2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)
Virtual Consultation 4: Update on development of Enterotoxigenic E.coli (ETEC) vaccines
18 June 2020
<table>
<thead>
<tr>
<th>Time (Geneva CEST)</th>
<th>Topic</th>
<th>Duration</th>
<th>Detail</th>
<th>Moderators, speakers</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.00 – 15.10</td>
<td>Welcome and roll call</td>
<td></td>
<td></td>
<td>David Kaslow / Birgitte Giersing</td>
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<tr>
<td>15.10 – 15.25</td>
<td>PDVAC/IVB engagement in ETEC vaccine</td>
<td>(10 + 5)</td>
<td>• Retrospective context of PDVAC engagement in ETEC; • Overview of cross-cutting portfolio activities that may help to inform product development and value • Summary of the ETEC preferred product characteristics (PPC) guidance following public consultation</td>
<td>Birgitte Giersing</td>
</tr>
<tr>
<td>15.25 – 15.40</td>
<td>Setting the scene: the current ETEC vaccine portfolio (10 + 5)</td>
<td>(10 + 5)</td>
<td>Overview of the current ETEC vaccine candidate portfolio and funding environment Challenges and opportunities</td>
<td>Lou Bourgeois (PATH)</td>
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<tr>
<td>15.40 – 16.00</td>
<td>Using controlled human infections and preclinical models to improve understanding of ETEC morbidity</td>
<td>(15 + 5)</td>
<td>AN overview of the status of controlled human infection models and preclinical models as tools to evaluate potential biomarkers for inflammation</td>
<td>Chad Porter (NMRC)</td>
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<tr>
<td>16.00 – 16.30</td>
<td>Product development overview of ETVAX</td>
<td>30min</td>
<td>Outcomes from Phase IIb Benin travellers study, current status of Phase II paediatric studies, currently envisaged formulation and presentation, manufacturing and licensure strategy</td>
<td>Bjorn Sjostrand &amp; Nils Carlin (Scandinavian Biopharma)</td>
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<tr>
<td>16.30 – 17.00</td>
<td>Discussion</td>
<td>30min</td>
<td>Open session</td>
<td>All</td>
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<tr>
<td>17.00 - 17.30</td>
<td>Discussion (closed session) – PDVAC only</td>
<td></td>
<td>• Does PDVAC endorse the PPC for ETEC vaccines? • Should ETEC vaccines remain a ‘priority’ for PDVAC and PDR/IVB? • In addition to the existing cross-cutting activities that PDR/PDVAC undertakes in support of ETEC, are there other specific activities that PDVAC should try to resource, to advance ETEC vaccines?</td>
<td>All</td>
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ETEC at PDVAC – historical perspective

- First discussed in 2015; ETVAX and ACE 527 most advanced
- Revisited in 2016; combination with Shigella was proposed; IVB award from BMGF to support vaccine development in late 2016.
  - 1st meeting in April 2017*: considerations for combination vaccine development
- Reviewed in 2017, joint with Shigella: robust pipeline for both antigens, key risks of a combination strategy debated, importance of defining burden of *morbidity*
- Discussed in 2018: IHME mortality estimates had declined to a level that was unlikely to warrant a stand-alone vaccine; uncertainty about the robustness/credibility of mortality estimates – call for WHO working group to look at data and methodology
  - Working group established in Q3 2018,
  - 2nd burden meeting in Nov 2018**: numerous recommendations
- Burden of enteric disease WG presented to PDVAC in April 2020.

*Considerations for using ETEC and *Shigella* disease burden estimates to guide vaccine development strategy (Hosangadi et al, 2019)
*WHO Consultation on ETEC and Shigella Burden of Disease, Geneva, 6-7th April 2017: Meeting Report (Hosangadi et al, 2019)
Establishing burden is fundamental to WHO concept of “full value of vaccines assessment” (FVVA)

The FVVA for vaccines is a concept that describes the global value of a vaccine, including from an LMIC perspective.

It aims to articulate the full direct (individual) and indirect (population) effects of a vaccine.

The intent of FVVA assessment is to support decision-making across the continuum of vaccine development and uptake...

...with a line-of-sight to sustainable socio-economic and public health impact.
Other cross cutting workstreams related to ETEC vaccine development and defining the FVVA

& the **AMR Value Attribution Framework:**

- a semi-quantitative framework to articulate the value of vaccines for their impact on AMR

Prioritise innovations in **vaccine delivery** attributes to provide greater clarity to manufacturers and immunisation partners to make investment decisions.
ETEC at PDVAC: development of preferred product characteristics (PPCs)

<table>
<thead>
<tr>
<th>ETEC PPC WG member</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td>George Armah</td>
<td>University of Ghana</td>
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<tr>
<td>(Norman Baylor)</td>
<td>Independent</td>
</tr>
<tr>
<td>Lou Bourgeois</td>
<td>PATH</td>
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<tr>
<td>Roma Chilengi</td>
<td>CIDRZ</td>
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<tr>
<td>Alejandro Cravioto</td>
<td>Universidad Nacional Autónoma de México (UNAM)</td>
</tr>
<tr>
<td>Dick Guerrant</td>
<td>University of Virginia</td>
</tr>
<tr>
<td>Ann-Mari Svennerholm</td>
<td>University of Gothenburg</td>
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<tr>
<td>Gagadeep Kang</td>
<td>THSTI</td>
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<tr>
<td>Margaret Kosek</td>
<td>University of Virginia</td>
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<tr>
<td>Ann-Mari Svennerholm</td>
<td>University of Gothenburg</td>
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<tr>
<td>Thomas Wierzba</td>
<td>Wake Forest School of Medicine</td>
</tr>
<tr>
<td>Ibrahim Khalil</td>
<td>WHO consultant</td>
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Seeking final endorsement for publication, following public consultation
ETEC at PDVAC: development of preferred product characteristics (PPCs)

Primary strategic public health goal: to develop a safe, effective and affordable ETEC vaccine that reduces mortality and morbidity due to moderate to severe diarrhoeal disease in infants and children under 5 years of age in LMICs.

