DRAFT WHO Preferred Product Characteristics for Vaccines against *Shigella*

Written comments proposing modifications to this text must be received by **28 May 2020** and entered in the Comment Form (available separately), and should be addressed to the Responsible Officer: Dr Birgitte Giersing at giessingb@who.int.
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The draft preferred product characteristics (PPCs) for *Shigella* was prepared by Birgitte Giersing and Ibrahim Khalil (consultant), in the Department of Immunizations, Vaccines and Biologicals (IVB) at WHO, with review by and contributions from a global expert working group. All working group members declared any conflicts of interest for the record. Sincere appreciation to the members of this group for their assistance and input, as well as additional reviewers.

Thanks to those who provided input through this public consultation which is open from 30 April to 28 May 2020.
# Abbreviations and glossary

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<tr>
<td>AMR</td>
<td>Anti-microbial resistance</td>
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<td>CoP</td>
<td>Correlates of protection</td>
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<td>CHIM</td>
<td>Controlled Human Infection Models</td>
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<td>CF</td>
<td>Colonization Factor</td>
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<td>DALYs</td>
<td>Disability Adjusted Life Years</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>ETEC</td>
<td>Enterotoxigenic <em>Escherichia coli</em></td>
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<td>EIEC</td>
<td>Enteroinvasive <em>Escherichia coli</em></td>
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<td>EED</td>
<td>Environmental Enteric Dysfunction</td>
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<td>FVVA</td>
<td>Full Vaccine Value Assessment</td>
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<td>GBD</td>
<td>Global Burden of Disease</td>
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<td>HIC</td>
<td>High-income country</td>
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<td>IVB</td>
<td>Immunizations, Vaccines &amp; Biologicals</td>
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<td>IHME</td>
<td>Institute for Health Metrics and Evaluation</td>
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<td>LMIC</td>
<td>Low and middle-income country</td>
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<td>MCEE</td>
<td>Maternal Child Epidemiology Estimation</td>
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<td>qPCR</td>
<td>quantitative Polymerase chain reaction</td>
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<td>PDVAC</td>
<td>Product Development for Vaccines Advisory Committee</td>
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<td>PPCs</td>
<td>Preferred product characteristics</td>
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<td>PQ</td>
<td>Pre-qualification</td>
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<td>R&amp;D</td>
<td>Research and Development</td>
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<td>SAGE</td>
<td>Strategic Advisory Group of Experts (on Immunization)</td>
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<td>TPP</td>
<td>Target Product Profile</td>
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<td>WHO</td>
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Executive summary

Diarrhoal diseases are among the leading causes of morbidity and mortality worldwide. Among children younger than 5 years, it is estimated that diarrhoea is responsible for about 446,000 deaths, which are geographically concentrated in sub-Saharan Africa and South Asia. Significant reductions in diarrhoeal disease mortality have been achieved over the last 20 years, however these have not been paralleled by declines in diarrhoea associated morbidity, which continues to negatively impact 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, like vaccines, remains a public health priority for 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, across all age groups with broad geographical distribution, the greatest burden is among children in LMICs where it is estimated to be responsible for between 28,000 (MCEE estimates) and 64,000 deaths (Global Burden of Disease study estimates), among children under 5 years of age. It is also an important cause of diarrhoea and dysentery in people older than 5 years, with an estimated 270 million episodes occurring annually among all ages.

*Shigella* infections spread easily in areas with poor sanitation and hygiene, where there is limited access to clean water. For young children, repeated infections due to these pathogens - that may be symptomatic or asymptomatic - can result in malnutrition and induce or exacerbate stunting. This has long-term implications, and adverse consequences on physical and cognitive development. In addition, *Shigella* can cause severe illness among travelers, deployed military personnel and expatriates in LMICs, and is associated with irritable bowel disease in these populations. *Shigella* infections also have epidemic potential in both younger and older age groups, especially with *S. dysenteriae* type 1.

Treatment options for shigellosis include oral rehydration salts and, when dysentery is present, antimicrobials are used. 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 anti-microbial resistance (AMR). In addition, considering the potential for herd immunity and protection from all cause diarrhoea, a phenomenon that has been observed with rotavirus vaccine use, 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 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 exist. Vaccine development has faced significant technical challenges but has also been impeded by a lack of prioritization by global level stakeholders, and an unclear commercial value proposition to inform investment. The World Health Organization (WHO) develops Preferred product characteristics (PPCs) that are intended to provide strategic guidance on preferences for new vaccines, specifically from a LMIC perspective. The articulation of PPCs for Shigella vaccines is intended to help advance product development and support policy assessment for the use in areas where the vaccine is most needed. To frame the development of Shigella vaccine PPCs, the 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 years olds would also offer significant, under recognised public health value to older children, adolescents and adults by reducing long term morbidity 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 WHO PPCs

The mission of WHO’s department of Immunization, Vaccines and Biologicals (IVB) is to accelerate the development and uptake of safe and effective 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 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, 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 candidates’ specific target product profiles (TPPs). Selected 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 LMIC stakeholders, and technical feasibility.² They may be updated in the event of product or technology innovations, or any other change in the identified need or 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.
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 to i) reduce mortality and morbidity from vaccine preventable diseases across the life course, and ii) 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 diarrhoea5,6 with high case-fatality rates in children with severe disease.7, 8

In addition, diarrhoea due to *Shigella* among travelers and military recruits can cause significant morbidity, including being incapacitated or placed sick in quarters by their illness, requiring intravenous fluids, and requiring hospitalization.9 Acquiring *Shigella* infection during travel can introduce antimicrobial-resistant *Shigella* into new populations,10 and can cause post-infection complications, such as reactive arthritis11 and irritable bowel syndrome,12 and there is potential for outbreaks in tourist groups and military deployment settings. The rise of antibiotic-resistant enteric bacteria has made the prevention of infectious diarrhoea, and the need for an effective vaccine against *Shigella*, an even greater public health priority.13

