Status of Vaccine Development for ETEC and *Shigella*

Presentation to WHO Product Development for Vaccine Advisory Committee (PDVAC)
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Geneva, Switzerland

A. Louis Bourgeois, PhD, MPH
Scientific Director
Enteric Vaccine Initiative
Presentation overview

- Dynamic field with priorities in transition; high level of activity and progress since PDVAC 2016
- ETEC and Shigella disease burden debate and implications on vaccine development
  - Overview of recent WHO ETEC/Shigella burden consultation – April 2017
- Standalone vaccines versus combination product considerations
  - Technical feasibility, Clinical data and Funding; Risk and Time of development
- Updates on most advanced candidates with emphasis on progress since last PDVAC Mtg.
- Highlights from other WHO and PATH sponsored meetings on ETEC and Shigella vaccines
  - WHO-PATH vaccine formulation and delivery mtg; introduction of VTIA tool - DEC 2016
- Overview of current issues and challenges
- How can WHO continue to help move this development effort forward
WHO consultation on ETEC and Shigella disease burden of Disease Estimates – 6 and 7 April 2017

- BoD estimates are variable (mortality) and incomplete (morbidity)
  - Direct observational studies versus modeling: GEMS, MAL-ED, MCEE, IHME
  - Currently mortality is the primary development driver
  - Agent specific DALYS currently not available but coming
  - Estimates further complicate by regional, national and sub-national level differences in ETEC and Shigella burden
  - Better diagnostics tools may also help resolve apparent conflicts: Taqman and LAMP

- Burden estimates likely to change further between now and licensure and will need to be well characterized to support policy recommendation

- Leading with a combination strategy is high risk and will take longer (5-10 yrs) for approval versus standalone products. Consequently development of standalone vaccines as well as combinations should be continued

- WHO WG will review model methodology to better define model uncertainties and ultimately make recommendations on best metrics to serve as development priorities going forward
Potential impact of *Shigella* & ETEC vaccine

- Together account for roughly 15% of under-5 diarrhea deaths (100,000 deaths) and 17-20% of all diarrhea deaths (240,000 deaths)

- *Shigella* is the third leading cause of under-5 diarrhea mortality and ETEC the 8\textsuperscript{th} but together ETEC and Shigella combined are the second, passing *Cryptosporidium*

- Efforts underway to better estimate pathogen specific DALYS and other metrics of long-term health impacts associated with these pathogens

- Early YLD estimates already available – top 5 agents associated with diarrhea YLD’s – Rotavirus, Crypto, ETEC, Shigella and Adenovirus (Colambara et al. 2016. Amer. J. Gastroenterol. 3(2): 4-11; doi:10.1038/ajgsup.2016.9)

Slide developed from I. Khalil of IHME at WHO ETEC and Shigella Burden Consultation of April 2017
Disease heterogeneity in 11 east African countries: Focal hot spots

- Intra- and inter-country disease heterogeneity is likely to exist.
- Possible for a country to contain areas encompassing the entire spectrum for ETEC and *Shigella* deaths/100,000 children (3.7 – 160 deaths/100,000 children).
- Understanding potential risk for death and disease is critical for country policymakers to decide where to introduce vaccines.
- Sub-national introduction of different vaccine products may be needed.

Analysis from R. Rheingans
## Current ETEC vaccine landscape – Standalones and combinations

### Oral administration

- **ETVAX inactivated** (SBH, PATH)
- **ACE527 live attenuated** (PATH; NVSI; UGA)

### Parenteral injection

- **FTA** (PATH, NMRC, Sanofi, IDRI)

### Clinical candidates

- CVD GuaBA mutants expressing ETEC antigens (UMB)
- ShigTEC (EVELIQURE)

### Preclinical candidates

- Ty21a expressing *Shigella* LPS and MEFA (Protein Potential)
- MEFA (KSU, JHU, PATH)
- LT/ST Fusion/conjugate (ENTVAC Consortium, PATH)
- Flagellin, EtpA, EatA, EaeH, YghJ (WASHU)

