Title: Defining cases of severe pediatric diarrhea for an efficacy trial of an enterotoxigenic *Escherichia coli* (ETEC) vaccine: Report on an international workshop, Washington DC, March 2016

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Abstract

Enterotoxigenic *Escherichia coli* (ETEC) causes severe acute watery diarrhea. No ETEC vaccine is available but candidates are in development, including ETVAX, an oral, whole-cell inactivated vaccine. ETVAX is being tested in a descending-age trial in Bangladesh. If found safe and immunogenic, investigators may test it for efficacy in children. Like oral rotavirus vaccines, we expect that ETVAX will be most effective at decreasing the incidence of moderate-to-severe ETEC episodes. Thus, for an efficacy trial outcome, it will be necessary to triage patients into moderate-to-severe versus mild disease. A severity scale specific to ETEC does not exist. To develop this scale, PATH convened a committee of international experts for a two-day meeting to strategize on diagnostic scale development. The workshop began with four presentations. The first described existing scales, item selection, and issues related to validation, reliability, and ease of use. The other three presentations provided details on the following published scores: the DHAKA score, validated for use with Bangladeshi children seeking diarrhea treatment; a modified-Vesikari score for evaluating North American outpatient children with diarrhea; and the Community Diarrhea Assessment (CODA) score developed for passive-case surveillance of Peruvian children with diarrhea. Following the presentations and discussion, the committee made several recommendations including: modifying existing scores to make them ETEC-centric; evaluating scoring systems against an objective measure of dehydration (i.e., the percent change in a child's bodyweight following rehydration); and adding an item to the scale measuring ETEC effects on growth faltering. The committee also discussed using available data sets to evaluate scores, but was concerned that if investigators characterized patients using different procedures than prescribed by the score, the results would be difficult to interpret. Committee members suggested new data collection and recommended conducting studies in Sub-Saharan Africa. The study results would be presented for peer-review and to regulatory authorities.

Background

Enterotoxigenic *Escherichia coli* (ETEC) are rod-shaped, gram-negative bacteria that induce acute, sometimes profuse, life-threatening watery diarrhea, especially among children living in low-resource areas. ETEC cause disease by using fimbrial adhesins to adhere to enterocytes along the proximal small intestine and by releasing heat-stable (ST) and/or heat-labile enterotoxin (LT). As these enteropathogens transmit via the fecal-oral route, ETEC burden is highest in areas with poor hygiene practices and with limited access to sanitation and potable water.

Recent studies in sub-Saharan Africa and South Asia showed that ETEC is one of four leading agents of moderate-to-severe diarrhea among children less than five years of age seeking diarrhea treatment at health centers [1]. The World Health Organization's (WHO's) Child Health Epidemiology Reference Group estimated 42,000 (95% CI: 20,000–76,000) global ETEC-associated deaths of children under five years of age in 2013 [2]. In older age groups, a meta-analysis of hospitalization and stool culture data projected that ETEC contributes an additional 89,000 deaths annually among persons older than five years of age in Africa and South Asia [3]. Besides death, moderate-to-severe diarrhea, as that caused by ETEC, is associated with linear growth faltering[1]. The disease is also frequent among travelers from non-endemic regions visiting ETEC-endemic countries [4, 5].

Universal global access to clean water and sanitation as well as improvements in personal hygiene would dramatically reduce ETEC global burden. The use of a highly effective and low-cost vaccine would also greatly benefit at-risk populations by bringing rapid protection to large, impoverished, and often inaccessible populations. No such vaccine is currently available. However, there are many candidates in preclinical and clinical development that offer hope for a licensed and WHO-prequalified vaccine [6].

One lead vaccine candidate is ETVAX, which is under development by Scandinavian Biopharma (SBH) and partners, including the international nonprofit organization PATH. ETVAX is a multivalent, oral, whole-cell, inactivated vaccine given with recombinant protein LCTBA, a hybrid between the binding subunits of *E. coli* heat labile toxin (LTB) and cholera toxin (CTB), and with double-mutant heat-labile enterotoxin adjuvant (dmLT). Investigators tested ETVAX in healthy Swedish adults and found it safe and immunogenic [7]. For the pediatric indication, investigators are currently evaluating the vaccine candidate in a placebo-controlled, dose-escalating, age-descending trial in Bangladesh. If they identify a safe and immunogenic dose, they will then evaluate ETVAX in a field efficacy trial among children less than six months old in one or more ETEC-endemic countries.

