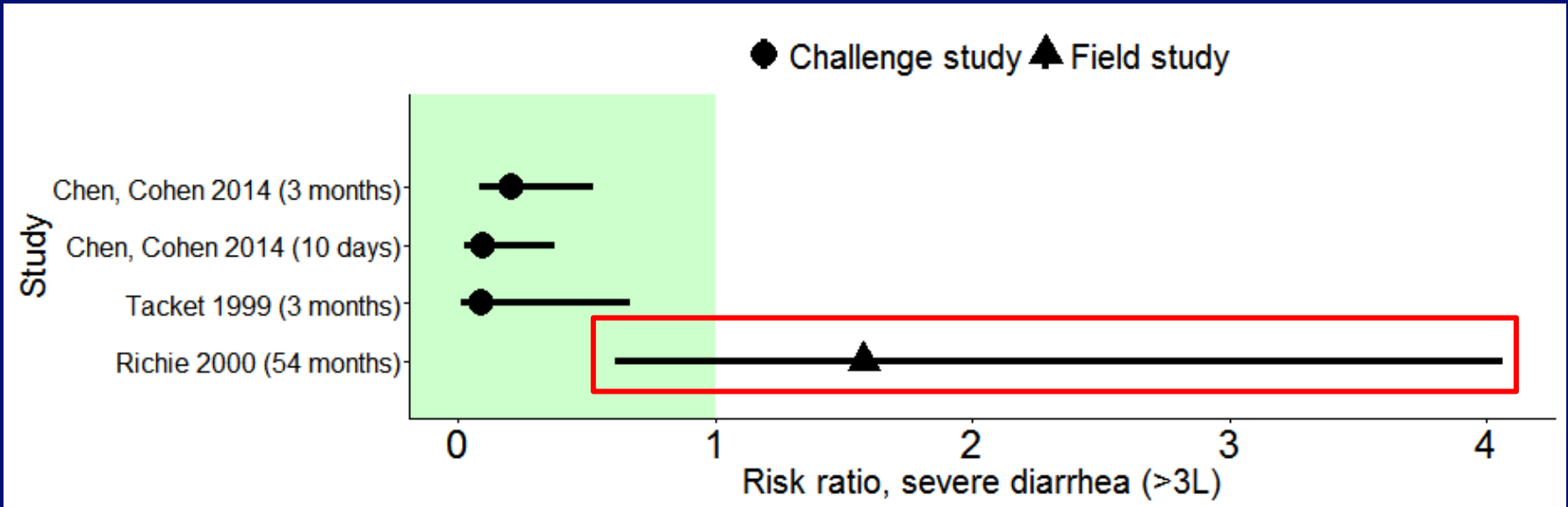
- 3 RCTs addressed outcome
- 2 challenge RCTs showed a strong consistent reduction in severe cholera diarrhea among vaccinated vs. comparison individuals



Note: Chen, Cohen 2014 study assessed outcome at multiple time points after vaccination

Evidence of benefits: prevention of severe (>3L) cholera diarrhea

- Field RCT: No significant difference in severe cholera diarrhea in vaccinated vs. comparison individuals
  - Conducted in Indonesia among children and adults
  - Individuals rather than clusters randomized
  - Cholera outcomes assessed by sentinel surveillance over 4 years
  - Incidence of cholera low during study period



Note: Chen, Cohen 2014 study assessed outcome at multiple time points after vaccination

Evidence type: prevention of severe (>3L) cholera diarrhea (critical outcome)

