Shigellosis

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Lancet 2025; 406: 1508–19
Published Online September 4, 2025
https://doi.org/10.1016/S0140-6736(25)01033-5

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Shigella **is a Gram-negative, facultative intracellular, gastric acid-resistant bacterium of the Enterobacteriaceae family, which includes four serogroups: *Shigella dysenteriae*, *Shigella sonnei*, *Shigella flexneri*, and *Shigella boydii*. Globally, shigellosis is the most common cause of invasive bloody diarrhoea in children younger than 5 years. Humans are the only natural reservoir and an inoculum of only 10–100 organisms is required for infection. Rising antibiotic resistance rates increasingly reduce the ability to adequately treat severe disease. The prevention of infection with vaccination and sanitation strategies remains a crucial step in reducing worldwide morbidity and mortality.**

Introduction

Although there has been improvement in diarrhoeal illness over the last 30 years, mostly in adults as measured by disability-adjusted life-years, it remains within the top three causes of morbidity and mortality globally among children younger than 9 years.[1] Shigellosis, an infection due to the bacteria *Shigella*, is the most common cause of invasive bloody diarrhoea in children younger than 5 years in low-income and middle-income countries (LMICs) where water, sanitation, and hygiene practices are minimal.[2] As few as 10–100 *Shigella* isolates are required for transmission, which occurs by person-to-person contact (including sexual contact), faecal–oral route due to contaminated food, drinking water, and recreational water, fomite, or flyborne transmission.[3–5] There has been an increase in antimicrobial resistance to *Shigella* species, particularly to WHO-recommended fluoroquinolone therapy, such that WHO has deemed shigellosis a top priority for research and drug development.[6] Given the substantial morbidity and mortality associated with shigellosis and there being no preventive vaccine for it, understanding the pathophysiology of this disease continues to be of great importance.

Epidemiology and antimicrobial resistance

Endemicity of shigellosis in tropical countries is well documented; however, localised geographical areas with endemicity have also been reported in temperate climates.[7] Global risk mapping and prediction modelling show that climate factors influence the geographical distribution of *Shigella* spp, including temperature, precipitation, and soil moisture of a region.[8] Although most shigellosis cases occur in children younger than 5 years, it can also occur in adults, particularly in travellers, men who have sex with men (MSM), those living with HIV, military personnel deployed to endemic settings, and those who are immunocompromised.[3,9,10]

The Global Enteric Multicenter Study (GEMS) was a 3-year (2007–11) case–control study, conducted at seven sites in Africa and Asia in more than 22 000 children. It identified four pathogens responsible for the majority of moderate-to-severe diarrhoea cases: rotavirus, *Cryptosporidium*, *Shigella*, and enterotoxigenic *Escherichia coli*.[11] Of those with culture-positive *Shigella*, *Shigella flexneri* (65·9%) was the most identified serogroup at all sites followed by *Shigella sonnei* (23·7%), *Shigella boydii* (5·4%), and *Shigella dysenteriae* (5·0%).[12] The Vaccine Impact on Diarrhea in Africa (VIDA) study (2015–18), a follow-on study from the GEMS, re-estimated pathogen-specific burden in children younger than 5 years from three of the GEMS African sites: The Gambia, Kenya, and Mali.[13] In this study, 359 (7·4%) of 4840 moderate-to-severe diarrhoea cases were due to *Shigella* spp as determined by culture, and 1641 (33·9%) of 4836 moderate-to-severe diarrhoea cases were due to *Shigella* spp as determined by quantitative polymerase chain reaction (qPCR). The predominant serogroups identified were considered relatively stable compared with the GEMS; only site-specific changes and a decrease in *S dysenteriae* prevalence were noted. Of the *Shigella* isolates obtained, 67·6% were *S flexneri*, 18·2% were *S sonnei*, 11·8% were *S boydii*, and 2·3% were *S dysenteriae*.[13] Community-based, multiyear cohort studies conducted in Peru have also shown relative stability in the distribution of serogroups over time.[14]

