Status of Vaccine Development for Shigella

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Uniformed Services University

burden of disease snapshot
PPC Development
Pipeline status
critical efforts, partnership and funding landscape
Burden of Disease Snapshot

Lucerne, Switzerland (2018)
MORTALITY

Ebola × 4
DALYS

ABX RESISTANCE

To develop a safe, effective, affordable vaccine to reduce diarrhea, dysentery and morbidity caused by Shigella in children under 5 years of age, in LMICs
Expected serotype immunity from O-antigen based vaccines


<table>
<thead>
<tr>
<th>S. sonnei and S. flexneri serotypes (% all Shigella case isolates)</th>
<th>1a (0.3)</th>
<th>1b (7.5)</th>
<th>2a (20.2)</th>
<th>2b (10.9)</th>
<th>3a (9.4)</th>
<th>3b (0.1)</th>
<th>4a (2.9)</th>
<th>4b (0)</th>
<th>5a (0)</th>
<th>5b (0.3)</th>
<th>6 (11.0)</th>
<th>7a (2.0)</th>
<th>7b (0)</th>
<th>X (1.0)</th>
<th>Y (0.4)</th>
<th>Ss (23.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. sonnei</strong></td>
<td>✅</td>
<td></td>
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<td></td>
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<tr>
<td><strong>S. flex 2a</strong></td>
<td>✅</td>
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</tr>
<tr>
<td><strong>S. flex 3a</strong></td>
<td>✅</td>
<td>✅</td>
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<tr>
<td><strong>S. flex 6</strong></td>
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</tr>
<tr>
<td><strong>Quadri-valent</strong></td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
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</tbody>
</table>

A quadrivalent mixture would protect against 88% of all *Shigella* (theoretically)
### Pipeline status overview

#### Phase 1

<table>
<thead>
<tr>
<th>Live</th>
<th>Killed</th>
<th>Subunit</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD1208S (S. flex 2a) U Maryland/PATH</td>
<td>TSWC (S. flex 2a) WRAIR/NIH</td>
<td>Oag synthetic conjug. (S. flex 2a) Pasteur Institute</td>
<td>NIH vaccine never licensed despite efficacy in phase 3</td>
</tr>
<tr>
<td>WRSs2/3 (S. sonnei) WRAIR/NIH</td>
<td>Invaplex-Detox IM (S. flex 2a) WRAIR/PATH/DFID</td>
<td>InvaplexAR-intranasal (S. flex 2a) WRAIR</td>
<td>Development halted, novel O-ag truncate under develop.</td>
</tr>
</tbody>
</table>

#### Phase 2

| Oag Bioconjugate (S. flex 2a) Limmatech (GSK) | GMMA (S. sonnei) GVGH (GSK) | Oag-TT conjugate (S. sonnei) NIH |

#### Phase 3

<table>
<thead>
<tr>
<th>Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin-dep LAV (historic/various) (Yugoslav Army/other)</td>
</tr>
</tbody>
</table>

#### Notes

- Historic LAVs no longer in use
- BMGF funded
- Wellcome funded
- US Gov Funded
- EU funded
- DFID, industry, Acad
From GMMA theory to GVGH examples

Simple to prepare but capable of sophisticated manipulation

GMMA
(una gemma: Italian for bud or jewel)

Remove, modify toxic components
- LPS

Delete antigens / genes
- Shigella virG

Modify composition
- Multivalent vaccine

Induce blebbing

Break links
GMMA manufacturing – Generic, simple and robust

Building on Shigella GMMA and a technology suited to sub-Saharan Africa

Genetic modifications
1. Increase GMMA production $\Delta tolR$
2. Decrease LPS innate immune stimulation $\Delta htrB$ or $\Delta msbB$
3. Other mutations virG nadA/B knock-in

Fermentation

Purification
- Micro-filtration Collect 0.22 $\mu$m permeate
- Ultra-filtration Collect 300 kD retentate

Formulation
Adsorption on Alhydrogel

Sterile filtration 0.22 $\mu$m

DS and DP characterization
- Generic panel of release tests
- CQA

References:
Building the *S. sonnei* GMMA vaccine experience

1790GAHB is safe and immunogenic in Shigella naïve and exposed adult populations

Status of 4-component GMMA Shigella vaccine

Key activities *S. sonnei* 1790GAHB and 4-component GMMA

2017

1790GAHB in sonnei CHIM

2018

Interim VE

4-component

GO

2019

APR CSR

2020

2021

2022

Immunogenicity & formulation development

Site & lab selection

Tox lot

GLP tox

3x GMP *S. flex* MCB & GMMA lots

Clinical GMP lot

CTA

4-component GMMA, 2 staged phase 1/2

Stage 1

EU adults

Stage 2

LMIC age descending & dose finding

APR CSR

LBMartin | GSK GMMA project |

9 May 2018 | WHO Shigella vaccine consultation | Geneva
Flexyn2a: bioconjugate vaccine that conjugates the O antigen of Shigella flexneri 2a (Sfl2a) to the Phase 1 trial: safe and immunogenic in US adults (Riddle '16)