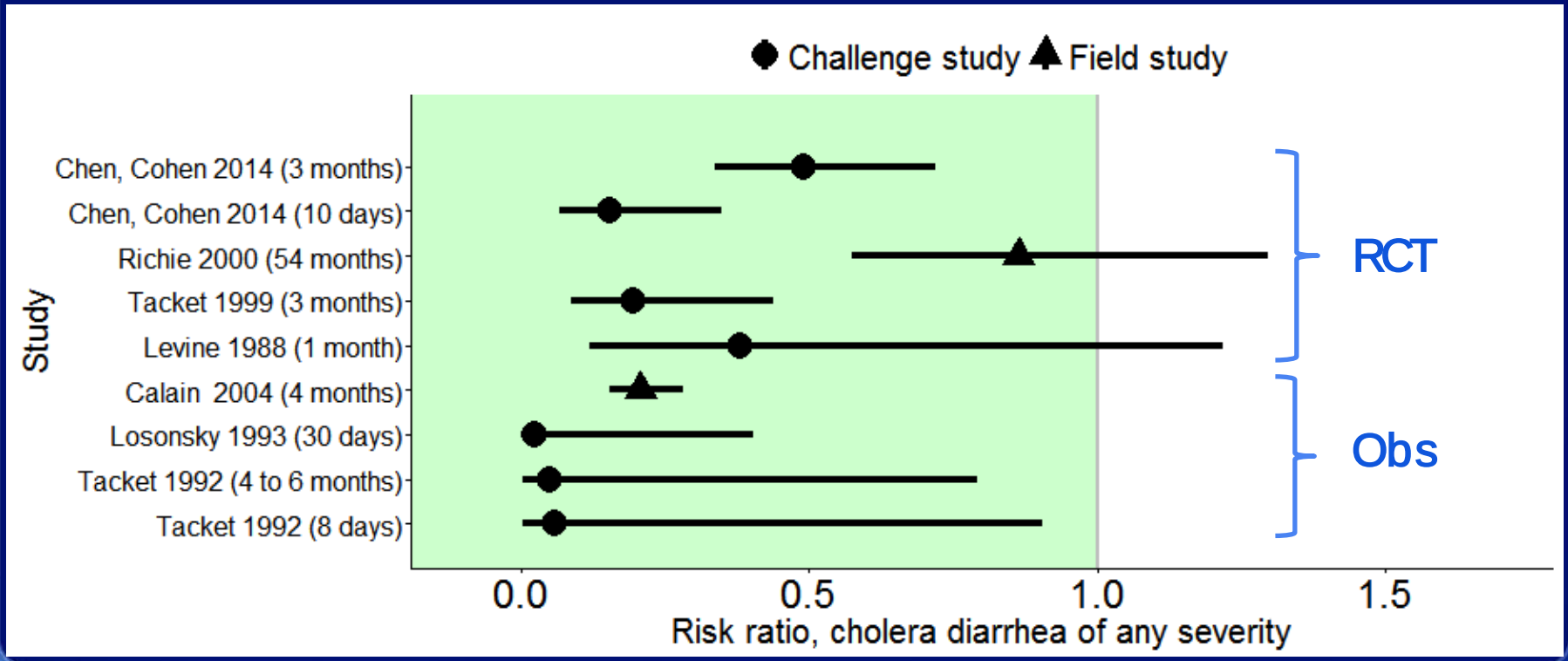
- Downgraded for inconsistency: 1 large field trial showed no effect
- Strong evidence from studies with old and new vaccine formulations that CVD 103-HgR prevents severe (>3L) cholera diarrhea

Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Final evidence	Overall evidence type
3 RCTs*	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1

