Controlled Human Infection Models and Enteric Vaccine Development

2018 Global Vaccine and Immunization Research Forum
March 20, 2018
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The University of Vermont

Objectives:

- What are Controlled Human Infection/Challenge Models (CHIM)?
- What utility is a CHIM to enteric vaccine development?
- Typhoid and Cholera models lead the way.
- ETEC and Shigella models re-evaluate standardization.
- Other enteric CHIM, briefly.
- The landscape for enteric CHIMs and vaccine development.

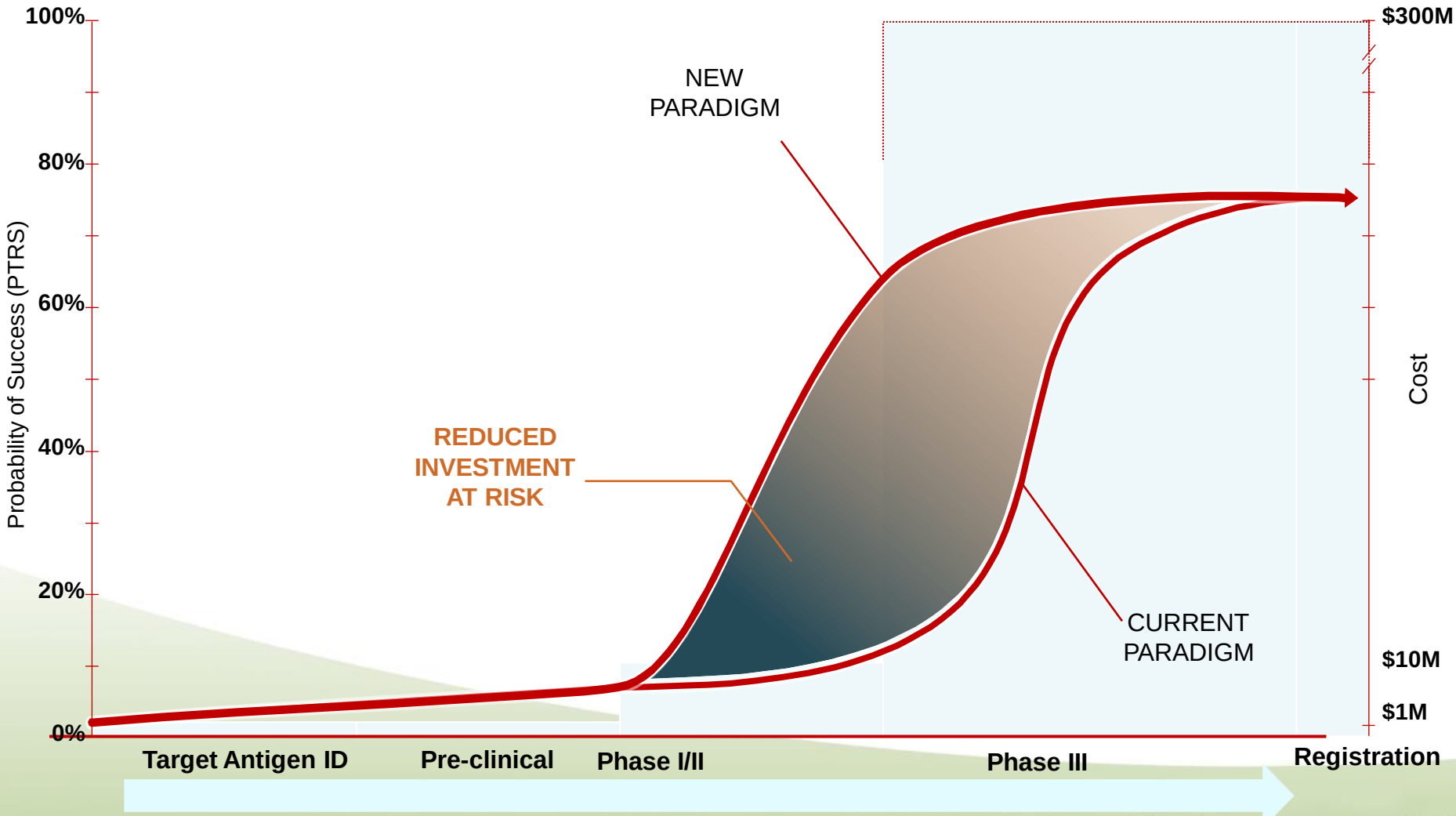
What is a controlled human infection/ challenge model?

- An establish model which purposefully infects humans with an infectious agent in a controlled situation to achieve:
  - Relevant and generalizable endpoints of infection or disease.
  - A reproducible attack rate.
- Meets all safety and ethical standards and has received regulatory approval.
- Uses a well-studied (GMP-produced and stored) inoculum, dose, and route.

How are CHIM *used* for vaccine development?

- A “vaccine-CHIM” study uses the model as an early test of vaccine efficacy.
  - Used as an instrument for vaccine candidate down-selection or advancement.
  - May replace a Phase III efficacy trial.
  - Is hoped to accelerate and de-risk the process of development, overall.
- CHIM studies also provide critical data to inform vaccine development.
  - Natural history of disease and disease pathogenesis.
  - Immune correlates of protection (not all are mechanistic).

