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Vaccines against *Shigella* and enterotoxigenic *Escherichia coli*: A summary of the 2016 VASE Conference

Richard I. Walker [a,*], Thomas F. Wierzba [a], Sachin Mani [a], A. Louis Bourgeois [b]

[a] *PATH, Washington, DC, USA*
[b] *Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA*

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ABSTRACT

PATH hosted the inaugural Vaccines Against *Shigella* and Enterotoxigenic *Escherichia coli* (VASE) Conference in Washington, DC in June 2016, bringing together experts from around the world for a highly collaborative forum to discuss progress in the development of new enteric vaccines. Diarrheal disease and long-term sequelae caused by infections with the bacterial pathogens *Shigella* and enterotoxigenic *E. coli* (ETEC) pose a significant public health burden in low-income communities. There are currently no licensed vaccines against these pathogens, and the global health community has recently prioritized their development. The 2016 VASE Conference aimed to accelerate communication and progress among those working in the enteric vaccine field to make *Shigella* and ETEC vaccines a reality as quickly as possible. Research presented in oral and poster presentations at the VASE Conference covered a range of topics, including: the global burden of disease and public health case for *Shigella* and ETEC vaccines; current vaccine candidates in development; immunology and host responses to the pathogens; and the rationale for and status of combined *Shigella*-ETEC vaccine candidates. This article reviews key points and highlighted research presented in each of the plenary conference sessions and poster presentations at the 2016 conference. Planning for the 2018 VASE Conference is underway and will likely provide an important platform for sharing the latest updates on *Shigella* and ETEC vaccine research efforts and maintaining the momentum for accelerating this work. It is also expected that the VASE Conference will continue to provide a unique opportunity for those in the enteric vaccine field to share ideas, make connections, and create workable plans to make *Shigella* and ETEC vaccines a reality. (Updates available at: www.vaseconference.org.)

1. Introduction

On June 28–30, 2016, PATH hosted the inaugural Vaccines Against *Shigella* and Enterotoxigenic *Escherichia coli* (VASE) Conference in Washington, DC, representing the first meeting in a new biennial scientific conference series. The 2016 VASE Conference brought together more than 250 scientists, public health professionals, immunization leaders, vaccine industry representatives, donors, and other experts from approximately 30 countries to discuss the development and introduction of new enteric vaccines.

The 2016 VASE Conference featured a distinctive and varied agenda, including three keynote speakers covering unique topics related to the enteric vaccine field. Dr. Richard Heinzl, founder of Doctors Without Borders Canada, opened the meeting with personal stories about delivering health services to people living in the midst of war, refugee camps, and other challenges. He described diarrheal diseases as a daily problem facing these populations. Dr. John Tsang from the US National Institutes of Health delivered the second keynote on systems biology of vaccination responses in humans. He described how, in his laboratory, he applies multiple approaches combining computation, modeling, and experiments to study the immune system at both organismal and cellular levels. The final keynote was delivered by Dr. Roma Chilengi from the Centre for Infectious Disease Research in Zambia. He provided an appropriate conclusion to the 2016 VASE Conference by sharing his experiences with treating children in Africa with diarrheal diseases and lessons learned from testing and introducing rotavirus vaccines to address diarrhea in these vulnerable populations.

For the scientific content of the meeting, more than 70 abstracts were received for consideration, and the final conference program featured a total of 23 abstract-based oral presentations and 32

* Corresponding author at: PATH, 455 Massachusetts Ave., NW, Suite 1000, Washington, DC 20001, USA.
E-mail address: rwalker@path.org (R.I. Walker).

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abstract-based poster presentations, representing a wide range of research and topics related to enteric diseases and vaccines. In addition, several partners and colleagues organized nine breakout workshop discussions, which allowed conference participants to engage in deeper discussions on key topics related to enteric vaccines that were of the most interest to them.

This supplement of *Vaccine* provides an overview of the major topics presented at the 2016 VASE Conference in an effort to share the content of the meeting more broadly with the enteric vaccine field. This article reviews key points and highlighted research presented in each of the plenary conference sessions and poster presentations. The final conference agenda and abstracts booklet are available on the VASE Conference website (www.vaseconference.org), and each presentation mentioned in this article is referenced using its assigned identifier code. The additional articles that follow this overview recap the presentations and discussions that took place in the breakout workshop sessions.

2. Global burden of disease and the case for vaccines

2.1. Global burden

While relative frequency may differ, diarrheal diseases strike persons of all ages and in all countries. Still, the greatest diarrheal disease burden is in low-resource countries. To quantify the magnitude of health loss, the Institute of Health Metrics and Evaluation (IHME) is conducting a Global Burden of Disease Study covering all major diseases, including diarrhea (GB05). While they estimate that diarrheal disease mortality is decreasing from year to year, it is clear that the heaviest toll remains in low-resource settings. IHME presented their estimates from both 2013 and 2015 for diarrheal disease mortality and morbidity and the specific burdens of *Shigella* and enterotoxigenic *Escherichia coli* (ETEC).

