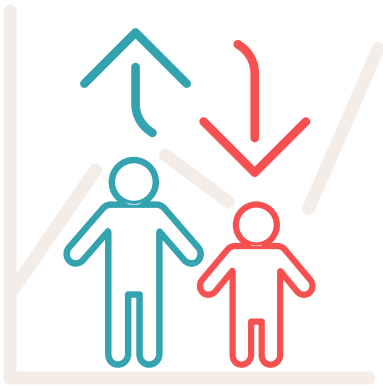
The potential health and economic impact of *Shigella* vaccines



***Shigella* is the leading bacterial cause of childhood diarrhea, causing more than 60,000 deaths and millions of hospitalizations each year.[1] *Shigella* infections in children also have long-term effects on growth and development.[2] No licensed *Shigella* vaccines currently exist, but several promising candidates in development could become available in a few years. PATH conducted a series of studies to better understand the public health value of potential *Shigella* vaccines and help inform decisions by international agencies, funders, vaccine developers, and national policymakers. As part of this work, PATH 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 measures cost-effectiveness based on health outcomes, and the other measures the long-term societal economic benefit of reducing stunting, focusing on its impact on future wages and productivity. (Manuscripts have been submitted to peer-reviewed journals.)**

Key takeaways

- The latest epidemiological evidence shows that even less-severe enteric infections, including by *Shigella*, can hamper long-term growth outcomes.
- These new vaccine impact models are the first to incorporate less-severe *Shigella* diarrhea and its impact on stunting. This significantly enhances cost-effectiveness, approaching that of rotavirus vaccines in some scenarios.
- In regions with high rates of stunting, *Shigella* vaccination could pay for itself due to increases in population productivity. In most scenarios, even vaccines that are only somewhat effective against stunting could yield significant economic returns.

Shigella and stunting

Although the vast majority of children will survive repeated enteric infections, some will unfortunately suffer long-term health issues associated with stunted growth. The link between *Shigella* and stunting among children living in low- and middle-income countries (LMICs) is stronger than other common enteric pathogens.[3] PATH synthesized the latest evidence that demonstrates even less-severe diarrhea (LSD), including LSD caused by *Shigella*, contributes to stunting. This is especially true in infants and toddlers when *Shigella* infection is most common.

In March 2021, PATH convened a panel of experts who confirmed the strength of the evidence associating LSD and stunting and explored the potential magnitude of a *Shigella* vaccine's impact against one or both outcomes. While preventing *Shigella* infection through vaccination is expected to reduce stunting, the experts agreed that vaccine probe trials should include measures of growth faltering as an *a priori* outcome to gauge the magnitude of impact.[4]

Methods

Traditional vaccine impact models focus on acute disease burden reduction, but the evidence on *Shigella* and stunting calls for a more expansive approach. PATH and partners designed a vaccine impact and cost-effectiveness model to assess the performance of *Shigella* vaccination in 102 LMICs over 20 years starting from 2025. The model incorporated new disease burden findings on the link between *Shigella* LSD and stunting, updated cost data, and high and low ranges for estimated vaccine efficacy and price.

PATH and partners also designed a second economic impact model based on principles such as country economic growth rate, gross national income, and returns on investment to measure long-term benefits of reduced stunting. A sensitivity analysis shed light on which inputs in this model have the strongest influence on the outcomes.

Results

Incorporating the impact of LSD and LSD-attributable stunting enhances the cost-effectiveness of potential *Shigella* vaccines (Figure 1), especially in the lowest income countries where the diarrheal burden is highest and vaccination would impact more diarrhea and stunting cases (Figure 2). In countries eligible for support from Gavi, the Vaccine Alliance, the incremental cost-effectiveness ratios (ICERs) for potential *Shigella* vaccines approach that of rotavirus vaccines (US$308/DALY averted vs. US$264/DALY averted,[5] respectively).

The long-term economic impact model is the first to estimate the impact of a vaccine that reduces stunting on adult economic productivity. The model found that the benefit-cost ratio is greater than one (i.e., the economic return outweighs the costs of *Shigella* vaccination) in all regions, with the highest return estimated for the Southeast Asia and Africa Regions based on high rates of stunting, relatively low intervention costs, and opportunities to improve productivity (Table 1). Preventing the long-term economic consequences of *Shigella*-attributable stunting may pay for the vaccine through future productivity gains in some regions.

