Cholera Vaccine Research from Johns Hopkins University, Departments of International Health and Epidemiology with Collaborators

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Acknowledgement to collaborations with scientists in
Cameroon, Nigeria, Uganda, Kenya, Tanzania, Zambia, Malawi, Democratic Republic of Congo
as well as
Harvard University and the University of Illinois Campaign-Urbana.

Flexibility in OCV dose intervals

Current recommendations:

- Two doses – 2 to 4 weeks apart
- Second dose is often delayed

Question:

- How does vibriocidal serum response differ if the second dose is significantly delayed

Previous knowledge from Kolkata study

- 2-week and 4-week intervals show no difference in vibriocidal responses 2-weeks after second dose
- Both result in a single peak antibody response
- Duration of elevated titer was not defined
- Response in young children (<5) not defined

New findings on Dose Intervals from Zambia and Cameroon

Both studies:

- Randomized and age stratified subjects
- Primary outcome is GMT vibriocidal titre 2-weeks after 2nd dose
- Subjects followed for up to 9 months

Zambia (CIRDZ)

- 2 weeks or 6 months
- 6-month interval was not inferior
- 6-month interval resulted in two vibriocidal peakss
- Titer fell by 3 months

Cameroon (MA Sante)

- 2 weeks or 6 months or 11.5 months
- 6-month and 11.5-month intervals appeared superior to 2-week interval
- Resulted in two vibriocidal peaks
- Titer fell by 3 months

Special note: Both studies required establishing vibriocidal assays in country with local strains made possible by South-South Tech Transfer between Zambia and Cameroon

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Trade-offs when delaying second dose: more people get at least one dose, more people get only one dose, more dropouts

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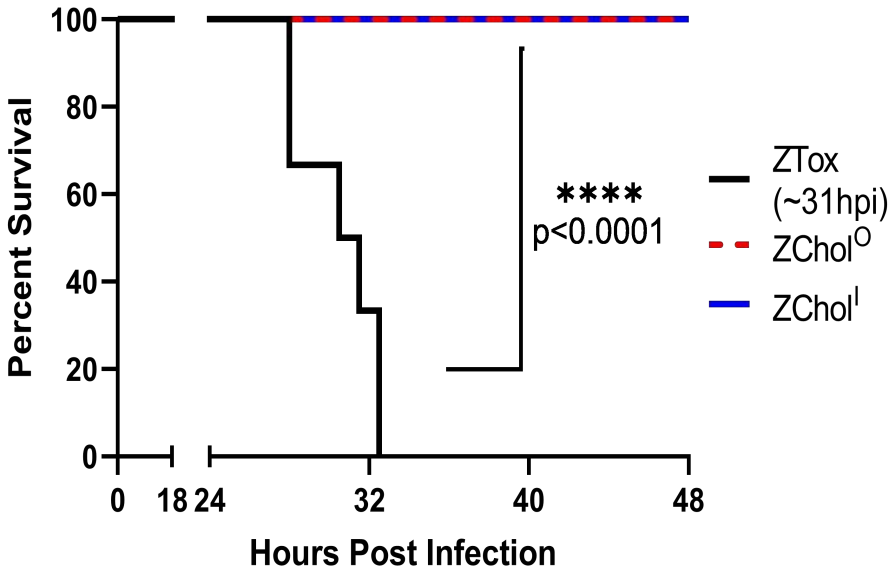
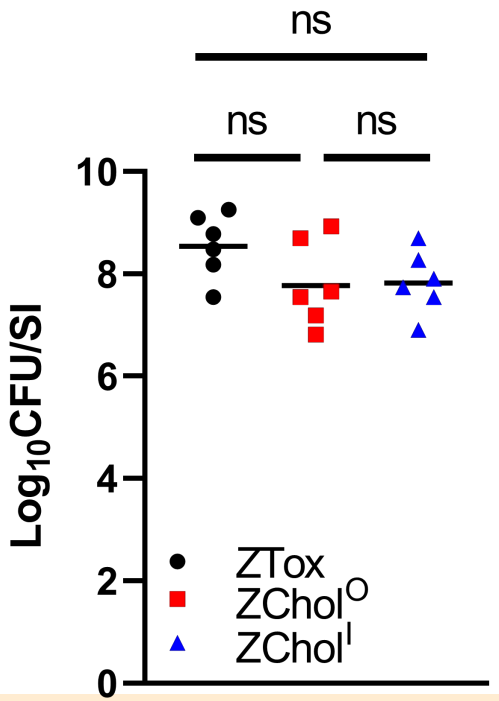
'Developing new safe cholera CHIM* challenge strains'
Collaboration: Harvard, CIDRZ and JHU*
*(*Controlled Human Infection Model)*