In the 2016 Global Burden of Disease (GBD) study, *Shigella* spp were the second leading cause of diarrhoeal mortality across all ages, accounting for 212 438 (13·2%) diarrhoeal deaths worldwide, most notably in children younger than 5 years.[15] In the 2021 GBD study, shigellosis accounted for 81 800 deaths of children younger than 5 years and had a fatal population attributable fraction of 24% in this age

Search strategy and selection criteria

We searched Embase, PubMed, and Cochrane databases from Jan 1, 2024 to May 15, 2025 for articles with the terms "Shigella", "Shigellosis", and "dysentery" cross-referenced with the terms "microbiology", "epidemiology", "serogroup", "serotype", "resistance", "antibiotic susceptibility", "mortality", "clinical severity", "pathogenesis", "innate", "adaptive", "immune response", "clinical manifestations", "prevention", "transmission", "complications", "reactive arthritis", "hemolytic uremic syndrome", "diagnosis", "antimicrobial therapy", "management", "molecular testing", "correlates of protection", "antibody", and "vaccines". There was no date restriction. Only articles published in English were included.

group.[16] The Maternal and Child Epidemiology Estimation project found that *Shigella* spp was responsible for the second largest percentage of attributable diarrhoeal deaths in children younger than 5 years in LMICs in 2021 (36 082 deaths; 8·1%), with the highest rates in southeast Asia. This proportion was noted to have increased since the 2000 estimate of 6·6% (78 753 deaths), which was attributed to higher detection rates with newer molecular testing.[17] In high-income countries, 170 (3·4%) diarrhoeal deaths in children younger than 5 years were attributable to *Shigella* spp. Although there were notable mortality differences between the GBD and the Maternal and Child Epidemiology Estimation studies, differences in data collection and interpretation methods make them difficult to compare; for example, multiple causes could be attributed to one death in the GBD study, whereas only one cause was attributed to each death in the Maternal and Child Epidemiology Estimation analyses.[17]

Shigella spp are a common cause of foodborne and waterborne outbreaks of disease in high-income and low-income countries and have been shown to spread between household members. A US Centers for Disease Control and Prevention report, summarising over 13 000 cases of foodborne outbreaks in the USA, found that over 3800 cases were due to *Shigella* spp, which were associated with eggs, roots, and vine consumption.[18] A study conducted across 20 provinces in Iran found that 118 (11·2%) of 1055 foodborne illness cases were attributed to *Shigella* spp.[19] In a review of untreated recreational water disease outbreaks in the USA, 14 (15·0%) of 95 outbreaks with confirmed causes were triggered by *Shigella* spp.[20] A retrospective cohort assessment of laboratory-confirmed *Shigella* cases households in Amsterdam, the Netherlands, found that secondary *Shigella* infection occurred in 7·4% of household members.[21]

First recognised at the start of the AIDS epidemic, sexual transmission of shigellosis has become increasingly common among MSM. A 2022 surveillance study in the UK reported a substantial increase in sexually transmitted *Shigella* infections following a decline during the COVID-19 pandemic.[22,23] Importantly, this has also included a rise in extremely drug-resistant *S sonnei*, which has also been reported in at least nine additional countries in Europe[23,24] (appendix p 2). Transfer of plasmid-encoded β-lactamase ($bla_{CTX\text{-}M\text{-}27}$) from *S sonnei* to *S flexneri* has also been shown in the UK; Thorley and colleagues identified that of the 26 *S flexneri* $bla_{CTX\text{-}M\text{-}27}$ cases identified, ten (77%) of 13 individuals who completed the questionnaire identified as MSM.[25]

