WHO PREFERRED PRODUCT CHARACTERISTICS FOR vaccines against Shigella
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### Abbreviations and glossary

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AMR</td>
<td>antimicrobial resistance</td>
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<tr>
<td>CoP</td>
<td>correlates of protection</td>
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<tr>
<td>CHIM</td>
<td>controlled human infection models</td>
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<tr>
<td>CF</td>
<td>colonization factor</td>
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<tr>
<td>DALY</td>
<td>disability-adjusted life-year</td>
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<tr>
<td>EPI</td>
<td>expanded programme on immunization</td>
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<tr>
<td>ETEC</td>
<td>enterotoxigenic <em>Escherichia coli</em></td>
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<tr>
<td>EIEC</td>
<td>enteroinvasive <em>Escherichia coli</em></td>
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<tr>
<td>EED</td>
<td>environmental enteric dysfunction</td>
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<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbant assay</td>
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<tr>
<td>FVVA</td>
<td>full value of vaccine assessment</td>
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<tr>
<td>GBD</td>
<td>global burden of disease</td>
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<tr>
<td>GEMS</td>
<td>Global Enteric Multicenter Study</td>
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<tr>
<td>HIC</td>
<td>high-income country</td>
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<tr>
<td>IVB</td>
<td>Department of Immunization, Vaccines and Biologicals, WHO</td>
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<tr>
<td>IHME</td>
<td>Institute for Health Metrics and Evaluation</td>
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<tr>
<td>LMIC</td>
<td>low- and middle-income country</td>
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<tr>
<td>LSD</td>
<td>less severe diarrhoea</td>
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<tr>
<td>MAL-ED</td>
<td>The Aetiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development Project</td>
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<tr>
<td>MCEE</td>
<td>Maternal Child Epidemiology Estimation</td>
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<tr>
<td>MSD</td>
<td>moderate-to-severe diarrhoea</td>
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<td>MSM</td>
<td>men who have sex with men</td>
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<tr>
<td>qPCR</td>
<td>quantitative polymerase chain reaction</td>
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<tr>
<td>PDVAC</td>
<td>Product Development for Vaccines Advisory Committee</td>
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<tr>
<td>PPCs</td>
<td>preferred product characteristics</td>
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<tr>
<td>PQ</td>
<td>pre-qualification</td>
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<tr>
<td>R&amp;D</td>
<td>research and development</td>
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<tr>
<td>SAGE</td>
<td>Strategic Advisory Group of Experts (on Immunization)</td>
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<tr>
<td>TPP</td>
<td>target product profile</td>
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<tr>
<td>US</td>
<td>United States</td>
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<td>WHO</td>
<td>World Health Organization</td>
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Diarrhoeal diseases are among the leading causes of morbidity and mortality worldwide. Among children younger than 5 years of age, diarrhoea is responsible for an estimated 441 100 (WHO and the Maternal Child Epidemiology Estimation (MCEE) 2000-2017) - 446 000 deaths (Institute for Health Metrics and Evaluation (IHME) 1990-2016) annually, which are geographically concentrated in the WHO African Region and South-East Asia Region. Significant reductions in diarrhoeal disease mortality have been achieved over the last 20 years; however, these reductions have not been paralleled by similar declines in diarrhoea-associated morbidity, which continues to impact negatively infant and child health, costing households and health systems millions of dollars each year in many low- and middle-income countries (LMICs). Consequently, the need to develop better and more equitable diarrhoeal prevention and control measures, such as vaccines, remains a public health priority for the World Health Organization (WHO).

Shigella was the second leading cause of diarrhoeal mortality in 2016 among all ages, and the leading bacterial cause of diarrhoea, accounting for approximately 212 000 deaths and about 13% of all diarrhoea deaths. Although Shigella infections occur worldwide, with broad geographical distribution and across all age groups, the greatest burden is among children in low- and middle-income countries (LMICs). Here, annually, it is responsible for an estimated 28 000 (MCEE) to 64 000 (IHME) deaths among children under 5 years of age. It is also an important cause of diarrhoea with or without dysentery in people older than 5 years of age, with an estimated 270 million episodes occurring annually among all ages, according to IHME’s 2016 Global Burden of Disease study.

Shigella infections spread easily in areas with poor sanitation and hygiene, where there is limited access to clean water. For young children, symptomatic or asymptomatic infections due to this pathogen can result in malnutrition and induce or exacerbate stunting. Both malnutrition and growth stunting have long-term adverse consequences on physical and cognitive development. In addition, Shigella can cause severe illness among travellers, deployed military personnel and expatriates in LMICs, and is associated with reactive arthritis and irritable bowel disease. Shigella infections also have the potential to cause large outbreaks in both younger and older age groups, especially with S. dysenteriae type 1.

Treatment options for shigellosis include oral rehydration salts, therapeutic zinc and, when dysentery is present, antimicrobials are recommended. The rise of antibiotic-resistant enteric bacteria, particularly Shigella spp, means that, in addition to the potential direct effects on morbidity and mortality, a Shigella vaccine might also have indirect effects on reducing the use of antibiotics and consequent emergence of antimicrobial resistance (AMR). Accordingly, WHO and the Centers for Disease Control and Prevention (CDC) have declared antibiotic-resistant Shigella spp. to be a public health threat requiring innovative interventions. Moreover, considering the potential for inducing herd effect and broad protection against Shigella-attributable disease, the development of a Shigella vaccine is an important goal for public health. It would also be of benefit to international travellers to endemic areas who are at risk of enteric illness associated with Shigella.

Although several candidate Shigella vaccines are being evaluated at different stages of preclinical and clinical development, currently no licensed vaccines against Shigella diarrhoea are available. Vaccine development has faced significant technical challenges, but has
WHO preferred product characteristics for vaccines against Shigella
WHO preferred product characteristics for vaccines against Shigella also been impeded by a lack of prioritization by global level stakeholders and an unclear commercial value proposition to inform investment. WHO develops preferred product characteristics (PPCs) to provide strategic guidance on preferences for new vaccines, specifically from a LMIC perspective.

“The greatest burden of Shigella infections is among children under 5 years of age, in low- and middle-income countries (LMICs)”

The articulation of PPCs for Shigella vaccines is intended to help advance product development and support policy assessment for use in areas where Shigella vaccines are most needed. To frame the development of Shigella vaccine PPCs, WHO convened a global stakeholder consultation to assess the priority public health needs, particularly in endemic areas. The outcome of this consultation was a consensus statement that the primary goal is to develop a safe, effective and affordable vaccine to reduce mortality and morbidity due to dysentery and diarrhoea caused by Shigella in children under 5 years of age in LMICs.