Phase 2b trial (controlled human infection model): safe, immunogenic and efficacious against 'shigellosis' (Talaat '17)

**Phase 2b trial design**

VACCINATION

- Flexyn2a: n=34
- Placebo: n=33

CHALLENGE

- 1500 CFU S. flexneri 2a 2457T

**Primary endpoint**

- Severe Diarrhea
- Moderate diarrhea & fever or ≥ 1 moderate const/enteric symptom
- Dysentery

## Flexyn2a Immunogenicity

### Serum Sf2a-LPS IgG

- Injection
- Challenge

<table>
<thead>
<tr>
<th>2a-LPS serum IgG titer (log10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

- Flexyn2a
- Placebo

Mean +/- 95% CI

*: p<0.05, t-test

### Serum Sf2a-LPS IgA

- Injection
- Challenge

<table>
<thead>
<tr>
<th>2a-LPS serum IgA titer (log10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

- Flexyn2a
- Placebo

Mean +/- 95% CI

*: p<0.05, t-test

### Serum Bactericidal Activity (SBA)

- Injection
- Challenge

<table>
<thead>
<tr>
<th>SBA titer (log10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

*: p<0.05, t-test

### ≥4-fold rise from baseline

<table>
<thead>
<tr>
<th></th>
<th>Serum Sf2a-LPS IgG</th>
<th>Serum Sf2a-LPS IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexyn2a</td>
<td>26/34 (76.5%)</td>
<td>26/34 (76.5%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0/30 (0%)</td>
<td>1/30 (3.3%)</td>
</tr>
<tr>
<td>Flexyn2a</td>
<td>27/33 (81.1%)</td>
<td>26/33 (78.8%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1/30 (3.3%)</td>
<td>1/30 (3.3%)</td>
</tr>
</tbody>
</table>

Day 0 to Day 28
Day 0 to Day 55
### Flexyn2a protects against severe shigellosis outcomes

<table>
<thead>
<tr>
<th>Attack Rate N(%)</th>
<th>Vaccine Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
</tr>
<tr>
<td>Flexyn2a N=30</td>
<td>Placebo N=29</td>
</tr>
<tr>
<td>Shigella (primary endpoint)</td>
<td>13 (43.3)</td>
</tr>
</tbody>
</table>

**Secondary Endpoints:**

- More Severe Diarrhea: 2 (6.7) vs. 7 (24.1), *p*-value = 0.07
- Received Early Administration of Antibiotics: 9 (30.0) vs. 18 (62.1), *p*-value = 0.01
- Received IV Fluids: 7 (23.3) vs. 13 (44.8), *p*-value = 0.05

- More Severe Shigellosis* (post hoc analysis): 8 (27.6) vs. 16 (53.3), *p*-value = 0.015

*Difference between the shigellosis primary endpoint and more severe shigellosis analysis is the inclusion of severe symptoms.

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**Multivalent P2 Descending Age Study**

**Confidential** 12
SF2a-TT15
A synthetic carbohydrate-based
*Shigella flexneri* 2a vaccine candidate

ClinicalTrials.gov Identifier: NCT02797236

**Phase I trial**
Randomized, single blind, placebo controlled, dose escalation study in healthy adults

**Investigator**: Jacob Atsmon - Tel Aviv Sourasky Medical Center

**Sponsor**: Institut Pasteur
(Clinical management: Cécile Artaud)

**Primary outcome**: safety

**Secondary outcome**: immunogenicity
Dani Cohen (TAU), Marie-Lise Gougeon (IP)

Laurence Mulard,
*Head, Chemistry of Biomolecules Laboratory*

Armelle Phalipon
*Group Leader, Molecular Microbial Pathogenesis Unit*
Study design

- Pre-screen included anti-SF2a IgG assessment – highest 20% excluded
- Single blinded with clinical and lab staff masked on study agents
- 46 males & 18 females, mean age: 22.7 (SD=5.9)