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<thead>
<tr>
<th>Parameter</th>
<th>Preferred characteristic</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Indication</td>
<td>Prevention of moderate-to-severe diarrhoea (MSD) due to ETEC infection</td>
<td>Primarily prevention of moderate-to-severe (MSD) diarrhoea due to ETEC is considered the optimal clinical end point to provide a measurable impact. Prevention of mild disease is also considered important; however, this is unlikely pre-licensure. Other possible indications: Direct effects include reduction of stunting, prevention of malnutrition, risk reduction of ETEC associated infections, prevention of all cause diarrhoea. Indirect effects include decrease in antibiotic use, decrease in ETEC AMR, induction of herd protection and financial risk protection. While these are important outcomes that will contribute to the value assessment for ETEC vaccines, they are challenging to assess as primary clinical endpoints pre-licensure. Where feasible, exploratory endpoints related to these indications should be collected during clinical studies.</td>
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<tr>
<td>Target Population</td>
<td>For initial licensure: Infants from 6 months and children up to 24 months.</td>
<td>The goal is full protection of infants by the end of 9 months, to cover peak incidence and mortality through the first 24 months of life and the greatest burden in children in LMICs up to 5 years of age. Prevention of MSD in this group would significantly reduce death and morbidity due to both immediate and long-term sequelae, such as growth stunting associated with infection. Other target populations that would likely benefit from a vaccine that is efficacious in infants are older children, adolescents, adults and older adults in LMICs and emerging markets, as well as travellers and military recruits to endemic areas.</td>
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<td>Parameter</td>
<td>Preferred characteristic</td>
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<td>Clinical Endpoints</td>
<td>Primary: Reduction of MSD diarrhoea caused by ETEC, according to the case definition for MSD</td>
<td>Although there is alignment on the need to prevent MSD due to ETEC in the target population, there is a lack of consensus on the case definition (and associated severity score) for MSD in community settings. This consensus is needed to compare studies and candidates. Alternatively, trials could assess vaccine impact on medically attended MSD using a passive surveillance study design.</td>
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<td></td>
<td>Secondary and Exploratory: Reduction in acute Less Severe Diarrhea (LSD)- diarrhoea leading to care seeking but without dehydration.</td>
<td>Since demonstration of vaccine impact on morbidity is expected to be needed for policy recommendation, secondary endpoints should include initial and follow up HAZ to measure potential impact on growth stunting, with or without overt diarrhoea. Direct effects: vaccine preventable ETEC strains, however cross-protection against CFs not in the vaccine or other defined conserved putative protective antigens may be beneficial; protection against LSD; immune correlates of protection; microbiological correlates of protection (PCR vs culture); mortality. Indirect effects: all ETEC diarrhea, reduction in shedding, herd protection, reduction in antibiotic use, reduction in ETEC AMR or other bacteria, reduction in hospitalization, improved linear growth and other nutritional parameters, cost-effectiveness</td>
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<tr>
<td>Efficacy</td>
<td>Efficacy of 60% or more against moderate-to-severe ETEC diarrhoea.</td>
<td>Values proposed are based on observed lower performance of enteric vaccines in endemic paediatric settings. Based on protection against VPOs (vaccine preventable outcomes) defined as other strains that have same putative protective antigens. Moderate efficacy (approximately 50 %) is considered clinically meaningful and would be comparable to rotavirus vaccine in some lower-middle-income countries.</td>
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## ETEC at PDVAC: development of preferred product characteristics (PPCs)

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<th>Parameter</th>
<th>Preferred characteristic</th>
<th>Notes</th>
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<tr>
<td>Dose Regimen &amp; Schedule</td>
<td>At least 2 doses are expected to be needed for primary immunization, <strong>between the ages of 6 to 9 months</strong>. An <strong>additional booster dose may be required</strong> to maintain effective and long-lasting immunity through the first 5 years of age.</td>
<td>The schedule should provide protection prior to the peak of infection to prevent the majority of ETEC infection and disease, and thus prevent the initiation of the EED pathogenic process. Depending on the vaccine platform and formulation, <strong>two or three doses</strong>, might be needed for primary immunization, with the first dose ideally at 6 months concomitantly with other EPI vaccines, and final dose in the primary series to be given with measles containing vaccine (MCV) at 9 months. This vaccine is expected to be delivered through the routine immunization schedule, although it may be implemented on a sub-regional or sub-national level in areas of heterogenous endemicity. A booster dose, after the primary series may be needed in the second year of life and could be given with the second MCV at 15 months. In some situations, such as outbreak, the ETEC vaccine may be delivered through special immunization campaigns. It could be also delivered pre-emptively with oral cholera vaccine and or typhoid vaccine.</td>
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Objectives of this meeting

➢ To provide a status update on candidate and funding landscape for ETEC vaccines
➢ To evaluate the outcomes of the ETVAX efficacy study in adult travellers and plans for the paediatric indication
➢ To determine if ETEC should remain a “priority” pathogen for PDVAC and if yes, whether there are activities that WHO/PDVAC should engage in going forward?