**Note:** Most candidates based on formulations that will induce immunity against LT toxin and primary and secondary bacterial adhesins or proteins aiding toxin delivery; LT-ST toxoid is not seen as standalone vaccine but as a potential supplement to both whole cell or subunit approaches.
ETVAX/dmLT: Most advanced ETEC candidate in clinical development

- First-generation showed efficacy against severe travelers’ diarrhea, but not protective in Egyptian infants (impact on more severe illness could not be determined).
- WHO recommended that CF/CS content of vaccine be increased; add CS6 to formulation; and assess impact of adding adjuvant (dmLT) – all addressed in current candidate.
- 2nd generation vaccine exceeded immunologic expectation in Ph1 trial in Swedish adults and this success justified moving the vaccine to a descending age study in Bangladesh (down to 6 mths of age)
ETVAX Clinical Development (Stage-Gate)

1. Descending Age OEV-122 (Aug ’15 to Dec ’17)
   - Target Age OEV-124 (2Q2018-3Q2020)
   - Travelers Trial OEV-123 (May ’17 to 1Q2020)
   - Development of self-contained presentation
   - Severe Score
   - Site Development

2. Phase 1/2

3. Phase 1/2

4. Phase 2b

#1 #2 #3 #4

Note: Initiation pending full analysis of OEV-122 immunology and securing adequate funds

Notes:
- Major timeline assumptions:
  - An ETVAX standalone vaccine is technically feasible
  - Funding will be adequate and available
  - Clinical results will support product licensure and WHO policy recommendation

- WHO Policy Recommendation (PR) – 2028
- Timeline is optimistic for standalone ETVAX vaccine but more complex and extended if combination is target
ETVAX update (Pediatric studies)

- **OEV-122**: Descending age study down to 6 mths of age
  - Clinical phase to be completed Jul 2017; no serious safety issues encountered to date
  - Tolerability improved by fractional dosing; dmLT (2.5, 5, and 10ug) did not add to reactogenicity
  - Assessment of mucosal and systemic antibody responses still ongoing; introduction of MSD platform enabled testing of ALS samples against all 5 vaccine key antigens
  - Early analysis of ALS may suggest age-dependency that highlights the need to further optimize immunization regimen in target age-group ( <1 yr) – additional dose; interval adjustment; settle on dmLT dose

- **OEV-124** is anticipated to look at ETVAX given on EPI schedule as stepping stone to Ph3 trials
  - New vaccine lot (reduced dose volume) manufactured, released, and available for trial
  - IND amendment for trial submitted and no “hold” issues identified; site IRB approval obtained; DGDA pending
  - Poised to begin, pending 122 immunology review and full funding

- Process development work ongoing at PATH to develop self-contained 1-2 components presentation for bridging study needed for start of Ph3.
OEV-123: Ph2b safety, immunogenicity and efficacy study in Finnish travelers to Benin

- **Overview**
  - Lab and clinic built in Benin site (Grand Popo) to support study; inaugurated on 4 Apr 2017
  - Ethics and FEMEA approval in Apr; Recruiting begun in May

  - **Dosing began June 13th and 1st subjects (20) are traveling to Benin on July 2nd**
  - Randomized, placebo-controlled Ph2b trial in consecutively cohorts of 20-30 Finnish travelers going to Benin under Finnish cultural exchange program; up to 800 subjects will be enrolled (1:1 randomization)
  - Immunization: 2 doses (days 0 and 14) of ETVAX buffer; last dose 7-30 days before travel
  - Stay in Benin – 12 nights/13 days; all subjects at one location with study clinic and lab on site to carry out in-country surveillance for Traveler’s diarrhea
  - With success, Ph3 likely to be carried out in British troops on training exercises in Kenya