Shigellosis was listed as a serious threat in the US Centers for Disease Control and Prevention 2019 Antibiotic Resistance Threat Report, with antimicrobial resistance rates as high as 24% for azithromycin and 10% for ciprofloxacin.[26] Analysis of 171 cases from a shigellosis outbreak in Seattle, WA, USA, from 2017 to 2022, found that 50·6% of isolates (65·5% of which were *S flexneri* and 32·2% were *S sonnei*) were resistant to at least three classes of antibiotics.[27] Resistance rates were 51·5% for azithromycin, 35·7% for ciprofloxacin, and 19·3% for ceftriaxone. In this cohort, 45·6% of patients were MSM and 51·5% were people experiencing homelessness.[27] A systematic review and meta-analysis of over 44 000 *Shigella* isolates collected in Bangladesh from 1979 to 2020 found antibiotic resistance rates of 61·9% for any fluoroquinolone, 38·8% for azithromycin, and 10·8% for ceftriaxone.[28] Non-susceptibility to ciprofloxacin was reported to be increasing by an average of 18·4% annually in a study of 79 548 *Shigella* isolates from 19 countries in central America and South America collected between 2000 and 2015, with highest increase rates in Honduras, Dominican Republic, Venezuela, and Chile.[29] In the VIDA study, antibiotic resistance was found in 353 *Shigella* isolates (98·3% with antimicrobial resistance data) mostly to co-trimoxazole (94·9%), ampicillin (48·4%), and nalidixic acid (1·7%). Resistance to ceftriaxone (0·3%) and azithromycin (0·3%) was minimal. Interestingly, no isolates were resistant to ciprofloxacin.[13] Lower rates of ciprofloxacin resistance in *Shigella* isolates from African countries have also been seen in other studies.[30]

Causative agent

Shigella is a Gram-negative, non-spore-forming, and non-motile bacterium from the family of Enterobacteriaceae. It is a facultative, intracellular bacteria with varying ability to survive extracellularly depending on the serogroup.[31] Humans are the only natural reservoir, although challenging non-human primates can result in disease.[32] *Shigella spp* are classified by serogroups and serotypes based on the O antigen in their outer membrane lipopolysaccharides: serogroup A (*S dysenteriae*, 15 serotypes); serogroup B (*S flexneri*, 19 serotypes and subserotypes); serogroup C (*S boydii*, 19 serotypes); and serogroup D (*S sonnei*, one serotype).[33] *S flexneri* is the most common serogroup and cause of shigellosis in LMICs, with *S sonnei* most often seen in high-income countries. However, in the last decade there has been a shift towards *S sonnei* predominance in rapidly developing countries in Asia, Latin America, and the Middle East.[3,34]

Shigella serogroups and serotypes collected from moderate-to-severe diarrhoea cases in the GEMS are listed in the appendix (p 3).[12] Serotypes found in the VIDA study (the GEMS African sites from 2015 to 2018) were similar in distribution over time compared with the GEMS (2007–11).[12,13] In the VIDA study, *S flexneri* was, again, the most common serogroup (67·7% of isolates) and the most commonly identified *S flexneri* serotypes were 2a (40·6%), 1b (18·8%), 6 (17·5%), 3a (9·0%), and 4a (5·1%).[35] A community-based diarrhoeal disease surveillance study conducted in children in the Peruvian Amazon found the most common *Shigella* serogroup to be *S flexneri* (67·1% of total isolates) with the most

See Online for appendix

common *S flexneri* serotypes being 2a (33·1%), 3a (19·4%), and 6 (16·5%).[35]

S flexneri can convert its serotype to evade host immunity, mostly through phage-mediated O-antigenic variation, which has led to the global emergence of novel and atypical serotypes from natural infection. Notably, these new subserotypes have been shown to exhibit greater antibiotic resistance than typical serotypes.[33] *S dysenteriae* type 1 (Sd1), the only serotype that produces Shiga toxin, has historically resulted in epidemics of dysentery with high rates of mortality and is most commonly found in southeast Asia and Africa.[32] Sd1 was also associated with epidemics in Central America between 1968 and 1972, with a high fatality rate in all age groups.[36]

As *Shigella* spp and *E coli* have a high degree of genomic homology, it is generally believed that pathogenic *Shigella* spp evolved from non-pathogenic *E coli*. Acquisition of a virulence plasmid and evolution of acid resistance pathways has allowed for *Shigella* survival in low pH environments. As a result, *Shigella* spp can survive gastric acidity with an inoculum of only 10–100 organisms required to cause infection.[37]

