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Summary of workshop "global burden of diarrheal diseases among children in developing countries: Incidence, etiology, and insights from new molecular diagnostic techniques"

Karen L. Kotloff [a,b,*], James A. Platts-Mills [c], Dilruba Nasrin [b], Anna Roose [a], William C. Blackwelder [b], Myron M. Levine [a,b]

[a] Departments of Pediatrics, Center for Vaccine Development, Institute for Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
[b] Departments of Medicine, Center for Vaccine Development, Institute for Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
[c] Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA, USA

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ABSTRACT

The Global Enteric Multicenter Study (GEMS) demonstrated that *Shigella* and enterotoxigenic *Escherichia coli* (ETEC) producing heat stable toxin (ST) (either alone or in combination with heat labile toxin) are among the most important pathogens associated with moderate-to-severe diarrhea (MSD) in children younger than 5 years of age living in developing countries. To inform the design of vaccines and other interventions, we reviewed published data and new results from GEMS characterizing the burden of *Shigella* and ST-ETEC infections. Clinical parameters were assessed to examine the value of various case definitions as indicators of MSD associated with *Shigella* and ST-ETEC for use in clinical trials. We discussed advantages and disadvantages of culture-based and culture-independent molecular diagnostics for detecting clinically and epidemiologically relevant disease. *Shigella* serotyping data from GEMS were examined to identify desirable components of *Shigella* and ETEC vaccines likely to confer broad protection. These findings can inform the development and implementation of vaccines to prevent these important infections among infants and children in developing countries.

1. Introduction

In 2015, diarrheal disease caused an estimated 688 million illnesses and 499,000 deaths worldwide among children younger than 5 years [1]. Although mortality rates have fallen during the past three decades, improvement has lagged in sub-Saharan Africa and South Asia where 90% of diarrheal deaths occur [1,2]. Survivors face an elevated risk of growth faltering [3] and other health effects. This is particularly important because declines in disease incidence have been marginal.

Rotavirus has been estimated to cause 25% of moderate-to-severe diarrhea (MSD) illnesses [3] and 30% of diarrheal deaths, most of which occur during the first 2 years of life [2]. Undoubtedly, this burden will be reduced considerably following introduction of rotavirus vaccines into the infant immunization programs of many Gavi-eligible countries. As a result, public health efforts will increasingly focus on diminishing the burden and ameliorating the adverse clinical effects of the remaining major etiologies of MSD in infants and young children. *Shigella* and enterotoxigenic *Escherichia coli* producing heat stable toxin (ST-ETEC, i.e. ETEC producing ST alone or together with heat labile toxin) are major contributors to this burden [3]. A concern is that the interventions currently recommended for case management of diarrhea, primarily rehydration therapy, continued feeding, and zinc, which have been very effective in managing rotavirus, will have more limited effectiveness against pathogens such as *Shigella* and ST-ETEC that have a predilection for inducing intestinal injury, persistent diarrhea, and growth faltering [3–5]. Moreover, the effectiveness of antibiotics recommended by WHO for treatment of dysentery is threatened by the global spread of multiple antibiotic resistances. It is uncertain whether antibiotics benefit children with watery diarrhea associated with *Shigella* or ST-ETEC and no specific therapy is recommended. For these reasons, prevention of these infections by development of a safe and effective vaccine would be a valuable public health intervention.

Abbreviations: GEMS, Global Enteric Multicenter Study; ETEC, enterotoxigenic *Escherichia coli*; ST, heat stable toxin; MSD, moderate-to severe diarrhea; ST-ETEC, ETEC producing ST alone or in combination with heat labile toxin; qPCR, quantitative polymerase chain reaction; AF, attributable fraction.

* Corresponding author at: University of Maryland School of Medicine, Center for Vaccine Development, 685 W. Baltimore Street, HSF 480, Baltimore, MD 21201, USA.
E-mail address: kkotloff@som.umaryland.edu (K.L. Kotloff).

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This workshop at the 2016 VASE Conference examined data describing the burden, epidemiology, and adverse clinical consequences of MSD associated with *Shigella* and ST-ETEC as elucidated by the Global Enteric Multicenter Study (GEMS), a large, 3-year, population-based, case-control study of acute, medically-attended, MSD among children younger than 5 years living in sub-Saharan Africa and South Asia. We focused on factors that might inform vaccine development and implementation for these important pathogens. We presented etiology results in GEMS derived from culture-based techniques and then reanalyzed using quantitative real-time PCR (qPCR) molecular diagnostics in an attempt to reconcile the most useful methods for detecting clinically and epidemiologically relevant disease. We examined *Shigella* serotyping data from GEMS to inform vaccine development. These presentations provided the basis for discussions of the optimal composition of a vaccine to prevent *Shigella* and/or ETEC, the most relevant clinical outcomes to target using vaccination, and the advantages and disadvantages of culture-based and culture-independent molecular methods for measurement of vaccine-preventable disease burden and microbiological outcomes of vaccination. Together this information can contribute to a rational approach for development of safe and broadly effective multivalent *Shigella* and ST-ETEC vaccines.