Interventions that prevent Shigella infection in under 5-year-olds might also offer significant, under-recognized public health value to older children, adolescents and adults by reducing long-term morbidity through both individual (direct) and population-based (indirect) herd effects, thereby contributing to improved social and economic development. This is the foundation for development of WHO’s Shigella vaccine PPC guidance.
1. Background and purpose of the World Health Organization’s preferred product characteristics

The mission of the World Health Organization’s (WHO’s) Department of Immunization, Vaccines and Biologicals (IVB) is to accelerate the development and uptake of safe, effective and affordable vaccines and related technologies that could have global public health impact. Priority areas for IVB include developing guidance and co-ordinating activities that enable: 1) prioritization and acceleration of vaccine candidates towards licensure; and 2) identification and generation of evidence to inform policy recommendations for candidate vaccines as they progress to advanced stages of development, in order to avoid a delay between licensure and vaccine implementation.

Vaccine preferred product characteristics (PPCs), published by WHO IVB, are intended to encourage innovation and promote development of vaccines for use in settings most relevant to the global unmet public health needs. They describe preferred parameters pertaining to vaccine indications, target populations, use case(s) and immunization strategies, as well as data that should be collected for safety and efficacy evaluation and policy consideration (1). PPCs are pathogen-specific and do not include minimally acceptable characteristics; they are intended to provide early guidance to inform subsequent candidate-specific target product profiles (TPPs).

Disease areas for vaccine PPC development are identified by WHO’s Product Development for Vaccines Advisory Committee (PDVAC), based on the unmet public health need for a vaccine, interest and demand for a vaccine from low- and middle-income countries’ (LMICs) stakeholders and technical feasibility (2). They may be updated in the event of product or technology innovations, or if there is any change in the identified need or in the research and development (R&D) landscape.

The primary target audience for WHO PPCs is any entity intending to eventually seek WHO policy recommendation and prequalification (PQ) for their products. Communication of WHO preferences can be useful to all those involved in vaccine development, including academic groups, funders and manufacturers. However, it is important to note that a vaccine that offers the preferred characteristics and is intended for use in LMICs will also undergo evidence-based assessment by WHO’s Strategic Advisory Group of Experts (SAGE) on Immunization (3). As such, WHO PPCs offer early guidance and complement, but do not supersede, existing WHO processes for vaccine development and evaluation for a particular vaccine class or product.

“Vaccine preferred product characteristics (PPCs), published by WHO, describe preferred parameters for vaccines intended for use in settings that are most relevant to the global unmet public health needs”
2. Development of a Shigella vaccine for LMICs – a strategic priority for WHO

The immunization agenda 2030 (IA2030) is a global stakeholder strategy for the decade of 2021–2030, to Leave No-one Behind (4). It includes primary goals: 1) reduce mortality and morbidity from vaccine preventable diseases across the life course, and 2) decrease disease burden by increasing access to and uptake of new vaccines. In resource-limited settings, Shigella species (Shigella) are a leading cause of childhood diarrhoea (5, 6) with high case-fatality rates in children with severe disease (7, 8). In addition to its impact in endemic settings, diarrhoea due to Shigella among travellers and military recruits can cause significant morbidity, including incapacitation, and may require antibiotics, intravenous fluids and hospitalization (9). Acquiring Shigella infection during travel can introduce antimicrobial-resistant Shigella into new populations (10), and has the potential to cause post-infection complications, such as reactive arthritis (11) and irritable bowel syndrome (12), as well as outbreaks in tourist groups and military deployment settings. Antibiotic-resistant Shigella strains have been found to circulate as sexually transmitted infections in men who have sex with men (13), particularly those living with HIV (14).

Shigella is considered a significant antimicrobial resistance (AMR) threat by WHO and the US CDC. The WHO Global Antimicrobial Resistance Surveillance System (15) identified Shigella as a priority pathogen for the development of new interventions. In addition, a recent Wellcome Trust-BCG report recommended that vaccine development for Shigella be accelerated because of its high global burden of illness and the difficulty in achieving effective treatment with commonly available antibiotics (16).

On the basis of public health stakeholder input and the scientific community’s understanding of the predominant burden of Shigella infection, including its adverse long-term sequelae, the WHO priority public health goal for Shigella vaccine development is to develop a safe, effective and affordable vaccine to reduce mortality and morbidity due to dysentery and diarrhoea caused by Shigella in children under 5 years of age in LMICs.”

“...the primary goal is to develop a safe, effective and affordable vaccine to reduce mortality and morbidity due to dysentery and diarrhoea caused by Shigella in children under 5 years of age in LMICs.”

At the time of writing, the Shigella vaccine candidates in clinical development include multivalent blends of O-antigen-based, subcellular complexes and whole cell-based candidates (17). Other innovative approaches being investigated include exploitation of conserved protein antigens of Shigella and the concept of hybrid constructs with antigens against other pathogens of diarrhoeal disease. The approach of developing combination vaccines against different pathogens would offer significant delivery advantages, considering the congested schedule within the expanded programme on immunisation (EPI) (18). The Shigella candidates in development would benefit from guidance regarding WHO and LMIC vaccine preferences as they are evaluated for future investment, and to position them for policy recommendation and introduction.
3. Background of Shigella diarrhoea

3.1 Shigella species and diarrhoea

*Shigella* is a facultatively anaerobic, non-motile Gram-negative rod, from the family Enterobacteriaceae. It is an antigenically diverse pathogen that comprises four species with various serotypes distinguished by components of the lipopolysaccharide O-antigen repeats; they have differing geographical distribution and epidemiological significance. There are 14 well established types of *S. dysenteriae*, 15 of *Shigella flexneri*, and 19 of *Shigella boydii*, but only one serotype of *Shigella sonnei* (7). The incubation period of *Shigella* infection is typically 1–4 days, but up to 8 days with *S. dysenteriae* type 1 (19). The proportion of *Shigella* infections that occur asymptotically in young children has not been fully established, however it is suggested to increase with age (20).

3.2 Shigella in children

The case control, healthcare facility-based Global Enterics Multicenter Study (GEMS) measured *Shigella*-attributed moderate-to-severe diarrhoea (MSD) that led to care-seeking and one or more of the following: dehydration, dysentery or hospital admission in children under 5 years of age (21). The incidence varied by age group across the seven field sites in sub-Saharan Africa and South Asia. When the results were extrapolated to the catchment population, the estimated incidences were 2.0 (95%CI: 1.4–2.6), 7.0 (95%CI: 5.0–9.0) and 2.3 (95%CI 1.2–3.4) *Shigella*-attributed MSD cases per 100 child-years, in children aged 0-11, 12-23 and 24-59 months respectively, based on diagnosis using quantitative polymerase chain reaction (qPCR) (22). The incidences using culture confirmation were 1.2, 2.8 and 1.1 *Shigella*-attributed MSD cases per 100 child-years in these same age groups (21).

The Aetiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) multisite, community-based, birth cohort study found the incidence of molecularly-determined *Shigella*-attributed diarrhoea, of any severity, to be 26.1 cases per 100-child years (95%CI: 23.8–29.9) in the first two years of life, with site-specific estimates ranging from 4.2–65.2 cases per 100-child years (23).