Questions for PDVAC:

➢ Should ETEC vaccines remain a ‘priority’ for PDVAC and PDR/IVB?
➢ In addition to the existing cross-cutting activities that PDR/PDVAC undertakes in support of ETEC, are there other specific activities that PDVAC should try to resource, to advance ETEC vaccines?
➢ Does PDVAC endorse the PPC for ETEC vaccines?
Update on the ETEC Vaccine Landscape and Factors Impacting Further Development

2020 WHO Product Development for Vaccines Advisory Committee (PDVAC) Consultation

Dr. A. Louis Bourgeois, PhD, MPH
Science Officer, Enteric and Diarrheal Diseases
PATH's Center for Vaccine Innovation and Access
ETEC vaccine landscape: Factors impacting the development and status of lead candidates—Setting the scene

• Uncertainty and transition have been the earmarks of ETEC vaccine development over the last four years.

• Uncertainty regarding FVVA* for ETEC vaccines stems from questions regarding:
  • Morbidity burden: Does ETEC play a sufficient role in acute illness and the pathogenic pathway leading to EED, stunting, and malnutrition; is it an AMR threat?
  • Technical feasibility: Will candidates (oral or parenteral) be sufficiently immunogenic and protective in the target age-group (6–9 months)?
  • Do we have the right antigens to provide broad protection against important ETEC pathotypes?
  • Are development timelines adequate to ensure vaccines will be available while they are still needed?

• FVVA uncertainty led to reconsideration of funder investments, with at least one major donor de-prioritizing ETEC.

• Despite these issues, the vaccine portfolio remains robust with an impressive level of activity and progress since last reviewed at PDVAC in 2018.

• The ETEC vaccine community remains optimistic that global burden estimates will become more robust and include further etiological evaluation of acute and more long-term morbidity.

• Further positive trial results should also help strengthen the case for ETEC as a priority WHO vaccine target.

* FVVA = Full Value of Vaccine Assessment
**Current ETEC vaccine and funding landscape**

### Clinical candidates
- **Oral administration**
  - ETVAX inactivated (SBH, UG, PATH)
  - ShigETEC (EveliQure)

- **Parenteral injection**
  - FTA (PATH, NMRC)

### Preclinical candidates
- **Oral administration**
  - CVD GuaBA mutants expressing ETEC Ags.; CVD1208-122 (CVD, Emergent)
  - Ty21a expressing *Shigella* LPS and MEFA (Protein Potential)
  - STM expressing ETEC, Campy Ags. (IVI, UGA, NMRC, WASHU, WRAIR, Tulane, PATH) (New candidate)

- **Parenteral injection**
  - MEFA (ILLU, JHU)
  - LT/ST conjugate toxoids (Univ. of Bergen, Tulane)
  - Flagellin, EtpA, EatA, YghJ, EaeH (WASHU, Univ. of Bergen, GlyProVac)

### Current funding landscape stabilizing:
- Europe/UK—Horizon 2020, EDCTP, EVI, DfID, Wellcome Trust;
- USA—NIAID, NIH, DoD/VA, BMGF

= candidates in or poised to begin clinical trials; STM = inactivated mutant *Shigella* with truncated LPS giving conserved protein Ags. greater exposure; ST toxoid and novel conserved antigens are not seen as standalone vaccines
ETVAX/dmLT: Most advanced ETEC candidate in clinical development

The vaccine candidate exceeded immunologic expectations in 6- to 11-month-old infants; an age-group difficult to immunize by the oral route. This success highlights the value of increasing and controlling antigens/dose and adding dmLT.

Total: $10^{11}$ bacteria, (ca $2 \times 10^{10}$ bacteria/strain)
Combined *Shigella*-ETEC candidates poised for Phase 1*

**ShigETEC**

- **Shigella platform**: Removal of LPS O-antigen induces broad antibody responses to cross-protect against *Shigella* and ETEC

- **ETEC coverage**: Addition of LT-B/STm(h) fusion protein to *Shigella* vaccine to induce immunity against ETEC diarrhea

- ShigETEC moving into the clinic in 2020 with support by Horizon 2020 grant and Wellcome Innovator award

- **Scope**:
  - Ph 1 study in Europe, regulatory approval in May 2020; trial start in Q3 2020 pending easing of COVID restrictions
  - Ph 1 in Bangladesh after European study completion
  - Seroepidemiology study and formulation development
  - Partners: European Vaccine Initiative (EVI), University of Göteborg, iccdrB and PATH

**CVD 1208S-122**

- Attenuated *Shigella* strains express ETEC colonization factors

- *Shigella* vector protects against homologous challenge in Sereny model

- Induces functional antibodies: SBA, HAI, and LT toxin neutralizing

- Protects against both ETEC and *Shigella* in UVA’s antibiotic treated mouse model (Medeiros et al. 2020. *npj Vaccines*)

- Prototype cGMP manufactured; Ph1 poised to begin pending easing of COVID restrictions
ETEC adhesin vaccine components: Candidate status and parenteral delivery proof-of-concept

ETEC FTA program overview

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<tr>
<th>CF class</th>
<th>Molecule</th>
<th>Biochemical</th>
<th>Immunogenicity</th>
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<td>+</td>
<td>+</td>
<td>Ph 1</td>
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</table>

a CfaE+MLT given ID significantly impacts on incidence and severity of H1047-associated illness in CHIMs

CssBA+dmLT Phase 1 trial (intramuscular)

- Addition of dmLT had significant impact on serum (IgG and IgA) and mucosal anti-CssBA IgA responses (see panels A and B)
- Increasing doses of CssBA up to 45 µg + 0.5 µg of dmLT lead to 100% of subjects being positive for anti-CssBA IgA α4β7 positive PBMCs and fecal IgA
- The fold rise in anti-CssBA fecal IgA correlated with the peak number α4β7 positive PBMCs in peripheral blood (r=0.81 by Spearmen's; p = 0.0013)
Multi-epitope fusion technology* (MEFA) vaccine candidate against ETEC