- **Primary, secondary and exploratory endpoints:**
  - Safety – frequency and severity of AE post-dosing
  - Immunogenicity – serum IgA/IgG responses to LTB and 078 as measure of vaccine “take” and marker for protection
  - Efficacy – prevention of moderate to severe TD due to VPO ETEC
  - Diagnostics – can TaqMan replace culture based methods for detecting ETEC and determine VPO’s?
  - Biorepository of study samples will also be established to facilitate later “deeper dive” into CoP
OEV 123 – Trial site, new study Lab/Clinic and sampling schedule

Finnish tourists to Benin

ETEC data is limited from Benin but previous Finnish study indicates potential for high TD (~70-80%) and ETEC infection rates (~50% of visitor); Shigella also may be common (~18% of cases); results based on PCR detections (Lääveri, T. et al. 2014. BMC Infect. Dis. 14:81-88)
ETEC Fimbrial Tip Adhesin (FTA) Vaccine: Current multivalent concept

- Concept: Antibodies to adhesive fimbrial subunits will abrogate initial step of intestinal adherence minimizing or preventing subsequent disease. Disease can be further minimized by elicitation of anti-LT antibody responses.
- Partners: NMRC, IDRI, Sanofi, PATH and BMGF.
- A multivalent vaccine approach covering four of the most prevalent colonization factors plus and LT component is the current proposed approach; estimated to provide 75-80% coverage for most common ETEC strains.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>CfaEB</th>
<th>CotDA</th>
<th>CsbDA-CooA</th>
<th>CssBA</th>
</tr>
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<tbody>
<tr>
<td>Structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated coverage</td>
<td>Class 5a</td>
<td>Class 5c</td>
<td>Class 5b</td>
<td>CS6</td>
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<tr>
<td></td>
<td>CFA/I, CS14, CS4</td>
<td>CS2</td>
<td>CS1, PCF071, CS17, CS19</td>
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</tr>
</tbody>
</table>

FTA update since PDVAC 2016

- All components protective (PE = 45-100%) in NHP after ID immunization.
- Anti-CssBA passive protection CHIMS study just completed to provide further support for CssBA as protective antigen – results to be presented at VED 2017.
- CssBA cGMP lot made; toxicology ongoing; needed for planned PH1/PH2b immunization and challenge study.
- B7A (LT+, ST+, CS6+) challenge model being refined for use in coming Ph2B study.
Current *Shigella* vaccine candidates – Standalones and combinations

**Oral Administration**

- TSWC—killed (PATH)
- WR VirG series live attenuated (PATH, WRAIR)
- CVD Guaba series live attenuated (UMB; PATH)

**Parenteral Injection**

- *E. coli* - expressed Glycoconjugate (LimmaTech Biologics) –Ph2b done
- GMMA (SBVGH)-2b
- Invaplex (WRAIR; PATH)
- Synthetic glycoconjugate (Institut Pasteur, PATH)

**Clinical Candidates**

- CVD Guaba mutants expressing ETEC antigens (UMB)

**Preclinical Candidates**

- ShigETEC (EVELIQURE)
- Ty21a expressing *Shigella* LPS (CombiVax)
- Truncated *Shigella* (IVI, PATH)
- Hilleman WC candidate – NICED

Note: Candidates based on formulations that will induce immunity against serotype specific O antigens and/or conserved proteins, like Ipa’s
TSWC – trivalent inactivated whole cell vaccine


- From initial Ph1 with SF2a - doses in \( \sim 3 \times 10^{11} \) range (cohort 4) more immunogenic than lower doses \( \leq 3 \times 10^{10} \) (cohort 3) in adults

- Final component of TSWC vaccine (Sf3a strain) undergoing cGMP manufacture; Sf2a and *S. sonnei* strain completed and released

- FDA permission to proceed with Ph2b CHIM protocol to evaluate protective efficacy of inactivated WC Sf2a component against challenge with 2457T is pending