For 2013, IHME estimated 1.3 million deaths due to diarrhea among all age groups. More than 99% of these fatalities occurred in low-resource countries. *Shigella* and ETEC ranked second and fourth, respectively, among the pathogens causing these deaths. IHME estimated that shigellosis induced nearly 74,000 deaths (95% uncertainty interval [UI]: 59,000–94,000), which was associated with 4.1 million Years of Life Lost (YLL). ETEC was estimated to have induced 59,000 deaths (UI: 44,000–78,000) with 3 million years YLL.

In their 2015 analysis, the global number of diarrheal deaths remained around 1.3 million, but due to the use of more sensitive, culture-independent laboratory methods (i.e., TaqMan multiplex PCR), the estimated number of *Shigella* deaths increased to 188,000 (UI: 83,000–292,000) with 295 million cases (UI: 131–684 million) among all age groups. The *Shigella* attributable fraction—or the proportion of diarrhea cases attributed to *Shigella*—was 13%. ETEC deaths and cases were estimated at 84,000 (UI: 30,000–143,000) and 128 million (UI: 38–591 million), respectively. The ETEC attributable fraction of all diarrhea cases was 6%. Among children under five years old, shigellosis was responsible for 73,000 deaths (UI: 27–118,000) and 99 million cases (UI: 43–231 million), while ETEC was responsible for 31,000 deaths (UI: 9–53,000) and 44 million cases (UI: 14–193 million). The attributable fraction of all diarrhea cases among children less than 5 years of age was 11% and 5% for *Shigella* and ETEC, respectively.

2.2. National burden, at-risk populations, and surveillance

As noted above, diarrheal disease burden is highest in low-resource countries, and sub-Saharan Africa in particular suffers disproportionately. As an example, in Nyahururu County, Kenya, diarrheal diseases are significantly affecting child health (GB13). Medical staff treated 669 children with diarrhea as outpatients at the county hospital in 2015. Of the children admitted to the pediatric ward, 200 were infants, 20 of whom died, and 150 were aged one to four years, 10 of whom died. Local data like these are critical to controlling diarrheal disease, as surveillance data is often limited or non-existent in low-resource countries. As an added layer of concern, climatologists consider climate change especially consequential to Africa, and such changes may lead to increases in diarrheal disease burden there as studies suggest that higher temperatures and more extreme weather conditions (e.g., droughts, increased rainfall) will exacerbate diarrhea rates in much of the developing world (GB12).

To help fill the gap in surveillance for diarrheal diseases, researchers in Bangladesh are establishing a nationwide program that will supplement surveillance activities and study the problems of symptomatic and asymptomatic ETEC infections (GB09). Diarrhea stools from different sites located around Bangladesh are being screened for ETEC using phenotypic and genotypic methods. From these cases, researchers are collecting demographic and clinical data useful to understanding disease epidemiology as well as evaluating potential vaccine impact.

In addition, researchers are conducting a study in Leon, Nicaragua, to clarify the ETEC disease burden by understanding ETEC phenotypic characteristics (GB04). ETEC isolates were obtained from children less than 60 months of age from a variety of sites (regional hospital, primary care clinics, and population-based cohort). Using the polymerase chain reaction (PCR) method, researchers detected at least one colonization factor (CF) among 65% of samples, of which CS19 was the most common, either alone or in combination with another CF. Among all CFs, 55% were members of the Class 5 fimbrial family.

Diarrheal diseases, including *Shigella* and ETEC, are also a health concern in high-resource countries. In the United States, shigellosis is the third most common enteric bacterial infection with an estimated 500,000 infections occurring annually (GB03). Children and adults within some communities have experienced large, protracted *S. sonnei* outbreaks, with the highest shigellosis rates in southern states and among children less than ten years old. As reported by the US Centers for Disease Control and Prevention, from 2003 to 2013, the proportion of *S. sonnei*, *flexneri*, *boydii*, and *dysenteriae* were 75%, 12%, 1%, and 0.3%, respectively, among 112,581 *Shigella* isolates. Culture-confirmed shigellosis cases decreased from 2003 (n = 15,951) to 2013 (n = 5,983).

Also in the United States, from 2011 to 2015, a study of 35 clusters of shigellosis cases found a wide distribution of transmission routes (GB08). Ten clusters involved childcare centers, camps, or schools. Ten clusters involved cases among men who have sex with men (MSM), seven clusters occurred among other person-to-person transmission routes, six clusters were foodborne, and two clusters were from recreational water. Nine clusters were caused by *S. sonnei* (n = 8) and *flexneri* (n = 1) that were resistant to more than one of the first-line treatments (i.e., ciprofloxacin, ceftriaxone, azithromycin). Of the nine antibiotic-resistant clusters, seven occurred among MSM-associated clusters and two among the other 25 clusters (prevalence ratio = 12.5, $p < 0.001$). This analysis showed that MSM are at high risk for antibiotic-resistant *Shigella* strains.

In Israel, over the last two decades, countrywide propagated epidemics of *S. sonnei* shigellosis occurred every two to three years (GB01). Ultraorthodox towns and communities with good sanitary infrastructure but with crowding were outbreak epicenters. In these high-risk towns, from the years 2000 to 2012, the mean incidence among children less than five years old was 413 and 1930 per 100,000 during non-epidemic and epidemic years, respectively. The incidence in the rest of the district was 278 and 662 per 100,000, respectively. High-risk towns were characterized by a

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