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.**

At the time of writing, the *Shigella* vaccine candidates in clinical development include multivalent blends of O-antigen-based and whole cell based candidates. Multivalent vaccines against the four most common circulating *Shigella* serotypes are expected to achieve about 64% coverage, which could increase to over 85% depending upon the degree of cross-protection elicited among *S. flexneri* strains not contained in the vaccine.14 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. Such approaches using combinations of vaccines against different pathogens would offer significant advantages considering the congested EPI schedule. The *Shigella* candidates will likely benefit from guidance regarding WHO and LMIC vaccine preferences as they navigate stage gates for future investment and evidence-based decision making.
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. *Shigella* is an antigenically diverse pathogen that comprises four species, or subgroups. The four *Shigella* species and their various serotypes have differing geographical distribution and epidemiological significance. Each species is subdivided into serotypes and sub-serotypes, distinguished by components of the lipopolysaccharide O antigen repeats. In addition to Shiga bacillus, now known as serotype 1 of *Shigella dysenteriae*, 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*. The incubation period of *Shigella* infection is typically 1–4 days, but up to 8 days with *S. dysenteriae* type 1. The proportion of *Shigella* infections that occur asymptotically in young children has not been fully established, however it is suggested to increase with age. In 2017, WHO recommended that ciprofloxacin be the first choice for treating adults and children with *Shigella* dysentery, and azithromycin, cefixime, and ceftriaxone should be considered as second choices. WHO also suggested trimethoprim-sulfamethoxazole as another second choice; however, resistance is widespread to this drug combination and other drugs that are otherwise considered efficacious (e.g., ampicillin, nalidixic acid, and pivmecillinam).

3.2. *Shigella* in Children

The Global Enterics Multicenter Study (GEMS) found the incidence of *Shigella*-attributed moderate-to-severe diarrhoea (MSD), diarrhoea that led to care seeking and one or more of dehydration, dysentery, or hospital admission, varied by age group. 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, using qPCR. 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.

The Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) multisite 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 sites-specific estimates ranging from 4.2-65.2 cases per 100-child years.
3.3.  *Shigella* in Adults and travelers

*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.\(^{21}\) Although this strain was multidrug-resistant before introduction into MSM, sub-lineages acquired additional plasmid-mediated resistance to azithromycin and ciprofloxacin, possibly from selective pressure exerted by treatment of sexually transmitted co-infections.\(^{22}\) Along with multidrug-resistant *S. flexneri* 3a, distinct multidrug-resistant *S. sonnei* and *S. flexneri* 2a strains emerged among MSM. These strains included clusters of ciprofloxacin-resistant *S. sonnei* in Australia, azithromycin resistant *S. flexneri* in the USA,\(^{23}\) and azithromycin-resistant *S. sonnei* strains producing extended-spectrum β-lactamase in the UK.\(^{24}\)

3.4. Mode of Transmission of *Shigella*

Humans are the only natural host for *Shigella*, and it is transmitted mainly through the fecal-oral route via direct person-to-person transmission, contaminated food and water, and fomites.\(^7\) The low infectious dose facilitates person-to-person spread. As few as ten *S. dysenteriae* type 1 and 180 *S. flexneri* or *S. sonnei* colony-forming units produce symptomatic infection in volunteers.\(^{15}\) Poor sanitation and hygiene conditions increase the likelihood of disease transmission. Outbreaks can disseminate rapidly, sometimes initiated by a food or waterborne locus, and then propagated by person-to-person contact.\(^7\) Houseflies were suggested as a mechanical vector for transmission in settings where disposal of human faeces is inadequate.\(^{25}\)

3.5. Pathogenesis, Clinical Presentation, and Complications

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. Processes that enable *Shigella* to overcome these barriers include proton consumption systems, resistance to locally-produced antimicrobial peptides, and production of mucinases.\(^7\) *Shigella* uses a range of bacterial effector proteins to invade (e.g., IpaA-D), replicate, and disseminate throughout the intestinal epithelium (e.g., VirG/IcsA). These effectors, and the needle-like type III secretion system through which they are injected into the host cell cytosol, are encoded by a virulence plasmid common to all *Shigella* species. The aggressive watery or mucoid/bloody diarrhoea is a direct consequence of *Shigella* invasion and destruction of the large intestinal epithelium.\(^{26}\)
Most illnesses in otherwise healthy individuals are mild and symptoms subside in a few days. In a few cases, there is progression within hours to days, to frank dysentery with frequent small stools containing blood and mucus, accompanied by lower abdominal cramps and tenesmus. Patients with severe infection might pass 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.

*Shigella* occasionally causes invasive infections such as meningitis, osteomyelitis, arthritis, and splenic abscess. *Shigella* sepsis, rare in otherwise healthy people, occurs most often in young or malnourished infants and children and people with HIV, and carries a poor prognosis. Intestinal complications of shigellosis are uncommon but often severe and include rectal prolapse, intestinal obstruction, toxic megacolon, and perforation; all these complications are more common with *S. dysenteriae* type 1 infections. The most frequent extraintestinal manifestation is seizures, which are generally reported in 5–30% of children hospitalized with shigellosis, and are reported most often in young children with fever or metabolic derangements known to precipitate seizures.

Haematological manifestations of shigellosis include leukaemoid reaction (neutrophil counts >50 000 per μL) and haemolytic uremic syndrome. *Shigella* vaginitis is well described, particularly in prepubertal children. Pregnant women with *Shigella* infection have had preterm labour and can transmit the infection to the new-born.

### 3.6. Diagnosis of *Shigella*

Conventional bacterial culture is the gold standard for diagnosing *Shigella* infection. Culture also enables serotyping, which is a key feature to identifying priority *Shigella* vaccine targets and important for defining microbiologic endpoints of *Shigella* vaccine trials. Furthermore, culture allows for identification of antibiotic susceptibility, which is becoming crucial as antimicrobial resistance evolves. However, *Shigella* is a fastidious organism to culture; when a delay between stool collection and plating is anticipated, transport media is needed to help maintain organism viability.