### Serum and Mucosal antibody responses to Sf2a inactivated whole cell vaccine

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Serum IgA &gt;2-fold (%)</th>
<th>Serum IgG &gt;2-fold (%)</th>
<th>ALS IgA &gt;4-fold (%)</th>
<th>ALS IgG &gt;4-fold (%)</th>
<th>Fecal IgA &gt;4-fold (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=10</td>
<td>1/10 (10)</td>
<td>3/10 (30)</td>
<td>0/10 (0)</td>
<td>0/10 (0)</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>Vaccine Cohort 3 N=20</td>
<td>10/18 (56)</td>
<td>6/18 (33)</td>
<td>8/18 (44)</td>
<td>ND</td>
<td>8/18 (44)</td>
</tr>
<tr>
<td>Vaccine Cohort 4 N=18</td>
<td>15/20 (75)</td>
<td>14/20 (70)</td>
<td>19/20 (95)</td>
<td>16/20 (80)</td>
<td>11/20 (55)</td>
</tr>
</tbody>
</table>
Live, attenuated *Shigella* vaccine: VirG series

- **WRSS1** is the *S. sonnei* component of a multivalent vaccine being developed at Walter Reed Army Institute of Research (WRAIR)
- Attenuated by VirG deletion which limits cell-to-cell spread of bacteria – protects in CHIMS
- Update since PDVAC 2016 – VAC 008
  - Vaccine safe and well tolerated in 5-9 yr olds at doses of $10^5$ and $10^6$
  - Cumulative local and serum Ab responses highest in $10^6$ group (82%). SBA response also seen in this group and in $10^5$ groups
  - Given results, moving to 12-23 mth. olds is reasonable
  - VAC 049: 12-23 mth. cohort began in 1Q2017 and study is ongoing

- WRSs2 and WRSs3 are Shet-1 and Shet2 + MsbB2 Mutants for greater attenuation: in Phase 1 trial.
Bioconjugation: Simplified manufacturing of a safe and efficacious vaccine

- Simple product
- Periplasmic production
- Site specific, enzymatic conjugation
- Purified «like a protein»
- Platform technology
Shigella Bioconjugate Vaccine – Development Status

- *S. dysenteriae* O1 phase 1 in 2010 *(Hatz et al., Vaccine 2015)*
- *S. flexneri* 2a phase 1 and 2b (Wellcome Trust program) 2014-2016
  - Phase 1 results obtained:
    - Safety and immunogenicity *(Riddle et al., Clin Vaccine Immunol 2016)*
  - Phase 2b results obtained:
    - Proof of concept for early indication of efficacy (results will be presented at VED 2017 and Human Challenge Workshop 2017)
    - Supportive data of serological correlation with protection against clinical shigellosis

- Development of a multivalent Shigella conjugate including the most-dominant serotypes currently ongoing; projected coverage - SF2a, Sf3a, Sf6 and *S. sonnei*
Flexyn 2a_Phase 1: Immunogenicity

Phase 1: 30 naïve adult volunteers, 10 µg conjugated PS +/- aluminum hydroxide, 2 doses IM, 1 month apart

Riddle et al., Clin Vaccine Immunol 2016

Mucosal immune response

Analysis of a sample-subset showed that parenteral immunization with Flexyn2a specifically induces α4β7+ PBMCs producing 2a-LPS IgG (ALS titers)
Generalized Module for Membrane Antigens (GMMA) Platform

- Pure outer membrane buds by genetic engineering → efficacy & affordability of whole cell vaccine without the side effects
- Remove / modify toxic components
  - Lipid A of LOS or LPS
- Delete unwanted antigens
  - surface polysaccharides, capsule
- Add new antigens
  - overexpress homologous antigens
  - add heterologous antigens
- 4-valent GMMA formulation (S. sonnei, S. flexneri 2a, 3a and 6) immunogenic in mice
- S. sonnei prototype safe and immunogenic in phase 1; descending age and challenge trial start 2017

