

2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)
Virtual Consultation 4: Update on development of Enterotoxigenic *E.coli* (ETEC) vaccines
18 June 2020
CHAIR: David Kaslow

Concept note

Enterotoxigenic *Escherichia coli* (ETEC) is one of the leading bacterial causes of diarrhoea, especially among children in low resource settings, as well as travelers and military personnel from high-income countries. It is estimated that ETEC causes about 220 million diarrhoea episodes globally, with about 75 million episodes in children under 5 years of age, and between 18,700 (IHME estimates) and 42,000 deaths (MCEE estimates) in children younger than 5 years. Although mortality rates for ETEC and other diarrhoeal pathogens are declining due to improvements in economic development and availability of safe water and sanitation, these reductions have not been paralleled by significant declines in diarrhoea-associated morbidity, which continue to impact negatively on infant and child health and prosperity in many low- and middle-income countries (LMICs).

Current ETEC vaccine development efforts are focused on inducing antitoxin and anti-colonization immunity. There are both oral and parenteral candidates in clinical studies. The leading whole cell based vaccine candidate, ETVAX, is an oral quadrivalent inactivated vaccine, consisting of four *E. coli* strains overexpressing the most prevalent colonization factors (CFA/I, CS3, CS5, and CS6) and a hybrid LTB-CTB toxoid (LCTBA) administered with a double-mutant heat-labile enterotoxin (dmLT) as an adjuvant. This quadrivalent candidate has progressed to descending-age studies in Bangladeshi infants, 6-11 months of age, with fractional doses of both vaccine (1/2, 1/4th or 1/8th of the adult dose) and dmLT adjuvant (2.5 ug, 5 ug or 10 ug). A Phase I age descending trial in Zambia in healthy adults and children is underway and a Phase IIb field pediatric efficacy trial is planned in The Gambia. In addition, ETVAX has just completed a Phase IIb efficacy study in Finish travellers, demonstrating safety, immunogenicity and significant protective efficacy of 56% against all severe diarrhea, independent of pathogen.

ETEC was identified as a priority pathogen by PDVAC in 2016. To date, efforts have focused on evaluating the data and methodology to derive the global mortality estimates for ETEC, and attention will now focus on the approach to determine robust morbidity estimates. In addition, preferred product characteristics (PPCs) for ETEC vaccines have been drafted by an expert working group and are near finalization. This session seeks to review the status of candidates in development, the tools, assays and models that are available to facilitate that development and the data from the recent ETVAX studies, including the Phase IIb efficacy study in travelers. Of particular interest are the intended 'next steps' for the pediatric indication, and whether, or what, facilitation from PDVAC/IVB is needed.

Objectives of the 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?

2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)
Virtual Consultation 4: Update on development of Enterotoxigenic *E.coli* (ETEC) vaccines
18 June 2020
CHAIR: David Kaslow

Background reading:

- DRAFT WHO Preferred Product Characteristics for Vaccines against Enterotoxigenic *E.coli*
- Barry E, Cassels F, Riddle M, Walker R, Wierzba T. 2019. Vaccines against Shigella and enterotoxigenic *Escherichia coli*: A summary of the 2018 VASE conference. *Vaccine*. 37:4768-4774
- Qadri F, Akhtar M, Bhuiyan TR, Chowdhury MI, Ahmed T, Rafique TA, et al. 2020. Safety and immunogenicity of the oral, inactivated, enterotoxigenic *Escherichia coli* vaccine ETVAX in Bangladeshi children and infants; A double-blind, randomized, placebo-controlled phase 1/2 trial. *Lancet Infect. Dis.* (Internet), Feb 20:20(2):208-219; doi.org/10.1016/S1473-3099 (19) 30571-7

2020 WHO Product Development for Vaccines Advisory Committee (PDVAC)
Virtual Consultation 4: Update on development of Enterotoxigenic *E.coli* (ETEC) vaccines
18 June 2020
CHAIR: David Kaslow

06:00 Seattle; 8:00 Lima; 9:00 Washington DC; 14:00 London; 15:00 Johannesburg; 15:00 Geneva; 18:30 New Delhi, 21:00 Beijing; 22:00 Seoul

Time (Geneva CEST)	Topic	Duration	Detail	Moderators, speakers
15.00 – 15.10	Welcome and roll call			David Kaslow / Birgitte Giersing
15.10 – 15.25	PDVAC/IVB engagement in ETEC vaccine	(10 + 5)	<ul style="list-style-type: none"> 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 	Birgitte Giersing (WHO)
15.25 – 15.40	Setting the scene: the current ETEC vaccine portfolio (10 + 5)	(10 + 5)	<ul style="list-style-type: none"> Overview of the current ETEC vaccine candidate portfolio and funding environment Challenges and opportunities 	Lou Bourgeois (PATH)
15.40 – 16.00	Using controlled human infections and preclinical models to improve understanding of ETEC morbidity	(15 + 5)	<ul style="list-style-type: none"> Overview of the status of controlled human infection models and preclinical models as tools to evaluate potential biomarkers for inflammation and morbidity 	Chad Porter (NMRC)
16.00- 16.30	Product development overview of ETVAX	30min	<ul style="list-style-type: none"> Outcomes from Phase IIb Benin travellers study, current status of Phase II paediatric studies, currently envisaged formulation and presentation, manufacturing and licensure strategy 	Bjorn Sjostrand & Nils Carlin (Scandinavian Biopharma)
16.30 – 17.00	Discussion	30min	Open session	All
17.00 - 17.30	Discussion (closed session) – PDVAC only <ul style="list-style-type: none"> 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? 			