- CFA MEFA expresses neutralizing epitopes of major CFAs on surface of a single protein
- Toxoid fusion MEFA expresses neutralizing ST and LT toxoids
- Safe and strongly immunogenic in mice, pigs, and rabbits; protective against disease in pigs and rabbits
- Can be co-administered with *Shigella* MEFA for combined protection against all species and serotypes of *Shigella* and all types of ETEC
- Currently in discussions with industrial partner(s); NIH supporting development of GMP materials
- Parenteral or oral vaccine on a vector such as Ty21a (commercial partner: Protein Potential)

Novel ETEC proteins have important burden implications and vaccine potential

Non-conserved ETEC proteins

- **EtpA** – accessory adhesin on flagella
- **EatA** – serine protease (*mucinase*); 80% homology with SepA of *S. flexneri*
- Both virulence factors contributing to pathogenesis/severity (see bar graph)
  - No CFA (50% express EtpA and/or EatA) – may help better define ETEC pathotypes
  - ST only strains (85% express EtpA and/or EatA)
  - LT only strains (50% express EtpA and/or EatA)
- Antibody against these proteins significantly reduce colonization in animal models and block toxin delivery *in vitro*.
- **YghJ** – metalloprotease (*mucinase*); specific glycosylation may distinguish pathogens from commensal (GlyProVac)
- Application of ETEC proteomic array technology strengthens the case for these proteins as vaccine antigens that complement anti-LT and anti-CFA immunity (H10407 and B7A CHIMs)

Data courtesy of M Kuhlmann, F Qadri and J Fleckenstein, WASHU/icddr,b

ETEC vaccine and funding landscapes: Summary of current status, promise, and challenges ahead (1)

- Recent field, laboratory, and CHIMs data indicate that conserved ETEC antigens, like EtpA, EatA, and YghJ, should get stronger consideration for inclusion in vaccines.
  - Can improve coverage for ETEC strains that lack CFAs, such as ST- or LT-only strains.
  - Expression of EtpA and EatA may help define a broader paradigm for ETEC pathotypes as efforts expand to explore ETEC’s contribution to EED, stunting, and malnutrition in LMICs.
  - Virulence of LT-only strains expressing major or minor CFAs and/or EtpE and EatA needs further assessment to determine role in ETEC morbidity.

- New animal model and CHIMs data to follow also indicate that ETEC strains can trigger elevation in intestinal inflammatory factors (i.e., MPO), which are risk factors for EED and stunting.

- New proteomic array data profiling mucosal antibody responses to conserved proteins as well as class 5 fimbriae are encouraging since they suggest vaccine coverage could be broader than expected.
ETEC vaccine and funding landscapes: Summary of current status, promise, and challenges ahead (2)

- Despite uncertainty of ETEC burden and concerns about complexity and timelines for vaccine development, the pipeline has remained robust with promising oral and parenteral candidates in clinical development.

- European funders have helped to maintain and stabilize funding for ETEC vaccine development.

- Four ETEC candidates are in Phase 1/2B studies or poised to begin Phase 1; progress impacted by COVID-19 pandemic.

- Encouraging results for lead oral (ETVAX) and parenteral (FTA) candidates indicate both are effective at inducing strong mucosal immune responses to key antigens and dmLT can improve these responses.

- With continued success, ETVAX licensure and WHO prequalification may be possible in about five years.

- All lead candidates are compatible with combination vaccine strategies that may improve FVVA.

- Resolving ETEC’s status as a WHO vaccine target and maintaining funding is critical to ensure continued progress of the most promising candidates.
Backup Slides
Application of ETEC proteomic arrays to characterize ALS-IgA mucosal antibody responses to novel ETEC antigens as well as CFA/I and related class 5 fimbriae post-challenge with ETEC strain H10407 (LT⁺ ST⁺ CFA/I⁺)

- ALS-IgA responses were induced to novel ETEC proteins: YghJ, EtpA, and EatA in most subjects; fecal extracts showed a similar pattern.
- Intestinal infection with H10407 induced a broader than expected ALS-IgA response to CFA/I and LTB, as well as other related class 5 fimbriae: CS14, CS1, CS2, CS17, CS19 and PCF 071; analysis of fecal extracts showed a similar pattern.
Using controlled human infections and preclinical models to improve understanding of ETEC morbidity

Chad Porter, PhD, MPH
Enteric Diseases Department
Naval Medical Research Center
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ETEC CHIM

• Results of first CHIM published in 1971
• Since then:
  – Over 1500 participants
  – Approximately 15 different strains
    • Various colonization factors (CFs)
    • Various toxin profiles (LT only, ST only, LT+ST)
• Applications to date
  – Efficacy
    • Vaccines
    • Immunoprophylactics
    • Chemoprophylaxis
  – Antigen discovery
• Newly evolving applications
  – Novel (‘conserved’) antigen discovery
  – Subclinical endpoints
Similarities to natural infection

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# loose stools

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<td>P</td>
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Duration (days)

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<td>P</td>
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= Challenge model point estimate and 95% CI

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Updated from: Vaccine 29 (35): 5869-5885
Survival Distribution Function

0.00
0.25
0.50
0.75
1.00

Time (hrs) to first loose stool

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<th>Onset</th>
<th>Strains*</th>
<th>Median time (hrs)</th>
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<td>Rapid</td>
<td>B7A, LSN03-016011/A</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>WS0115A</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>E24377A, TW10598</td>
<td>24.9</td>
</tr>
<tr>
<td>Delayed</td>
<td>H10407</td>
<td>47.0</td>
</tr>
</tbody>
</table>

*Excludes strain DS26-1 (only 2 subjects with loose stools)