It is expected that an oral ETEC vaccine will be most effective against preventing moderate-to-severe ETEC episodes. An earlier study with the first-generation of ETVAX showed no protection against ETEC diarrhea of any severity, and the study had an insufficient number of diarrhea episodes to explore protection against moderate-to-severe disease only [8]. In a parallel efficacy study in travelers to Guatemala and Mexico, the first generation vaccine did provide protection against moderate-to-severe forms of ETEC diarrhea[9]. Oral rotavirus vaccines have also demonstrated increased efficacy against moderate-to-severe rotavirus diarrhea compared to rotavirus diarrhea of any severity[10].

For rotavirus vaccine trials, investigators developed several clinical scoring systems to classify mild, moderate, and severe rotavirus-associated diarrhea. The most widely used scale is the Vesikari Score [10], which is a measure of clinical severity, but not degree of dehydration. It is not used for patient care. With this score, study personnel evaluate each patient based on the presence and severity of seven items: diarrhea duration, maximum stools in 24 hours, days vomiting, times vomited in 24 hours, fever, percent dehydration, and prior treatment. Patients are scored on a scale of 1 to 20, with a score

greater than 11 classified as moderate-to-severe rotavirus. No one has validated this score for use with ETEC diarrhea, which may differ from rotavirus diarrhea by clinical presentation (e.g., frequency of vomiting, mucoid stools, fever), age-specific incidence, and prevalence among at-risk populations.

In preparation for the expected Phase 3 trial of ETVAX, PATH is initiating the development of a severity scale relevant to ETEC diarrhea. First, we established a Steering Committee comprised of health scale developers and diarrheal disease experts to provide guidance to developing or revising a scoring system. We then sponsored a two-day international workshop (1 and 2 March 2016), with support from the Bill & Melinda Gates Foundation, to make recommendations for identification of a valid, reliable, and easy-to-use scoring system appropriate for an ETEC vaccine efficacy trial in an ETEC-endemic country. We divided the workshop into two sessions. The first day was an open session for Steering Committee members and invited guests. It included a presentation on the theory of scale development and three presentations on existing scores for pediatric patients. We followed this open session with a closed session where the Steering Committee members reviewed presentations, discussed scales and scores, and made specific recommendations. (See Table 1 for a list of presenters and the names and affiliations of the Steering Committee members.)

Summary of Open Session

Dr. Thomas Wierzba, Steering Committee Chair, opened the workshop by explaining that PATH is working with SBH and the Bill & Medina Gates Foundation to develop a vaccine against ETEC-associated diarrhea. This vaccine would have a pediatric indication for developing-country populations. He noted that the lead candidate was ETVAX, a multivalent whole-cell killed vaccine, and that developers are preparing for a Phase 3 trial in an ETEC-endemic area. With the expectation that ETVAX will prevent severe ETEC diarrhea, Dr. Wierzba explained that the purpose of this workshop was to address issues

regarding the case definition for severe ETEC-associated diarrhea, specifically developing a scale for health workers to score a patient's degree of diarrhea severity for ETEC episodes. He further noted that while the Vesikari Score had been widely used in rotavirus vaccine trials, this scoring system was weighted on vomiting and fever, which may be less prominent for ETEC-associated diarrhea.

This introduction was followed by the open sessions' first main speaker, Dr. David Streiner, who provided the theoretical basis for developing a scoring system based on his extensive work in health measurement scales [11]. He explained that, for scales like a severity score, items correlate statistically to some degree and, because of the correlated nature of items, not every item needs to be included in the score; that is, items in the scale are a sample of all possible ones. On the other hand, an index, such as the Apgar scale, a 10-point score to assess the health of newborn children based on five criteria (i.e., heart rate, respiratory effort, muscle tone, reflex irritability, and color) consists of uncorrelated items[12, 13]. In this case, it is very important that the items constitute the full universe of relevant characteristics. Scale attributes include validity, reliability, and ease of use. Valid scales accurately measure what they were designed to evaluate. Reliability includes measurements of individuals on different occasions, by different observers, or by similar or parallel test producing the same or similar results. Reliability includes, but is not limited to, internal consistency, test-retest, and inter-rater reliability. Scales should also be easy to deploy. Importantly, Dr. Streiner advised that one does not validate a test, but validates the use to which a scale is put. In other words, the scale may be valid for one group or for one purpose but not for other groups or purposes.