Status of GSK’s GMMA vaccine project targeting Shigella

PD-VAC update provided by GVGH to EVI PATH

*Shigella sonnei* GMMA vaccine, 1790GAHB

- Phase 1 studies in EU adults demonstrated tolerability and antigenicity when delivered intramuscularly of up to 5.9 µg OAg / 100 µg protein per dose (NCT02017899, NCT02034500)
- Further development of 1790GAHB alone, or when included in a multivalent formulation, will use 1.5 µg OAg / 25 µg protein per dose
  - Generating median specific anti-LPS serum IgG at least as high as observed after natural infection
- Evaluation of booster dose in EU adults ongoing (NCT03089879)
- Phase 2 study in Kenyan adults complete (NCT02676895). Clinical study report in preparation.
- Phase 2b evaluation in experimental human infection mode of *S. sonnei* will start following definitive definition of challenge dose by CCHMC

**Note added:** 53G model being refined for coming Ph2b using lyophilized strain for greater standardization

4-valent Shigella vaccine

- Extends the technical and clinical data of 1790GAHB
- Composition includes GMMA from *S. sonnei* and 3 GMMA of *S. flexneri* serotypes
- Ongoing activities include formulation for GLP toxicology and GMP manufacture of vaccine components

Work supported by GSK, EU FP7 (STOPENTERICS & ADITEC), Bill & Melinda Gates Foundation
**S. flexneri 2a Artificial Invaplex given IM protects against shigellosis in the guinea pig rectocolitis challenge model**

Invaplex is a unique subunit *Shigella* vaccine

- **Composition**: Serotype-specific LPS in a macromolecular complex with broadly conserved Ipa proteins. Only candidate specifically targeting both key polysaccharide and protein antigens.

- **Highly immunogenic**: Inducing immune responses directed to LPS and Ipa proteins, mimicking responses to natural infection.

- Pre-IND package being prepared for FDA; tox pending FDA ok; FIH Ph1 projected for 2Q2018; complete vaccine – trivalent formulation.

<table>
<thead>
<tr>
<th>Treatment IM</th>
<th>Protected*/Total</th>
<th>Percent Protection**</th>
<th>P value (compared to saline)***</th>
<th>P value (compared to dmLT)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sfl2a Invaplex_AR + dmLT****</td>
<td>4/6</td>
<td>67%</td>
<td>0.0082</td>
<td>0.02</td>
</tr>
<tr>
<td>dmLT****</td>
<td>0/8</td>
<td>0</td>
<td>Not significant</td>
<td>---</td>
</tr>
<tr>
<td>saline</td>
<td>0/10</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

* Protection defined as a composite disease score less than 8.0; protection also seen in mouse lung model and Sereny

** Percent protection calculated as [([(disease controls - % disease vaccines) / % disease controls] x 100).

*** The levels of protection were evaluated by the Fisher’s exact test to determine the P-value.

**** Invaplex_AR concentration was 25 ug; the dmLT concentration was 0.1 ng; similar protection seen with detoxified formulation.

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Additional promising vaccine platforms and supportive studies and technologies

- Mutants
- Vectors
- Protein carriers
- Severity score
- Formulation/Presentation
Truncated mutant: *Shigella* strains with shorter O-polysaccharide unit

**Update since PDVAC 2016**

- Increased 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 being investigated in the Sereny GP model
- Vaccine is envisioned to include at least 2 strains: Sf2a and *S. sonnei*

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

Data Courtesy of Jae-Ouk Kim, IVI
Update since PDVAC 2016

1. Application of new immunological tools (ETEC proteomic arrays and Cytoff T cell analysis) have identified antigen specific antibody (EatA) and T cell responses (T_{EM}) that appear more common in the protected subjects given the dmLT adjuvanted vaccine

2. NVSI in China has made encouraging progress in improving fermentation and stabilization of vaccine strains that improve prospect for co-formulation product

3. In new work, UGA and UA will evaluate vaccine strains as vectors for a conserved *Campylobacter* glycan antigen; approach builds on recent success in significantly reducing colonization in poultry (up to 10 logs) using avian *E. coli* to deliver same glycan antigen.
Multi-epitope Fusion Antigen (MEFA) Vaccine – platform for ETEC, Shigella other enteric pathogen antigens