USE OF CHALLENGE MODELS



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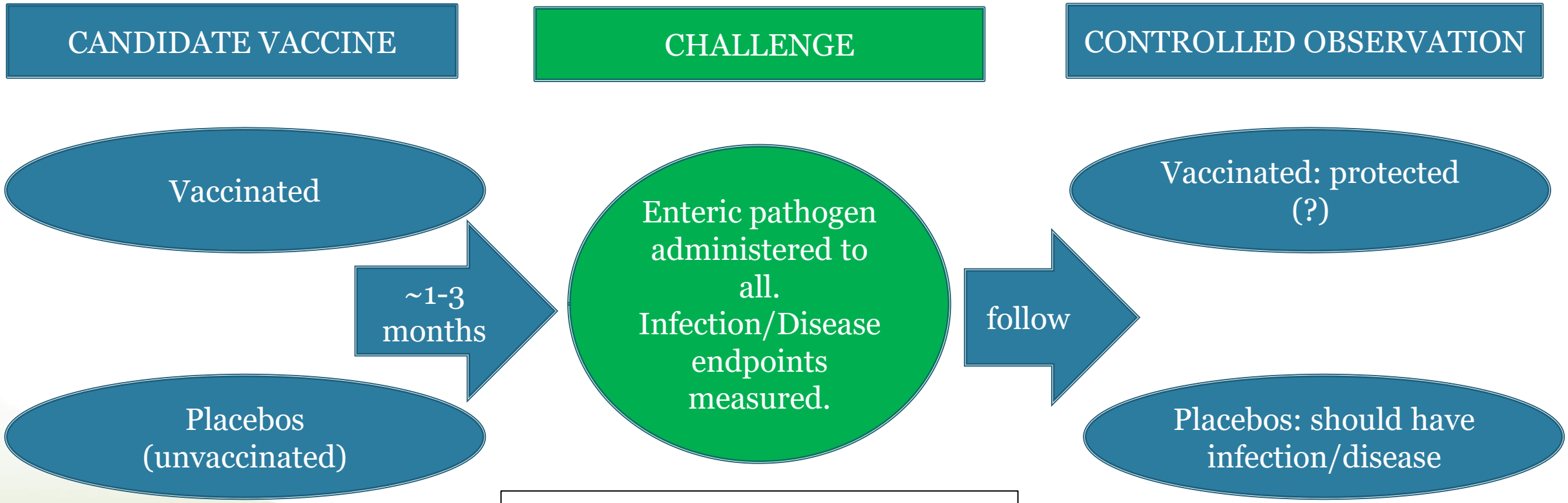
Vaccine-Challenge Studies



$$VE = \frac{ARU - ARV}{ARU} \quad (\times 100),$$

with

- VE = Vaccine efficacy,
- ARU = Attack rate of unvaccinated people,
- ARV = Attack rate of vaccinated people.

Cholera…from 1969

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 129, NO. 1 • JANUARY 1974

Response of Man to Infection with *Vibrio cholerae*. I. Clinical, Serologic, and Bacteriologic Responses to a Known Inoculum

Richard A. Cash, Stanley I. Music,* Joseph P. Libonati, Merrill J. Snyder, Richard P. Wenzel,† and Richard B. Hornick

From the Division of Infectious Diseases, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland

The spectrum of illness and the immunologic response produced by cholera in volunteers were studied. The strains of *Vibrio cholerae* used were classical Inaba 569B and classical Ogawa 395. An oral dose of 10^8 organisms in buffered saline was required to induce the diarrhea of cholera. When given with live organisms, $NaHCO_3$ lowered the infecting dose from 10^8 to 10^4 organisms. Clinical manifestations of infection varied from culturally positive formed stools to "rice water" diarrhea. Severe diarrhea did not have an explosive onset but rather progressively increased in volume during a 24-hr period. In 45% of cases the stool was positive for *V. cholerae* before the onset of diarrhea. Titers of vibriocidal antibody rose after diarrhea, peaked the second week after challenge, and rapidly fell during the next four weeks.

- Early Cholera models (**1969**-):
  - Strived for a reproducible attack rate
  - Demonstrated protection of volunteers after homologous re-challenge 4-12 months later.

- El Tor N16961 CHIM standardized at three centers, **1998**.The final model:
  - Challenge dose of 10^5 wild-type *V. cholera* 01 El Tor biotype, Inaba serotype,>85% Attack rate.
  - Challenge strain lots made by GMP, open to the field.

~16 years later…

- Oral live attenuated (CVD 103-HgR, Vaxchora) previously licensed outside US until 2004. PaxVax purchases to redevelop for travelers in **2009**.
- Vaccine-CHIM
  - volunteers challenged at 10 or 90 days after vaccination.
  - Inpatient for 9-10 days for close fluid management.
- **Straightforward endpoint for efficacy:**
  - Moderate (>3L) to severe (>5L) cholera diarrhea

Vaccine Efficacy (95% CI) or *P* Value	
Day 10	3 mo
93.3% (56.2%–100%)	85.7% (46.2%–100%

CID 2016:62 (1 June) • Chen et al

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Cholera Vaccine-CHIM

- First vaccine to received FDA approval (**2016**) without a Phase III efficacy trial, for use in travelers.
- 2009-1026 (7rs) vs. 1969-2016 (47 years)