* Includes ≥1 study with new formulation of CVD 103-HgR vaccine

Evidence of benefits: prevention of cholera diarrhea of any severity

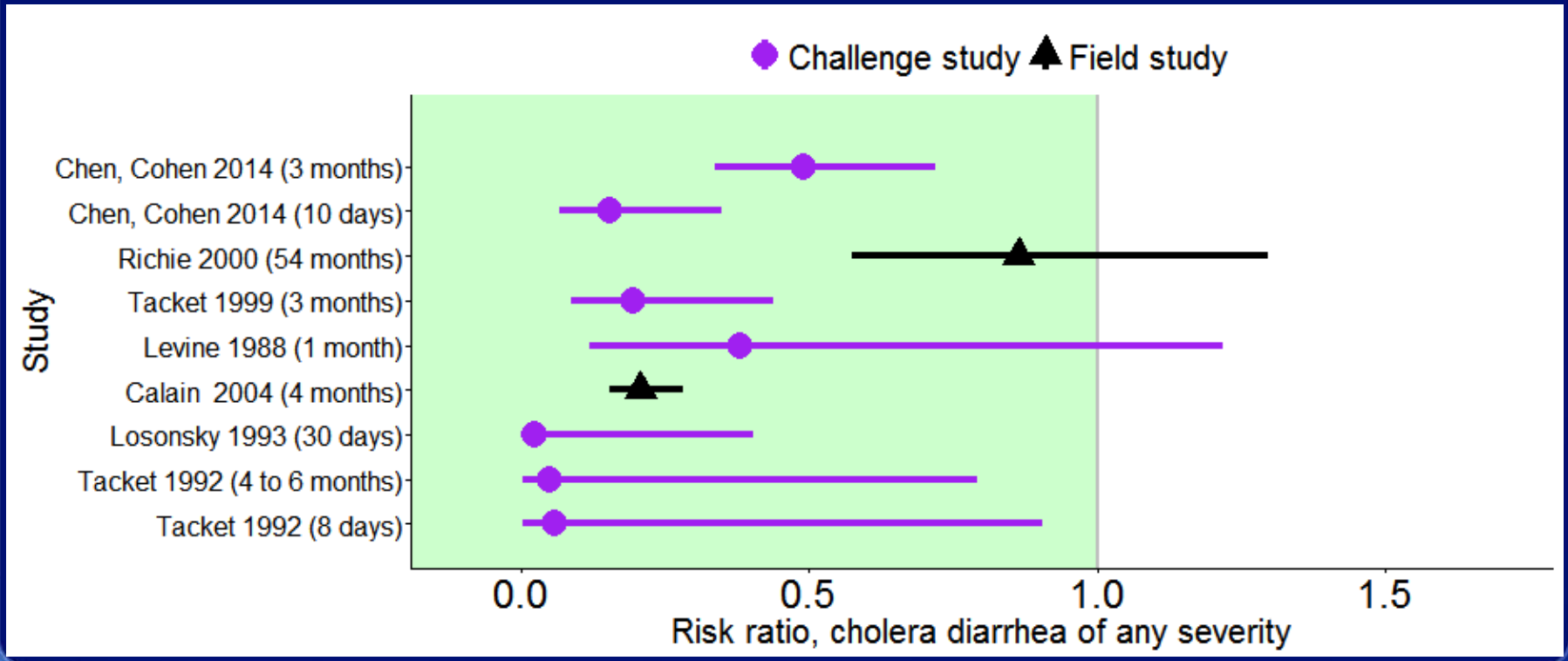
- 4 RCTs, 3 observational studies addressed outcome



Note: Chen, Cohen 2014 and Tacket 1992 studies assessed outcome at multiple time points after vaccination