For ETEC
- One MEFA expresses the dominant epitopes of CFAs in a single protein
- One MEFA expresses non-toxic LTA LTB and ST in a single protein
- MEFA vaccines stimulate neutralizing antibodies against each of these virulence antigens
- 3 of 3 piglets immunized with MEFA –K88ac vaccine remained healthy following challenge
- Quantitative culture of piglet ileum showed reduced colonization following immunization
  - **Immunized group**: 3.2 x10^8 CFU  **Control group**: 1.6 x 10^9 CFU

For Shigella
- Ipa protein epitopes inserted in CFA/I backbone are immunogenic in mice

In General
- MEFA proteins are easily purified at high yield; stable at room temperature
- Readily used in combination vaccine as vector expressed (oral) or as parenterally injected antigen with other subunit vaccines

Data courtesy of Weiping Zhang, KSU
Status of Severity Score development for support of future ETEC and Shigella vaccine Phase III field trials – cont.

- The Vesikari severity score has played an important role in assessing efficacy of Rotavirus vaccines
- More recently, an ETEC severity score has been developed for use in evaluating candidate vaccines in Ph2b immunization and challenge studies (Porter, C. et al. 2016. PLoS ONE 11(3):e0149358.doi:10.1371/journal.pome.0149358)
- ETEC and Shigella vaccines currently under development likely to be most effective at decreasing the incidence of MSD; thus field methods are needed to triage participants into MSD vs. mild disease outcomes for interpretation of study results
- Neither the Vesikari or CHIM severity scoring systems will be applicable for ETEC/Shigella Ph3 field studies, so a new score is needed
- To address this gap, PATH convened a committee of experts to strategize on options for score development. The results of this 2 day workshop were recently published in the journal “Vaccine” (Wierzba et al. 2017. Vaccine. 35:503-507)
  - Workshop consider 3 score options that needed to be adapted to ETEC/Shigella
  - Committee recommended evaluating scoring options vs. an objective measure of dehydration (% change in child’s body weight)
  - Score evaluation should be done prospectively in Africa and a rapid screening tool for ETEC and Shigella was needed to help control study costs.

<table>
<thead>
<tr>
<th>Immunization Group</th>
<th>Number of Subjects</th>
<th>Challenge strain</th>
<th>Protective efficacy</th>
<th>Mean (std) Severity Score</th>
<th>2-sides p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve/Placebos</td>
<td>31</td>
<td>H10407</td>
<td>-</td>
<td>4.35 (2.70)</td>
<td>-</td>
</tr>
<tr>
<td>ACE527</td>
<td>13</td>
<td></td>
<td>20.5%</td>
<td>3.92</td>
<td>0.64</td>
</tr>
<tr>
<td>ACE527 + dmLT</td>
<td>13</td>
<td></td>
<td>65.9%</td>
<td>2.38 (2.60)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

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- Neither the Vesikari or CHIM severity scoring systems will be applicable for ETEC/Shigella Ph3 field studies, so a new score is needed
ETEC/Shigella diarrhea severity score development: key project goals and milestone update since PDVAC 2016

• **Project Goal**: Identify a sensitive and specific, easy to administer score to identify moderate to severe ETEC/Shigella cases
  
  • Use percent weight change from admission to discharge as proxy for degree of dehydration
  • Evaluate LAMP as fieldable semi-quantitative rapid screen tool for ETEC and Shigella

• Milestones:

  1. Evaluate feasibility of LAMP$_{ES}$ as a rapid screening test for ETEC/Shigella through laboratory testing at JHU through 4Q 2017
     - Work ongoing; initial LAMP results indicate high degree of sensitivity and specificity for ETEC and *Shigella* (>85%) versus RT-PCR in evaluation of CHIMS and diarrhea samples from Bangladesh

  2. Field evaluate/validation of LAMP$_{ES}$ pending in West Africa of India in 4Q 2017 - 2Q2018; based on success of field validation studies LAMP$_{ES}$ could be used to help develop new severity score
Options for Oral Presentation of ETVAX and Shigella Vaccines

