

A public health value proposition for prospective *Shigella* vaccines

Shigella is the leading bacterial cause of childhood diarrhea globally, resulting in more than 60,000 deaths and millions of hospitalizations each year, mostly in low- and middle-income countries (LMICs).¹ It is also a major cause of diarrhea among travelers and military personnel from high-income countries visiting LMICs. In addition, there is growing evidence of long-term health and economic impacts related to *Shigella* infections, as well as increasing antimicrobial resistance (AMR). No licensed *Shigella* vaccines currently exist, but several promising candidates in development could become available in a few years. While the World Health Organization has identified *Shigella* as a priority disease for which vaccines are urgently needed, past experiences show that the development of an effective vaccine does not automatically result in sufficient commercial interest and country demand. In the context of an increasingly crowded and expensive immunization schedule, and with competing demands for new vaccines against other pathogens, *Shigella* vaccines may simply not be prioritized over other public health interventions.² To help inform decisions by international agencies, funders, vaccine developers, and national policymakers, PATH conducted a series of studies to understand the potential public health value of prospective *Shigella* vaccines (Figure 1). This brief provides a comprehensive summary of the results. (Manuscripts have been submitted to peer-reviewed journals.)

Key takeaways

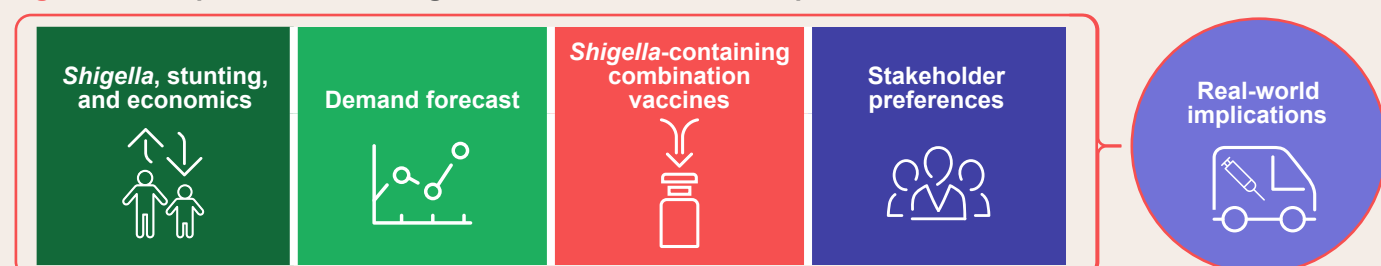
- ◆ The potential health impact and economic value of effective *Shigella* vaccines appear greater than previously estimated, due to *Shigella*'s increasingly recognized contribution to long-term effects such as growth faltering and stunting in young children in LMICs and its growing resistance to antibiotics.
- ◆ There is significant awareness of *Shigella* among LMIC national stakeholders, but the attractiveness and prioritization of *Shigella* vaccines appear highly dependent on vaccine presentation and the actual magnitude of vaccine impact on diarrheal disease, stunting, and AMR.
- ◆ *Shigella*-containing combination vaccines are likely to markedly increase attractiveness to LMIC decision-makers, and their development could be greatly facilitated by modifications in the regulatory, policy, and financial ecosystems to make them more relevant for combination products.
- ◆ There appears to be significant interest within the travel medicine and military communities for effective *Shigella* vaccines, whether standalone or in combination with another antigen.

Background

Shigella typically causes severe or bloody diarrhea (“dysentery”) and is now considered responsible for a broader spectrum of diarrheal disease than historically thought. In addition, repeated *Shigella* infections contribute to an increasing number of negative long-term effects on growth and development among children in LMICs, including severe malnutrition, stunting and metabolic disorders, as well as increased mortality from other infectious diseases.^{3,4,5} There is also strong evidence of growing AMR to *Shigella*,⁶ making treatment increasingly complex and expensive.