Vaccine 37(34): 4814-4822.
Time to resolution

Survival Distribution Function

Time (hrs) from treatment to last unformed stool

Time (hrs) to antibiotic treatment

All other strains

H10407

14 hours

100
125
150
175
0
25
50
75
100
125
150
175
0.00
0.25
0.50
0.75
1.00
0.00
0.25
0.50
0.75
1.00
LT ETEC and disease

<table>
<thead>
<tr>
<th>Dose (cfu)</th>
<th>N</th>
<th>% with diarrhea</th>
<th>Median (IQR) time to diarrhea (hr)</th>
<th>Diarrhea output in g; median (IQR)</th>
<th>Other gastrointestinal signs/symptoms, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total (Max. 24 h)</td>
<td>Ab. cramps</td>
</tr>
<tr>
<td>7×10^8</td>
<td>5</td>
<td>60</td>
<td>14 (7, 25)</td>
<td>787 (384, 1139)</td>
<td>556 (326, 845)</td>
</tr>
<tr>
<td>6×10^9</td>
<td>8</td>
<td>88</td>
<td>14 (12, 15)</td>
<td>1001 (517, 1429)</td>
<td>508 (429, 717)</td>
</tr>
</tbody>
</table>

Disease Severity Score

- **p=0.002**
- **p=0.05**

ETEC and fecal inflammatory markers


NCT02773446 (M. Maciel, unpublished)
What about the microbiome

Cognitive function
(psychomotor vigilance testing)

• Background
  – Cognitive function test
  – Historically used to study sleep deprivation
• Generally interpreted as a measure of attention state
• Methods
  – Response time to external stimulus
  – Cues occur on 2-10 second intervals
  – Test lasts 10 minutes
  – Subjects complete 3x daily with vital signs
• Benefit
  – Random testing cues (suitable for repeated testing over time)
  – Easy to perform
  – Rough measure of one’s ability to perform daily tasks

NCT03040687 (TJ Doty, unpublished)
## Blood group – CHIM

<table>
<thead>
<tr>
<th>Blood group</th>
<th>Diarrhea severity</th>
<th>O or B</th>
<th>A or AB</th>
<th>total subjects (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H10407</strong></td>
<td>none-mild</td>
<td>35 (44%)</td>
<td>5 (19%)</td>
<td>40 (38%)</td>
</tr>
<tr>
<td>(p=0.017)</td>
<td>moderate-severe</td>
<td>44 (56%)</td>
<td>22 (81%)</td>
<td>66 (62%)</td>
</tr>
<tr>
<td></td>
<td>total subjects</td>
<td>79</td>
<td>27</td>
<td>106</td>
</tr>
<tr>
<td><strong>B7A</strong></td>
<td>none-mild</td>
<td>8 (30%)</td>
<td>10 (48%)</td>
<td>18 (38%)</td>
</tr>
<tr>
<td>(p=0.2)</td>
<td>moderate-severe</td>
<td>19 (70%)</td>
<td>11 (52%)</td>
<td>30 (62%)</td>
</tr>
<tr>
<td></td>
<td>total subjects</td>
<td>27</td>
<td>21</td>
<td>48</td>
</tr>
</tbody>
</table>

- H10407 secretes EtpA
- EtpA interacts with glycans on intestinal epithelial cells from blood group A accelerating adhesion and toxin delivery

A. nancymae model

- NAMRU-6 in Lima, Peru
  - AAALAC accredited facility
  - Four primate rooms with total holding capacity of 140 animals
- Aotus nancymae (owl monkey)
  - 1 kg, typical adult weight
  - Supplied by IVITA (Iquitos, Peru), a captive-breeding facility operated by the Universidad Nacional Mayor de San Marcos
- Data collection menu
  - Age, Sex
  - Weights, temperatures, blood chemistry, hematology throughout study
  - Stool for consistency, colonization, etc
  - Small bowel endoscopy
- Model used to demonstrate efficacy of adhesin-based vaccines targeting Class 5a (CFA/I), 5b (CS17), 5c (CS2) fimbriae as well as CS6

<table>
<thead>
<tr>
<th>Challenge strain</th>
<th>CF</th>
<th>Diarrhea rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H10407 (LTSThSTp)</td>
<td>CFA/I</td>
<td>90*</td>
</tr>
<tr>
<td>WS3294A (STh)</td>
<td>CS14</td>
<td>75</td>
</tr>
<tr>
<td>LSN03/016011A (LT)</td>
<td>CS17</td>
<td>75*</td>
</tr>
<tr>
<td>WS0115A (LTSTp)</td>
<td>CS19</td>
<td>87*</td>
</tr>
<tr>
<td>DS26-1 (LT)</td>
<td>CS19</td>
<td>80</td>
</tr>
<tr>
<td>B2C (LTSTh)</td>
<td>CS2+CS3</td>
<td>77*</td>
</tr>
<tr>
<td>B7A (LTSThSTp)</td>
<td>CS6</td>
<td>75*</td>
</tr>
<tr>
<td>E. coli HS</td>
<td>none</td>
<td>12*</td>
</tr>
</tbody>
</table>

* Data represent cumulative values from >1 cohort
Murine model

- Fecal myeloperoxidase (MPO) levels increase with ETEC infection
- Higher levels of MPO in stool of mice receiving zinc-deficient diet
- Reduced in MPO levels in an LT knock-out ETEC mutant

- ETEC strain H10407 (LT⁺ ST⁺ CFA/I⁺) wild type (ETEC WT) or LT-toxin knockout (LTKO)
- Diets: HC = house chow; dZD – zinc deficient chow; all mice were pre-treated with antibiotics for days prior to H10407 challenge

