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Status of vaccine research and development for *Shigella*☆

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ABSTRACT

Shigella are gram-negative bacteria that cause severe diarrhea and dysentery. In 2013, *Shigella* infections caused an estimated 34,400 deaths in children less than five years old and, in 2010, an estimated 40,000 deaths in persons older than five years globally. New disease burden estimates from newly deployed molecular diagnostic assays with increased sensitivity suggest that *Shigella*-associated morbidity may be much greater than previous disease estimates from culture-based methods. Primary prevention of this disease should be based on universal provision of potable water and sanitation methods and improved personal and food hygiene. However, an efficacious and low-cost vaccine would complement and accelerate disease reduction while waiting for universal access to water, sanitation, and hygiene improvements. This review article provides a landscape of *Shigella* vaccine development efforts. No vaccine is yet available, but human and animal challenge–rechallenge trials with virulent *Shigella* as well as observational studies in *Shigella*-endemic areas have shown that the incidence of disease decreases following *Shigella* infection, pointing to biological feasibility of a vaccine. Immunity to *Shigella* appears to be strain-specific, so a vaccine that covers the most commonly detected strains (i.e., *S. flexneri* 2a, 3a, 6, and *S. sonnei*) or a vaccine using cross-species conserved antigens would likely be most effective. Vaccine development and testing may be accelerated by use of animal models, such as the guinea pig keratoconjunctivitis or murine pneumonia models. Because there is no correlate of protection, however, human studies will be necessary to evaluate vaccine efficacy prior to deployment. A diversity of *Shigella* vaccine constructs are under development, including live attenuated, formalin-killed whole-cell, glycoconjugate, subunit, and novel antigen vaccines (e.g., Type III secretion system and outer membrane proteins).

1. About the disease and pathogen

Shigellosis is caused by the ingestion of bacteria of the genus *Shigella*. Three species of *Shigella* are responsible for the majority of infections: *S. flexneri* is the most frequently isolated species worldwide, accounting for most cases in the least-developed countries; *S. sonnei* is more common in low- and middle-income countries; and *S. dysenteriae* has historically caused epidemics of dysentery, particularly in confined populations such as refugee camps. A fourth species, *S. boydii*, a cause of infection in less-developed countries, accounts for 6 percent or less of *Shigella* cases [1].

Shigellosis is an important cause of morbidity and mortality among preschool-aged children, older children, and adults. Recent studies in sub-Saharan Africa and South Asia conducted under the Global Enteric Multicenter Study (GEMS) reaffirmed the importance of *Shigella* as a major cause of moderate-to-severe diarrhea (MSD). Among children less than five years old brought to a center for treatment of diarrhea, *Shigella* was among the top four causes of potentially life-threatening diarrheal illness in both regions [2]. In a birth cohort study that followed children twice-weekly at home to detect diarrhea episodes conducted at sites in sub-Saharan Africa, South Asia, and South America, researchers found that *Shigella*, especially in the second year of life, was one of four pathogens associated with the highest burden of diarrheal diseases [3]. When assessing *Shigella*-associated mortality, despite differences in methodology (systematic literature review versus 187-country vital records review), two other recent studies resulted in similar estimates of global mortality from shigellosis for children less than five years old: 28,000 deaths in 2011 by the Child Health Epidemiology Reference Group [4] and 34,400 deaths in 2013 by the Institute for Health Metrics and Evaluation (IHME)

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[5]. In addition, a meta-analysis of hospitalization and stool culture data projected that *Shigella* may contribute to an additional 40,000 deaths per year among age groups older than five years in Africa and South Asia [6]. This analysis also estimated that, in 2010, shigellosis was more common in these older age groups than cholera and typhoid combined, with 88.4 million shigellosis cases versus 9 million typhoid and cholera cases (approximately 6 million and 3 million, respectively), with school-age children being at the highest risk for all illnesses. Supporting these findings, IHME also estimated 40,500 deaths in 2013 from *Shigella* infection in persons older than five years of age [7]. In addition to mortality, IHME found that, in 2010, shigellosis disability-adjusted life years (DALYs) were estimated at 7 million (7.8 percent of all diarrhea DALYs) and years lived with disability (YLDs) due to shigellosis were estimated at 744,000 (9 percent of all diarrhea YLDs) [8,9]. Travelers and deployed military service members visiting *Shigella*-endemic areas also frequently suffer from shigellosis and contribute to the overall disease burden.

A recent evaluation of a new quantitative polymerase chain reaction (qPCR) assay for *Shigella* diagnosis confirms that traditional culture methods may seriously underestimate the global burden of *Shigella*-associated illness [10]. Using samples from GEMS, investigators found that use of qPCR almost doubled the percentage of MSD cases attributable to *Shigella*, from 9.6 percent by traditional culture methods to 17.6 percent by qPCR [10].