2. Presentations

2.1. Major etiologic agents and clinical consequences of moderate-to-severe diarrhea among children 0–59 months of age living in sub-Saharan Africa and South Asia, areas of the world where most under-5 deaths occur

2.1.1. Design of GEMS

The first presentation described the results of GEMS with emphasis on the etiology, manifestations, and clinical consequences of MSD associated with *Shigella* and ETEC. Key subject areas included elucidation of the disease burden to guide prioritization of vaccine development, examination of clinical presentation and complications to define the most relevant endpoints to target for prevention, and examination of the age-specific attributable fraction (AF) and incidence rates to guide vaccine trial design and implementation strategies. As described in detail elsewhere [3,6–9], GEMS was undertaken at study sites located in The Gambia, Mali, Mozambique, Kenya, India, Bangladesh, and Pakistan [3,6]. At enrolment, cases and matched controls provided clinical and epidemiological data and a stool sample for detection of a broad array of enteropathogens [9]. Cases and controls underwent a single follow-up visit and assessment of vital status 2–3 months after enrolment. The etiologic endpoints, AF and attributable incidence, were estimated only for pathogens that were significantly ($p < 0.05$) associated with MSD in conditional logistic regression models after adjusting for the presence of other pathogens [7]. Notably, GEMS took place before introduction of rotavirus vaccine.

We assessed the clinical data collected in GEMS using a modified Vesikari scale. The definitions of parameters in GEMS and in the Vesikari scale differed regarding the maximum number of stools and the maximum number of emesis episodes per day, and GEMS did not collect the duration (in days) of emesis. We rescaled the severity cutoffs normally used to classify children as having mild, moderate or severe disease in the Vesikari scoring system to account for the new number of points in the scale (now 16 vs the original 20). A two-sided p-value < 0.05 was taken to indicate statistical significance. No adjustment was made for multiple comparisons.

2.1.2. Age at infection

A total of 9439 cases and 13,129 matched controls were included in the primary GEMS analysis of AF and attributable incidence [3]. The median age of MSD cases with ST-ETEC was 14 months (Fig. 1a) compared to 20 months for *Shigella* (Fig. 1b).

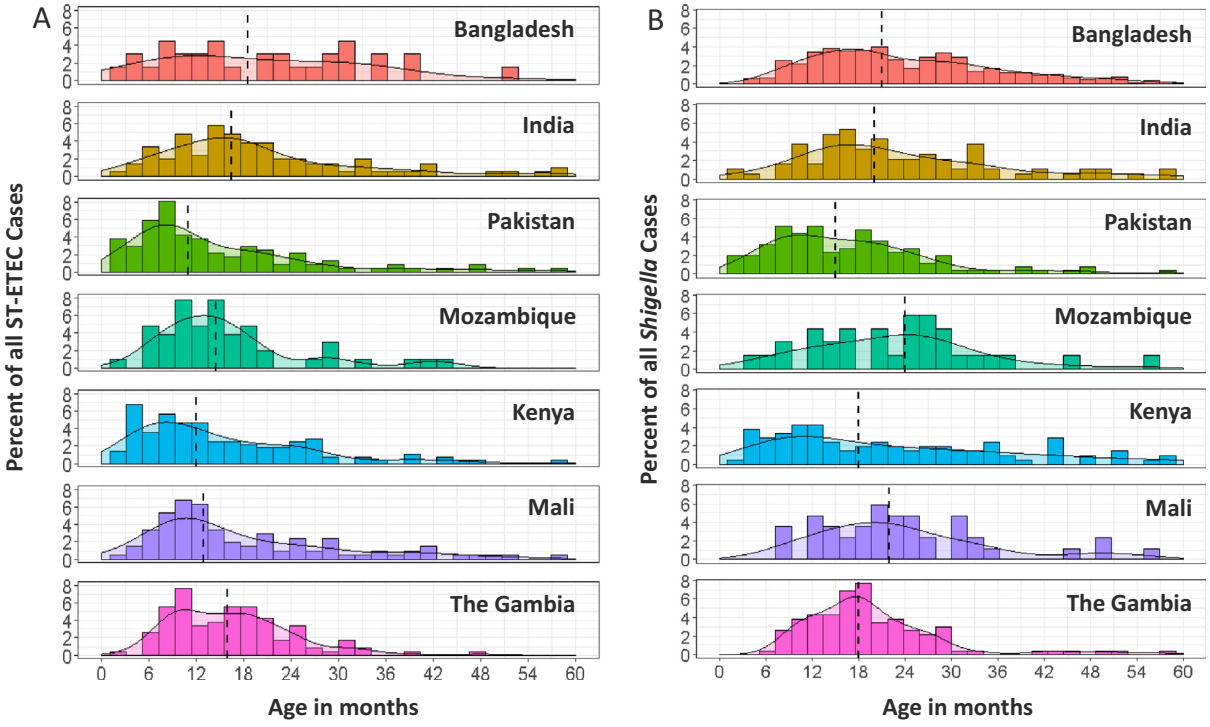

Fig. 1. Age distribution of children experiencing an episode of moderate-to-severe diarrhea associated with ST-ETEC (A) and *Shigella* (B). Bars indicate the percent of episodes at each site attributed to each age, in months, in 2-month bins. Lines show the median age of cases. Shaded areas show the density function estimating the smoothed distribution of cases with the pathogen by age.

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