3.3 Shigella in adults and travellers

*Shigella* is a common cause of diarrhoea in travellers and military recruits, affecting individuals from high-income countries who visit endemic areas in LMICs (9, 24). A systematic review suggests that diarrhoeal disease among long-term travellers remains a frequent occurrence, and the associated morbidity is significant, even though a high percentage of cases are not brought to medical attention (25). In addition, patients with traveller’s diarrhoea could introduce antibiotic-resistant *Shigella* strains, and thereby change the antimicrobial profile of susceptibility to most antimicrobial agents (26).

*Shigella* also emerged in the 1970s as a sexually transmitted infection among men who have sex with men (MSM). In 2009, an outbreak of an unusual serotype (*S. flexneri* 3a) appeared in England and Wales among MSM and spread intercontinentally within the MSM population to regions considered low risk for *Shigella* infection (27). Along with multidrug-resistant *S. flexneri* 3a, distinct multidrug-resistant *S. sonnei* and *S. flexneri* 2a strains emerged among MSM and HIV-positive populations (28, 29).

"The WHO Global Antimicrobial Resistance Surveillance System identified *Shigella* as a priority pathogen for the development of new interventions."
3.4 Mode of transmission and pathogenesis of Shigella

Humans are the only natural host for Shigella, and it is transmitted mainly through the faecal-oral route via direct person-to-person transmission, contaminated food and water, and fomites (7). A low infectious dose facilitates person-to-person spread, and the likelihood of disease transmission is increased by poor sanitation and hygiene conditions. Outbreaks can disseminate rapidly, then propagate by person-to-person contact (7). Houseflies have been suggested as a mechanical vector for transmission in settings where disposal of human faeces is inadequate (30).

After oral ingestion, Shigella survives the acidic environment of the stomach and the competitive intestinal microbiota to reach the terminal ileum, colon and rectum, where it penetrates the mucous layer. The aggressive watery or mucoid/bloody diarrhoea is a direct consequence of Shigella invasion and destruction of the large intestinal epithelium (31).

Most illnesses in otherwise healthy individuals are mild and symptoms subside in a few days; however, in young or malnourished infants and children (32) and people with HIV (33), Shigella infection frequently carries a poor prognosis. There can be progression within hours or days to frank dysentery with frequent small stools containing blood and mucus, accompanied by lower abdominal cramps and tenesmus (7), with more than 20 dysenteric stools in one day. Abdominal pain, often a prominent feature, might simulate appendicitis or, in young infants and neonates, intussusception or necrotizing enterocolitis (34). The significant intestinal inflammation induced by Shigella infection and local invasion is also a risk factor for subsequent development of gut enteropathy, malnutrition and stunting (35, 36).

3.5 Diagnosis of Shigella

The gold standard for diagnosing Shigella infection is conventional bacterial culture, since it enables serotyping, which is key to identifying priority Shigella vaccine targets and important for defining microbiologic endpoints of Shigella vaccine trials. Culture also allows for identification of phenotypic antibiotic susceptibility in Shigella, which is becoming crucial as antimicrobial resistance evolves (37). However, Shigella is a fastidious organism to culture, and when a delay between stool collection and plating is anticipated, appropriate transport media is needed to help maintain organism viability. Because of the poor sensitivity of culture for Shigella, as well as the difficulty in standardizing culture techniques between laboratories, qPCR has emerged as an alternative method for detection and case ascertainment.

Since 2013, several nucleic acid-based diagnostic panels have been developed and approved by the US Food and Drug Administration (FDA) for detection of enteric pathogens, including Shigella; however, these nucleic acid-based diagnostics do not require live pathogens for a positive result (38). The application of qPCR in diarrhoeal surveillance and case ascertainment has led to substantial increases in estimates of Shigella infection incidence in the GEMS and MAL-ED multisite diarrhoea aetiology studies in children in low-resource settings (23, 22). Thus, adoption of qPCR, rather than culture, as the primary microbiological outcome, could significantly increase the statistical power and decrease the sample size of clinical endpoint efficacy trials.

Quantitative PCR also has the potential to detect novel antimicrobial resistance genes (39), and is able to differentiate Shigella serotypes (40) and species (40). While there is some concern that the IpaH gene target is conserved between Shigella and enteroinvasive E. coli (EIEC) (41), and that this may obscure the assessment of Shigella vaccine efficacy, recent analysis suggests that only approximately 5% of IpaH is due to EIEC (42, 39). For these samples, this limitation could be overcome by pairing IpaH with detection of S. sonnei or S. flexneri serotypes to confirm Shigella presence. At the time of writing, there's a proposal for discussion with national regulatory agencies on the acceptability of qPCR as the primary microbiological outcome for field-efficacy studies.

3.6 Prevention and treatment of Shigella

Global access to improved sanitation and meticulous hand washing represent the ideal solution to preventing transmission of Shigella and other faecally-transmitted organisms. However, this can be difficult to achieve in the short term, and challenging to sustain given the financial and logistical constraints in low-resource regions (43). Breastfeeding is also one of the most effective prevention interventions for diarrhoeal diseases, and it provides a wide array of proven benefits to infants and young children (44, 45); however, breastfeeding is not universal (46). Moreover, the peak incidence of shigellosis occurs in 12–23-month-olds when complementary food and liquids are used and breastfeeding is less emphasized as a public health measure.

The cornerstone of Shigella treatment is maintenance of hydration and electrolyte balance. WHO recommends
antibiotic treatment for all children with dysentery, with the assumption that most cases are caused by *Shigella*. Evidence supports the use of antibiotics to treat *Shigella* dysentery to reduce the duration of fever and diarrhoea, interrupt pathogen shedding and help reduce the risk of person-to-person transmission (47). The benefit of antibiotics for non-dysenteric *Shigella* diarrhoea is unknown. Nonetheless, it is suggested that if antibiotic treatment is started early, disease is aborted and does not progress to dysentery. Early antibiotic treatment has also been suggested to help avert the significant linear growth faltering that may result from *Shigella* diarrhoea and dysentery (48, 49). Provision of adequate nutrition is critical in children in low-resource settings, and it has been found that zinc treatment can speed up recovery time. While the available treatment strategies have been used successfully over the past decades, there are notable limitations and issues with coverage and sustainability.

Antibiotics are often prescribed empirically for diarrhoea treatment in many settings, contributing to the rise in AMR. In 2017, WHO recommended that ciprofloxacin be the first choice for treating adults and children with *Shigella* dysentery; however, there is an increasing trend towards resistance (50). While azithromycin, cefixime and ceftriaxone are second-line options (51), resistance to these drugs is also emerging. Trimethoprim-sulfamethoxazole was considered as an alternative; resistance to this drug, however, is widespread (52). Therefore a new intervention, such as *Shigella* vaccines, is a critical element of both the short-term and long-term preventive strategies required to alleviate the burden of diarrhoeal disease morbidity and mortality in areas of the world where new interventions are most needed.