- Formulation and Delivery Strategies for Oral Immunization of Infants in Low-to-Middle Income Countries, 12-13 Dec 2016, Geneva – optimize presentation to enhance uptake in LIMCs


**Aqueous Presentation**
- Saline suspension of bacteria in plastic tube

**Hybrid Presentation**
- Dry cake in vial (buffer, dmLT, LCTBA)
- Saline suspension of bacteria
- MCT oil suspension of buffer, LCTBA, dmLT

**Non aqueous Presentation**
- MCT oil suspension of bacteria, buffer, LCTBA, dmLT
Summary of current issues and challenges ahead

- Morbidity becoming more recognized for impact on early development and long-term health, but mortality remains primary driver of development decision making by funders.
- Mortality for *Shigella* felt to be high enough to support development of standalone vaccine; ETEC mortality perceived as lower bringing its impact as a standalone vaccine into question
  - Recent WHO consultation in April 2017 called to better understand burden and give guidance for setting ETEC and *Shigella* vaccine priorities in the context of their impact on child health particularly in Africa and South Asia
- Good news – increased funding for *Shigella* and ETEC vaccine development over last 10 yrs. has lead to several candidates moving into more advanced clinical trials and field testing
  - Most promising candidates include both oral and parenteral approaches
  - Sustained funding is critical to ensure continued progress of the most promising candidates
Summary of current issues and challenges ahead – cont.

- Remaining challenges being addressed:
  - Severity score to aid in vaccine efficacy evaluation under development
  - Encouraging progress being made on standardization of antigens and assays for assessing vaccine immunogenicity and functional capabilities
  - Novel formulation and delivery approaches more suitable for vaccine immunization are actively being investigated
  - Research tools to better define the health impact of ETEC and *Shigella* beyond mortality and understand how to more effectively immunize infants under one year of age are now on the horizon
What can WHO do to further facilitate ETEC and *Shigella* vaccine development?

- Establish a burden of disease working group to better understand variation in estimates—already in progress
- Developed Preferred Product Characteristics (PPC’s) for ETEC, *Shigella*, and combined vaccines—cleared to begin shortly
- Coordinate assay development activities, including development of a correlate of protection and facilitating assay harmonization/standardization—consultation being planned for Fall
- Coordinate harmonization and standardization of vaccine efficacy endpoint—case definition for mild–moderate and severe diarrhea and dysentery
- Clinical and regulatory pathways
- Provide input into programmatic suitability of vaccine presentations
Review of recent WHO meetings associated with formulation and delivery of ETEC and *Shigella* vaccine development

- **Formulation and Delivery Strategies for Oral Immunization of Infants in Low-to-Middle Income Countries, 12-13 Dec 2016, Geneva** – optimize presentation to enhance uptake in LIMCs

Recommendations/Goals from end-user, manufacturer and regulatory perspective:

- 1 or 2 component vs. 3; total volume of 1.5 to 2 mLs including buffer; early WHO review of delivery device advised
- Thermostabiilty profile matching with current WHO-approved VVM type
- No need for exogenous water
- Controlled Temperature Chain (CTC) qualification encouraged
- Meet or approach Programmatic Suitability for Prequalification (PSPQ) requirements

- Novel delivery strategies are needed to help improve vaccine uptake but it has been difficult to compare the overall total systems’ effectiveness of the most innovative and competitive approaches.

- To address this gap, a new Vaccine Technology Impact Assessment tool (VTIA) has recently been developed.

- VTIA is envisioned to facilitate a “pull” strategy that will help target investment into the most “game-changing” technologies with the greatest impact on vaccine coverage.