Evidence of benefits: prevention of cholera diarrhea of any severity

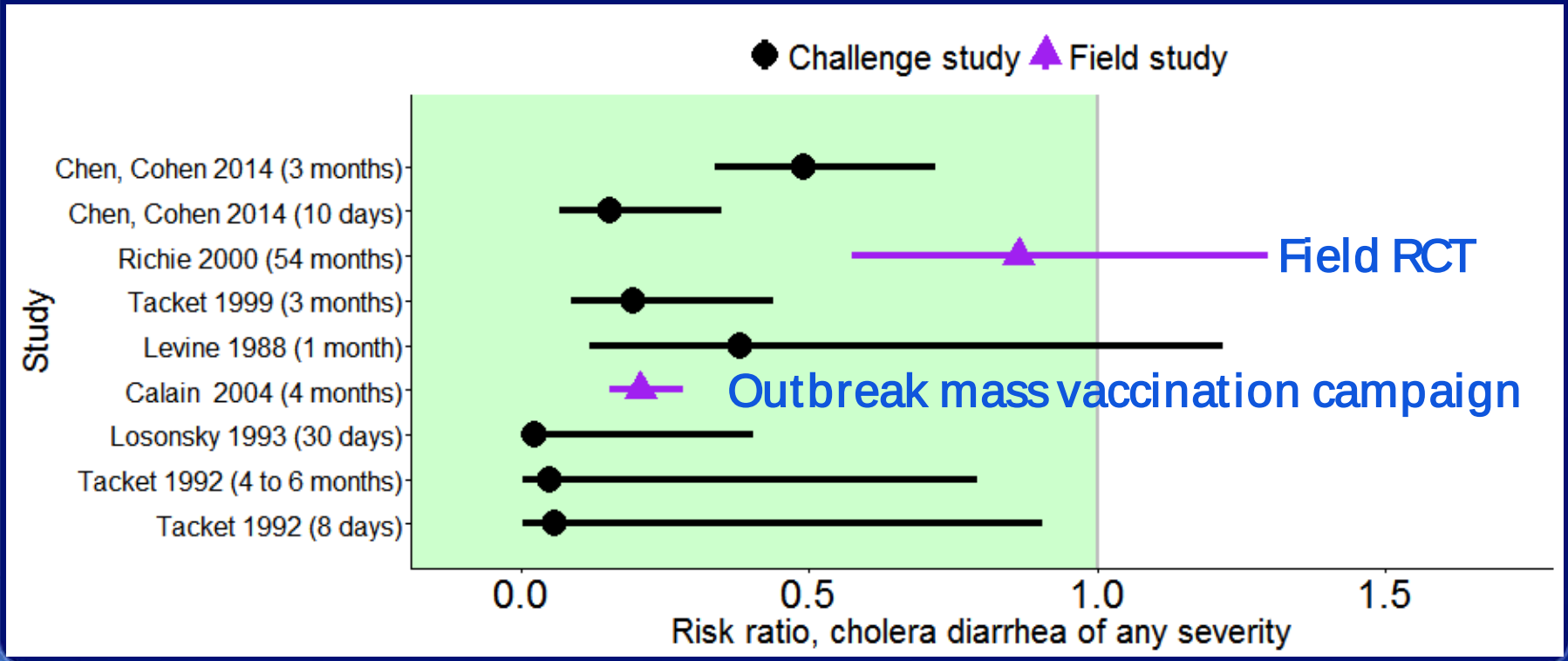
- 5 challenge studies
- 4 showed significant reduction in proportion developing cholera diarrhea (VE51–100%)



Note: Chen, Cohen 2014 and Tacket 1992 studies assessed outcome at multiple time points after vaccination

Evidence of benefits: prevention of cholera diarrhea of any severity

- **1 field RCT:** No difference between vaccinated and comparison populations in cholera diarrhea detected by sentinel surveillance over 4 years
- **1 mass vaccination campaign during outbreak:** Incidence of cholera diarrhea lower in vaccinated vs. comparison populations



Note: Chen, Cohen 2014 and Tacket 1992 studies assessed outcome at multiple time points after vaccination

Evidence type: prevention of cholera diarrhea of any severity (important outcome)

- Downgraded for inconsistency: 1 large field trial showed no effect
- Strong evidence from studies with old and new vaccine formulations that CVD 103-HgR prevents cholera diarrhea of any severity

Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Final evidence	Overall evidence type
4 RCTs*	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
3 Obs	3	Serious (-1)	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	3	