There is no animal reservoir for *Shigella*, and infection is transmitted person-to-person, via fomites, and from ingestion of contaminated food or water. Shigellosis is therefore associated with poor sanitation and hygiene and limited access to clean drinking water. Transmission control under these circumstances is made more difficult by the relatively low infectious dose of this pathogen [11]. Furthermore, the variety of species and serotypes associated with shigellosis makes it possible for reinfections to occur locally or during travel to areas where other serotypes predominate. For example, the heterogeneous distribution of *Shigella* serotypes found in cases from urban and rural areas of Bangladesh suggest that multivalent vaccines will be needed to prevent shigellosis in these settings [12]. Healthy individuals with mild infections usually recover without specific treatment, but because *Shigella* invades the mucosal lining of the colon, it often causes dysentery, which is not amenable to oral rehydration. Antibiotic treatment is recommended for dysentery, severe shigellosis, and individuals with compromised immune systems. However, the emergence of multi-drug-resistant strains of *Shigella* further complicates antibiotic treatment, making prevention of infection critical.

Based on the emerging qPCR data mentioned above that indicate a higher *Shigella* disease burden than previously estimated, the introduction of a cost-effective, broadly protective *Shigella* vaccine could have a significant public health impact [13]. An effective *Shigella* vaccine could substantially reduce the global burden of shigellosis and also reduce *Shigella*-associated mortality and complications associated with diarrhea and dysentery due to this pathogen. In low- and middle-income endemic countries with inadequate access to proper sanitation, safe water, and treatment options for severe diarrhea that may be resistant to common antibiotics, a *Shigella* vaccine would become an ideal choice in diarrheal disease management. It is important to note that *Shigella* infections are rare during the first six months of life, possibly due to the presence of maternal immunity and the relatively low direct interaction with the environment. Incidence increases after this age, peaking at 12–23 months and decreasing moderately afterwards [2]. Therefore, any potential *Shigella* vaccine would need to be safe and effective in children at least up to five years of age and administered within the current Expanded Programme on Immunization vaccination schedule (at 6, 10, and 14 weeks of age, possibly with a later booster dose given at the time of measles vaccination). In addition, due to the number of other enteric pathogens that also affect children in early life, another important goal for a *Shigella* vaccine is compatibility for combination with other enteric vaccines to be given by the same route.

2. Overview of current efforts

2.1. Biological feasibility for vaccine development

A successful strategy to control childhood diarrhea caused by *Shigella* would need to employ all effective diarrheal disease prevention and treatment interventions—including not only vaccines but also improved sanitation and hygiene, access to clean and potable water, and exclusive breastfeeding for the first six months of life—to help ensure long-term success and maximum impact. While a comprehensive approach to diarrhea prevention and control is the ideal solution, cost–benefit analyses show that water and sanitation infrastructure development can be cost-prohibitive and time-consuming, particularly for low-income countries. In the near term, many public health stakeholders view vaccination as a much more equitable and cost-effective preventive intervention.

At present, there are no licensed vaccines available for *Shigella.* However, studies in animals and humans have demonstrated that protection by vaccination is feasible. Among 12 non-human primates, a challenge/rechallenge study with virulent *S. flexneri* 2a demonstrated 100 percent protection [14]. Similarly, in controlled human challenge models, protection was suggested for adults given attenuated *S. flexneri* 2a strains and challenged with virulent *S. flexneri* 2a [15]. In one model using six adult volunteers, 100 percent protection was observed against fever and diarrhea associated with clinical *S. sonnei* infection in all volunteers who were rechallenged with a virulent *S. sonnei* strain, and 70 percent protection was observed in volunteers challenged and rechallenged with virulent *S. flexneri* 2a [16]. Field epidemiology studies suggest a chronological association of protection with age in younger individuals due to a decrease in age-specific incidence rates and the development of adaptive immunity through natural exposures [7,17,18]. Seroepidemology studies also indicate that the presence of serum antibody correlates with protection from homologous strains [19,20].

Multiple factors affect the development of long-lasting protective immunity to *Shigella* infection. A key factor is that serum and mucosal antibody responses to *Shigella* are predominantly homologous, i.e., directed against a serotype-specific *Shigella* lipopolysaccharide (LPS)-associated O antigen [21]. While these responses are robust and lead to the induction of memory B-cell responses, evidence of their ability to cross-protect against diverse serotypes is inconclusive [13,22]. While other antigens such as the conserved invasion plasmid antigens (Ipas) do induce serum and mucosal antibody responses against *Shigella*, they are usually produced in lower quantities compared to anti-LPS antibodies. This could possibly be due to the sequestration of conserved epitopes in a way that evades T-cell recognition during natural *Shigella* infections.

With four major species and 50 different serotypes of *Shigella*, the task of developing an all-encompassing vaccine, while scientifically feasible, might become an impractical and expensive endeavor. Based on the serotype distribution from the seven sites of the GEMS study, *Shigella flexneri* and *Shigella sonnei* comprised nearly 90 percent of all *Shigella* isolates [13]. About 24 percent of all isolates were *Shigella sonnei*. Of the *Shigella flexneri* serotypes, 2a and 3a comprise nearly 30 percent of the isolates and serotype 6 comprises about 11 percent. *S. flexneri* 2a, *S. flexneri* 3a, and *S. flexneri* 6 strains also share O-antigen group determinants with the remaining 11 *S. flexneri* serotypes and its subserotypes [23–26]. Hence, an ideal multivalent vaccine that would provide maximal coverage would incorporate the three *S. flexneri* serotypes and *S. sonnei*.