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2μg/OS</td>
<td>10μg/OS</td>
</tr>
<tr>
<td>2μg/OS + alum</td>
<td>10μg/OS + alum</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

- 3 IM injections on days 0, 28, 56
- Nine follow up visits for safety and immunogenicity, last visit 3 month after 3rd dose
Results

- SF2a-TT15 is safe and well tolerated.
- 1 immunization with 10 µg SF2a-TT15 (dose per synthetic OS) induces an impressive serum anti-SF2a LPS IgG response in 100% of the vaccinees (x 27 fold as compared to placebo baseline (similar results with the other immune parameters measured).
- SBA correlation with the level of serum IgG antibodies to SF2a LPS indicates functional capabilities of these antibodies.
- SF2a-TT15 also elicits a significant rise in the percent of specific B memory cells to SF2a LPS suggesting priming for a sustained immune response.
- At the lower dose, alum increases SF2a-TT15 immunogenicity.

Future plans:

<table>
<thead>
<tr>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
</tr>
<tr>
<td>07 08 09 10 11 12 01 02 03 04 05 06 07 08 09 10 11 12</td>
<td>07 08 09 10 11 12 01 02 03 04 05 06 07 08 09 10 11 12</td>
<td>07 08 09 10 11 12 01 02 03 04 05 06 07 08 09 10 11 12</td>
<td>07 08 09 10 11 12 01 02 03 04 05 06 07 08 09 10 11 12</td>
<td>07 08 09 10 11 12 01 02 03 04 05 06 07 08 09 10 11 12</td>
</tr>
</tbody>
</table>

SF2a-TT15 monovalent

Flex 2a CHIM

Flex 2a Descending Age Study
**Shigella Invasin Complex (Invaplex) Vaccine**

Invaplex is a unique subunit *Shigella* vaccine

- **Composition:** Serotype-specific LPS in a macromolecular complex with broadly conserved Ipa proteins.
- **Highly immunogenic:** Inducing immune responses directed to LPS and Ipa proteins, mimicking responses to natural infection.
- **Biologically active:** Induces endocytosis.
- **Safe:** Delivered to > 100 volunteers with no Significant Adverse Events.
- **Multivalent *Shigella* vaccine:** Multiple options for constructing tri- or quadrivalent serotype-specific vaccine.
- **Combination Vaccine Potential:** Can be administered with other enteric vaccines. Functions as an adjuvant for protein and DNA vaccines.
- **Gap Filling:** The Ipa protein components helps to “fill the gap” between conjugate (LPS-driven) and whole cell (live-attenuated or inactivated) vaccine approaches.
Shigella Invaplex Vaccines (AR = Artificially Recombined)

**Phase 1/2b: tbd**

**MUCOSAL**

- IpaB + IpaC + LPS → Invaplex

**PARENTERAL**

- IpaB + IpaC + Detoxified LPS → Invaplex

Phase 1 planned: Jan 2019 (DFID/US DoD Funded; PATH Sponsor)

- IpaB + IpaC + Detoxified LPS → Invaplex

**Invaplex_{AR}** and **Invaplex_{AR-DETOX}**
Shigella live-attenuated approaches

<table>
<thead>
<tr>
<th>Primary attenuation strategy</th>
<th>UMD-CVD</th>
<th>DoD-WRAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔguaBA - enzymes employed in the distal de novo purine biosynthesis pathway</td>
<td></td>
<td>ΔvirG-responsible for inter- and intra-cellular spread</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional attenuation deletions</th>
<th>UMD-CVD</th>
<th>DoD-WRAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δset (Shigella entertoxin 1), Δsen (shigella enterotoxin 2)</td>
<td></td>
<td>Δset + Δsen (2nd), ΔmsbB2 (3rd, reduces pyrogenicity by deleting the lipid A acyltransferase)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most recent trial (year)</th>
<th>UMD-CVD</th>
<th>DoD-WRAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 with lyophilized 1208S (2013)</td>
<td></td>
<td>Phase 1 with WRSs2/3 (2017)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary results</th>
<th>UMD-CVD</th>
<th>DoD-WRAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safe, with 3 doses (0, 28, 56) at $10^8$ CFU 42% serconversion</td>
<td></td>
<td>Safe at single dose with better immunogenicity for WRSs2&gt;WRSs3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Next steps</th>
<th>UMD-CVD</th>
<th>DoD-WRAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>No current trials planned</td>
<td></td>
<td>Phase 2b with 2 doses of WRSs2 (NIAID/US-DoD)</td>
</tr>
</tbody>
</table>
Next Generation: Strain CVD 1208S-122