Since 2013, several nucleic acid-based diagnostic panels have been developed and approved by the US Food and Drug Administration for detection of enteric pathogens, including *Shigella*, however this method does not require a living organism to be positive, and like culture methods, it cannot differentiate between symptomatic and asymptomatic cases. Also as of this writing, most molecular panels did not distinguish between *Shigella* and rare enteroinvasive *Escherichia coli* (EIEC), which share the same gene target, *ipaH*. Although PCR assays are not able to provide susceptibility data to
inform antimicrobial treatment, they increase the diagnostic yield and rapid PCR assays could guide pathogen-specific management if affordable and feasible in LMIC settings. Identification of specific resistant gene targets that correlate closely with phenotypic antibiotic resistance to *Shigella* is an area of active research that is needed before molecular tools can completely replace culture in Point of Care health facilities.

3.7. **Prevention and treatment of* Shigella*

Proven, lifesaving interventions to prevent and treat diarrhoeal disease, including illness caused by *Shigella*, already exist. Prevention methods include improved sanitation and hygiene, access to safe drinking water, exclusive breastfeeding, optimal complementary feeding and micronutrient programs, and vaccines against other pathogens (e.g., rotavirus and measles). 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.

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; however, breastfeeding during a child’s first hour of life, exclusively for six months of age, and for two years overall is well short of universal. Moreover, the peak incidence of shigellosis occurs in the 12-23 month age group when breastfeeding is no longer emphasized as a public health message.

The cornerstone of *Shigella* treatment is maintenance of hydration and electrolyte balance, with antibiotics for dysentery for children in LMIC. Since shigellosis among otherwise healthy children in High Income Countries (HIC) is often self-limited, antibiotic use should be restricted to children with, or at risk for, severe disease. In either case, antibiotic therapy should be guided by available antibiotic resistance data whenever possible. In young children, oral rehydration with a reduced osmolarity solution is indicated to treat the WHO-defined category of ‘some dehydration’ and is preferable to intravenous fluids unless severe dehydration is present. Provision of adequate nutrition is critical in children in low resource settings and it has been found that zinc treatment can speed 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.
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. The benefit of antibiotics for non-dysenteric *shigella* diarrhoea is unknown. However it is suggested that if antibiotic treatment is started early, disease is aborted and does not progress to dysentery.\textsuperscript{46} WHO recommends antibiotic treatment for all children with dysentery, with the assumption that most cases are caused by *Shigella*. The rise of antibiotic-resistant enteric bacteria has made the prevention of infectious diarrhoea, and the need for an effective vaccine, an even greater public health priority to prevent the spread of AMR.\textsuperscript{47} The WHO Global Antimicrobial Resistance Surveillance System\textsuperscript{48} identified *Shigella* as a priority pathogen for the development of new interventions. In addition, growing concerns over increasing antibiotic resistance among *Shigella species* has led Wellcome to recommend that vaccine development should be accelerated.\textsuperscript{13}

Therefore, an intervention like a new *Shigella* vaccine is a critical element of both the short-term and long-term preventive strategies, to alleviate the burden of diarrhoeal disease morbidity and mortality in areas of the world, where it is most needed.
4. Full Value of Vaccines Assessment (FVVA) for Shigella Vaccines

The value proposition of a vaccine candidate defines its epidemiologic, product development, economic, market, policy, financing, delivery and regulatory environments to guide investment in that product. Value propositions seek to identify the major stakeholders and beneficiaries, who may value the product differently, and articulate how the envisaged product will address their unmet need, as well as identify gaps in evidence to justify the product’s uptake.49 The fundamental elements that are expected to inform the Shigella vaccine value proposition include a robust assessment of the current, and future, mortality and morbidity-related socio- and macroeconomic burden of disease and the impact of a vaccine on emerging AMR. It is therefore imperative to capture the full, i.e. direct (individual) and indirect (population associated) burden of Shigella disease.

A cost-effectiveness model for two ETEC and Shigella vaccine candidates was developed to evaluate vaccine impact on long-term sequelae of diarrhoeal diseases over the first ten years after vaccine introduction in children under five years old living in 79 low and low-middle income countries.50 However, to date, burden estimates have not included comprehensive estimates of disability adjusted life years (DALYs) that specifically assess long-term sequelae such as stunting, malnutrition, and cognitive impairment, as well as an increased risk of death due to other infectious disease causes.

Travelers, deployed military personnel, and expatriates in LMICs51,52 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 adult travelers and the military are likely not compatible with the programmatic requirements for a vaccine to be suitable for pediatric use in LMICs. There are a larger number of constraints related to product presentations (dimensions of packaging, thermostability), duration of protection and number of doses for vaccines intended for implementation in the expanded programme of immunization. Target populations that could potentially benefit from the availability of an effective vaccine, in addition to infants and young children in LMIC include travellers and the military, the private sector in emerging middle-income countries, older children, adolescents, and adults. 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.3,53

In order to determine the potential market size and most cost-effective implementation strategy for Shigella vaccines, the disease burden needs to be characterized at regional, national levels and
potentially sub-national levels for large, disparate populations. Co-infecting enteric pathogens, asymptomatic infections, antigenic diversity, and variability of diagnostic methods can complicate the determination of diarrhoeal aetiology for children in LMICs. The global burden of enteric diseases, including *Shigella* estimates, are currently being modeled by 2 groups: The Institute for Health Metrics and Evaluation (IHME) and Maternal Child Epidemiology Estimation (MCEE). Each disease burden model has its strengths and limitations.\(^{54}\) Factors such as inclusion/exclusion criteria for studies, model inputs and adjustments, assessment of pathogenicity, geographical representativeness, and country or regional extrapolation affect conclusions about the attributable burden. An additional contributor to uncertainty intervals in these estimates is the geographic heterogeneity that exists for the *Shigella* species, their various serotypes and respective disease burden. 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. Nevertheless, recent evidence points to the emergence of *S. sonnei* in economically transitional states, effectively replacing *S. flexneri* to become the predominant shigellosis aetiology.\(^{55, 56}\) Neither IHME nor MCEE estimates account for these different *Shigella* species and their geographic distribution.