Clinical presentation and complications

The hallmark of *Shigella* infection is dysentery, which is the frequent (often up to ten stools per day) passage of small-volume stool containing blood, inflammatory cells, and mucous. This can present with fever, abdominal pain, and tenesmus.[32] Intestinal complications, including rectal prolapse, toxic megacolon, obstruction, and perforation are rare and associated most often with Sd1.[38,39] Diarrhoea occurs within 1–3 days post innoculation.[32,40] Clinical presentation is variable and depends on age, geographical area, and infecting serogroup. In the VIDA study, *Shigella*-associated dysentery was more common in children aged 24–59 months (50·1%) compared with infants younger than 11 months (39·5%) and varied by geographical site. Dysentery was more common in children infected with *S flexneri* (60·3%) compared with children infected with *S sonnei* (44·4%).[13]

Systemic complications of shigellosis include bacteraemia; fluid, electrolyte, or nutritional imbalance; leukemoid reaction (white blood cell count ≥50 000 per mm³) neurological disease; reactive arthritis; and haemolytic uremic syndrome.[32] Bacteraemia occurs in less than 10% of cases of *Shigella* infection and occurs most commonly in malnourished children younger than 1 year.[41] Although rare, bacteraemia in adults is seen most often in those older than 65 years with multiple comorbidities or immunocompromising conditions.[42] A shigellosis surveillance study of all ages conducted from 2002 to 2012 in Georgia, USA, found secondary bacteraemia in 0·64% of cases, about half of which were in patients who were HIV positive. In this study, most faecal isolates were *S sonnei*, but blood isolates were equal numbers of S *sonnei* and S *flexneri*, suggesting a higher invasive potential for *S flexneri*.[43] *S flexneri* serotype 2a was also identified in 30% of invasive shigellosis cases in South Africa between 2003 and 2009. In this study, those with invasive shigellosis and HIV infection (67%) were 4·1 times more likely to die from shigellosis than those without concomitant HIV infection.[44]

A common neurological complication from *Shigella* infection is seizures, which is associated with poor outcomes and almost exclusively seen in children younger than 15 years.[45] A case–control study investigating children hospitalised with gastroenteritis in Israel found that convulsions in toddlers were associated with elevated body temperature and *Shigella* infection.[46] Other neurological complications include encephalopathy, obtundation, and death, which occur with a lethal form of shigellosis, known as Ekiri syndrome. Ekiri syndrome was associated with *S sonnei* and historically resulted in 15 000 deaths per year in Japan before and immediately following World War 2.[38]

Reactive arthritis, a diffuse inflammatory arthritis sometimes accompanied by conjunctivitis or urethritis, is rarely seen with *Shigella* infection. A meta-analysis of pathogen-associated reactive arthritis found that 36 of 6415 confirmed *Shigella* cases developed reactive arthritis.[47] Haemolytic uremic syndrome, a clinical syndrome defined by a triad of haemolytic anaemia, renal insufficiency, and thrombocytopenia, most commonly occurs in children younger than 5 years with dysentery, and has a pooled case fatality rate of 36%. It is associated with *E coli* 0157:H7 and Sd1 infection, both of which are known to produce high levels of Shiga toxins during infection. Both appropriate and inappropriate antibiotic use has been associated with haemolytic uremic syndrome. Hypotheses for the mechanism of haemolytic uremic syndrome include antimicrobial-induced bacterial toxin release and disruption of host protective gut microbiota. However, further investigations have suggested that early (within 4 days of symptom onset) and appropriate antibiotic administration for Sd1 infection is likely beneficial and prevents worsening of disease.[48]