FDA News Release

FDA approves vaccine to prevent cholera for travelers

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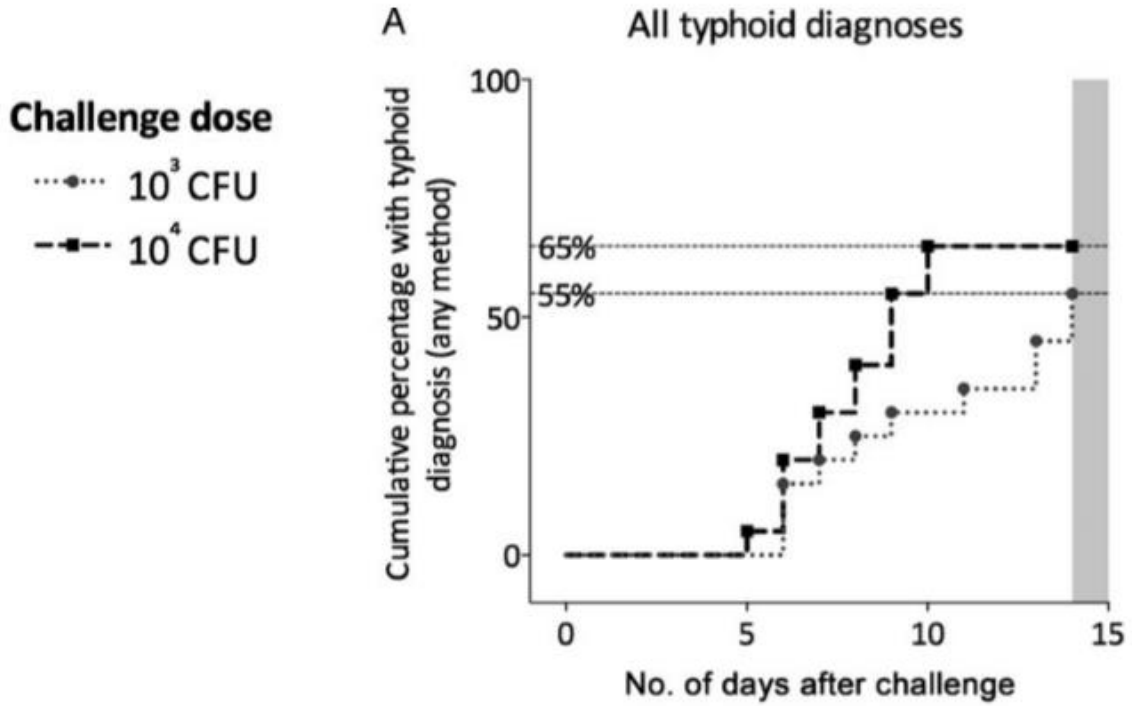
For Immediate Release June 10, 2016

Oxford updates the Typhoid CHIM

- 1952-1974, >1600 volunteers in early models. Quailes strain (Vi+).
- At Oxford, 40 years later.
  - Strain sequenced to confirm virulence factors
  - New GMP cell bank
- **Clear endpoints**: fever or bacteremia
- Balance safety, possibility of 'overwhelming' vaccine and desire for high attack rate.



CID 2014:58 (1 May) • Waddington et al

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CHIM and Vi-TT protein conjugate vaccine (TCV) testing

	Control group (n=34)	Vi-TT group (n=41)	Vi-PS group (n=37)
Primary outcome			
Completed challenged	31	37	35
Total diagnosed (composite definition, clinical or microbiological typhoid diagnosis)	24/31 (77%)	13/37 (35%)	13/35 (37%)
Relative risk (95% CI)	..	0·45 (0·28–0·73)	0·48 (0·30–0·77)
Vaccine efficacy (%, 95% CI)	..	54·6% (26·8–71·8)	52·0% (23·2–70·0)
p value	..	0·0005	0·0010

Post-hoc: " The diagnostic criteria were not designed to mirror field trial definitions of typhoid fever. [Field efficacy of Vi-PS is 69%.] If …[these criteria any fever>38 before positive BC] were applied to Vi-TT, estimated efficacy of Vi-TT would be **87.1%**"

TCV recommended by SAGE Prequalified by WHO

October 2017

Summary of the October 2017 meeting of the Strategic Advisory Group of Experts on Immunization

Typhoid vaccines

SAGE noted the continued high burden of typhoid fever and the alarming increase in antimicrobial resistance of *Salmonella* Typhi (*S.* Typhi) in low- and middle-income countries. SAGE re-emphasized the importance of programmatic use of typhoid vaccines for controlling endemic disease. Following review of the available data, SAGE recommended the introduction of typhoid conjugate vaccine(TCV) for infants and children over 6 months of age as a single dose in typhoid endemic countries. Introduction of TCV should first be prioritized to countries with the highest burden of disease or a high burden of antimicrobial resistant *S.* Typhi. SAGE also recommended catch-up vaccination wherever feasible, with priority for catch-up in the youngest age groups (up to 15 years of age), depending on local epidemiology.

Typhoid vaccination is recommended in response to confirmed outbreaks of typhoid fever. Typhoid vaccination may be considered in humanitarian emergencies depending on risk assessment in the local setting.

January 2018

World Health Organization

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Essential medicines and health products

Typhoid vaccine prequalified

3 JANUARY 2018 - WHO has prequalified the first conjugate vaccine to prevent typhoid fever called Typbar-TCV® developed by Indian pharmaceutical company Bharat Biotech.

The vaccine has long-lasting immunity, requires only one dose and can be given to children as young as 6 months through routine childhood immunization programmes. Other Typhoid vaccines are recommended for children over 2 years of age.

Prequalification by WHO means that the vaccine meets standards of quality, safety and efficacy, thus making it eligible for procurement by United Nations agencies, such as the United Nations Children's Fund.

A conjugate vaccine is one that is composed of a polysaccharide antigen that is fused to a carrier molecule.