Conclusions / Points for discussion

• The ETEC CHIM is well-established method to evaluate human-pathogen interaction
  – Acute disease with specific phenotypes
  – Host susceptibility: blood group antigens, other?
  – Inflammatory markers: fecal, serologic?
  – ‘Other’ effects: cognitive, microbiome, others
  – Efficacy of treatment or preventive interventions

• Non-human primate models
  – Established for multiple strains
  – Acute diarrheal illness
  – Opportunity for colonscopy, pathology, etc
  – Can protect with active vaccination and passive prophylaxis

• Murine model
  – Measurable affects on diarrhea, weight and inflammatory markers (role of diet; role of toxin)
  – Can protect with active vaccination
We are developing the first vaccine for protection against diarrhea caused by ETEC in both travelers and endemic populations.
Diarrheal disease is the second biggest killer of children below age of five in LMIC

- Diarrheal disease has the highest incidence among children under five years of age
- 1.7 billion annual diarrheal episodes leading to approximately 712,000 deaths in children below five years of age
- Strong link between diarrheal disease and poor physical and cognitive development among infants in LMIC
- ETEC is a major cause of diarrheal disease and accounts for approximately 400,000 deaths in children <5 / year

6. WHO's 5th Product Development for Vaccines Advisory committee, PDVAC, Executive Summary
7. Future directions for research on enterotoxigenic Escherichia coli vaccines for developing countries, 2006
ETEC - the major cause of travelers diarrhea (TD)

- 642 million arrivals to emerging economies (UNWTO 2018)<sup>9</sup>
- > 80 million travelers from developed countries visit tropical/subtropical destinations annually and the most common illness affecting them is TD<sup>10-12</sup>
- At least 35 million travelers per year are affected by TD<sup>13-15</sup>
- ETEC is the major cause of TD<sup>13,16</sup>
- In up to 3-17% of travelers, TD causes further health complications, including irritable bowel syndrome<sup>15, 17-19</sup>

Incidence of Enterotoxigenic Escherichia coli (ETEC)

- High risk 20-90%
- Intermediate risk 8-20%

---

13. CDCP. The Pretravel Consultation: Self-Treatable Conditions.
Vaccine composition

A multivalent vaccine containing four of the most common colonization factors plus an LT toxoid and a dmLT adjuvant.

Giving the vaccine together with an adjuvant enhanced the magnitude, breadth and kinetics of the intestinal immune responses in infants.

ETVAX® being an inactivated vaccine potentially lends itself for co-administration with other vaccines. Potential targets already identified.
ETVAX® travelers formulation
An oral 2 dose vaccine

A full immunization requires 2 doses orally taken at least 1 week apart, with the last dose taken at least 1 week before travel.
ETVAX® pediatric indication
An oral 3 dose vaccine

Evaluate three vs two doses of the ETVAX® vaccine in phase III trials

Phase IIB in the Gambia
Present endemic pediatric formulation
~11 ml
2.5 µg dmLT

Whole cell bulk + LCTBA

Phase III in Zambia and commercial presentation
Endemic pediatric formulation all-in-one
~10 ml

The contents of the mixed powder, monovalent bulks and PBS constitutes a complete dose, no further additions are required
ETVAX® - The leading ETEC vaccine candidate in the world

Offers two lines of defense

- Prevents colonization of ETEC bacteria in the intestine
- Induces antibodies that neutralize the heat-labile toxin (LT) produced by the bacteria
ETVAX® - Great vaccine coverage

ETVAX® is estimated to have the potential to protect against at least 80% of all clinical ETEC strains

85 % vaccine coverage shown in clinical field trial in Benin (data on file)

Potential cross-protection against other CF’s as suggested from serological cross-reactivity in adults (S Leach et al 2017) and in children (Qadri & Svennerholm unpublished)

Isidean et al 2011, Vaccine 29: 6167-6178
ETVAX® containing dmLT significantly enhance the immune response and the LT toxin neutralization.

<table>
<thead>
<tr>
<th></th>
<th>IgG</th>
<th>IgA</th>
<th>Toxin neutralization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resp. freq:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fold rises (GM + SEM)</td>
<td>93%*</td>
<td>70%</td>
<td>97%</td>
</tr>
<tr>
<td>(C) Vacc. (LCTBA) + 10 µg dmLT</td>
<td>Ref. vacc. (CTB)</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>(C) Vacc. (LCTBA) + 10 µg dmLT</td>
<td>Ref. vacc. (CTB)</td>
<td>80%</td>
<td>55%</td>
</tr>
</tbody>
</table>

* Significant difference
** Highly significant difference

Lundgren et al. Vaccine 2014
Results from published clinical studies show strong immunogenicity and excellent safety

**PHASE I - SWEDEN**
- 60 participants
- Conceptual composition, prototype vaccine

**PHASE I - US**
- 36 participants
- Excellent safety
- The trial under an US IND

**PHASE I - SWEDEN**
- 140 participants
- Placebo controlled study on final composition
- All primary endpoints were met and exceeded, excellent safety and impressive frequency of

**PHASE I - SWEDEN**
- 60 participants
- Phase I booster and memory study in Swedish volunteers.
- Strong boostable immunological memory for at least two years

**PHASE I/II - BANGLADESH**
- 495 participants
- Age descending safety and immunogenicity trial in adults, toddlers and infants in an endemic region down to 6 months of age
- Strong immune response exceeding expectations
- dmLT driven significant early onset of immunity in youngest age group
Development plan of ETVAX® Travelers and Pediatrics