- VTIA is now being used to evaluate 3 delivery/presentation options for ETEC and TWSC vaccines (3 component, 2 component – aqueous and non-aqueous or all in one).
ETEC and Shigella: Two diseases with different modes of pathogenicity and vaccine targets

Potential lines of defense:
1. Protect against colonization of the small intestine
2. Induce antibodies that neutralize heat-labile toxin (LT)
3. Blocking invasion and cell-cell spread
4. Induction of bactericidal and opsinophagocytic Ab

*ST, which is a small peptide, does not elicit neutralizing antibodies following natural infection.
Anti-CTB serum IgA titer\(^1\) at arrival in Guatemala/Mexico as a marker for reduced risk of developing moderate to severe ETEC travelers diarrhea

<table>
<thead>
<tr>
<th>Anti-CTB IgA Titer at arrival</th>
<th># of Travelers</th>
<th>Mod-Sev TD VPO</th>
<th>No or Mild TD VPO</th>
<th>Relative Risk(^2)</th>
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</thead>
<tbody>
<tr>
<td>(&lt;40)</td>
<td>279</td>
<td>10</td>
<td>269</td>
<td>Reference</td>
</tr>
<tr>
<td>41-120</td>
<td>31</td>
<td>2</td>
<td>29</td>
<td>1.80 (0.41, 7.85)</td>
</tr>
<tr>
<td>121-360</td>
<td>73</td>
<td>2</td>
<td>71</td>
<td>0.76 (0.17, 3.41)</td>
</tr>
<tr>
<td>361-1080</td>
<td>81</td>
<td>0</td>
<td>81</td>
<td>0.16 (0.01, 2.75)</td>
</tr>
<tr>
<td>(&gt; 1080)</td>
<td>185</td>
<td>1</td>
<td>184</td>
<td>0.15 (0.02, 1.17)</td>
</tr>
</tbody>
</table>

\(^1\) Range of anti-CTB IgA titers in arrival serum samples collected from U.S. adults traveling to Guatemala and Mexico regardless of vaccination status; subjects with reciprocal anti-CTB titer < 40 were negative.

\(^2\) Cochran-Armitage test for trend (p-value = 0.01); using dichotomous cut-point at 360, RR = 0.10 (95%CI: 0.01 – 0.78)

CD4\(^+\) T\(_{EM}\) net IL-17A production \textit{pre-challenge} following stimulation with ETEC homogenate

Data courtesy of S. Grahek, JHBSPH and M. McArthur and M. Sztein, CVD

OEV-123 exploratory immunology: More in-depth of humoral and cellular immunity may give field greater insights into ETEC CoP – application of traditional and novel tools
Diarrhea associated YLD’s by agent – Colombara et al 2016

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Etiology Attribution</th>
<th>95% UI[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>3.35%</td>
<td>(2.46%-3.96%)</td>
</tr>
<tr>
<td>Aeromonas</td>
<td>0.60%</td>
<td>(0.42%-0.77%)</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>0.00%</td>
<td>(0.0018%-0.0021%)</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>0.68%</td>
<td>(0.34%-1.01%)</td>
</tr>
<tr>
<td>Cholera</td>
<td>0.56%</td>
<td>(0.55%-0.58%)</td>
</tr>
<tr>
<td><em>Cryptosporidium</em></td>
<td>4.43%</td>
<td>(3.67%-5.03%)</td>
</tr>
<tr>
<td>Entamoeba</td>
<td>0.38%</td>
<td>(0.14%-0.55%)</td>
</tr>
<tr>
<td>enteropathogenic <em>E. coli</em></td>
<td>0.59%</td>
<td>(0.026%-0.09%)</td>
</tr>
<tr>
<td>enterotoxigenic <em>E. coli</em></td>
<td>3.99%</td>
<td>(2.99%-4.70%)</td>
</tr>
<tr>
<td>norovirus</td>
<td>0.47%</td>
<td>(0.13%-0.75%)</td>
</tr>
<tr>
<td>Other <em>Salmonella</em></td>
<td>0.32%</td>
<td>(0.18%-0.46%)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>15.15%</td>
<td>(13.44%-16.49%)</td>
</tr>
<tr>
<td><em>Shigella</em></td>
<td>3.21%</td>
<td>(2.75%-3.63%)</td>
</tr>
</tbody>
</table>