NB: 1952-2017=65 years

http://www.who.int/medicines/news/2017/WHOprequalifies-breakthrough-typhoid-vaccine/en/

Vaccine-CHIM success stories

- The biology of pathogen is well understood.
- Vaccine feasibility is strong.
- An established CHIM exists.
- A GMP strain is available.
- The CHIM is safe with:
  - clear and distinct endpoints.
  - A relatively high and consistent attack rate.

J. Diggins

TYPHOID CHALLENGE MODELS

- Determine the dose of *Salmonella* Typhi required to produce an AR of 60-75%
- Clinical and laboratory features
  - Time course
  - Bacteraemia
  - Inflammatory response
- Development of immunity
  - Innate & humoral
  - Cell mediated immunity
  - Long-term immunity after treatment
- Diagnostics
  - PCR-based
  - Mass spectrometry
- Variation in genomic response
- Research mechanisms for related pathogens
- Correlates of protection

VACCINE STUDIES

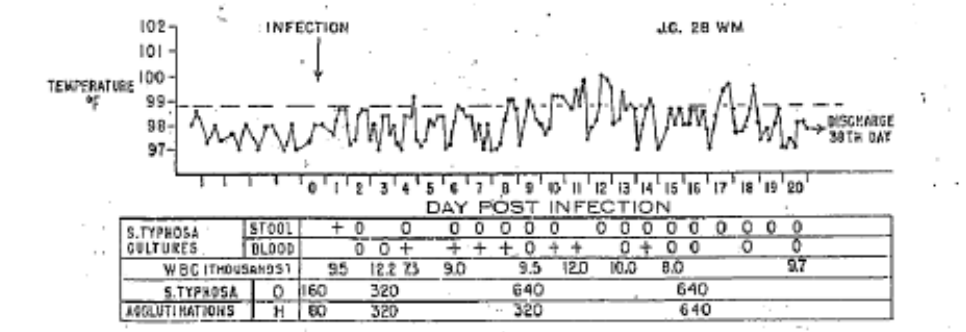
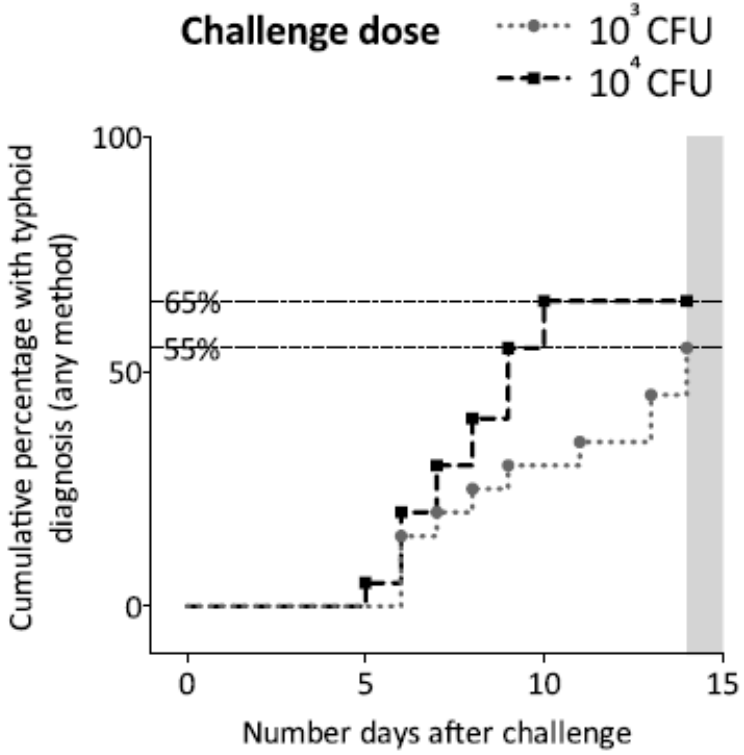


FIG. 1. *Clinical summary of volunteer no. 9, J. G., after the ingestion of 10^8 viable Salmonella typhosa Quailes strain. Rectal temperatures are recorded.*