“Adoption of qPCR, rather than culture, as the primary microbiological outcome, could significantly increase the statistical power and decrease the sample size of clinical endpoint efficacy trials.”
4. Full value of vaccines assessment for Shigella vaccines

The value proposition of a vaccine candidate defines its epidemiologic, product development, regulatory, economic, market, policy, financing and delivery environments to guide investment in that product. Value propositions seek to identify the major stakeholders and beneficiaries who may value the product differently. They articulate how the envisaged product will address both the common and the non-overlapping, unmet needs of key stakeholders and beneficiaries, as well as identify gaps in evidence needed to justify recommending and financing the product’s uptake (53).

The full value of vaccines assessment (FVVA) concept aims to address the vaccine value from the perspective of stakeholders in LMICs, and to assess both the individual (direct) and population-based (indirect) benefits (54). The fundamental elements that are expected to inform the Shigella FVVA include both a robust assessment of the current and future mortality- and morbidity-related health and socioeconomic burden of disease, as well as the impact of a vaccine on emerging AMR.

To determine the potential market size and most cost-effective implementation strategy for Shigella vaccines, the disease burden needs to be characterized at regional and national levels, and potentially at subnational levels, for large, disparate populations that experience health and socio-economic inequity. Global Shigella mortality-estimates are currently being modelled by two groups: the Institute for Health Metrics and Evaluation (IHME) and Maternal Child Epidemiology Estimation (MCEE). The current global epidemiological burden for shigellosis is mainly attributed to two species, S. flexneri and S. sonnei, which were conventionally associated with low- and middle-income contexts respectively. The emergence of S. sonnei in economically transitional states is commonly observed, effectively replacing S. flexneri to become the predominant shigellosis aetiology (55, 56). Neither IHME nor MCEE estimates account for these different Shigella species or for their geographic distribution.

Whereas the adverse clinical consequences of symptomatic shigellosis are well described, recent findings suggest that asymptomatic infection with Shigella spp. also contributes to the pathogenic pathway leading to stunting (35), and these negative health outcomes also increase the risk that affected infants and young children will die of other infectious disease causes (57). Shigella is also a significant cause of morbidity and mortality in older age groups (> 5 years of age), and it contributes to school absenteeism, especially among older children of 5–14 years of age, and to lost productivity among adults (58, 59). An assessment of Shigella vaccine impact on long-term sequelae in children under 5-years-old living in LMICs, on both direct and Shigella-induced stunting deaths (60), has been done. However, to date, the global burden estimates have not included comprehensive estimates of disability-adjusted life-years (DALYs) that specifically assess the impacts of stunting, malnutrition and cognitive impairment, as well as an increased risk of death due to other infectious diseases.

The determination of Shigella-associated diarrhoeal aetiology, especially for children in LMICs, is complicated by coinfecting enteric pathogens, asymptomatic infections and variability of diagnostic methods. An additional contributor to the uncertainty intervals in the burden estimates is the geographic heterogeneity that exists for the Shigella species, their various
serotypes and respective disease burden. A recent analysis (61) explored how, when one accounts for subnational and economic heterogeneity in Shigella and enterotoxigenic Escherichia coli (ETEC) disease burden, it affects the projected vaccine impact and cost-effectiveness of ETEC and Shigella vaccines after their introduction in four sub-Saharan African countries. The results suggested that vaccination was most cost-effective for children living in the lower wealth quintiles in underserved, high-burden provinces. Therefore, Shigella vaccines may be appropriate for use in high-burden areas at subnational levels in some countries, and not necessarily be appropriate for introduction into national routine EPI immunization programmes. Reliable, Shigella-specific surveillance data will be essential to guide an optimal vaccine implementation strategy.

Where possible, attributes that serve all target markets should be identified and prioritized in order for these vaccines to have global reach and impact on reducing Shigella disease and transmission (3, 64). Target populations that could potentially benefit from the availability of effective Shigella vaccines, in addition to infants and young children in LMICs, include the following: travellers and the military; young children living in crowded communities in high- or upper middle-income countries endemic for shigellosis; immunocompromised children; MSM; people living with HIV (PLHIV); the private sector in emerging middle-income countries; and older children, adolescents and adults in LMICs.

To fully capture the value of Shigella vaccines, multiple aspects should be considered in the context of other interventions. Shigella vaccine candidates should be formulated so as to facilitate future combinations with other vaccines, since this strategy will likely enhance uptake in public-sector markets of LMICs, where ease of vaccine delivery is critical to achieving equitable coverage (65). The rise of antibiotic-resistant enteric bacteria has made the need for effective vaccines against Shigella an even greater public health priority (16) and, in combination with other bacterial enteric pathogens such as Salmonella spp. or ETEC, could result in a significant reduction of antibiotic use. Disease burden, cost-effectiveness, programmatic suitability, feasibility and customer demand are all issues that need to be considered early in vaccine development, in addition to safety, efficacy and impact.

Endemic-country awareness of the true impact that a disease has, or may have, on a country’s population is fundamental to informing impactful health-policy decisions on vaccine implementation. While policymakers in some endemic nations are highly attuned to overall diarrhoeal burden, they may be unaware of the significance of the Shigella-specific burden of diarrhoeal illness (6). Considering that the first vaccines may be 5–10 years from licensure, the level of awareness must improve in the near term, otherwise the potential impact of Shigella vaccines may be limited due to lack of demand and uptake (66, 67).

"Shigella is also a significant cause of morbidity and mortality in older age groups (> 5 years of age), and it contributes to school absenteeism, especially among older children of 5–14 years of age, and to lost productivity among adults."

Travellers, deployed military personnel and expatriates in LMICs (62, 63) represent substantial, but typically middle–high income market segments that contribute to the value proposition for Shigella vaccines. However, the target product profiles for vaccines that are developed for these populations may not be compatible with the programmatic requirements that will enable paediatric use in LMICs. There are a larger number of constraints related to product presentations (for example, dimensions of packaging, thermostability), duration of protection and number of doses/regimen for vaccines intended for implementation in the EPI.
5. The burden of *Shigella* diarrhoea

5.1 MCEE group mortality estimates
The MCEE group, previously known as the Child Health Epidemiology Group (CHERG), published its most recent diarrheal estimates of 441,000 deaths based on data from 2000-2017 (68). It published pathogen-specific mortality for children under 5 years of age, using aetiologic data from hospital inpatient studies as a proxy for the pathogen distribution (70). MCEE (1990 – 2011) estimated 712 000 diarrhoea deaths in all age groups and 28 000 (12 000–53 000) *Shigella* deaths per year in children younger than 5 years of age.