2020
2021
2022
2023
2024
2025

Development Plan Travelers

Submission FDA Q2 2025

Clinical Consistency Q3 2023- Q3 2024

Phll (Bridging) OEV-125
Q2 2021-Q4 2021

OEV-127 (Ped)
Q2 2023- Q1 2024

Phll Travelers
OEV-126
Q1 2022- Q3 2023

Submission EMA Q2 2024

Phll Pediatric Efficacy
OEV-129 (Zambia)
Q1 2022- Q1 2025

Phlb 6- 23 months age
OEV-128 (The Gambia)
Q3 2020-Q4 2022

Development Plan Pediatric, endemic regions

Phll Travelers
OEV-123 (Benin)

Phll Pediatric
Bangladesh
OEV-122

Phi Age descending
OEV-124
(Zambia) Q3 2019- Q4 2020

Submission WHO PQ

Complete d studies

DMID 09-0066

OEV-121A

OEV-120

OEV-121

OEV-125

OEV-126

OEV-127

OEV-128

OEV-129

OEV-130
# OEV-122 Study Design

**PART A:** 18-45 years, inclusive
- **Cohort ETVAX dmLT N**
  - Full dose: 15
  - 10 µg: 15
  - Placebo: 15
  - Total: 45

**PART B:** 24-59 months, inclusive
- **Cohort ETVAX dmLT (N)**
  - ½ dose: 15
  - Placebo: 10
  - ½ dose: 15
  - Placebo: 10
  - Full dose: 15
  - Placebo: 10
  - Highest safe dose: 2.5 µg: 15
  - Placebo: 10
  - Highest safe dose: 5 µg: 15
  - Placebo: 10
  - Highest safe dose: 10 µg: 15
  - Placebo: 10
  - Total: 150

**PART C:** 13-23 months, inclusive
- **Cohort ETVAX dmLT (N)**
  - ½ dose: 15
  - Placebo: 10
  - ½ dose: 15
  - Placebo: 10
  - Full dose: 15
  - Placebo: 10
  - Highest safe dose: 2.5 µg: 15
  - Placebo: 10
  - Highest safe dose: 5 µg: 15
  - Placebo: 10
  - Highest safe dose: 10 µg: 15
  - Placebo: 10
  - Total: 100

**PART D:** 6-12 months, inclusive
- **Cohort ETVAX dmLT (N)**
  - 1/8 dose: 30
  - Placebo: 10
  - ¼ dose: 30
  - Placebo: 10
  - ½ dose: 30
  - Placebo: 10
  - Highest safe dose: 2.5 µg: 30
  - Placebo: 10
  - Highest safe dose: 5 µg: 30
  - Placebo: 10
  - Total: 200

Highest safe dose: ½ dose 10 µg dmLT

X = AE:s at this dose

- Vaccination Schedule: Day 0, 14 ± 2

Qadri et al. Lancet Infect Dis 2020
Frequencies of mucosal IgA antibody responses against the 5 primary vaccine antigens in different age groups in Bangladesh

Determined in ALS specimens; for 6-11 months old children in ALS and/or feces

Qadri et al. Lancet Infect Dis 2020
Frequencies of fecal IgA antibody responses

Fecal IgA responses (≥2-fold) among infants 6 to 11 months old to ETVAX antigens given placebo or ¼ adult dose with and without dmLT on day 7 and day 28

Qadri et al Lancet Infect Dis 2020
Development plan of ETVAX® Travelers and Pediatrics

**Development Plan Travelers**
- **OEV-120**
  - **PhI/II**
  - Pediatric, Bangladesh
- **OEV-121**
  - **PhII (Bridging)**
  - OEV-123 (Benin)
- **OEV-122**
  - **PhII**
  - Pediatric, Bangladesh
- **OEV-125 (Benin)**
  - **PhII**
  - Travelers
- **OEV-126**
  - **PhII**
  - Travelers
  - OEV-123 (Benin)
  - **PhIIb**
  - 6-23 months age
- **OEV-128 (The Gambia)**
  - **PhI Age descending**
  - OEV-124 (Zambia)
  - Q3 2019- Q4 2020
- **OEV-127 (Zambia)**
  - **PhII**
  - Travelers
  - OEV-126
  - Q1 2022- Q3 2023
- **Clinical Consistency**
  - Q3 2023- Q3 2024
- **Submission FDA**
  - Q2 2022
- **Submission EMA**
  - Q2 2024
- **Submission WHO PQ**
  - Q1 2025

**Development Plan Pediatric, endemic regions**
- **OEV-121A**
  - **PhIII Pediatric Efficacy**
  - OEV-129 (Zambia)
  - Q1 2022- Q1 2025
- **Submission EMA**
  - Q2 2024
- **Submission WHO PQ**
  - Q1 2025

Complete studies

- **2020**
- **2021**
- **2022**
- **2023**
- **2024**
- **2025**
Study design Phase IIB

- 743 Finnish travelers spent a fortnight in Benin
- 2 dose Placebo-controlled trial
  - 50% Vaccinated
  - 50% Placebo
- Study period 14 days + 6 days after returning home
The safety of the vaccine was excellent.

Overall vaccine immunogenicity was good, strong IgA and IgG serum antibody responses to LTB (the B-subunit of ETEC heat-labile enterotoxin).

The overall median magnitude of the IgA response was 33-fold; however, the overall vaccine take rate (defined as ≥4-fold IgA response to LTB) was lower than expected based on prior studies, 76% versus the 90% seen previously among Swedish adults [1].

The reduced response rate was restricted to cohorts vaccinated during a certain period (P=0.0015) suggesting that the dosing procedure used for mixing dmLT and vaccine in that period was inconsistent and merits further investigation and standardization.
Promising findings Benin
ETEC is very common and causes severe disease

- A secondary objective of the study was evaluation of protective efficacy (PE) against vaccine-preventable outcome (VPO). Our goal of 70% PE was not met.