A recent analysis\(^ {57}\) explored how accounting for subnational and economic heterogeneity in *Shigella* and ETEC disease burden affects the projected vaccine impact and cost-effectiveness of ETEC and *Shigella* vaccines after introduction in four sub-Saharan African countries, using dynamic models for provincial areas and socioeconomic status. It was suggested that impact and cost-effectiveness were more favorable if vaccinations reach the most vulnerable children in underserved provinces. Therefore, a *Shigella* vaccine may be appropriate for use in high burden areas at sub-national level in some countries, and not necessarily for introduction into the national routine EPI immunization program. Surveillance data will be essential to guide vaccine implementation, and to inform the implementation strategy, either as a single vaccine, or co-administered or combined with other vaccines. In addition, *Shigella* vaccine candidates should be formulated in such a way as to facilitate their use in future combination vaccine strategies that will likely serve to enhance uptake in public-sector markets of LMICs, where ease of vaccine delivery is critical to achieving equitable coverage.\(^ {58}\)

In order to fully capture the value of a *Shigella* vaccine, multiple aspects should be considered in the context of other interventions. 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.
5. The burden of *Shigella* Diarrhoea

5.1. IHME Global Burden of Disease (GBD) study Mortality Estimates

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

5.2. The Maternal Child Epidemiology Estimation (MCEE) group Mortality Estimates

The MCEE group (previously known as CHERG), published estimates of pathogen-specific mortality for children under 5 years of age using etiologic data from hospital inpatient studies as a proxy for the pathogen distribution.\(^6\) MCEE estimated 712,000 diarrhoea deaths in all age groups and 28,000 (12,000–53,000) *Shigella* deaths in children younger than 5 years of age.

5.3. Diarrhoeal Diseases and *Shigella* Morbidity Burden Estimates

The limitations and discrepancies in mortality estimates pose challenges for vaccine developers, funders and policy makers in prioritizing the relative importance of intervention strategies against *Shigella*. Mortality modelling and diagnostic methods are continually undergoing optimization, resulting in variation of the estimates for each iteration. Both estimates indicate an unacceptable burden of acute disease leading to mortality. In addition, the potential value of a *Shigella* vaccine should not just account for impact on death during the acute phase of the illness; the burden estimates and associated vaccine impact should also incorporate the benefits that a vaccine could have on reduction of the long term morbidity and indirect effects, as well as reduction the use of antibiotics for treatment. 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.\(^6\),\(^6\),\(^6\) Repeated infections, which are common among children in LMICs because of the multiple species, serotypes and subtypes, can induce or exacerbate growth stunting and other forms of malnutrition, and reduced immune function. These infections can also hinder cognitive development, with adverse consequences on school performance and economic status.\(^6\),\(^6\),\(^6\)
There are gaps in our knowledge base related to linking the causes of post-infectious sequelae with specific pathogens. The long term impact of *Shigella* on individual health, cognitive function, and macroeconomic effects would also benefit from further study.\(^{66}\) In an effort to quantify a proportion of this morbidity burden for diarrhoeal diseases, IHME conducted a study to quantify the long-term sequelae due to growth faltering, using disability-adjusted life years (DALYs). DALYs is the sum of the number of years of life lost due to premature mortality (YLL) and the number of years lived with disability (YLD).\(^{59}\) This metric is widely used in public health practice to assess and monitor population health and to set health priorities in a given country. The study showed that the global burden of diarrhoea is substantially underestimated when only incidence and mortality are considered, and that accounting for long-term sequelae associated with growth impairment increased the number of diarrhoea DALYs among children younger than 5 years 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, surpassing malaria and neonatal encephalopathy in the number of DALYs in this age group.\(^{67}\) To date, there is no *Shigella* specific analysis to account for the additional DALYs burden due to long term sequelae. Such an analysis will help to refine the pathogen specific burden estimates and the full value of a vaccine for *Shigella*.

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 vaccines implementation. While policymakers in some endemic nations are very 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 an *Shigella* vaccine may be limited due to lack of uptake.

### 6. *Shigella* vaccine development

#### 6.1. *Shigella* Vaccine feasibility and Approach

Human and animal challenge trials with virulent *Shigella*, as well as observational studies in endemic areas, have shown that the incidence of disease decreases following *Shigella* infection, supporting biological feasibility of a vaccine. A challenge/rechallenge study with virulent *S. flexneri* 2a in 12 non-human primates demonstrated 100% protection.\(^{68}\) Similarly, in a controlled human challenge model, protection was demonstrated for adults given attenuated *S. flexneri* 2a strains and challenged with virulent *S. flexneri* 2a. Protection was also demonstrated in volunteers who were rechallenged with wild
type *S. flexneri* 2a.\(^9\) In one model using six adult volunteers, 100% protection was observed against fever and diarrhoea associated with clinical *S. sonnei* infection in all volunteers who were rechallenged with a virulent *S. sonnei* strain, and 70% protection was observed in volunteers challenged and rechallenged with virulent *S. flexneri* 2a.\(^7\) Field epidemiology studies suggest a chronological association of protection with age; younger individuals are more susceptible as indicated by high incidence rates and this is compatible with the concept that acquired immunity against *Shigella* is developed in time through natural exposure.\(^7\), \(^2\), \(^3\) The MAL-ED study found a 15-33% reduction in risk of *Shigella*-attributed diarrhea after 1 or more *Shigella* infections,\(^7\) which was similar to the 14% protection reported among children in Chile (72% serotype specific protection).\(^7\)

Although vaccine development is clearly feasible from the evidence generated from these studies, several challenges remain before success can be achieved. There are more than 50 serotypes of *Shigella* based on the diversity in protective O-antigen, the polysaccharide component of the outer membrane lipopolysaccharide (LPS), that increases antigenic variability. While there are efforts to consolidate evidence and a consensus for firm correlates of protective immunity,\(^7\) additional challenges still exist, such as the lack of robust and informative animal models, and unclear commercial interest.