5.2 IHME Global Burden of Disease study mortality estimates
According to the IHME’s 2016 Global Burden of Disease (GBD) study estimates (1990-2016), diarrhoea accounts for more than 1 million deaths and about 4% of the total global DALYs per year across all age groups (69). *Shigella* was the second-leading cause of diarrhoeal mortality among all ages, accounting for approximately 212 000 deaths (136 979–326 913) and about 13% (9.2–17.4) of all diarrhoea deaths annually (6), and was responsible for 64 000 annual deaths (41 191–93 611) among children under 5 years of age. It was frequently associated with diarrhoea across all adult age groups, increasing in elderly people, and with broad geographical distribution.

5.3 *Shigella* burden estimates
The limitations and discrepancies in mortality estimates pose challenges for vaccine developers, funders and policymakers in prioritizing the relative importance of intervention strategies against *Shigella* compared to other pathogens. Mortality modelling and diagnostic methods are continually undergoing reassessment, resulting in variation of the estimates for each iteration. The two disease burden models have their strengths and limitations, and efforts are underway to harmonize the data informing the models, and to ensure the model assumptions are explicit (71). Factors such as inclusion/exclusion criteria for studies used to provide data; model inputs and adjustments; assessment of pathogenicity; geographical representativeness; and country or regional extrapolation affect conclusions about the attributable burden. Regardless, both estimates indicate an unacceptably high burden of acute disease leading to mortality.

Beyond its potentially devastating and immediate impacts on health, *Shigella* infection and diarrhoea can also have long-term implications, including malnutrition and adverse consequences on physical and cognitive development (72, 73, 74). Repeated infections, which are common among children in LMICs because of the multiple species, serotypes and subtypes of *Shigella*, can induce or exacerbate growth stunting and other forms of malnutrition, and reduce immune function. These infections can also impair cognitive development, with adverse consequences for school performance and economic status (75, 76, 77).

The long-term impact of *Shigella* on individual health, cognitive function and macroeconomic effects would benefit from further study (77). In an effort to quantify a proportion of this morbidity burden for diarrhoeal diseases, IHME conducted a study using DALYs to quantify the long-term sequelae due to growth faltering. Based on the 2016 estimates, the study showed that the global burden of diarrhoea is substantially underestimated when only incidence and mortality are considered; when long-term sequelae associated with growth impairment are accounted for, it increased the number of diarrhoea-associated DALYs among

“Beyond its potentially devastating and immediate impacts on health, *Shigella* infection and diarrhoea can also have long-term implications, including malnutrition and adverse consequences on physical and cognitive development.”
children younger than 5 years of age by about 40%. After inclusion of these long-term sequelae, diarrhoea moves from the fifth-leading to the third-leading cause of DALYs among children younger than 5 years of age, surpassing malaria and neonatal encephalopathy in the number of DALYs in this age group (78). However, to date, there is no GBD Shigella-specific analysis to account for the additional DALYs burden due to long-term sequelae. Such an analysis is needed to refine the pathogen-specific burden estimates and the full value of vaccines for Shigella.
6. Shigella vaccine development

6.1 Shigella vaccine feasibility and approaches

Several lines of evidence support the favourable biological feasibility of developing effective Shigella vaccines. Both human and animal challenge trials with virulent Shigella, as well as observational studies in endemic areas, reveal that the risk of subsequent disease decreases following Shigella infection, consistent with acquired immunity. A challenge/rechallenge study with virulent S. flexneri 2a in 12 non-human primates demonstrated 100% protection from the primary infection (79). Similarly, controlled human infection model studies (CHIMs) have demonstrated the protective efficacy of experimental infection with wild type S. sonnei (80) and S. flexneri 2a (81, 82) against development of symptomatic shigellosis upon rechallenge. These human challenge studies indicate that vaccine-induced protection against homologous serotypes is feasible.

Field epidemiology studies suggest a chronological association of protection with age. Younger individuals have higher incidence rates and appear more susceptible to disease. While innate factors may contribute to less susceptibility over time (83, 84, 85), the evidence also supports the concept that acquired immunity against Shigella develops through natural exposure (81, 86).

In the past 3 decades, the first-generation candidate, consisting of O-antigen of S. sonnei lipopolysaccharide chemically conjugated to recombinant exotoxin of Pseudomonas aeruginosa (rEPA) (87), advanced to efficacy trials, and it was shown to induce protection in Israeli adults (88) and children older than 3 years of age (89). However, the candidate failed to protect in the very young (87, 89). Lack of protection was associated with a decrease in serum O-antigen IgG levels induced by immunization with descending age. This efficacy study expanded upon evidence generated by human challenge studies, field observations (90, 82) and early vaccine trials in Yugoslavia (91), demonstrating that serotype-specific immunity to Shigella can be elicited and that efficacy can be correlated with the level of serum IgG titer to O-antigen (82, 92). However, a protective threshold has yet to be determined for any Shigella serotype.

Live oral vaccines are also in development either alone or in combination with ETEC antigens (93). Oral vaccines may more closely mimic the immunoprotective effects of natural infection; however, additional challenges still exist. Suboptimal efficacy and effectiveness performance of both viral and bacterial vaccines have been observed in many countries in Asia and Africa, and are most apparent with oral vaccines (94, 95, 96). Several hypotheses for these observations have been suggested, including underlying gut enteropathy, coinfections and malnutrition (72, 97), and potentially they are also a consequence of the variable force of infection in different settings (98).

Although vaccine development appears biologically feasible, several hurdles must be overcome on the road to safe, effective, affordable Shigella vaccines. One of those difficulties is that more than 50 O-antigen-based serotypes of Shigella drive serotype-specific protective immunity. Accordingly, the development of all-encompassing, O-antigen-based Shigella vaccines faces challenges (99).

The GEMS surveillance studies indicate that S. sonnei (which has only one serotype) and S. flexneri (which has 15 serotypes) are the predominant species, comprising 24% and 66% of episodes respectively, while Shigella dysenteriae and S. boydii each account for only about 5% of isolates (100, 93). Based on animal challenge studies (101) and observations from GEMS (100), researchers have suggested that a multivalent vaccine construct targeting the O-antigens of S. flexneri 2a, 3a and 6 (and possibly 1b) and S. sonnei would provide direct protection against at least 72% of Shigella strains. It would also provide cross-protection for up to 89% of all strains.

S. dysenteriae type 1 could be considered for inclusion in Shigella vaccines if concerns arise about recrudescence of this notoriously virulent serotype that has been associated with epidemic outbreaks and pandemic spread, with high case fatality in all age groups. Given the approximately 10-year periodicity of S. dysenteriae type 1 epidemics, the absence of this dangerous serotype since the late 1990s should be viewed with guarded optimism. This strain is not included in most serotype-specific vaccine constructs (7).