A prototype *Shigella* live vector expressing ETEC antigens

CVD 1208S::P_{mLpp}-CFA/I-LThA2B

- chromosomal integration of CFA/I and LThA2B expression, by mLpp promoter
- renamed as **CVD 1208S-122**

CVD’s Portfolio of *Shigella*-ETEC vaccine strains

<table>
<thead>
<tr>
<th>Attenuated live vector strain</th>
<th>serogroups and serotypes</th>
<th>ETEC Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD 1208S-122</td>
<td><em>S. flexneri</em> 2a</td>
<td>CFA/I &amp; LTA2B</td>
</tr>
<tr>
<td>CVD 1213S-210</td>
<td><em>S. flexneri</em> 3a</td>
<td>CS1 &amp; CS5</td>
</tr>
<tr>
<td>CVD 1215S-310</td>
<td><em>S. flexneri</em> 6</td>
<td>CS4 &amp; CS6</td>
</tr>
<tr>
<td>CVD 1233S-410</td>
<td><em>S. sonnei</em></td>
<td>CS2 &amp; CS3</td>
</tr>
<tr>
<td>CVD 1254S</td>
<td><em>S. dysenteriae</em> 1</td>
<td>Stx1B &amp; CS17</td>
</tr>
</tbody>
</table>

Note: The trc promoter did not result in efficient expression of ETEC antigens
Truncated mutant: *Shigella* strains with shorter O-polysaccharide unit

*IcsP is masked by lipopolysaccharide (LPS) O-antigen on the wild type *Shigella* surface

**Update since PDVAC 2017**

- Truncated O side chains of LPS Increase exposure of conserved IcsP outer membrane protein on *Shigella* surface without affecting expression level
- In mice, immunization with mutant strains:
  - induced elevated IgA and IgG immune responses to whole cells and outer membrane proteins (PSSP 1 and Ipa’s)
  - Induction of heterologous protection noted in mouse lung model
- Heterologous protection will be investigated in the Sereny GP model
- Vaccine is envisioned to include at least 2 strains: Sf2a and *S. sonnei*
- RO1 pending with NIH for cGMP production of pilot lot of the truncated mutant to enable approach to move into Ph1/2b trials

Data Courtesy of Jae-Ouk Kim, IVI
<table>
<thead>
<tr>
<th>2017</th>
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<tr>
<td>07</td>
<td>08</td>
<td>09</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

**STRATEGY**
- SME WS
- Funders Mtg
- Strategy endorsed

**REGULATORY**
- WHO PPC WS
- WHO PD & Policy Pathway
- WHO Engagement on ETEC & Shigella OPP1135836

**ASSAYS & STDs**
- ELISA WS
- IgG Thresholds OPP1189564 (Tel Aviv University)
- IgG stds flex 2a & S. Sonnei ELISA assay (NIBSC)

**EPIDEMIOLOGY**
- Burden WS

**CHIM**
- CHIM Clinical & Assays WS
- Endpt Consensus
- CHIM Endpt & Assays Papers submitted

**Bioconjugate Vaccine (Limmatech)**
- Multivalent P2 Descending Age Study

**GMMA (GVGH) OPP1133860**
- S. Sonnei CHIM
- Multivalent P2 Descending Age Study

**Synthetic GP Vaccine (IP)**
- Flex 2a CHIM
- Flex 2a Descending Age Study

Slide courtesy: Cal MacLennan, BMGF
Points for discussion

- Regulatory/LMIC/WHO consensus for accelerated development pathway?
- Stewardship of field site development in support of phase III planning
- LMIC/industry engagement on vaccine development, value and adoption
- Pipeline robustness, sustainment of enteral approaches/strategies
- What should be the role/priority for WHO/IVR going forward?

ACKNOWLEDGEMENTS

- Birgitte Giersing (WHO)
- A. Louis Bourgeois (PATH)
- Veronica Gambillara (LimmaTech/GSK)
- Armelle Phalapon (Institute Pasteur)
- Laura Martin (GSK/GVGH)
- Rob Kaminski (WRAIR)
- Malabi Venkatessan (WRAIR)
- Calman MacLennan (BMGF)
# Shigella Vaccine Development: Critical Efforts, Partnership, and Funding Landscape

## Key Aspects

- **Vaccine Pipeline Generator**
- **Assay, Tools, Early Clin. Development**
- **Regulatory Path / Pivotal Trial Execution**
- **Disease Burden / Health Need**
- **Market Development / Buyer Demand**