Immunity to *Shigella* appears to be serotype-specific. With four major species and 50 different serotypes of *Shigella*, the task of developing an all-encompassing vaccine, even if scientifically feasible, poses challenges.\(^7\) However solutions have been found for other bacteria such as pneumococcus. Like *Shigella*, immunity must cover multiple serotypes and there is evidence that the same serotypes predominate across a wide geographic areas of S. Asia and sub-Saharan Africa. The four *Shigella* species and their respective serotypes are frequently isolated in diarrhoeal surveillance studies.\(^4\), \(^5\) A *Shigella* vaccine targeting the O-antigens of *S. flexneri* 2a, 3a, and 6 (and possibly 1b) and *S. sonnei* is expected to cover the majority of all *Shigella* illnesses.\(^7\) Researchers from GEMS have suggested that such a multivalent vaccine construct would provide direct protection against 72% of *Shigella* strains and cross-protection for up to 89% of all strains.\(^4\) Another species, *S. dysenteriae* type 1, has been considered for inclusion in a multivalent *Shigella* vaccine. *S. dysenteriae* type 1 has been associated with epidemic outbreaks and pandemic spread with high case fatality in all age groups. Given the circa 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, in order to provide the strain coverage, *Shigella* vaccines will likely need to be multi-component formulations. Vaccines must also be formulated and delivered in such a way that their costs
are reasonable, and their tolerability and immunogenicity is assured in the target populations, namely young children in LMICs under the age of 5 years. As described in section 4, consideration of the potential co-formulation of a *Shigella* vaccine with others that are administered in 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 co-administration of an adjuvant such as the double mutant labile toxin (dmLT). An additional challenge for vaccines in low resource settings is the sub-optimal performance of both viral and bacterial vaccines in terms of efficacy and effectiveness, especially with oral vaccines, as has been demonstrated in many countries in Asia and Africa. Several reasons for this phenomenon have been suggested, including underlying gut enteropathy, co-infections and malnutrition.

### 6.2. Shigella vaccine pipeline

In the past 3 decades, the first-generation chemical conjugate vaccine consisting of O-antigen of *Shigella sonnei* lipopolysaccharide conjugated to recombinant exotoxin of *Pseudomonas aeruginosa* (rEPA), was advanced to efficacy trials and was shown to induce protection in Israeli adults and children older than 3 years. However, the candidate failed to protect in the very young. Lack of protection was associated with a decrease in serum O-antigen IgG levels with descending age.

This study, and others, demonstrated proof of concept that immunity to *Shigella* is serotype specific and associated the level of protection observed with the serum IgG titer to O-antigen. Comparison of efficacy and immunogenicity data from the Controlled Human Infection Model (CHIM) study further supports serum O-antigen IgG as a correlate of protection.

These findings suggest that serum O-antigen IgG may be a surrogate or correlate of protection, and that a vaccine able to induce high levels of such antibodies among LMIC children will likely confer protection in this vulnerable population. However, parenteral immunization is known to benefit from previous mucosal priming, which may be present in the older vaccine recipients, but not in the infant population.

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. The use of this antigen in most candidates is based on the finding that *Shigella* immunity is serotype-specific. Numerous strategies, including live attenuated oral, killed oral, and subunit parenteral vaccines, are actively being explored.
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 new vaccine candidates are exploring the use of conserved antigens in addition to or instead of O-antigen. Recently, a core *Shigella* proteome microarray consisting of over 2000 antigen targets common to all *Shigella* species was used to assess serum samples from volunteers immunized with killed, attenuated and wild-type *S. flexneri 2a*. These studies identified a protein type three secretion system (T3SS) signature associated with clinical protection. It is hoped that the new candidates will demonstrate improved immunogenicity and efficacy in the target population of young children in LMICs.

### 6.2.1. Vaccine candidates in clinical trials

#### Polysaccharide-conjugate candidates

Three parenteral O-antigen-based glycoconjugate vaccines are currently in clinical development. The most advanced is a bioconjugate vaccine, with *Shigella* O-antigen of wild-type length covalently coupled in sun-type format to rEPA within genetically-engineered *E. coli*. A monovalent *S. flexneri 2a* bioconjugate was immunogenic in phase 1 clinical trial and although it did not protect against the primary endpoint, it protected against moderate to severe shigellosis/dysentery in a CHIM study in US adults. The quadrivalent formulation has entered a phase I/II study in Kenya.

Another candidate is a ‘GMMA’ (Generalized Modules for Membrane Antigens), an outer membrane vesicle vaccine which contains multiple *Shigella* protein antigens and is also considered an O-antigen-based vaccine, since the vesicles are serving as a delivery vehicle for O-antigen. The *S. sonnei* monovalent GMMA candidate was tested in phase 1 studies in France and the UK, and has subsequently been tested in Kenyan adults and a CHIM study.

The third vaccine candidate is a synthetic O-antigen conjugate, incorporating *S. flexneri 2a* O-antigen synthesized from 15 monosaccharide units and conjugated to tetanus toxoid. In a Phase 1 first-in-human study it was demonstrated to be safe and induced high levels of serum O-antigen IgG in adults, that appear to be significantly higher than *flexneri 2a-rEPA*. A CHIM study in the US and descending-age study in Kenya are planned for the near future using the monovalent *S. flexneri 2a* formulation, as well as Phase 1-2 studies of a quadrivalent formulation in due course in Kenya.
**Invaplex**

Artificial Invaplex (Invaplex<sub>AR</sub>) has been produced from a blend of under-acylated LPS and recombinant IpaB and IpaC<sup>98</sup> and this approach brings together important serotype-specific and conserved antigens of *Shigella*. The artificial formulation may be more immunogenic than naturally produced Invaplex preparations studied earlier<sup>99</sup>. This artificial Invaplex candidate completed a phase 1 trial in 2020.