The second presentation was given by Dr. Adam Levine, who noted that despite widespread use by medical personnel of clinical severity scores to assess severity and direct diarrhea treatment such as Integrated Management of Childhood Illness (IMCI)[14], a scoring system using clinical signs to classify

children for dehydration level, and Vesikari [10, 15, 16], researchers have not empirically validated any score in a resource-limited setting. With this context, he presented work on developing and validating a clinical dehydration scale, called the DHAKA score, for use among children in developing nations [12]. This score assesses clinical severity and guides treatment. The research was conducted at icddr,b, where Bangladeshi children with acute diarrhea were evaluated and classified by researcher-trained nursing staff. Children were evaluated upon admission for eight putative variables: depth of sunken eyes, general appearance, dryness of mucous membranes, heart rate, radial pulse, respiration, skin turgor, and tearing. Subsequently, investigators modeled patient results using multivariable logistic regression and identified score items that predicted percent dehydration. They calculated the percent weight change using the change in weight from admission to achievement of a stable, post-illness weight as a dehydration proxy. Four variables were found to be statistically independent predictors of severe dehydration: general appearance (normal, restless/irritable), respirations (normal or deep), skin pinch (normal, slow, and very slow), and tears (normal, decreased, or absent). Using these variables, the Area under the Curve (AuC), a composite measure of sensitivity and specificity, was 0.79 for severe dehydration. An AuC of 1.0 would indicate perfect discrimination. The four-item score was validated against a second pediatric cohort in Bangladesh and found to have similar results (AuC=0.82) to the first study, and outperformed the score of the IMCI score (AuC=0.76)[13]. The distribution of enteropathogens among cases was unknown.

Next, Dr. Stephen Freedman presented a modified Vesikari Score (MVS) [17]. He and others developed the score for use in outpatient studies of North American children where in-patient visits may be impractical. The MVS was consistent with items in the Vesikari Score except the degree of dehydration was removed and information on receipt of a post-baseline visit for care was added. The score items included diarrhea duration, maximum stools, and vomiting episodes in 24 hours, days vomiting duration,

maximum fever, post-baseline health care provider visit, and treatment. When tested among Canadian children seeking treatment, there was good correlation among items, no significant co-linearity, and results were normally distributed and were predictive of prolonged day care and work absenteeism ($p < 0.001$). Investigators validated the score in a second study in the United States with similar results. Information on the enteropathogens associated with diarrhea was not collected [18].

Dr. Margaret Kosek gave the final presentation during the open session, which focused on creating a severity score called CODA. This score is specific to community-based studies using active surveillance for case detection. She noted that in 138 randomized clinical trials involving acute diarrhea, investigators used 46 different definitions of acute diarrhea and 32 trials assessed diarrheal disease severity, of which eight used the Vesikari or a modified Vesikari. The same modification was not used for each trial. CODA was created to be unbiased to health-seeking behavior, not-etiological specific, simple, and predictive of clinical outcomes including hospitalization, and growth. Score items were selected based on a study of 442 children experiencing more than 3,900 diarrhea episodes. The outcome was change in weight measured over one month and change in length/height over nine months. Items in the score included: number of days with fever, anorexia, and vomiting and maximum number of stools in 24 hours. The total value of the score was 0 to 15. A high severity score (>7) predicted a 132 (95% CI: -213.6 to -50.7, $p = .0001$) gram weight loss over one month. The score was validated using data from MAL-ED, a multinational study of pediatric diarrhea episodes in eight developing countries [16]. The outcome was diarrhea hospitalization. A CODA score of 4 or more had an AuC of 0.87 with hospitalization as the criterion, which was marginally better than the MAL-ED score (0.85) or the Clark score (0.84).