Vaccines against *Shigella* are currently in clinical development and may be available in the next five years. The most advanced candidates for children are injectable and will likely require two doses given between the ages of six months to one year. Therefore, this is the ideal time to examine their public health value for a range of stakeholders. To this end, PATH first systematically reviewed the robustness of the evidence linking *Shigella* infection to stunting. These results were used to inform the development of two health impact and economic models to estimate the cost-effectiveness and potential long-term societal economic benefit of *Shigella* vaccines. PATH also conducted a study in five countries to improve understanding of the key drivers of country-level decision-making to help refine target product profiles to inform vaccine design, clinical evaluation, and donor and vaccine manufacturer investments. Finally, PATH organized an expert convening to examine opportunities for and barriers to the development of *Shigella*-containing combination vaccines.

Figure 1. Components of the *Shigella* Public Health Value Proposition.



Results



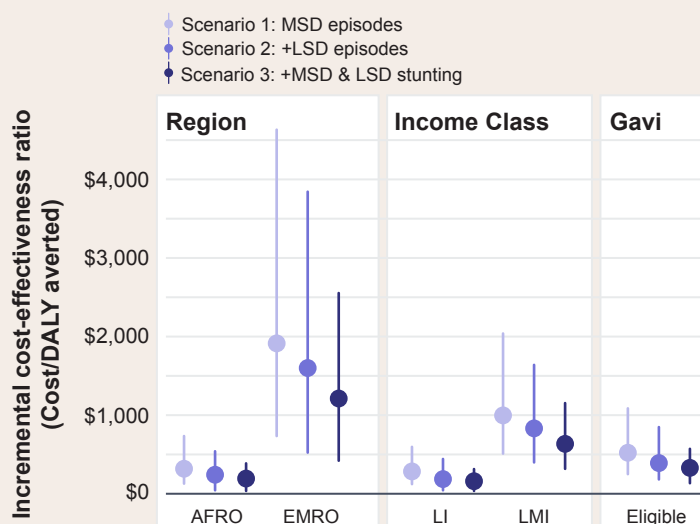
Shigella, stunting, and economics

The link between *Shigella* infection and subsequent stunting among children living in LMICs is uniquely well-demonstrated among the most common enteric pathogens, though the underlying mechanism through which this occurs remains unclear.⁷ PATH synthesized the latest evidence for this association, which has primarily been demonstrated with moderate-to-severe diarrhea (MSD), and included new evidence suggesting that the link extends to less-severe diarrhea (LSD). PATH summarized and presented the data to a panel of experts, who confirmed the strength of this evidence, considered *Shigella* vaccines' potential to prevent stunting due to MSD and LSD, and explored how to measure the long-term economic impact of stunting and its prevention. The experts concluded that, **while preventing *Shigella* disease through vaccination holds promise to reduce stunting, vaccine efficacy studies should directly assess the magnitude of impact on this outcome, if possible.**⁸

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PATH also supported the development of two vaccine impact models to estimate the effects of reducing not only *Shigella* diarrhea but also *Shigella*-attributable stunting. One model estimates the impact and cost-effectiveness of a *Shigella* vaccine on health outcomes in 102 LMICs over 20 years starting from 2025, and the other projects the long-term societal economic benefit of reducing stunting, focusing on its impact on future wages and productivity. These new models found that incorporating prevention of LSD and stunting due to *Shigella* significantly enhances the cost-effectiveness of *Shigella* vaccination such that the cost-effectiveness approaches that of rotavirus vaccines in some regions and scenarios (Figure 2). In fact, the long-term societal economic model indicates that in regions with high rates of stunting, *Shigella* vaccination could pay for itself due to increases in population productivity.

Figure 2. Incremental cost-effectiveness ratios (ICERs) indicate the cost of a vaccine per one year of healthy life gained, measured here as one disability-adjusted life year (DALY) averted (lower ICER = better cost-effectiveness). Preventing both MSD and LSD episodes (Scenario 2) notably improves cost-effectiveness; adding stunting prevention increases it further. ICERs were lowest in the World Health Organization African (AFRO) and Eastern Mediterranean (EMRO) Regions and in low- and lower-to-middle income countries (LI and LMI, respectively).