Therefore, to provide sufficient strain coverage for recommended use in LMICs, Shigella vaccines will likely need to be multicomponent formulations, and/
or encompass conserved antigens. Vaccines must also be formulated and delivered in such a way that their costs are affordable, and their tolerability and immunogenicity is assured in the target populations, namely young children in LMICs under the age of 5 years (53, 3, 64). As described in section 4, consideration of the potential coformulation of Shigella vaccine components with other vaccines, administered using a compatible schedule and implementation strategy, would potentially offer a significant advantage in terms of vaccine delivery cost and coverage. Shigella vaccines for both oral and parenteral delivery may be found to benefit from coadministration of an adjuvant (102).

Based on this evidence, most Shigella vaccine candidates, whether whole cell based, hybrid or subunit, include the LPS-associated, O-specific polysaccharide (O-SP) antigen, and are multivalent. Numerous strategies are actively being explored (103), and the Shigella vaccine pipeline is diverse, with both oral (live-attenuated and formalin-inactivated) and parenteral (subunit-based) approaches evaluated in clinical studies. Some vaccine candidates comprise conserved antigens such as IpaB and IpaD in addition to, or instead of, O-antigen (104, 105, 106). It is hoped that the new candidates will demonstrate improved immunogenicity and efficacy in the target population of young children in LMICs.

6.2 Shigella vaccine clinical development considerations

Human field studies are deemed necessary to evaluate vaccine safety and efficacy in target populations, particularly young children in LMICs, prior to licensure in these regions. However, vaccine development may be accelerated by use of animal models and CHIM studies to demonstrate clinical proof of concept, thereby prioritizing the most promising candidates and de-risking investments in product development. CHIM studies permit an early understanding of the efficacy of candidate vaccines under controlled infection conditions, and allow evaluation and exploration of immunological markers, one or more of which could be correlates of vaccine-induced protective immunity. In addition, CHIM studies have a potential role in vaccine regulatory approval, as in the case of the travellers’ vaccine Vaxchora, where efficacy was demonstrated in a CHIM study supplemented by immunogenicity data (107).

Shigella CHIM studies have traditionally been performed in naive adults in high-income countries (HIC). CHIMs with S. flexneri 2a (2457T strain) and/or S. sonnei (53G strain) are established at three centres in the US (108), but standardization of both CHIM protocols and the enzyme-linked immunosorbent assay (ELISA) methods is crucial to compare vaccine candidates. Recent efforts to harmonize the Shigella CHIM approach have resulted in published consensus documents on standardization of the primary clinical endpoints (108) and alignment of the clinical study design (109), including agreement on clinical sample collection and immunological assays (110).

Further guidance is being developed to standardize the manufacture of strains for CHIM, as CHIM may be particularly useful to demonstrate efficacy against Shigella strains for which it will not be practical to measure field efficacy. Indeed, it has been proposed that licensure of Shigella vaccines could be achieved on the basis of CHIM studies without field efficacy studies. However, there is no fully established correlate of protection as yet: adult CHIM studies conducted in endemic areas may not reflect responses to vaccines in children; CHIM studies cannot be performed on the target population of children in LMICs; and there is no licensed Shigella vaccine available for immunological bridging. Therefore, for a first-in-class Shigella vaccine that is intended for use in young children in LMIC populations, it is expected that WHO policy recommendation, PQ and LMIC licensure will require a field trial to demonstrate safety and effectiveness in the target population.

With respect to field efficacy studies among children in LMICs, consensus on the appropriate clinical endpoint definition of diarrhoea of various severities is needed to make comparisons between candidates and studies. Selection of an endpoint such as medically-attended diarrhoea, as defined in GEMS, can normalize endpoint ascertainment, and generally represents a more severe form of diarrhoea than community diarrhoea (111, 118). However, there may not be access to medical care in all settings, and care-seeking likely depends on factors unrelated to severity, such as proximity to a facility, income and trust in the healthcare system.

Stratification of medically-attended diarrhoea into various severities using a scoring system has the advantage of post-hoc comparisons of various score cut-offs, as has been done in rotavirus trials using the Vesikari score (112). Although useful in the context of rotavirus vaccines (113), the Vesikari score may not be an appropriate severity indicator for Shigella diarrhoea. A recently developed Shigella severity score using GEMS data, comprised of dehydration, hospitalization and diarrhoea duration, performed similarly to a modified Vesikari score in predicting death among children with Shigella (114). Other scores have been proposed (115, 116,
and one of them was designed for community diarrhoea in LMICs and validated by the MAL-ED study consortium (118). In addition, Porter and colleagues have developed a severity score specifically for shigellosis that has been validated for use in CHIM studies and suggested as a secondary endpoint to evaluate vaccine impact (119). However, the clinical endpoints suggested for CHIM studies are not necessarily applicable to, nor feasible to collect in, paediatric field-efficacy studies.

If a correlate and threshold of protection are established following a successful phase 3 efficacy study in children in a LMIC, this could potentially leverage a large phase 2 safety and immunogenicity study as the basis of licensure for subsequent Shigella vaccine candidates. Modelling could be used to extrapolate declines in the correlate over time to provide an indication of the durability of protection, and enable subsequent age escalation in the priority target population by immunobridging up to 5 years. If acceptable to regulators, such a strategy could accelerate licensure for these vaccines, reducing cost of late-stage clinical development and incentivizing product developers.

A critical consideration for all stakeholders developing a vaccine for infants and children in LMICs is whether the data to support the proposed licensure pathway would also provide sufficient evidence to support a policy recommendation for introduction. In preparation for approval in LMICs, it will be important to engage with LMIC regulators in the design of the phase 3 efficacy study, as well as policymakers, to understand what other data, in addition to safety and efficacy, will be needed for establishing national approval and recommendation for use.

“Human field studies are deemed necessary to evaluate vaccine safety and efficacy in target populations, particularly young children in LMICs”

6.3 Shigella vaccine formulation and delivery considerations for use in LMICs

It is imperative to begin the development of the optimal vaccine formulation and presentation early so that it can be evaluated in pivotal clinical trials. The number of doses per regimen also should be carefully considered, based on the safety and efficacy of the final vaccine presentation. For procurement, broad implementation and practical use of vaccines in LMICs, it will be crucial to develop a vaccine formulation that is cost-effective and enables use in the target population (65, 120). Therefore it is critical to optimize thermostability.

Oral vaccines avoid many of the challenges of injectable vaccines. They are relatively easy to administer, assuming a low volume and palatable formulation is identified. Oral vaccines, such as polio, have the capacity to induce local mucosal immunity in the intestine, and can be potentially produced at a relatively low cost (121). Although oral rotavirus vaccines have demonstrated safety, efficacy and impact in LMICs, the target population of infants and young children under 5 years of age has proved challenging to immunize effectively. To optimize efficacy and improve public health impact, parenteral delivery is being explored (103, 89). As parenteral vaccine candidates progress to licensure, it will be critical to evaluate their compatibility for combination with other vaccines administered by the same route with a similar dosing schedule.