- The attack rate of diarrhea was higher than expected based on experience from previous TD studies,
  - Overall, 61% of the volunteers experienced diarrhea (according to the classical TD definition),
  - moderate-to-severe diarrhea (≥4 loose stools/24 hours and at least one additional symptom) was found in 56% of all volunteers, of whom approximately 60% provided at least one ETEC-positive fecal sample.

- The contribution of ETEC to the diarrheal pathogen burden was even more evident when more severe cases (≥16 loose stools/24 hours) were considered; 75% of the pathogens associated with these episodes were ETEC, highlighting its importance as a cause of severe TD.

- The toxin profiles of all ETEC isolates from diarrheal stools were: LT only 34%, LT/ST 32%, and ST only 34%.
Promising findings
Benin
Secondary objective - efficacy

- Our goal of 70% PE was not met.
- Despite the higher than expected TD attack rate and severity of ETEC-associated disease, ETVAX® provided significant protection.
- Mixed infection with ETEC of another toxin and/or CF phenotype proved surprisingly common 18% of VPO ETEC cases

| Responders (≥4-fold seroconversion to LTB) | PE=52% (p=0.006; 95% CI=18-72%), PE=56% (p=0.025, CI= 9-83%), | PE=41%, p=0.02; 95% CI=7-63%), PE=43% (p=0.05) |
| All | Diarrhea of any cause (including viral pathogens) affecting daily activities among vaccine responders with ≥16 loose stools in 24 hours |

- Representing 25% of all TD
- Representing 22% of all TD
Promising findings Benin
Reduced antibiotic use

Antibiotic or antisecretory drug treatment was given to significantly fewer vaccine responders than to placebo recipients (p=0.03), indicating that ETVAX® reduced the severity of enteric illness.
Support for the pediatric indication of ETVAX®

• ETEC remains a significant contributor to diarrheal disease burden in children of low- and middle-income countries (LMICs),

• Presently, we are conducting an immunogenicity trial in Zambian children evaluating 1/4 or 1/8 dose in a three-dose schedule.

• A phase 2b efficacy trial in Gambian children is scheduled to start in September 2020. Preliminary data from the Zambian trial (OEV-124) show promising immunogenicity data for toxoid and colonization factor antigens in the vaccine.

• A pivotal Phase 3 efficacy trial in Zambian children with an all-in-one formulation.

• The good immunogenicity observed in Zambia and in the Bangladesh study (OEV-122) using fractional doses of the vaccine suggests a very favourable cost of goods estimate for ultimately making ETVAX® available for use in LMICs settings following licensure and prequalification by the World Health Organization.
Manufacturing

- EU Biologics Co., Ltd is a biopharmaceutical company situated in Chuncheon, Republic of Korea.

- EU Biologics has developed an oral cholera vaccine in two different presentations; Euvichol® and Euvichol-Plus®, that are prequalified by WHO.

- EU Biologics is increasing its production capacity by building a new vaccine manufacturing facility in Chuncheon. The facility has multipurpose capacity with 1000L production fermenters and down-stream capabilities. The manufacturer has set aside a production capacity of 8 million doses for ETVAX®, which can be increased by installation of more equipment.

- Currently production of tech-batches for all components including dmLT followed by GMP production of ETVAX® monovalent bulks is ongoing at EuBiologics.
Advanced in Regulatory

• Scientific advice from EMA and Swedish Medical product agency

• Pre-Q advise meeting with WHO

• Phase I/II study in Bangladesh conducted under an IND with US FDA

• ETVAX® is scaled up to commercial scale

• Stabile & Validated process

• 48 months stability of bulk and 60 months stability of vaccine
Scandinavian Biopharma is developing, together with researchers at the University of Gothenburg and the international non-profit organization PATH.

The programs are mainly funded by the European Union’s (EU) Research and Innovation Framework Program, Horizon 2020 through the EDCTP (European and developing countries clinical trial partnership) organization, DFID (Department for international development), and SME Instruments supporting innovative SMEs in the health care biotechnology sector.

We have a CRADA with USAMMDA (U.S. Army Medical Materiel Development Activity).

<table>
<thead>
<tr>
<th>Study number</th>
<th>Indication</th>
<th>Completed/Ongoing/Planned</th>
<th>Phase</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEV-124</td>
<td>Pediatric</td>
<td>Ongoing Q3 2019- Q4 2020</td>
<td>Phase I, Age descending</td>
<td>EDCTP</td>
</tr>
<tr>
<td>OEV-125</td>
<td>Pediatric/Travelers</td>
<td>Planned Q2 2021- Q4 2021</td>
<td>Phase II, Bridging</td>
<td>EDCTP</td>
</tr>
<tr>
<td>OEV-128</td>
<td>Pediatric</td>
<td>Planned Q3 2020-Q4 2022</td>
<td>Phase IIb</td>
<td>EDCTP</td>
</tr>
<tr>
<td>OEV-129</td>
<td>Pediatric</td>
<td>Planned Q1 2022- Q1 2025</td>
<td>Pivotal Phase III, Placebo-controlled</td>
<td>EDCTP</td>
</tr>
</tbody>
</table>
We are a research-based specialty biopharma company developing the first ETEC vaccine in the world

ETVAX® has a great potential
- Diarrhea is the second biggest killer of children under five years of age
- More than 35 million travellers are affected by TD every year.

Project supported by European Research and Innovation Program - Horizon 2020 (2.9, 7.4 & 10.6 MEuro) & PATH. CRADA with the USArmy.

ETVAX® is the only ETEC vaccine candidate in late-stage development. The strong immunogenicity and safety data, great coverage as well as the protective efficacy seen in Benin clearly distinguish ETVAX® from other vaccine candidates that are under development against ETEC-induced diarrhea.