Demand forecast

PATH conducted two demand forecast analyses to project the *Shigella* vaccine markets for LMICs and civilian/military travelers. The model for LMICs estimated demand in 102 low-income, lower-middle-income, and upper-middle-income countries. **Based on historical country-specific vaccine introduction timing for previous childhood vaccines and considering country variability in disease burden and cost-effective thresholds, the model estimated that *Shigella* vaccine demand could reach 60 to 100 million annual doses by 2044.** When disease burden and cost-effectiveness thresholds were combined with a slower than historical introduction pace, estimated demand further decreased to 20 to 50 million annual doses. Overall LMIC demand hinges heavily on the pace of introduction and whether only high-burden countries will introduce.

The civilian and military travelers' markets for *Shigella* vaccines were estimated independently for a pre-COVID pandemic *Shigella* vaccine in each of the market segments. In addition to publicly available information, researchers prospectively collected survey data from key stakeholders and travel medicine providers. Given the challenges of conducting clinical trials with travelers, most experts believed that human challenge models would be the most effective way to demonstrate clinical efficacy in that population. **Assuming pre-pandemic travel patterns, it was estimated that annual demand for a two-dose *Shigella* vaccine in civilian/military traveler markets combined could amount to nearly 12 million doses and generate at least US\$700 million.** Given the heterogeneity of *Shigella* disease burden in LMICs and the absence of a standard high-income country market for *Shigella* vaccines, this potential revenue could provide an important incentive to vaccine manufacturers and support tiered pricing for LMICs.



Shigella-containing combination vaccines

With an increasingly crowded immunization schedule in LMICs, combining a *Shigella* vaccine with an existing infant vaccine would conceivably increase its attractiveness. PATH convened an independent panel of 34 academic, industry, philanthropic, and global health experts to discuss the potential barriers to the development, licensure, policy recommendations and introduction of a hypothetical *Shigella* vaccine combined with one of three existing routine vaccinations.

The experts concluded that while development and manufacturing obstacles are significant, regulatory, policy, and commercialization issues in particular appear to represent major challenges. This is because current policy recommendations and financial incentives are not particularly attuned to the special risks associated with combination vaccine development. Yet, there was also much optimism. **Innovative technologies**

are advancing the development of new and better vaccines, and some (such as mRNA) may particularly lend themselves to facilitating combinations. With many new vaccines against multiple pathogens in development and increased emphasis on manufacturing partnerships, there is growing awareness that combination vaccines may be increasingly favored.

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Stakeholder preferences

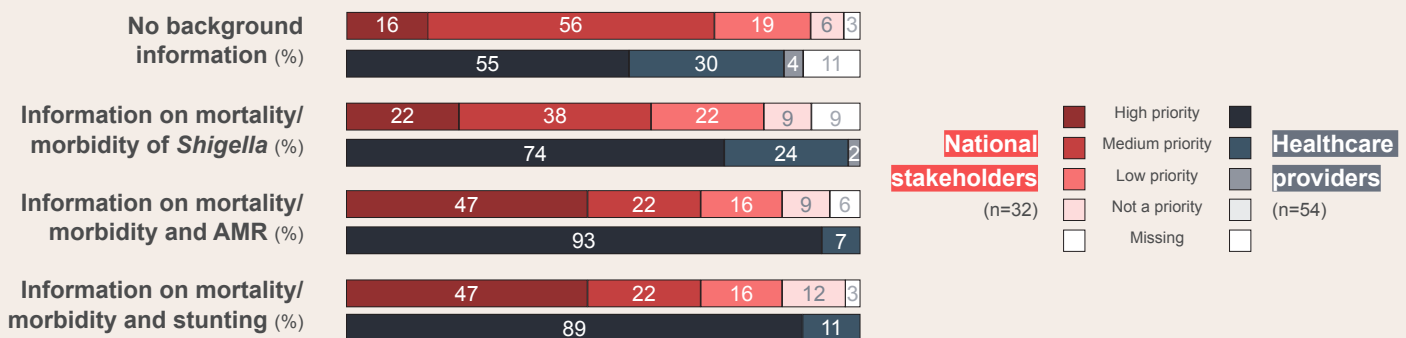
Given numerous competing disease prevention priorities in LMICs, input from key stakeholders is required to accurately understand and estimate country demand for *Shigella* vaccines. PATH conducted a feasibility and acceptability study involving interviews with **32 national stakeholders and 54 healthcare providers in Burkina Faso, Ghana, Kenya, Nepal, and Vietnam, as well as 3 regional stakeholders from the Pan American Health Organization's (PAHO's) headquarters** in Washington, DC, to identify preferences and priorities for future *Shigella* vaccines. Participants were asked about their prioritization of and preferred attributes for a *Shigella* vaccine based on their prior knowledge and after receiving progressively more information about the vaccine's potential impact in their country.