Clinical outcomes of shigellosis have improved over the last 30 years, owing to global decline in malnutrition, increased access to health care, and the substantial decline of Sd1 infections.[49] However, *Shigella* spp continue to be a leading cause of hospitalisation in children younger than 5 years in LMICs. The Global Pediatric Diarrhea Surveillance network, which enrolled at 33 sentinel surveillance hospitals in 28 LMICs, found that *Shigella* spp were the second leading cause of hospitalisation due to diarrhoea (9·7%).[50] In the GEMS, 42 deaths (2·8% of *Shigella*-attributable diarrhoea cases) were children younger than 1 year. Risk factors for *Shigella* associated with death included diarrhoea duration before presentation, vomiting, stunting, wasting, and hospitalisation.[51] A systematic review of the consequences

of shigellosis in children younger than 5 years in LMICs found that children with shigellosis were more likely to have persistent (>14 days) diarrhoea,[52] which ultimately leads to poorer health outcomes, including stunting, wasting, and death. In this study, persistent diarrhoea was more likely in children who were malnourished, had dysentery, or had multidrug-resistant shigellosis.

Diagnosis

The definitive diagnosis of shigellosis occurs with the identification of the organism in stool during disease. The presence of stool leukocytes and erythrocytes are additional evidence.[53] In LMICs, where the vast majority of *Shigella* infections occur, laboratory facilities for standard microbiological isolation of the organism are often not available. Diagnosis is therefore dependent on clinical evaluation and stool microscopy.

Primary screening agar for identification of *Shigella* spp by stool culture includes MacConkey, Hektoen enteric, Salmonella–Shigella, and xylose-lysine-deoxycholate agar.[54–56] Any suspicious, lactose non-fermenting, xylose non-fermenting, and sulphide non-producing colonies (consistent with *Shigella* spp) can then be subcultured onto secondary screening agar, which includes triple sugar iron, lysine iron agar, and urea agar. Serogroup and serotype are then determined using polyvalent or monovalent antisera.[54,55] Laboratory identification is complicated by the genetic similarity between *Shigella* and *E coli*, which causes overlapping reactions and misidentification. Additionally, stool culture yield is dependent on the sample type (rectal swab *vs* whole stool), transport medium (buffered glycerol saline *vs* Cary–Blair), quality of the specimen, bacterial load, time to culture after collection, incubation time, quality of laboratory performance, and preceding antibiotic use.[55,56] Therefore, extensive workflows have been developed for the identification of *Shigella* spp and now can include qPCR and matrix-assisted laser desorption ionization-time of flight mass spectrometry testing.[54] Molecular tests, including commercially available multiplex panels, are now in wide use, particularly in high-income countries (table 1), and have shown that culture underestimates Shigella burden.[2,57–59] However, molecular testing remains less useful compared with culture in some aspects, such as the inability to differentiate some Shigella subspecies, determine antibiotic susceptibilities, and allow for whole genome sequencing, although qPCR diagnostics to detect serotypes and resistance genes are being developed.[60,61]

The development of rapid and inexpensive point-of-care testing for determination of *Shigella* serogroups and susceptibilities is of great importance, particularly in LMICs. Although not widely available, immunochromatographic dipstick tests for *S flexneri* 2a, *S sonnei*, and *S dysenteriae* 1 have been successfully developed.[62] This rapid dipstick method requires minimal technical skill and was found to be highly specific.[63–65] Detection of *Shigella* spp in milk samples with multiple endonuclease restriction real-time loop-mediated isothermal amplification technology showed 10-fold more sensitivity than that of qPCR.[66] A rapid loop-mediated isothermal amplification-based diagnostic test has been developed and validated for rapid detection of Enterotoxigenic *E coli* (ETEC) and *Shigella* spp, which shows a sensitivity for *Shigella* of 93% and specificity for *Shigella* of 100% when compared with qPCR analysis of paediatric diarrhoeal stool samples in India.[68] Fluorescent microsphere-based immune-chromatographic test and multiple cross displacement amplification-based gold nanoparticles biosensor are two nucleic acid lateral flow-based immunoassays that have been developed for on-site and point-of-care testing for *Shigella*.[66,67] EZ-Shigella is a rapid test device manufactured by Biomerica (Irvine, CA, USA) for the qualitative determination of *Shigella* spp in human stool