Summary of Closed Session

182 Over the remainder of the workshop, the Steering Committee members met in a closed session. At the
183 start of the discussion, one member outlined the broader purpose of the scale and the far-reaching
184 context in which it would be used. The member noted that there is a need to distinguish between
185 regulatory and policy objectives. Industry focus is on licensure in high-income settings; however,
186 licensure does not guarantee uptake at the country level or in low-income settings. WHO has a primary
187 focus on prevention of severe diarrhea cases, and we will need to ensure that data from the Phase 3
188 study will be easily extractable to provide this information. Simply achieving outcomes for licensure
189 might not be enough to meet policy requirements for introduction set by WHO or Gavi, the Vaccine
190 Alliance. In regards to ETEC, the pathogen is well documented and known to be associated with
191 moderate to severe disease and mortality. As long as developers can provide robust data for the
192 prevention of moderate to severe disease, WHO may look favorably on introduction.

193

194 Members suggested that the selected severity scale will need to complement the Phase 3 trial and the
195 Chair briefly described its design. The trial will be placebo-controlled, employing passive case detection
196 at sentinel study sites to identify pediatric ETEC diarrhea cases seeking treatment. We will likely conduct
197 the trial in one or more ETEC-endemic countries. Children will be triaged for disease severity (i.e., mild,
198 moderate, and severe), treated, and enrolled once informed consent is obtained from a parent.

199

200 Committee members considered the use of a Vesikari Score for this trial. They observed that the
201 Vesikari Score was developed for rotavirus disease and has become widely accepted as a metric for
202 diarrheal disease severity in rotavirus trials. This score may not, however, be generalizable to ETEC
203 diarrhea as rotavirus diarrhea differs in clinical presentation. For example, the frequency and length of
204 vomiting are key characteristics of rotavirus diarrhea but are thought to be less common to ETEC
205 diarrhea. The possibility of modifying the 20-item Vesikari Score to remove or modify items that are not

206 relevant to ETEC disease such as vomiting was discussed in some detail. It was suggested that removing
207 such items might improve the performance of the Vesikari Score for ETEC diarrhea. However, the
208 committee members noted that simply removing or modifying Score items would essentially be
209 synonymous with developing a new scale for ETEC diarrhea and require score validation and reliability
210 studies, demonstration of its superiority over Vesikari and, finally, acceptance in the research
211 community.

212

213 Members considered that several scoring systems for diarrhea severity already exist, and a new scale
214 starting “from scratch” with identification of scale items is not needed. Instead, current scores, such as
215 CODA and DHAKA, should be further developed or revised. To this end, the DHAKA score was viewed
216 very favorably by the committee as it was developed and validated for passive surveillance (as used in
217 the proposed trial) and based on a measure of dehydration (e.g., percent change in body weight from
218 admission to discharge). However, developers have yet to validate the DHAKA score outside Bangladesh.
219 To demonstrate the DHAKA score’s utility across multiple geographic areas, the committee
220 recommended that a validation study be considered in sub-Saharan Africa.

221

222 Members also discussed the possibility of using current data sets to evaluate each score. While there is a
223 wealth of information such as that used in the multi-country MAL-ED study [19] and Global Enteric
224 Multicenter Study (GEMS) [1], data are not collected as prescribed by a score like DHAKA (e.g., patient
225 thermometry obtained) or CODA (e.g., mother-reported interviews). Due to these differences, it would
226 be challenging to use existing data to validate these scores and compare them head-to-head.
227 Furthermore, while MAL-ED and GEMS assessed diarrhea severity, they do not have an objective
228 measure of severity, as does the CODA or DHAKA scores. In summary, the committee recommended

229 considering a study that would allow for a direct comparison of sensitivity and specificity of each score
230 in a new study.