Diarrhea was most frequently mentioned by study participants as a key health concern for children younger than five years old. Though when asked to rate the severity of given health concerns, they rated related, longer-term issues—such as stunting and increased risk of AMR—as more serious concerns than diarrhea. Awareness of *Shigella* was high, but it was not considered a very high priority for most participants.

Study participants generally indicated a willingness to consider adding a *Shigella* vaccine to the immunization schedule, in theory (Figure 3). However, this was tempered by a lower perceived burden of *Shigella* relative to other vaccine-preventable diseases and heightened concern about the number of concomitant injections children already receive. **The overall priority of a *Shigella* vaccine rose among participants as they were provided with progressively more country-specific information about the possibility of preventing longer-term issues related to *Shigella*, notably reducing AMR and stunting.**

Figure 3. What is the priority of a potential *Shigella* vaccine?

(Results from all study countries.)



When asked to choose which vaccine delivery attributes would affect their willingness to introduce a *Shigella* vaccine, participants strongly preferred oral and *Shigella*-containing combination vaccines. Participants felt that a vaccine requiring -20°C cold chain storage would not be feasible, however lyophilization, single-dose packaging, and the requirement of a booster dose did not affect their willingness to introduce.



Conclusions and real-world implications

The collective results of these analyses conducted by PATH summarize the potential public health value of prospective *Shigella* vaccines, with several important themes emerging. ***Shigella* vaccines have the potential to be most cost-effective in areas with a high burden of *Shigella*-attributable diarrhea.** Designing clinical studies that demonstrate the extent to which *Shigella* vaccine candidates can reduce diarrhea and stunting would help refine these modeling results. Incorporating the effect of stunting could also help assess return on investment for other enteric vaccines in future models.

In addition, country-level stakeholders appear to have high awareness of *Shigella*, but its prevention by vaccination is only a moderate priority. However, this prioritization increased when accounting for potential impact on reducing stunting and AMR or the inclusion of *Shigella* in a combination vaccine that also targets other pathogens of importance. **These results highlight the clear need for improved *Shigella* surveillance within countries, as well as greater awareness of the global and local burden of *Shigella*,** especially with respect to its role in stunting and AMR, and the potential impact that a vaccine could have in addressing these issues.

These findings may help guide investment decisions by donors and vaccine developers to better meet LMIC needs, influence clinical trial designs, or help inform global policy guidance and national vaccine introduction decision-making in the future. They may also be applicable to other new vaccines in development, and **the resulting insights and recommendations from the convening on *Shigella*-containing combination vaccines particularly may help guide future combination vaccine development efforts.** While it is too early for countries to start considering the introduction of *Shigella* vaccines, the results from this public health value proposition indicate that there could be a substantial market for *Shigella* vaccines, particularly when part of a combination vaccine and if they can demonstrate impact on related health issues such as stunting and AMR.

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Recommendations

- ◆ Awareness of the disease burden attributable to *Shigella*, especially related long-term impacts, should be more broadly communicated to LMIC stakeholders.
- ◆ If possible, clinical studies of *Shigella* vaccine candidates should measure impact on additional endpoints that could also have major public health or economic implications, particularly stunting and AMR or antibiotic use.
- ◆ The public health community and international agencies should consider adapting current regulatory, policy, advocacy, and procurement processes in order to accelerate the development, licensure, and introduction of *Shigella*-containing combination vaccines for both LMIC populations and civilian/military travelers.

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