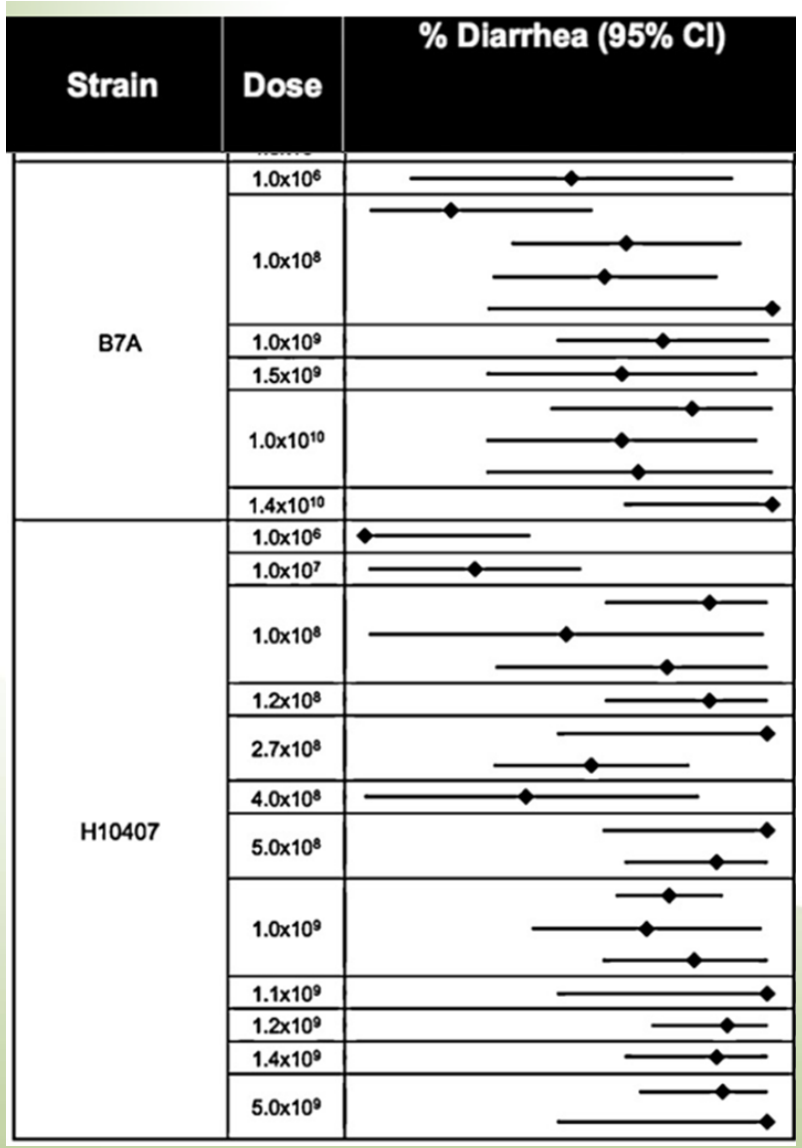
Waddington CS, et al. *Clin Infect Dis 2014;* 58: 1230-40

ETEC and Shigella CHIM

- Major contributors to acute diarrhea in low-middle income countries in young children. May contribute to long-term health outcomes. Clinical similarities.
- Complexity of biology: species, virulence factors, immune responses.
- Disease profile includes many non-diarrheal symptoms:
  - CHIM endpoints of moderate-severe diarrhea may not fully capture disease profile.
  - CHIM attack rates variable.

*and Campylobacter

ETEC Attack Rate Variability



- 27 studies of 11 strains of ETEC
- Attack rates variable, hard to compare between and within studies.
- Diarrhea and non-diarrhea symptoms differ by strain and presence of toxins.
- **H10407** and B7A models have undergone re-establishment for standardization (2011, 2018).

Vaccine 29 (2011) 5869–5885

ETEC Disease Severity Score

Table 5. Disease severity score components.

Parameter	Outcome		Score
Objective signs	>1 episode of vomiting/24 hrs ***OR*** any fever		2
	1 episode of vomiting ***AND*** no fever		1
	No vomiting ***AND*** no fever		0
Subjective symptoms	Moderate-severe lightheadedness ***OR***		2
	Severe: nausea, malaise, headache or abd cramps		2
	Mild lightheadedness ***OR***		1
	mild-mod: nausea, malaise, headache or abd cramps		1
	No 'subjective symptoms'		0
Diarrhea score (max 24 hr loose stools)	>1000 ml	>12 episodes	4
	>600 to ≤1000 ml	>7 to 12 episodes	3
	>400 to ≤600 ml	>4 to ≤7 episodes	2
	>0 to ≤400 ml	1 to 4 episodes	1
	No loose stools	No loose stools	0

PLOS ONE | DOI:10.1371/journal.pone.0149358 March 3, 2016

H10407 Model use in vaccine testing

ETEC fimbrial tip adhesion (FTA) vaccine

- Intradermal administration of recombinant FTA, 3 doses
- Donor strand-complemented CfaE, a stabilized form of the CFA/I fimbrial tip adhesion and LT
- Primary endpoint of mod/severe diarrhea.
- Results TBD