231

232 The committee commented on the design of such a study. To evaluate scores, the percent weight
233 change from admission to discharge could be used as a proxy for degree of dehydration. The sensitivity
234 and specificity to predict severe dehydration among scores methods could be compared. To ensure the
235 scale was specific to ETEC, the investigators would need to incorporate etiology data in this study. The
236 committee members noted in the recent GEMS results that diarrhea episodes, particularly ETEC-
237 associated diarrhea, correlated with increased mortality and poor linear growth over six months post
238 episode [1]. The committee recommended that a secondary objective of a severity scale could be to
239 include items associated with long-term sequelae, including stunting and mortality. The committee also
240 recommended that the scale should be tested using the same category of personnel that would use the
241 score in the trial to simulate real-life settings, and the study not be limited to only hospitalized infants,
242 but all pediatric patients seeking care for diarrhea. Investigators need to include measures of inter- and
243 intra-rater reliability.

244

245 One committee member proposed that we could leverage the Vaccine Impact on Diarrhea in Africa
246 (VIDA) study currently taking place the Gambia, Mali, and Kenya. Among other things, this study is
247 assessing the burden of pediatric diarrhea following the introduction of rotavirus vaccine. These studies
248 are observational and apply the Vesikari Score. There may be flexibility to enroll additional infants under
249 a separate protocol to compare DHAKA, CODA, IMCI, and Vesikari Scores based on data collected at
250 these sites. One committee member, Dr. Karen Kotloff, offered to explore using VIDA sites to validate
251 various scores to determine which best identifies ETEC diarrhea severity. The principal investigator for
252 the additional study could be the same as the VIDA studies, however additional personnel may be

needed, and the etiology component will result in additional costs. The sample size issue for these studies were revisited. Rough calculations for 0.80 sensitivity would necessitate a sample size of approximately 400 to 450 ETEC cases if a 5% difference between scores is to be excluded; 0.8 sensitivity would only require approximately 100 ETEC cases if a 10% difference was excluded.

The committee agreed that moderate-to-severe cases should be identified; however, there should be a method built-in to the scoring system that would allow for evaluation of severe cases only, as this will play a large role with WHO and vaccine uptake. Detecting only severe cases for a Phase 3 trial will undoubtedly have sample size implications that will also need to be evaluated.

When reviewing score presentations, several members noted that the AuC for scores were often similar. In the event that all scores performed similarly, investigators should develop a decision tree to down select to the best score. A few considerations for down-selection could include reverting to Vesikari, since it is already widely accepted, or employing whichever is the easiest to use score.

The workshop ended with plans for the Steering Committee to meet monthly going forward as the recommendations made are implemented.

Conclusions

ETEC induces severe acute diarrhea in large segments of pediatric populations in low-resource areas. Several vaccines are in preclinical and clinical development and one candidate, ETVAX, is rapidly progressing to a Phase 3 efficacy trial. As with rotavirus vaccines, protection from this ETEC vaccine is likely to be against moderate-to-severe disease. As the developers plan for the ETVAX efficacy trial, a valid, reliable, and easy-to-use scoring system is needed to identify moderate-to-severe pediatric cases of ETEC diarrhea during the study. Several scoring systems have been developed but most were not

277 tested against an objective measure of disease severity. Based on a measure of dehydration using
278 percent weight gain from hospital admission, the Steering Committee members recommended that
279 scores can be evaluated and compared for validity, reliability, and ease of use. As a concrete next step,
280 the committee recommended that a validation study be considered in sub-Saharan Africa. The results of
281 which would be published in a peer-reviewed journal and presented to national regulators for
282 acceptance, prior to being utilized in the Phase 3 ETVAX study.

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Table 1: Steering Committee Members and Speakers

Name	Role	Affiliation
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Thomas F. Wierzba, PhD, MPH	Chair	PATH
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Nils Carlin, PhD	Member	Scandinavian Biopharma
Jorge Flores, MD	Member	PATH
Birgitte Giersing, PHD, MRes	Observer	World Health Organization
Karen Kotloff, MD	Member	University of Maryland
Vasee Moorthy, BMBCh, PhD	Observer	World Health Organization
Duncan Steele, PhD	Member	Bill & Melinda Gates Foundation
David Streiner, PhD, MA	Member/speaker	McMaster University University of Toronto
Alexandra Bourgis, MS	Project Manager	PATH
Speakers		
Adam Levine, MD, MPH	Presenter	Brown University
Stephen Freedman, MDCM, MSc	Presenter	Alberta Children's Hospital
Margaret Kosek, MD	Presenter	Johns Hopkins University

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