	Approximate turnaround time to result (h)	Technology
RidaGene-kits (R-Biopharm, Darmstadt, Germany)	1·5	Multiplex real-time PCR
EntericBio real-time Gastro Panel I (Serosep, Limerick, Ireland)	1·5	Multiplex real-time PCR
Seeplex Diarrhea ACE detection (Seegene, Seoul, South Korea)	10·0	Multiplex real-time PCR
xTAG gastrointestinal pathogen panel (Luminex, Austin, TX, USA)	5·0	Multiplex real-time PCR and suspension array detection
CLART EnteroBac (Tabasmed, Tehran, Iran)	5·0	Multiplex PCR and array detection
Filmarray gastrointestinal panel (Biofire, Salt Lake City, UT, USA)	1·0	Nested PCR, multiplex real-time PCR, and melting curve analysis

Table 1: **Commercially available molecular tests that include *Shigella* spp**

Panel: Recommendations to prevent the spread of *Shigella* as per the US Centers for Disease Control and Prevention[3,73]

- Wash hands with soap and water (including parents, children, and caretakers) for at least 20 s after using the bathroom, changing nappies, or assisting anyone in the bathroom
- Avoid preparing food for others during illness
- Avoid swimming during illness
- Attempt to stay home during illness and if working in health care, childcare, or food service industries, follow guidance from the local health department on returning to work
- Children should not attend childcare, school, or group activities while having active diarrhoea and follow local health department guidelines on when it is safe to resume these activities
- Wait to have sex until 1 week after diarrhoea stops. When sex resumes, wash body and hands after sex and use barrier condoms

samples, reporting an assay sensitivity and specificity of 99% or more.[68] These tests are all available for clinical use to varying extents, depending on regulatory approvals and institutional resources.

Management and prevention

In both adults and children, shigellosis is typically self-limiting, with symptoms lasting around 5–7 days. Without antibiotic treatment, one in five infants can have persistent organism shedding up to 2 months after the onset of diarrhoea.[40] Management consists mainly of supportive care, including oral rehydration and electrolyte repletion.[69] Oral zinc supplementation is recommended, particularly for those with signs of malnutrition.[70] Feeding should continue during, or restart immediately after, the rehydration process.[71,72] Randomised controlled trials have shown that antibiotic use in adults with acute severe diarrhoea can reduce symptom duration by 1–3 days and organism shedding.[69] Antibiotic therapy is recommended in adults who are immunocompromised or have signs or symptoms of sepsis. As *Shigella* spp are highly contagious, antibiotic therapy is also recommended for those in close contact environments (nursing facilities, day care centres, etc)[69] regardless of clinical severity to reducing shedding duration. Recommendations for the prevention of disease spread are listed in the panel.[3,73]

WHO recommends the use of antibiotics for the treatment of dysentery in children, with ciprofloxacin as first-line therapy, and azithromycin, cefixime, trimethoprim-sulfamethoxazole, and ceftriaxone as second-line agents.[74,75] Systematic reviews have shown reduced clinical and bacteriological failure rates with the use of WHO-recommended empiric antibiotics in the early 2010s, mostly in children in LMICs.[76] Use of antimicrobials for children with shigellosis in the GEMS showed an association of antibiotic use and improved linear growth, suggesting their role in mitigating growth faltering.[77] These findings are further supported by the Azithromycin for Bacterial Watery Diarrhea trial, a placebo-controlled efficacy trial examining the effect of azithromycin use in seven countries in children aged 2–23 months with watery diarrhoea and dehydration or malnutrition. In a subgroup analysis of children with shigellosis, linear growth faltered less in those treated with azithromycin compared with those treated with placebo.[78]

Given the rising global antibiotic resistance rates, stool culture with antimicrobial susceptibility testing is recommended with initiation of antimicrobial treatment. Use of empiric antibiotics should take into consideration presentation severity and risk groups, including MSM, people experiencing homelessness, and returning travellers from areas with high resistance rates.[27,73,79] Difficulties with treatment and prevention strategies for shigellosis have also led to a renewed interest in the use of phage therapy.[80] A 2024 phase 1 randomised controlled trial investigating the use of an oral cocktail of five lytic bacteriophages targeting all four *Shigella* serogroups in healthy adult participants found the drug to be safe and tolerable without evidence of significant gut inflammation or microbiome disruption.[81]