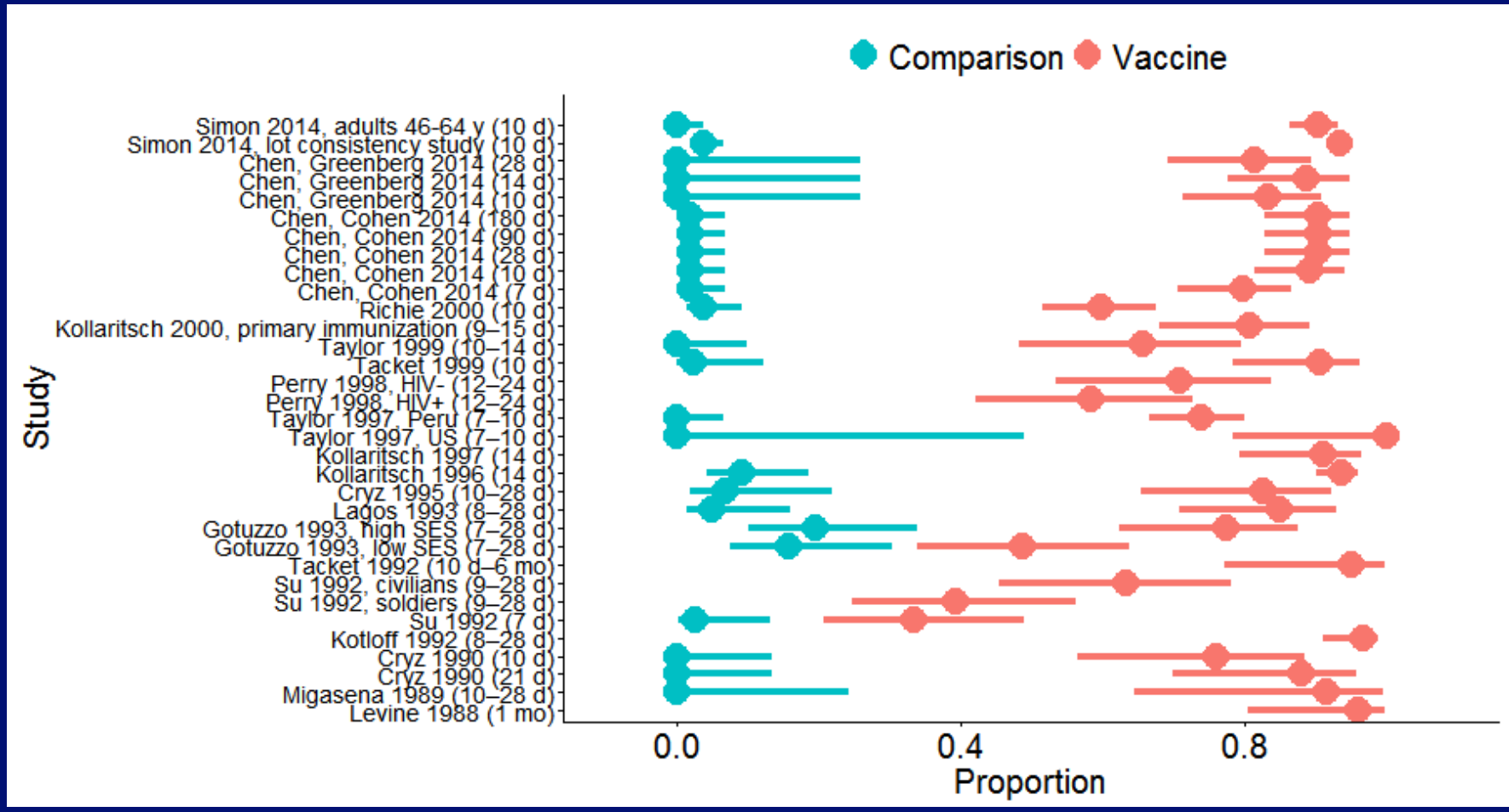
* Includes ≥1 study with new formulation of CVD 103-HgR vaccine

Evidence of benefits: vibriocidal antibody response

- Vibriocidal antibodies
  - best available marker for protection against cholera
  - serogroup-specific (O1 or O139) protection
  - protect against both biotypes (El Tor, Classical) and both serotypes (Inaba, Ogawa)