The positive economic impact estimates of potential *Shigella* vaccines proved resilient across many scenarios. While the model assumes that the vaccines will reduce stunting based on the extent to which they reduce diarrhea, a sensitivity analysis illustrated that even a vaccine with only 10 percent efficacy against stunting still showed positive benefit-cost ratios in several regions.

Conclusions

Shigella vaccines have the potential to be most cost-effective in areas with a high burden of less severe, *Shigella*-attributable diarrhea based on increased opportunity to reduce DALYs through vaccination. Reduced stunting increases cost-effectiveness to a rate comparable to rotavirus vaccines in some regions. Further, looking at adult productivity based on increased income, potential economic benefits of stunting reduction would make them cost-saving, meaning the economic benefits outweigh their costs. Designing clinical studies that demonstrate whether *Shigella* vaccine candidates can reduce diarrhea and stunting would help confirm these modeling results. Incorporating the effect of stunting could also help assess return on investment for other enteric vaccines in future models.

These results contribute to PATH's broader effort to evaluate the public health value of potential *Shigella* vaccines. These findings may help guide investment decisions by donors and vaccine developers, influence new clinical trial designs and endpoints, or help inform global policy guidance and national vaccine introduction decision-making in the future.

References

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Figure 1. 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 moderate-to-severe diarrhea (MSD) and LSD episodes (Scenario 2) notably increases 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).

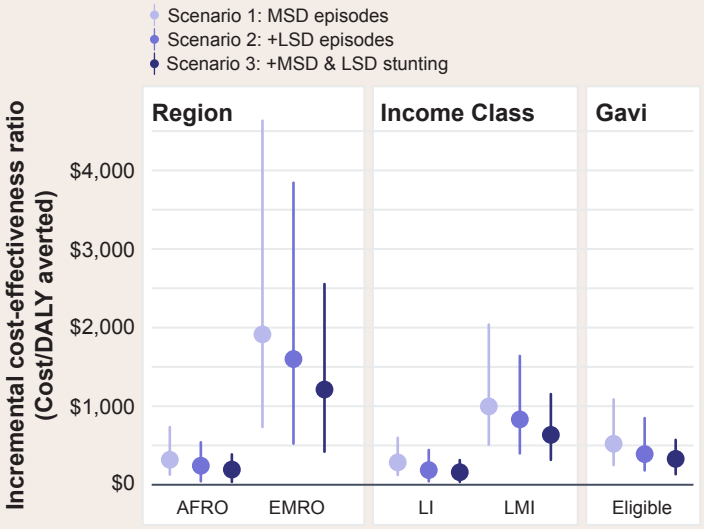

Figure 2. *Shigella* vaccination could potentially prevent almost half of *Shigella*-attributable DALYs, with the greatest impact in low-income countries and in Africa where disease burden is high.

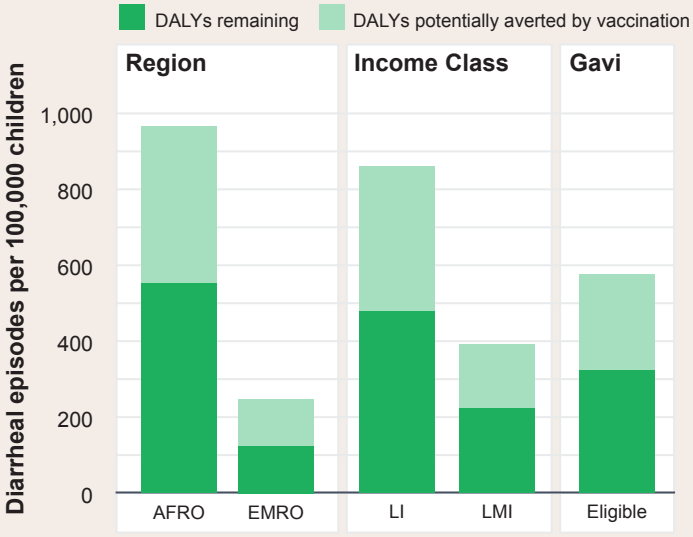

Table 1. A benefit-cost ratio greater than one indicates a positive return (i.e., greater than $1 return, or benefit, for every $1 cost). A standard 3 percent "discount" of economic returns takes into account the higher value of benefits today relative to benefits in the future.

WHO African Region	8.52
WHO Region of the Americas	3.32
WHO Eastern Mediterranean Region	2.90
WHO European Region	4.06
WHO Southeast Asia Region	21.67
WHO Western Pacific Region	6.56
All Gavi countries	14.45
Global	11.60