In addition, novel excipients that improve product shelf-life, as well as packaging technologies that allow inclusion of dry and liquid vaccine components in one container, would be helpful in addressing some of the presentation challenges, particularly for parenterally-administered vaccines (122, 123, 124). Several manufacturers have developed improved designs for dry and liquid vaccine presentations (125, 126). Where possible, innovative approaches, both for decreasing the storage footprint and to improve heat and freeze stability, should be evaluated to facilitate logistics and use in LMICs.

The optimal presentation, formulation and storage characteristics for infant vaccines to be used in LMICs (127) will be more constrained than those for adult travellers and the military. However, where possible, these attributes should be aligned, since the market for a traveller’s vaccine may help to provide an added economic incentive to vaccine manufacturers to also seek a paediatric indication.
## 7. PPCs for Shigella vaccines

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| **Indication** | Prevention of moderate-to-severe diarrhoea (MSD) due to *Shigella* infection. | Prevention of MSD caused by *Shigella* strains that have the same putative protective antigens as those in the vaccine. Prevention of long-term morbidity due to sequelae resulting from malnutrition and growth stunting is considered important to demonstrate effectiveness, and will likely be important for policy consideration. Although long-term morbidity may not be feasible to assess as primary endpoints pre-licensure, assessments of the reduction of long-term morbidity should be included as secondary and/or exploratory endpoints in pivotal efficacy studies.  
WHO encourages efforts to measure vaccine impact on antibiotic use as a secondary endpoint in vaccine trials and in vaccine impact studies.  
Prevention of less severe diarrhoea (LSD) is also considered important but, if measured in trials, should be as a secondary endpoint.  
Other anticipated vaccine benefits include the following: broad protection against *Shigella*-attributable disease, including strains not contained in the vaccine; reduction in impact of subsequent morbidity, including cognitive development; reduction of antimicrobial resistance; reduction of subclinical *Shigella* infections (carriage); herd effect; prevention of all-cause diarrhoea; and socio-economic benefits.  
While these anticipated benefits are important to demonstrate the value of *Shigella* vaccination, some may not be feasible to assess as robust endpoints within the constraints of a controlled pre-licensure clinical study. However, where feasible, exploratory endpoints related to these benefits should be collected during clinical studies. |
### Parameter | Preferred characteristic | Notes
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**Target population** | Infants from 6 months and children up to 36 months of age. Data supportive of longer-term effectiveness in children up to 5 years of age will be of interest for policy and introduction decision-making. | Infants and children under 5 years of age experience the highest incidence of *Shigella* disease. The peak of incidence is between 12–24 months of age. Some country and regional variation (+/- 6 months) in peak incidence is expected. The immunisation goal is full protection of infants by 12 months of age, thus covering both peak incidence in the second year of life and the greatest burden in children up to 5 years of age in LMICs. Additional potential target populations include the following: immunocompromised children; children under 5 years in crowded communities with high birth rates and recurrent propagated *Shigella* epidemics (i.e. subnational deployment, outbreak response); children over 5 years of age; adolescents and adults living in LMICs; travellers; military; MSM; PLHIV; and elderly and institutionalized persons. However, the preferred product characteristics for vaccines targeted at these populations may differ.

**Dose regimen and schedule** | 1–2 doses are expected to be needed for primary immunization, and are given during the first 12 months of life. An additional booster dose may be required to maintain effective, protective immunity through the first 5 years of life. | *Shigella* vaccines, it is assumed, will be implemented though the routine EPI vaccination schedules in LMICs. The schedule should be optimized to provide protection as maternal antibodies wane – with the first dose as early as 6 months and, if needed, the second dose by 12 months – prior to the peak of infection in the second year of life, to prevent the majority of *Shigella* disease, malnutrition and growth faltering. Every effort should be made to align the dose schedule with existing EPI vaccination schedules. The measles-containing vaccine (MCV) schedule may be compatible since this has a dose at around 9 months of age, and an additional MCV dose at 6 months is under consideration. If the vaccine demonstrates immunogenicity and durability, consideration could be given to administration within the EPI schedule prior to 6 months of age. The need for a booster dose will depend on the duration of protection conferred, and may be aligned with the MCV at 15 months, ideally for protection through the first 5 years of life. No more than one booster dose in the first 5 years of life is preferred. A single dose primary vaccination schedule is strongly preferred, and its feasibility should be assessed in the clinical development plan. Vaccine-impact modelling and pilot-implementation studies may be needed to inform and optimize the effectiveness of the implementation strategy and delivery schedule. Consideration for coformulation with EPI vaccines or other pipeline vaccines that have a compatible immunization schedule and delivery requirements would be advantageous.
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<td><strong>Safety</strong></td>
<td>A clinically acceptable safety and reactogenicity profile at least as favourable as current WHO-recommended routine vaccines for the given immunization age.</td>
<td>A favourable safety profile will need to be demonstrated in adults before progressing to younger ages and the target population. Contraindications should be restricted to known hypersensitivity to any of the vaccine components.</td>
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<tr>
<td><strong>Case definition of MSD</strong></td>
<td>Diarrhoea accompanied by dehydration, dysentery, or requiring hospitalization.</td>
<td>MSD is considered the most feasible measurement of desired vaccine impact for pivotal efficacy studies. Case ascertainment is therefore most practical in a medically attended context, where severity indicators can be systematically assessed and faecal samples collected. This proposed case definition needs validation with stakeholders and harmonization across clinical studies. A scoring system, instead of the case definition proposed, may provide a greater spectrum of disease, and could differentiate moderate from severe diarrhoea. Quantitative PCR (qPCR) of direct faecal samples more than doubles the likelihood of detecting putative <em>Shigella</em>, can detect novel antimicrobial resistance genes, and can differentiate <em>Shigella</em> species and serotypes. Misclassification due to the presence of IpaH gene in EIEC is a concern, though <em>Shigella</em> as an aetiological agent of MSD is far more common than EIEC. Serogrouping and serotyping PCR analysis could help confirm whether a pathogen is <em>Shigella</em> or EIEC. Microbiological culture is considered the “gold standard” for <em>Shigella</em> case detection; however, adoption of PCR as the primary microbiological outcome could significantly impact the statistical power and reduce the required size of the pivotal efficacy study. At the time of writing, there’s a proposal for discussion with the national regulatory agencies on the acceptability of qPCR as the primary outcome.</td>
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WHO preferred product characteristics for vaccines against Shigella