- 19 RCTs, 3 observational studies assessed immunogenicity

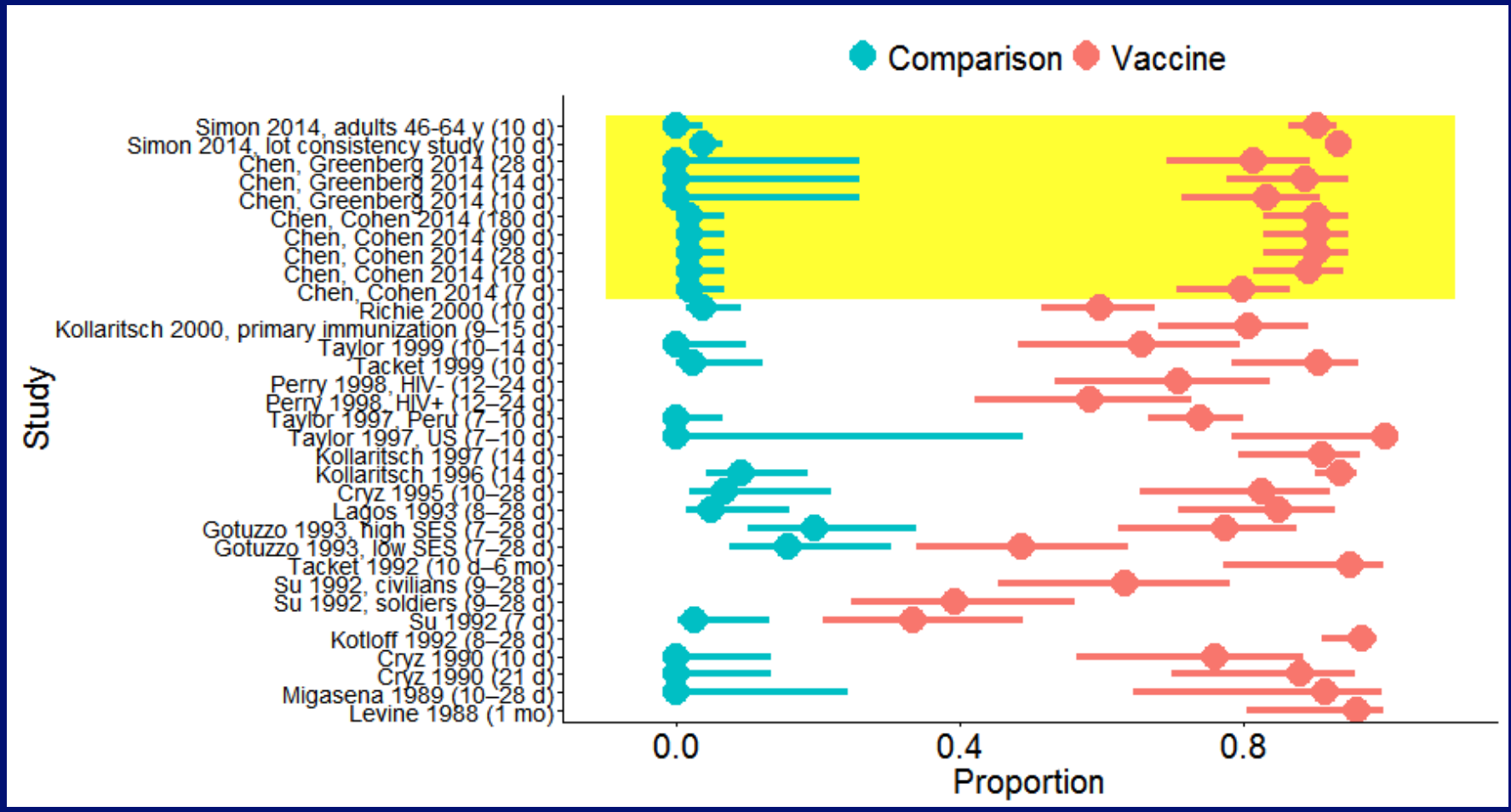
Vibriocidal antibody response (Inaba)



- Consistent vibriocidal antibody response seen with older and newer formulation of vaccine

Note: Some studies assessed outcome in >1 group and/or at multiple time points after vaccination

Vibriocidal antibody response (Inaba)



- VE with new formulation ≥98%

Note: Some studies assessed outcome in >1 group and/or at multiple time points after vaccination

Evidence type: vibriocidal antibody response (important outcome)

- Observational studies with older vaccine downgraded for indirectness
- Strong evidence from studies with old and new formulations that CVD 103-HgR vaccine induces vibriocidal antibody response

Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Final evidence	Overall evidence type
19 RCTs*	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
3 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	2	

* Includes ≥1 study with new formulation of CVD 103-HgR vaccine

Evidence of harms: serious and systemic adverse events

- 20 RCTs, 4 observational studies, and post-marketing surveillance data
- Serious adverse events
  - 1 field RCT: No difference in overall mortality in vaccinated vs. comparison population over 4 years
  - No differences detected between vaccinated and comparison populations for any serious adverse events
- Systemic adverse events
  - 1 unpublished RCT with new formulation found slightly higher proportion with diarrhea in vaccinated vs. comparison persons (0.8% vs. 0)
  - Systemic adverse events occur at similar rates in vaccinated and comparison populations

Orochol® Post-marketing, spontaneously reported, serious unexpected adverse events, 1994–2004

- **Of 528,765 Orochol® doses distributed:**
  - Hospitalization with fever, gastroenteritis, vomiting, hemorrhagic CSF in 11-mo infant (1)
  - Guillain-Barre syndrome (1)
    - Received CVD 103-HgR, YFV, Ty21a, diphtheria, polio vaccines
  - Angioedema (1)
  - Loss of hair (1)

- **Of 276,564 Orochol® E doses distributed (higher dose formulation):**
  - No spontaneously reported adverse reactions

Orochol: Spontaneously reported adverse reactions, January 12,1994 - March 31, 2004

Evidence type: serious and systemic adverse events (critical outcome)

- Most evidence from studies of older formulation of vaccine (downgraded for indirectness)
- Relatively few recipients of newer formulation of vaccine (downgraded for imprecision)
- Serious adverse events uncommon
- Studies with old and new formulations of vaccine suggest adverse events occur at similar rates in vaccinated and comparison populations

Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Final evidence	Overall evidence type
20 RCTs*	1	No serious	No serious	Serious (-1)	Serious (-1)	No serious	None	3	3
4 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	

* Includes ≥1 study with new formulation of CVD 103-HgR vaccine

Evidence of harms: decrease effectiveness of co-administered vaccines and medications

- 3 RCTs, 1 observational study evaluated outcome
- No effect identified on antibody response to live attenuated oral typhoid vaccine (Ty21a)
  - 62–83% given both vaccines (n=425) developed anti-Typhi antibodies vs. 66% given typhoid vaccine alone
- No effect identified on antibody response to yellow fever vaccine (17D)
  - 100% given both vaccines (n=58) developed anti-YF antibodies

Evidence of harms: decrease effectiveness of co-administered vaccines and medications

- 1 additional study evaluated CVD 103-HgR in combination with Ty21a, yellow fever vaccine, oral polio vaccine, mefloquine, chloroquine, and proguanil

- Lower vibriocidal seroconversion when chloroquine co-administered with CVD 103-HgR (67%) vs. CVD 103-HgR alone (91%)

Evidence type: decrease effectiveness of co-administered vaccines or medications (critical outcome)

- For typhoid or yellow fever vaccine: downgraded for indirectness (older formulation vaccine)
- No suggestion that CVD 103-HgR decreases effectiveness of typhoid (Ty21a) or yellow fever (17D) vaccines
- Insufficient evidence to determine effect on other co-administered vaccines or medications

Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Final evidence	Overall evidence type
3 RCTs	1	No serious	No serious	Serious (-1)	No serious	No serious	None	2	2
1 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	

GRADE summary

Outcome	Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other	Final evidence	Overall evidence type
Prevent cholera death	4 RCTs	1	N/A	N/A	N/A	Very serious (-2)	N/A	N/A	N/A	Insufficient evidence to evaluate outcome
	1 Obs	3	N/A	N/A	N/A	Very serious (-2)	N/A	N/A	N/A	
Prevent life-threatening cholera diarrhea	1 RCT	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
Prevent severe cholera diarrhea	3 RCTs	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
Prevent cholera diarrhea of any severity	4 RCTs	1	No serious	Serious (-1)	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
	3 Obs	3	Serious (-1)	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	3	
Induce vibriocidal antibody response	19 RCTs	1	No serious	No serious	No serious	No serious	No serious	Strength of assoc. (+2)	1	1
	3 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	Strength of assoc. (+2)	2	