**Whole-cell based candidates**

The main oral whole based cell candidates that were advanced in clinical trials are the trivalent *Shigella* killed whole cell, comprising formalin-inactivated *S. flexneri*<sub>2a</sub>, and *S. sonnei*, which proved to be safe and immunogenic<sup>100</sup>. This approach is now being further developed with a quadrivalent candidate. The live attenuated WRSS1 and WRSs2/3 are prototypes for the *S. sonnei* component of a multivalent vaccine being developed following attenuation by VirG deletion, which limits cell-to-cell spread of bacteria. Of the three, the WRSs2 mutant is being advanced in clinical development<sup>97,101</sup>. Another live *Shigella* vaccine candidate, attenuated by deletions in *guaBA*, and two *Shigella* enterotoxins *sen* and *set*, (CVD 1208S-GMP) was both well-tolerated and immunogenic in a Phase I study<sup>102</sup>.

**6.2.2. Vaccine candidates in Preclinical evaluation**

Several candidates are in preclinical development<sup>103</sup>, including a live LPS-free genetically attenuated *Shigella* vaccine strain (ShigETEC), that is amenable to the heterologous expression of diarrhoeal antigens such as ETEC<sup>77</sup>. The first Phase 1 study of this candidate is expected to start in Europe during the first half of 2020<sup>104</sup>. Other ‘hybrid’ approaches include aTy21a typhoid candidate expressing *Shigella* LPS and a combined Shigella-ETEC vaccine constructed from attenuated *Shigella*<sup>76</sup>. 
**6.3. Shigella Vaccine Immunogenicity and efficacy Considerations and the role of CHIM in advancement of Shigella vaccines**

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 to demonstrate clinical proof of concept, thereby prioritizing the most promising candidates and de-risking product development. CHIM studies permit an early understanding of the efficacy of candidate vaccines under controlled infection conditions and allow evaluation and exploration into immunological markers of vaccine-induced immunity. The model can be used to guide evidence-based decisions for candidate selection and inform investments required to take a candidate vaccine through late-stage clinical development.\(^{105}\) In addition, CHIM studies have a potential role in vaccine regulatory approval, as was demonstrated in the case of the travelers’ vaccine Vaxchora where efficacy was demonstrated in CHIM study supplemented by immunogenicity data.\(^{106}\)

*Shigella* CHIM studies have traditionally been performed in naïve adults in high income countries (HIC). The potential for undertaking CHIM studies in adult populations within LMICs, and in particular the relevance of results from adults CHIM studies to pediatric populations in endemic settings is being explored. These models must contend with the prevalence of endemic infection in these settings and the likelihood that the participants will be previously primed. There is significant debate regarding the feasibility of CHIM studies in pediatric populations, where the regulatory and ethical considerations with respect to risk vs benefit are complex. In preparation for approval in LMICs, it will be important to further familiarize LMIC regulators with CHIMs\(^{107}\) with clear presentation of the safety and efficacy data, as well other data that will be needed for establishing a WHO policy recommendation for use.

Although CHIM studies cannot currently be performed in children, limiting the direct applicability of findings to this population, CHIM data\(^{108}\) for the TypBar-TCV typhoid conjugate vaccine (Bharat Biotech) facilitated an immunologic ‘bridge’ to licensed polysaccharide vaccine.\(^{109}\) Data from this study using Typbar-TCV in a population of immunologically naïve adult volunteers produced an estimate of efficacy of 87.1% (95% CI 47.2-96.9%) based on an endpoint of persistent fever followed by positive blood culture. These data, in addition to previous field trials with other typhoid conjugate vaccines, were considered as good supporting evidence for WHO policy recommendation and prequalification of the vaccine.\(^{109}\) However, the expectation is that, for a first in class *Shigella* vaccine that is intended for use in
young children in LMIC populations, WHO policy recommendation, PQ and LMIC licensure will require field study to demonstrate safety and effectiveness in the target population.

Given the application of the *Shigella* CHIM to inform vaccine prioritization decisions, and its potential to support vaccine licensure and policy decisions as outlined above, efforts to harmonize the various CHIM models in the *Shigella* field are needed. The primary clinical endpoint in *Shigella* CHIM studies has varied across institutions, investigators, studies, and sponsors, ranging from mild to more severe disease, and a consistent and reproducible model to assess vaccine candidates across multiple trials and trial sites is necessary.

Recent efforts to harmonize the *Shigella* CHIM approach have resulted in published consensus documents on standardization of the primary clinical endpoints and alignment of the clinical study design, including agreement on clinical sample collection and immunological assays. It is intended that these consensus positions will be incorporated into future clinical protocols. Further guidance is being developed to standardize the manufacture of strains for CHIM. CHIM may be particularly useful to demonstrate efficacy against *Shigella* strains for which it will not be practical to measure field efficacy.