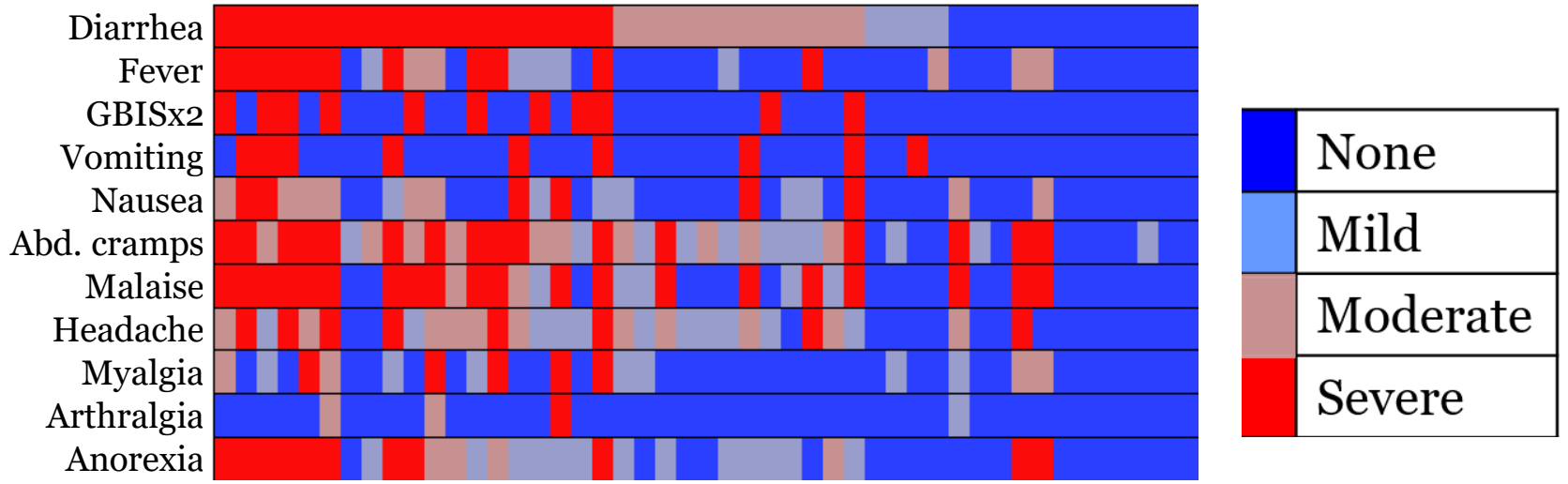
ACE 527 Vaccine

- Live-attenuated vaccine with 3 ETEC strains, deleted virulence factors and CFAI, CS1-3,5,6, LT
- 27% vaccine efficacy vs. mod/severe diarrhea, not significant vs. placebos.
- Vaccine development stopped.

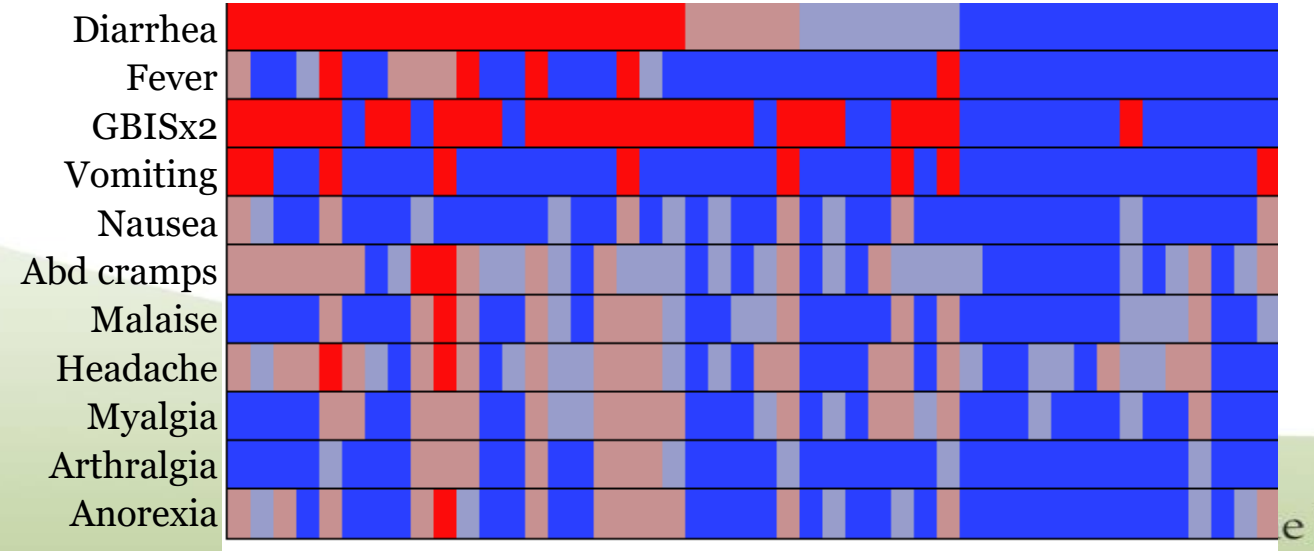
December 2012 Volume 19 Number 12 Clinical and Vaccine Immunology p. 1921–1931

Shigella CHIM: Signs and Symptoms

2457T (*S. flex* 2a)



53G (*S. sonnei*)



Shigella Endpoint problems

Shigellosis

- Diarrhea
- Diarrhea ***OR*** Dysentery
- Diarrhea ***AND*** Fever
- Diarrhea, Fever ***OR*** Dysentery
- Diarrhea, Fever, Dysentery ***OR*** *Severe* Abdominal Cramps
- Diarrhea, Fever ***OR*** Dysentery ***AND*** >1 *Severe* 'Intestinal Symptom' ***AND*** >1 *Severe* 'Constitutional Symptom'

Diarrhea

- 1 LS of >300ml ***OR*** ≥2 LS >200ml in 48 h
- ≥2 loose stools in 24 h
- ≥3 loose stools in 24 h
- ≥4 loose stools in 24 h
- 1 LS of >300ml ***AND*** ≥1 symptom/sign ***OR*** ≥2 LS totaling >200ml in 48 h ***AND*** ≥1 symptom/sign

Fever

- >37.8°C
- ≥37.8°C
- >38.0°C
- ≥38.0°C
- ≥38.1°C
- ≥38.3°C

Dysentery

- Occult blood in 1 LS
- Gross blood in 1 LS
- Gross blood in >1 LS
- Blood or mucus in 1 LS
- Blood and mucus >1 LS
- Gross blood in formed or LS
- Gross or occult blood in 1 LS
- Gross blood, occult confirmed in ≥ 2LS in 24 h

Chad Porter, US Navy Medical Research

Shigella CHIM Consensus Primary Endpoints

Primary Endpoint	Definition
1. Severe Diarrhea	≥6 loose stools* in 24 hours OR >800 G loose stools in 24 hours
2. Moderate Diarrhea	[4-5 loose stools in 24 hours OR 400-800 G loose stools in 24 hours] AND [oral temperature ≥38.0˚C† OR ≥1 moderate constitutional/enteric symptom‡ OR ≥2 episodes of vomiting in 24 hours]
3. Dysentery	≥2 loose stools with gross blood (hemoccult positive) in 24 hours AND [oral temperature ≥38.0˚C OR ≥1 moderate constitutional/enteric symptom OR ≥2 episodes of vomiting in 24 hours]