GRADE summary

Outcome	Studies	Initial evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Other	Final evidence	Overall evidence type
Serious/systemic adverse events	20 RCTs	1	No serious	No serious	Serious (-1)	Serious (-1)	No serious	None	3	3
	4 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	
Decrease effectiveness of co-administered vaccines and medications	3 RCTs	1	No serious	No serious	Serious (-1)	No serious	No serious	None	2	2
	1 Obs	3	No serious	No serious	Serious (-1)	No serious	No serious	None	4	

CONSIDERATIONS FOR FORMULATING RECOMMENDATIONS FOR USE

Cholera epidemiology, United States

- Cholera rare in the United States
- Fewer than 25 cases per year reported since 2012
  - 42 cases in 2011, during cholera epidemic in Haiti
  - Large outbreak on flight from Argentina → Peru → U.S. (1992)
- Cholera cases in United States likely underreported
- Infections that occur while traveling that resolve before return to the U.S. are not captured by U.S. surveillance
  - Short incubation period
  - Little information is available about cases that occur while traveling

Clinical features and risk factors

- Cholera can be severe and rapidly life-threatening
- Overall risk of cholera is very low for most U.S. travelers
- Treatable if medical services readily available
- Certain populations at higher risk of exposure
  - May include healthcare personnel, outbreak response workers, persons visiting friends or relatives, persons traveling or living in cholera-affected areas for extended periods
- Certain populations at higher risk of poor outcomes
  - Low gastric acidity, blood type O
  - Persons without ready access to medical services

- Note: Sanitation, hygiene, safe water/food remain critical to preventing cholera and other enteric infections

Evidence type for benefits and harms

- Overall evidence type 1 for prevention of cholera diarrhea and induction of vibriocidal antibody response
- Overall evidence type 3 for safety (assessed by serious/systemic adverse events) and 2 for decreasing the effectiveness of co-administered vaccines and medications
- Insufficient data to evaluate whether CVD 103-HgR prevents death from cholera
- No data available on safety and efficacy in pregnant women

Balance between benefits and harms

- Strong evidence that CVD 103-HgR prevents cholera diarrhea
- Serious adverse events uncommon with older formulation of vaccine; limited evidence with newer formulation
- Systemic adverse events occur at similar rates in vaccinated and comparison groups

Values related to outcomes

- Prevent a severe, life-threatening illness in travelers at risk of cholera exposure or severe cholera illness, especially if medical care not readily accessible

Cost-effectiveness

- Not evaluated
- Risk of cholera is very low for most travelers to cholera-affected areas
- Travel vaccines are paid for by employers or by the travelers themselves, depending on the circumstances

Options for draft recommendations

- **Broad:** Recommend or consider for adults ≥18 years age planning to travel to a cholera-affected area
- **Targeted:** Recommend or consider for adults ≥18 years of age at high risk of exposure (e.g., cholera outbreak response workers) or severe illness

Next steps

- Based on review of the evidence for critical and important outcomes, WG concludes that vaccine is safe and effective
- WG continuing to discuss category A versus category B recommendation and whether specific risk groups should be emphasized in the recommendations
- WG evaluating evidence for duration of protection and for re-immunization
- WG evaluating evidence from selected subgroups, such as immunocompromised persons, separately from GRADE review
- WG evaluating pediatric studies separately from GRADE review, as a summary of these data may be helpful to clinicians considering off-label use in persons <18 years of age

Category A recommendations are made for all persons in an age- or risk-factor-based group. Category B recommendations are made for individual clinical decision making.

Discussion

- Policy question: Should CVD 103-HgR be recommended for use in adults at risk of travel-related exposure to toxigenic *Vibrio cholerae* O1?
  - Should specific risk groups should be emphasized?
- Are there additional data that would be helpful to ACIP to inform future discussions?