Controlled Human Infection Models and Enteric Vaccine Development

2018 Global Vaccine and Immunization Research Forum
March 20, 2018
Beth Kirkpatrick, MD
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

- **CURRENT PARADIGM**
- **NEW PARADIGM**
- **REDUCED INVESTMENT AT RISK**

Cost

- $1M
- $10M
- $300M

Probability of Success (PTRS)

- 0%
- 20%
- 40%
- 60%
- 80%
- 100%

Target Antigen ID → Pre-clinical → Phase I/II → Phase III → Registration

© 2013 Bill & Melinda Gates Foundation (modified)
Vaccine-Challenge Studies

CANDIDATE VACCINE

Vaccinated

Placebos (unvaccinated)

~1-3 months

CHALLENGE

Enteric pathogen administered to all. Infection/Disease endpoints measured.

CONTROLLED OBSERVATION

Vaccinated: protected (?) follow

Placebos: should have infection/disease

\[
VE = \frac{ARU - ARV}{ARU} \times 100, \\
\]

with
- \(VE\) = Vaccine efficacy,
- \(ARU\) = Attack rate of unvaccinated people,
- \(ARV\) = Attack rate of vaccinated people.

The University of Vermont
Cholera...from 1969

- 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...


- 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

---

<table>
<thead>
<tr>
<th>Vaccine Efficacy (95% CI) or P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 10</td>
</tr>
<tr>
<td>93.3% (56.2%–100%)</td>
</tr>
<tr>
<td>3 mo</td>
</tr>
<tr>
<td>85.7% (46.2%–100%)</td>
</tr>
</tbody>
</table>
Cholera Vaccine-CHIM

- First vaccine to receive 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*

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

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

Essential medicines and health products

Typhoid vaccine prequalified

3 JANUARY 2018 - WHO has prequalified the first conjugate vaccine to prevent typhoid fever called Typhar-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

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

Variation in genomic response

Diagnostics
PCR-based
Mass spectrometry

Research mechanisms for related pathogens
Correlates of protection

VACCINE STUDIES

FIG. 1. Clinical summary of volunteer no. 9, J. C., after the ingestion of $10^8$ viable Salmonella typhi, with daily stool and blood cultures. Stool samples were collected, and stool and blood cultures were performed at the relevant time points.

Challenge dose
- $10^3$ CFU
- $10^4$ CFU

Cumulative percentage with typhoid diagnosis (any method)

© Bill & Melinda Gates Foundation

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).
# ETEC Disease Severity Score

## Table 5. Disease severity score components.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Outcome</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective signs</strong></td>
<td>&gt;1 episode of vomiting/24 hrs <strong>OR</strong> any fever</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1 episode of vomiting <strong>AND</strong> no fever</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No vomiting <strong>AND</strong> no fever</td>
<td>0</td>
</tr>
<tr>
<td><strong>Subjective symptoms</strong></td>
<td>Moderate-severe lightheadedness <strong>OR</strong></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe: nausea, malaise, headache or abd cramps</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Mild lightheadedness <strong>OR</strong></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>mild-mod: nausea, malaise, headache or abd cramps</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No ‘subjective symptoms’</td>
<td>0</td>
</tr>
<tr>
<td><strong>Diarrhea score (max 24 hr loose stools)</strong></td>
<td>&gt;1000 ml</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt;600 to ≤1000 ml</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;400 to ≤600 ml</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;0 to ≤400 ml</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No loose stools</td>
<td>0</td>
</tr>
</tbody>
</table>
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.
Shigella CHIM: Signs and Symptoms

2457T
(S. flex 2a)

53G
(S. sonnei)

Diarrhea
Fever
GBISx2
Vomiting
Nausea
Abd. cramps
Malaise
Headache
Myalgia
Arthralgia
Anorexia

None
Mild
Moderate
Severe
Shigella CHIM Consensus Primary Endpoints

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Severe Diarrhea</td>
<td>≥6 loose stools* in 24 hours OR &gt;800 G loose stools in 24 hours</td>
</tr>
<tr>
<td>2. Moderate Diarrhea</td>
<td>[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]</td>
</tr>
<tr>
<td>3. Dysentery</td>
<td>≥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]</td>
</tr>
</tbody>
</table>

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
Shigella Vaccine CHIM applications

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

*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
All models are wrong, but some are useful.

— George E. P. Box —

The first record of Box saying “all models are wrong” is in a 1976 paper published in the *Journal of the American Statistical Association* 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.