Constitutional/Enteric Symptoms
Nausea
Abdominal pain/cramping
Myalgia/arthralgia
Malaise

Shigella CHIM Working Group:
MacLennan CA, Riddle MS, Chen W,
Talaat K, Jain V, Bourgeois L, Frenck R, Kotloff K, Porter C

The University of Vermont

Shigella Vaccine CHIM applications

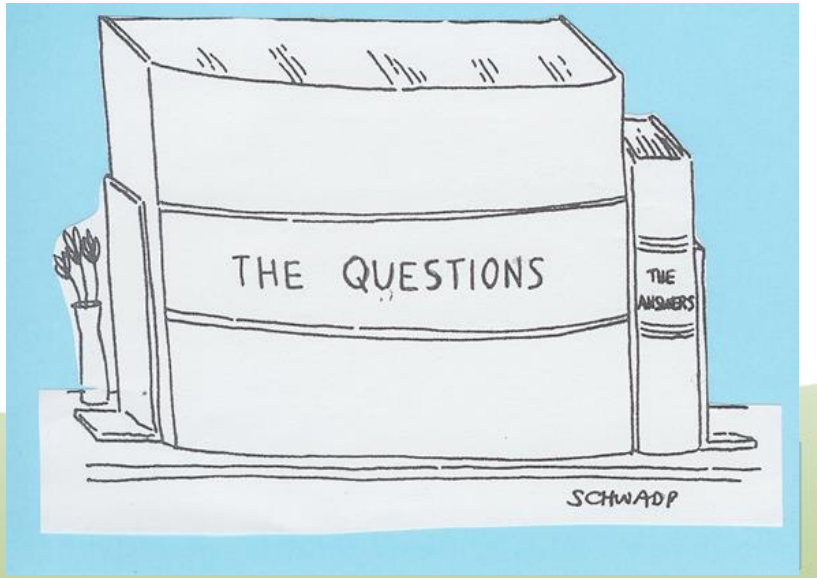
CHIM	Vaccine	Naïve AR (n/N)	Vaccine AR (n/n)	Efficacy (%)	Reference
Flex2A-2457T	SC602	6/7	0/7	100	Coster , IAI, 1999
Flex2A-2457T	EsSF2a-2*	12/14	10/16	27	Kotloff, Vaccine, 1995
Flex 2A-2457T	Proteosome	13/13	9/14	36	IDSA 2001
Flex2A-2457T	Invaplex-50	8/12	7/10	-5	NCT00485134
Sonnei-53G	WRSS1	1/10	0/10	*	NCT01080716
Flex2A-2457T	Flexyn2a**	< ***results pending*** >			NCT02646371

*Study performed in Thai adults yielded lower than anticipated naïve attack rates

** bioconjugate vaccine, 2 doses IM, 1500 CFU *S. flexneri 2A*

Campylobacter, *Cryptosporidium*, Polio/Rotavirus

- Campylobacter: Homologous protection not found in all strains, vaccine feasibility?
- *Cryptosporidium*: CHIM construction for drugs first; relevance for vaccines?
- Polio/Rotavirus: use of live oral vaccines as the challenge inoculum (i.e. an inactivated vaccine protects against a live vaccine).



Regulatory landscape

- Resurgence in interest in CHIMs has led to:
  - Meeting focused on standardization, regulation (IABS).
  - WHO documents, NIH guidance on ethics, etc.

- Requirements vary significantly by country/region

- Pathways to support licensure are evolving.
  - Support for moving vaccines into endemic pediatric populations.
  - Support of licensure for traveler indications.

What's next for Enteric vaccines+ CHIM?

- Standardization of models, endpoints, and inoculums for the whole field.
- A standard practice of publishing "negative" results is essential.
- Focus on end-target populations:
  - Application of Vaccine-CHIM data in healthy adults to target populations, especially children in low-middle income countries?
- Consideration of endemic site CHIMs: the impact of prior exposures, enteropathy, co-infections, microbiome.
- Application of advanced immunology for immune correlates
  - An immunologic bridging study >CHIM> Phase III efficacy trials