Rationale: Other than a field trial, CHIMs is best for validating immune protection. CHIMs are useful when testing

- New vaccines
- New vaccine schedules
- Duration of protection
- Efficacy of booster doses

Used Zambia Ogawa (2016) to create isogenic, non-toxigenic, Ogawa and Inaba strains





Current CHIMs

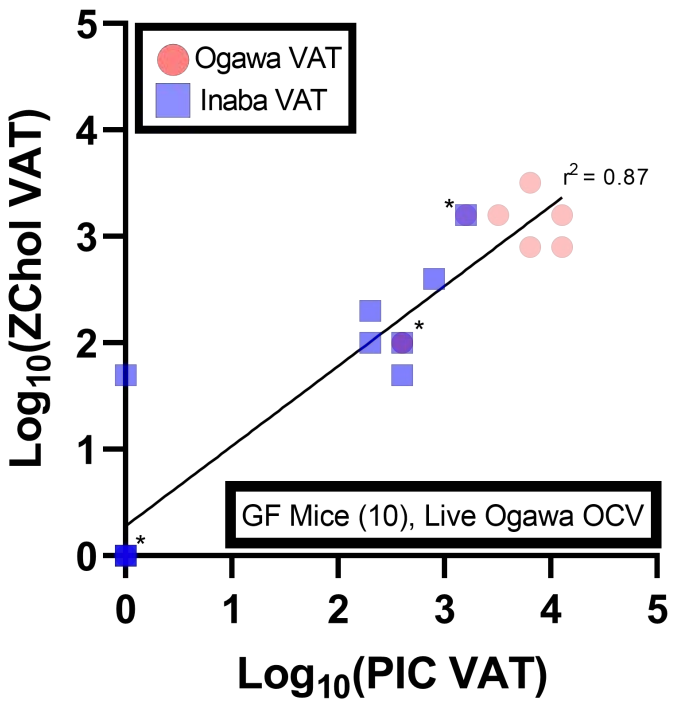
- Specialized inpatient units
- Makes volunteers ill
- Expensive
- Uses an Old Strain (Wave 1)

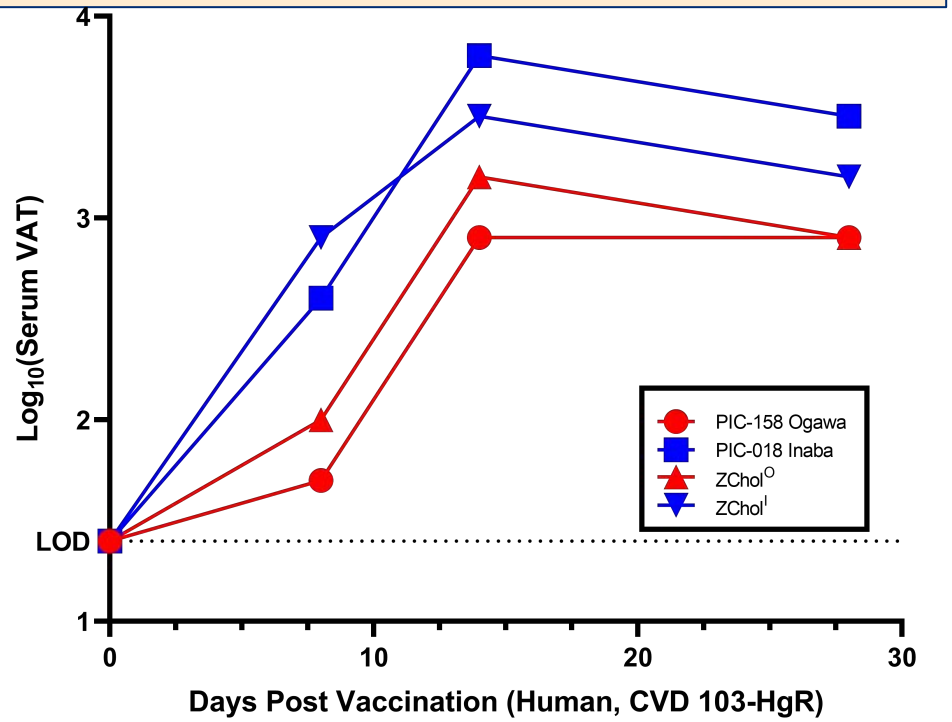
Mutants colonize infant mice, but are not virulent

Goal: Develop a safe, outpatient CHIM strain available for LMICs

**Investigators, Fakoya, Waldor, Chilengi, Simuyandi, Sack*

Non-toxigenic ZChol^{O} and ZChol^{I} are also useful for Vibriocidal Assay





Use of isogenic non-toxigenic strains may improve serotype specific vibriocidal assay and allow for distribution of these standard strains internationally