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| **Clinical endpoints** | **Primary:** Reduction in acute MSD caused by *Shigella* strains contained within the vaccine.  
**Secondary:** Reduction in Z-score for height-for-age (HAZ) as an indicator of growth stunting.  
Reduction in acute LSD due to *Shigella*, i.e. diarrhoea leading to care-seeking, but without dehydration or dysentery. | MSD is considered the optimal clinical endpoint to provide a measurable impact in endemic settings, although there is currently a lack of consensus on the case definition of this endpoint. The proposed primary clinical endpoint needs to be validated with stakeholders and harmonized across clinical studies, and the potential benefit of a scoring system should be explored.  
Secondary/exploratory endpoints should include initial and follow-up HAZ scores to measure potential impact on growth stunting, with or without overt diarrhoea, prevention of LSD and broad protection against *Shigella*-attributable disease. |
| **Efficacy**       | Efficacy of 60% (point estimate) or more against moderate-to-severe *Shigella* diarrhoea caused by serotype in vaccine-preventable *Shigella* diarrhoea.  
Assessment of field efficacy in response to all circulating serotypes would inform vaccine effectiveness. | For initial licensure, efficacy threshold will be based on prevention of disease caused by vaccine-preventable strains, i.e. those within the vaccine.  
Target value is based on observed lower performance of enteric vaccines, especially rotavirus, in endemic paediatric settings. Moderate efficacy is clinically meaningful and would be comparable to rotavirus vaccines in high-burden LMICs.  
Vaccine impact modelling can guide the acceptable efficacy. Ideally, assessment of vaccine efficacy, with data collected as early as possible from large field trials, should include factors such as the following: protection against serotypes not included in the vaccine; protection against all types of diarrhoea; impact on growth stunting; reduction in the use of antibiotics; and consequent AMR. However, it may not be possible to assess some of these data until post-licensure studies. |
<p>| <strong>Duration</strong>       | Duration of protection for 24 months following the last vaccine dose in the primary series, with protection up to 5 years desirable. | Efficacy trials should be designed to measure efficacy over at least a 2-year period. Duration of protection up to 5 years of age is optimal, but may have to be assessed in post-licensure studies. A booster dose may be required. Natural boosting due to asymptomatic exposure in endemic environments is also possible. |</p>
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<td><strong>Adjuvant requirement</strong></td>
<td>Preference for the absence of an adjuvant, unless there is clinical evidence of immunological benefit in the target population in low resource settings.</td>
<td>Evidence to justify an adjuvant inclusion with accepted safety profile is a prerequisite to add an adjuvant. Historical lack of efficacy of <em>Shigella</em> vaccines in infants provides a rationale for considering adjuvant to enhance immunogenicity.</td>
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<tr>
<td><strong>Immunogenicity</strong></td>
<td>Seek to establish correlate or surrogate of protection and threshold based on a validated assay measuring immune effector levels and functionality, which has been directly related to efficacy in the target population.</td>
<td>A correlate of protection would provide an immunological benchmark for the evaluation of <em>Shigella</em> vaccines and immunisation regimens. This would inform comparison of next generation vaccine candidates, including combination vaccines, as well as allow modelling of longevity of the immune response. The relationship to the duration of protection should be investigated. Serum IgG antibodies to <em>Shigella</em> O-antigen are proposed as a correlate of protection for O-antigen-containing vaccines (parenteral), based on association of protection observed in field efficacy studies, as well as CHIM studies. Confirmation is now required in the target population of LMIC infants in the context of a field efficacy study. However, this may not be a correlate for non-O-antigen-based (oral) vaccines, where other responses may be important to assess. Functional assays and cross-serotype responses should be evaluated in pivotal clinical studies. Seroconversion thresholds for immunologic responses that may be a surrogate marker, and ideally functional assays, should be validated within field clinical studies within the target population.</td>
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<td><strong>Non-interference</strong></td>
<td>Demonstration of favourable safety and immunologic non-interference upon coadministration with other vaccines recommended for use, including those within the EPI schedule.</td>
<td>There should be no significant interference in relation to safety and immunogenicity with concurrently administered or co-formulated vaccines. Vaccine formulations and schedules, potentially combinable with other EPI vaccines, should be considered and supported for the potential downstream, post-licensure, combination approaches.</td>
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<tr>
<td><strong>Route of administration</strong></td>
<td>Oral or injectable (IM, ID or SC), using standard volumes of administration, as specified in programmatic suitability for PQ or needle-free delivery.</td>
<td>Presentation and route must be suitable for use in the primary target population of 6 to 36 months of age. Where possible, innovative approaches to decrease the storage footprint and improve ease of use should be evaluated to facilitate logistics and use in LMICs.</td>
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<td><strong>Product stability and storage</strong></td>
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<td><em>Stability will depend on the final vaccine composition and state (dry or liquid). Some components that may need to be kept separate from other vaccine components until administration, for example, diluent, should be kept out of the cold chain.</em></td>
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<td>Two years at 2–8°C.</td>
<td><em>Innovative approaches to improve heat and freeze stability should be evaluated to facilitate logistics and use in LMICs.</em></td>
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<td>Vaccine vial monitor for at least 30 days at 37°C for stable solid formulation and may include adjuvant.</td>
<td><em>Additional data on controlled temperature chain (CTC) stability would be desirable.</em></td>
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<td></td>
<td>Vaccine vial monitor for 14 days at 37°C for stable liquid formulation, and may include adjuvant.</td>
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<td><strong>Vaccine presentation</strong></td>
<td>Provide vaccines, whenever possible, in &quot;ready-to-use&quot; presentations that do not require the mixing of components.</td>
<td><em>Provide vaccines in formats to minimize: 1) the number of preparation steps; 2) the potential for error during preparation and administration; and 3) the packaging footprint, particularly if a cold chain is required.</em></td>
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<td><em>Except for separately packed diluents, vial-filled presentations are strongly preferred over ampoule-filled presentations (127), as outlined in 2015 in WHO’s Generic preferred product profile for vaccines.</em></td>
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<td><em>Novel delivery technologies and packaging presentations may help to optimize and overcome the delivery challenges and increase vaccine effectiveness.</em></td>
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<tr>
<td><strong>Registration, PQ and programmatic suitability</strong></td>
<td>The vaccine should be PQ according to the process outlined.</td>
<td><em>WHO-defined criteria for programmatic suitability of vaccines should be met (128), as outlined in Assessing the programmatic suitability of vaccine candidates for WHO prequalification.</em></td>
</tr>
<tr>
<td><strong>Access and affordability</strong></td>
<td>The vaccine should be cost-effective and price should not be a significant barrier to access in LMICs.</td>
<td><em>It is imperative to capture the full burden of Shigella diarrhoea, including morbidity burden, in addition to the direct and indirect effects of infection. It is important to assess the broader societal and economic benefits of vaccination when articulating the value of a Shigella vaccine from a LMIC prospective.</em></td>
</tr>
<tr>
<td></td>
<td>Dosage, regimen and cost of goods amenable to affordable supply.</td>
<td><em>The vaccine’s potential impact on health systems and other aspects of implementation science should be evaluated pre- or post-licensure, as this will also contribute to the full value of vaccine assessment.</em></td>
</tr>
</tbody>
</table>
WHO preferred product characteristics for vaccines against Shigella

References


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