With respect to field efficacy studies among children in LMICs, consensus on the appropriate clinical endpoint definition of diarrhea of various severities is needed to make comparisons between candidates and studies. Medically-attended diarrhea can centralize endpoint ascertainment and generally represents a more severe form of diarrhea than community diarrhea. Stratification of medically-attended diarrhea into various severities may be done by using a scoring system. The Vesikari score is used in rotavirus vaccine trials, and although useful in that context, may not be an appropriate indicator of *Shigella* diarrhea-severity. Other scores have been proposed to grade diarrhoeal severity, and one of them was designed for community diarrhea in LMICs and validated by the MALED study consortium. The MSD definition used in GEMS, medically-attended diarrhea with one or more of: dysentery, dehydration, and/or hospital admission has also been proposed because of its high case-fatality rate. 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, however the clinical endpoints suggested for CHIM studies are not necessarily applicable to, or feasible to collect in, pediatric field efficacy studies.
6.4 *Shigella* Vaccine Safety considerations

*Shigella* vaccines will be expected to be well tolerated and acceptable to recipients, and to have a safety profile at least as favorable as those for current WHO-recommended vaccines. Live attenuated vaccines may encounter the greatest challenge for safety in infants and young children, whereas non-living (both killed and subunit approaches) may be better tolerated\textsuperscript{121} and can also have a more predictable immunogenicity profile since the antigen dose given to each vaccine recipient can be better standardized and controlled. Nonetheless, it is notable that to date live attenuated oral *Shigella* vaccines have appeared far more attenuated in children from LMIC than in adults from HIC.\textsuperscript{122, 123} However, the safety risk versus efficacy benefit evidence for each candidate will be evaluated through clinical effectiveness studies.
6.5 *Shigella* Vaccine Formulation and Delivery considerations for use in LMICs

It is imperative to begin the development of the optimal vaccine 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.58, 124

Oral vaccines avoid many of the challenges of injectable vaccines. They are relatively easy to administer, assuming a low volume, palatable formulation is identified. Oral vaccines have the capacity to induce local mucosal immunity in the intestine and can be potentially produced at a relatively low cost.125 Other formulation considerations include protection from gastric acidity, to prevent antigen degradation in passage through the stomach.126, 127

Although oral rotavirus vaccines have demonstrated safety, efficacy and impact in LMICs, the target population of infants and young children under 5 have proven challenging to immunize effectively. To optimise efficacy and improve public health impact, parenteral delivery is being explored to overcome the barriers to an efficacious oral vaccine.77, 85 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 schedule.

In addition, novel excipients that improve product shelf life and packaging technologies that allow inclusion of dry and liquid vaccine components in one container would be helpful to address some of the presentation challenges, particularly for parenterally-administered vaccines.128, 129, 130 Several manufacturers have developed more advanced designs for dry and liquid vaccine presentations.131, 132 Where possible, innovative approaches 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 an infant vaccine to be used in LMICs133 will be more constrained than those for adult travelers and military. However, where possible, these attributes should be aligned since the market for a traveler’s vaccine may help provide an added economic incentive to industry to also develop the pediatric indication.
### 7. PPCs for *Shigella* vaccines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preferred characteristic</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Prevention of diarrhoea and/or dysentery and morbidity due to <em>Shigella</em></td>
<td>Primarily, prevention of moderate-to-severe diarrheal disease/dysentery due to <em>Shigella</em>. Prevention of mild disease is also considered important; however, this will likely not be possible to assess as a primary endpoint pre-licensure. Consider as a potential secondary endpoint. Other anticipated vaccine benefits include: Prevention of all diarrhoea due to <em>Shigella</em>, reduction in morbidity due to long-term sequelae resulting from malnutrition and growth stunting, reduction in the use of antibiotics and associated antimicrobial resistance, risk reduction of <em>Shigella</em> associated infections, herd protection and prevention of all cause diarrhoea. While these are important outcomes of <em>Shigella</em> vaccination, they may not be feasible to assess as endpoints within the constraints of controlled clinical study and would be measured post licensure. However, where feasible, exploratory endpoints related to these indications, particularly those due to growth stunting, should be collected during clinical studies.</td>
</tr>
<tr>
<td><strong>Target Population</strong></td>
<td>For initial licensure: Infants and children up to 24 months. For introduction in LMICs: Children up to five years of age</td>
<td>The goal is full protection of infants by 12 months, to cover peak incidence in the second year of life and the greatest burden in children in LMICs up to 5 years of age. Some country and regional variation in peak incidence is expected. Additional potential populations include immunocompromised children, children under 5 in crowded communities with high birth rate and recurrent propagated <em>Shigella</em> epidemics (i.e. sub-national deployment), children over 5 years and adolescents, adult travellers, military recruits, elderly and the institutionalized. However, the preferred product characteristics for vaccines targeted to these populations may differ.</td>
</tr>
<tr>
<td><strong>Schedule and dose Regimen</strong></td>
<td>At least 2 doses are expected to be needed for primary immunization, given during the first 12 months of life. An additional booster/s dose may be required to maintain effective and long-lasting immunity through the first 5 years of life.</td>
<td>This vaccine is assumed to be implemented though the routine expanded programme of immunization. The schedule should provide protection prior to the peak of infection to prevent the majority of <em>Shigella</em> disease, malnutrition and growth faltering. Two-doses could be delivered at 6 and 9 months of age, in line with measles containing vaccine (MCV1 is given at 9 months and MCV2 at 15 months, however a MCV0 dose at 6 months is under consideration and could provide an opportunity for earlier immunisation. The need for a booster dose will depend on the duration of protection conferred and may be aligned with MCV2</td>
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<td>Parameter</td>
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<tr>
<td><strong>Safety</strong></td>
<td>A safety and reactogenicity profile at least as favourable and clinically acceptable, as current WHO-recommended routine vaccines.</td>
<td>A favorable safety profile will need to be demonstrated in adults before progressing to younger ages. Contraindications should be restricted to known hypersensitivity to any of the vaccine components.</td>
</tr>
<tr>
<td><strong>Case definition of MSD</strong></td>
<td>Diarrheal illnesses that would not be expected to resolve without medical intervention</td>
<td>Defined as cases of diarrhea accompanied by dehydration, requiring access to life-saving rehydration fluids, or hospital admission, or where there is evidence of destruction of the intestinal mucosa as determined by visible blood in stool, confirmed by culture. While highly sensitive quantitative PCR (qPCR) more than doubles the likelihood of detecting putative <em>Shigella</em>, to date it does not enable antimicrobial resistance interpretable without an isolate. There is also concern of cross-reactivity of the <em>ipaH</em> gene with EIEC and a lack of consensus regarding the interpretation of low quantity infections. qPCR is suggested as a secondary microbiologic outcome, though this should be reviewed as the technology is further refined.</td>
</tr>
<tr>
<td><strong>Clinical Endpoints (Primary)</strong></td>
<td>Primary: Reduction in acute MSD</td>
<td>There are no standardised clinical endpoints for moderate to severe <em>Shigella</em> diarrhoea in endemic settings. Primary Endpoints: Prevention of acute medically-attended <em>Shigella</em> diarrhoea is proposed, as care-seeking behaviour for diarrhoea is considered a surrogate for severity. Among those seeking care, the primary clinical endpoint should measure prevention of MSD as defined above. Prevention of community diarrhoea should be considered in post-licensure studies.</td>
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<tr>
<td></td>
<td>Secondary and Exploratory: Reduction in acute Less Severe Diarrhea (LSD)- diarrhoea leading to care seeking but without dehydration or dysentery.</td>
<td>Direct effects: all Shigella diarrhoea, cross-protection against <em>S. flex</em> serotypes not contained in the vaccine, sterilizing immunity, protection against LSD, immune correlates of protection, microbiological correlates of protection (PCR vs culture), mortality. Indirect effects: reduction in AMR, reduction in hospitalization, improved linear growth and other nutritional parameters, cost-effectiveness</td>
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<tr>
<td><strong>Efficacy</strong></td>
<td>Efficacy of 60% or more against moderate-to-severe vaccine preventable <em>Shigella</em> diarrhoea.</td>
<td>Target value is based on observed lower performance of enteric vaccines, especially rotavirus, in endemic pediatric settings. Moderate efficacy (approximately 50%) is clinically meaningful and would be comparable to rotavirus vaccines, in high burden LMICs. Efficacy threshold will be based on prevention of all vaccine-preventable serotypes. Assessment of field efficacy in response to all circulating serotypes would be inform vaccine effectiveness. Efficacy by 9 months is required to protect children who have been weaned and are susceptible to first <em>Shigella</em> infections and EED Vaccine Impact modelling can guide the acceptable efficacy. Ideally assessment of vaccine effectiveness with data collected as early as possible from large field trials, should include factors such as herd protection, reduction in the use of antibiotics and consequent AMR and protection against financial risk, however this data may not be available until post-licensure.</td>
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<tr>
<td><strong>Duration</strong></td>
<td>For initial licensure: Duration of protection 2 years, starting 14 days after vaccination. For introduction in LMICs: Booster dose can be considered to extend protection to the 5 year target.</td>
<td>Demonstrate protection for 2 years in pivotal efficacy study. An additional booster/s dose may be required to maintain effective and long-lasting immunity through the first 5 years of age. Natural boosting due to asymptomatic exposure in endemic environments is also possible. Duration of protection beyond 2 years will be informed by post licensure studies.</td>
</tr>
<tr>
<td><strong>Adjuvant requirement</strong></td>
<td>Preference for the absence of an adjuvant. Adjuvant preferred only if proven enhancement of efficacy to overcome reduced vaccine performance if observed in infants in low resource settings.</td>
<td>Evidence to justify an adjuvant inclusion with accepted safety profile is a prerequisite to add an adjuvant.</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Seek to establish correlate or surrogate of protection, based on a validated assay measuring immune effector levels and functionality that 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 immunization regimens. This would inform comparison of next generation vaccine candidates, including combination vaccines, as well as inform the longevity of the immune response, and the relationship to the duration of protection should be investigated. Serum IgG antibodies to Shigella O-antigen (parenteral vaccines) are proposed as a correlate of protection, for polysaccharide conjugate vaccines, based on association of protection observed in field efficacy studies, as well as CHIM studies. However, this may not be a correlate for</td>
</tr>
</tbody>
</table>
### Non-interference