Thank you

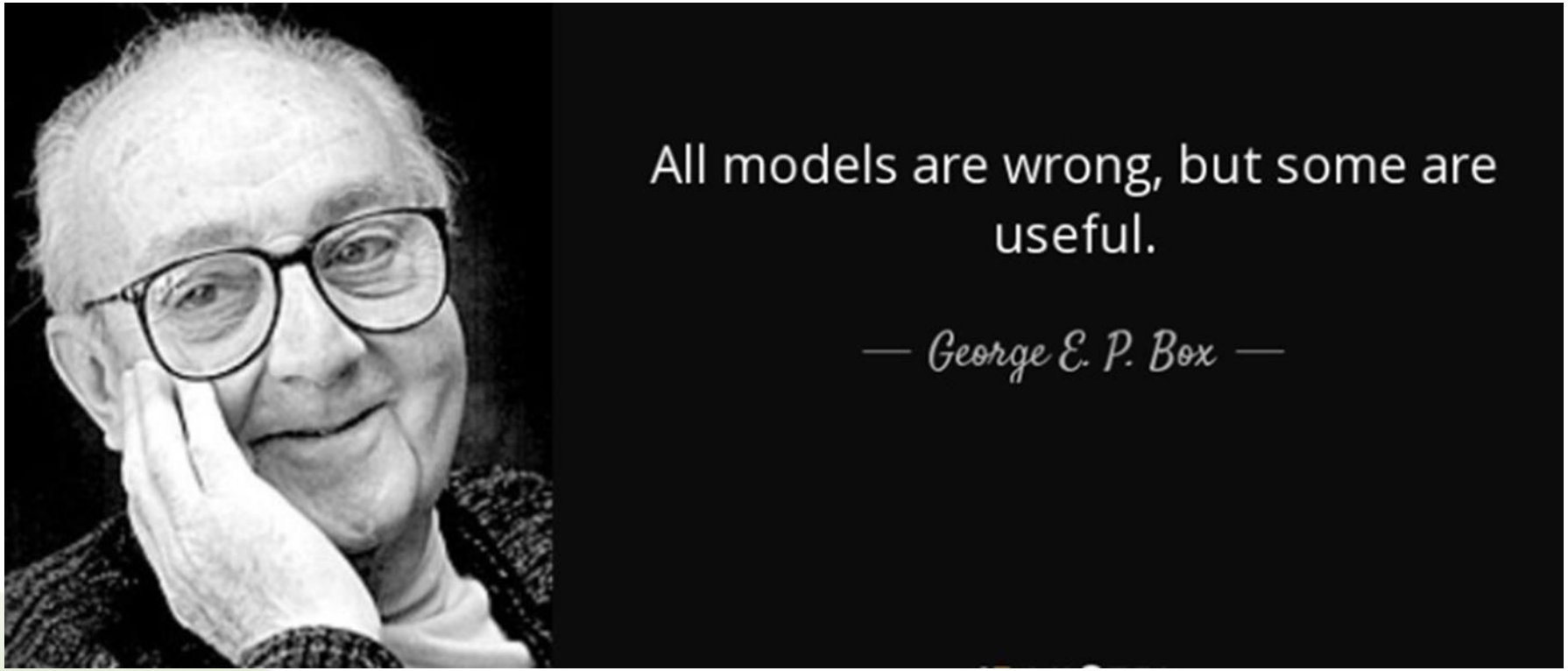
World Health Organization

National Institutes of Health

Bill & Melinda Gates foundation

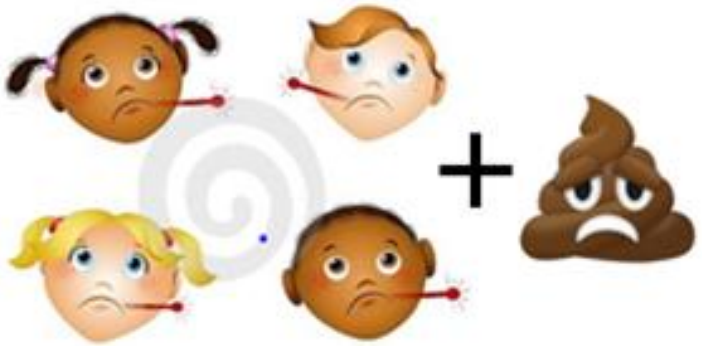
Shahida Baqar, PhD,
Chad Porter, PhD
UVM Vaccine Testing Center

EXTRA SLIDES



The first record of Box saying "all models are wrong" is in a 1976 paper published in the *Journal of the American Statistical Association*.[1] The paragraph containing the aphorism is below.

> Since all models are wrong the scientist cannot obtain a "correct" one by excessive elaboration. On the contrary following William of Occam he should seek an economical description of natural phenomena. Just as the ability to devise simple but evocative models is the signature of the great scientist so overelaboration and overparameterization is often the mark of mediocrity.



Design CHIM: Endpoints, Attack Rate

Identify challenge strain

GMP-inoculum

Regulatory, Ethical Approvals

Dose Ranging Studies

Safe, relevant model, consistent attack rate

Epidemiology
Natural history
Immune correlates
Microbiology

Vaccine Feasibility

Vaccin… goal*

…ccine candidate (TPP)*

Phase I/II clinical trials

Vaccine-CHIM*

Phase III Efficacy Trial*

TIME AND EXPENSE

Shigella and ETEC: re-thinking CHIM principles and standardization

Table 1
Discussion questions within each topic area.

Topic area	Discussion questions
Clinical outcomes	What attributes of clinical outcomes in human challenge studies would help better predict positive impact in endemic settings? What value have clinical outcomes demonstrated in advancing enteric vaccines to the end goal of licensure or prequalification is licensure/prequalification the end goal for all? What are the main challenges limiting the application of the best clinical outcomes in the human challenge model?
Non-clinical	What nonclinical outcomes are currently missing or lacking that would facilitate identification of immune correlates/surrogates and guide candidate down selection? What currently used non-clinical outcomes provide critical information to help advance the field of vaccinology? How can we advance from currently utilized non-clinical outcomes to those that would transform enteric vaccine trials?
Model standardization	How would standardized methodologies and outcomes best be developed and disseminated? What are key features of a challenge model that would ensure constant clinical and nonclinical outcomes across time and space? Should human challenge models be utilized for vaccine candidate down selection?

Who should be responsible for standardization?

How to we standardize doses for comparability?

Are we using doses (too high) which limit translation to natural settings?

Are models relevant to endemic settings?

Porter C, Bourgeois AL et al. Developing and utilizing controlled human models of infection. Vaccine 2017; 35: 6813-8