Developing a MEFA Cholera Vaccine

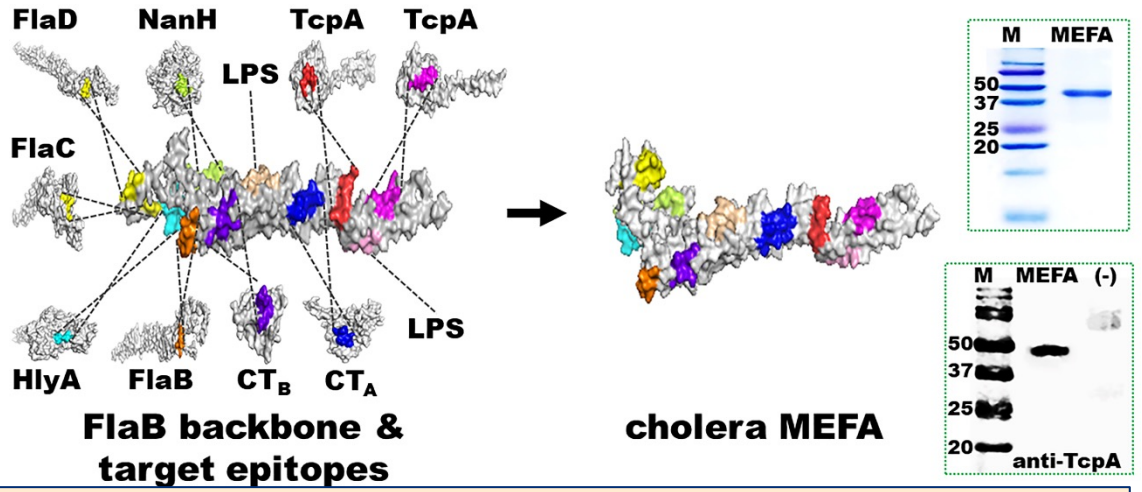
Collaboration University of Illinois and JHU*

Current Understanding: Protective immunity is based on LPS (OSP) and is best measured by vibriocidal antibody. Proteins play only a secondary role, if any.

This study challenges these assumptions:

- Based on development of a MEFA vaccine for ETEC, a similar approach was used to prepare a cholera MEFA immunogen
- MEFA: Multi-Epitope Fusion Antigen
- Epitopes from many of the potential virulence proteins fused to FlaB backbone
- When IM injected: stimulates antibodies including functional antibodies, to the proteins, but no antibodies to LPS and no vibriocidal response

- **Broadly protects rabbits (intestinal colonization in adults and disease in infant rabbits) without LPS immunity**



Protection in passive infant rabbit model

Challenge strain	# rabbits	Efficacy against any diarrhea	Efficacy against severe diarrhea
El Tor Inaba N16961	25	80%	100%
Classical Ogawa 395	16	100%	100%
O139	14	83%	100%
34-D 23 nonO1/non O139	13	100%	100%

*Investigators: Weiping Zhang, Ipshita Upadhyay, Siqi Li, Galen Ptacek, Hyesuk Seo, and David A Sack

Micro-hotspots to target OCV

Observations:

- Hotspots at the district level are too large and miss the true micro-hotspots within the "hot districts."

- Micro-hotspots also exist within cold districts, and these are missed by current methods.

Kenya	High risk county	Lower risk county
High risk subcounty	1.4 million	1.6 million
Lower risk subcounty	1.6 million	

Studies on Micro-hotspots in Kano State, Nigeria and Kenya

- Identification of micro-hotspots may more precisely identify true high-risk areas
- Identifying micro-hotspots also important when identifying risk factors, district-level analysis does not identify WASH risks.

Recommendation: Need to continue to improve methods for identifying micro-hotspots to improve OCV focus

The Impact of OCV in Uvira, DRC

1. Estimate the impact of mass oral cholera vaccination campaigns deployed in the city of Uvira on the incidence of confirmed clinical cholera cases and deaths from 2021 through 2026.

2. Describe changes in vaccine coverage, care seeking behavior, and serologically derived *V. cholerae* infections rates in the city of Uvira from 2021 to 2026

3. Describe *V. cholerae* contamination patterns and genetic diversity in patients, households, and the broader environment through microbiological analyses of clinical and environmental samples.

Ministère de la Santé
République Démocratique du Congo
Programme National d'Elimination du Choléra et de lutte contre les autres Maladies Diarrhéiques
(PNECHOL-MD)

Oxfam

Johns Hopkins Bloomberg School of Public Health

wellcome

Gavi
The Vaccine Alliance

London School of Hygiene & Tropical Medicine