- Demonstration of favourable safety and immunologic non-interference upon co-administration with other vaccines recommended for use.
- Demonstration of non-interference with immune responses to relevant vaccines from the EPI.

There should be no significant interference in relation to safety and immunogenicity with concurrently administered or co-formulated vaccines.

### Route of administration

- Oral or injectable (IM, ID, or SC), using standard volumes for injection, as specified in programmatic suitability for prequalification (PQ), or needle-free delivery.

Where possible, innovative approaches to decrease the storage footprint and improve ease of use should be evaluated to facilitate logistics and use in LMICs.

### Product stability and storage

- Three years at 2 to 8°C; vaccine vial monitor for 30 days at 40°C.
- Vaccine vial monitor for 7 days at 40°C for stable liquid formulation and may include adjuvant.

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.

Innovative approaches to improve heat and freeze stability should be evaluated to facilitate logistics and use in LMICs.

### Vaccine presentation

- Provide vaccines whenever possible, in "ready-to-use" presentations that do not require the mixing of components.

Provide vaccines in formats to minimize the (1) number of preparation steps and (2) potential for error during preparation and administration.

Except for separately packed diluents, vial-filled presentations are strongly preferred over ampoule-filled presentations. (Generic Preferred Product Profile for Vaccines, WHO 2015).

### Registration, PQ, and programmatic suitability

- The vaccine should be prequalified according to the process outlined

WHO-defined criteria for programmatic suitability of vaccines should be met: [Assessing the Programmatic Suitability of Vaccine Candidates for WHO Prequalification](https://www.who.int/vaccine_rbc/Vaccine_Suitability_Model/en/)

### Access and affordability

- The vaccine should be cost effective and price should not be a barrier to access, including in LMICs.
- Dosage, regimen and cost of goods amenable to affordable supply.

It is imperative to capture the full burden of *Shigella* diarrhea including morbidity burden, in addition to the direct and indirect effects of infection. Assessment of the broader societal and economic benefits of vaccination are important to articulate the value of an *Shigella* vaccine from an LMIC prospective.

The vaccine’s potential impact on health systems and other aspects of implementation science should be...
| evaluated pre- or post-approval, as this will also contribute to assessment of vaccine value. |
8. References:


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