<table>
<thead>
<tr>
<th>Academia</th>
<th>Govt R&amp;D</th>
<th>Industry</th>
<th>Regulatory Agencies</th>
<th>Philanthropic Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAV</td>
<td>LAV, synth conj, Invaplex</td>
<td>Bioconjugate, GMMA</td>
<td></td>
<td>Partner / Sponsor</td>
</tr>
<tr>
<td>Stand. ELISA, Phase 1/2b</td>
<td>Stand. ELISA, Phase 1/2b</td>
<td>Stand. ELISA, Phase 1/2b</td>
<td></td>
<td>Partner / Sponsor</td>
</tr>
<tr>
<td>Field site development</td>
<td>Field site development</td>
<td>Phase 3 trials</td>
<td></td>
<td>Partner / Sponsor</td>
</tr>
<tr>
<td>GEMS, BoD, Traveler Epi</td>
<td>Traveler Epi</td>
<td>Traveler Epi</td>
<td></td>
<td>GAVI</td>
</tr>
<tr>
<td>Country level assessments</td>
<td>Multi-country Network</td>
<td>Priority setting (WHO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAGE Recommend</td>
<td></td>
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</tbody>
</table>

- **Stand. ELISA, Phase 1/2b**
- **Field site development**
- **Phase 3 trials**
- **Key Partners**
- **Priority setting (WHO)**
- **SAGE Recommend**
- **GAVI**
# Target Product Profile for Shigella Vaccines (in revision)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Minimum</th>
<th>Optimistic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong>*</td>
<td>Prevention of moderate to severe diarrhea due to <em>Shigella</em> in children less than two years of age</td>
<td>Prevention of moderate to severe diarrhea due to <em>Shigella</em> in children less than two years of age</td>
</tr>
<tr>
<td><strong>Target Population</strong>*</td>
<td>Children up to two years of age</td>
<td>Children up to 5 years of age</td>
</tr>
<tr>
<td><strong>Schedule and Route of Administration</strong>*</td>
<td>EPI schedule: 2 or 3 dose + booster IM route.</td>
<td>EPI schedule - 1 dose IM route.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Safety and reactogenicity profile should be clinically acceptable. Contraindications should be restricted to known hypersensitivity to any of the vaccine components</td>
<td>Safety and reactogenicity profile should be clinically acceptable. Contraindications should be restricted to known hypersensitivity to any of the vaccine components</td>
</tr>
<tr>
<td><strong>Efficacy</strong>*</td>
<td>50% efficacy against moderate to severe diarrhea caused by <em>Shigella</em> strains in the vaccine</td>
<td>70% efficacy against moderate to severe diarrhea caused by all <em>Shigella</em> strains</td>
</tr>
<tr>
<td><strong>Duration of Protection</strong></td>
<td>2 years, w/ boosting possible to extend protection</td>
<td>To 5 years.</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$1 - $3</td>
<td>&lt; $1</td>
</tr>
<tr>
<td><strong>Co-administration</strong></td>
<td>With EPI vaccines without interference</td>
<td>With EPI vaccines without interference</td>
</tr>
<tr>
<td><strong>Vaccine volume</strong></td>
<td>0.5 ml/dose</td>
<td>0.5 ml/dose</td>
</tr>
<tr>
<td><strong>Target Countries</strong></td>
<td>GAVI-eligible and LMIC</td>
<td>GAVI-eligible and LMIC</td>
</tr>
<tr>
<td><strong>Onset of immunity</strong></td>
<td>2 weeks after 2 or 3 doses</td>
<td>2 weeks after 1 dose</td>
</tr>
<tr>
<td><strong>Indirect protection</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Accelerated pathway enablers

ADVANCES IN THE FIELD

2 CHIMs

STANDARDIZED CONTROLLED HUMAN CHALLENGE MODELS

Shigella sonnei (53G)
  • 53G lyophilized (DoD)
Shigella flexneri (2457T)
Multiple Sites Developed
  • CVD, JHU, Univ of Cincinnati
Standardization efforts underway
  • Definitions
  • Study procedures

4 ELISAs

INTERNATIONAL STANDARDIZED ELISA - 4 TARGET SEROTYPES

• Establish ‘notional’ role of O-antigen IgG in protection
• Development of standard laboratory method/SOP
• Reference laboratory establishment
• Develop supply of sera for international standard

1 Pathway

ROAD-MAP FOR CLINICAL & REGULATORY PATHWAY

• WHO/GAVI prioritization, good will and open-mindedness
• Developer commitment
• Research community collaboration
• Funder backing