Immunopathogenesis

The pathogenesis of *Shigella* depends on its ability to evade and exploit host immunity, permitting replication

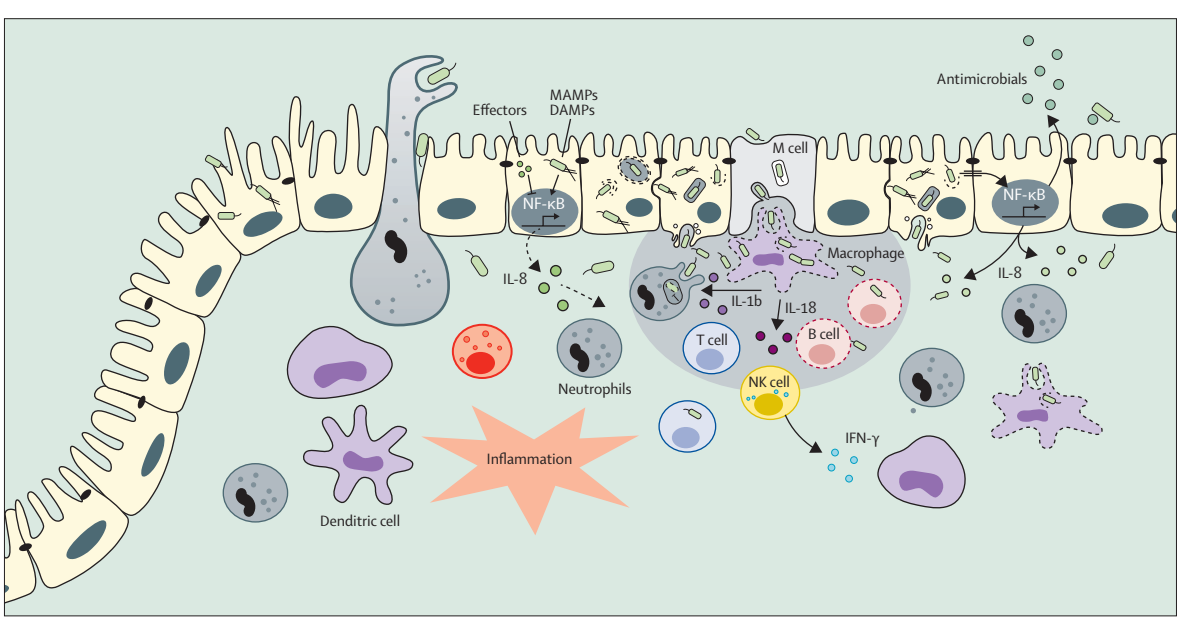

Figure: **The immunopathogenesis of *Shigella* infection in the colon**
MAMPs=microbe-associated molecular patterns. DAMPs=damage-associated molecular patterns. NK=natural killer. Adapted from Schnupf and Sansonetti.[82]

within the colon and leading to epithelial destruction (figure).[82,83] After oral ingestion, *Shigella* survives in the acidic environment of the stomach, aided by proton consumption systems and mucinase production; it overcomes the resident gut microbiota to reach the terminal ileum, colon, and rectum.[84,85] In the early stage of infection, HD5 induces filopodia formation to capture *Shigella* spp in epithelial cells. HD5 interacts with the epithelial P2Y11 receptor to promote *Shigella* spp invasion.[86] A study of human rectal biopsies showed that specialised epithelial cells overlying lymphoid follicles of Peyer's patches are the first to be damaged in shigellosis, followed by vascular injury and detachment of epithelial lining.[87] Most infections in this study were due to *S flexneri*, followed by *S dysenteriae*, and *S boydii*.[87]

Experiments with the rabbit ligated intestinal loop model confirmed that *S flexneri* crosses this epithelial barrier through transcytosis by microfold cells in the lymphoid follicle-associated epithelium.[88,89] Subepithelial resident macrophages phagocytose the bacteria, which induces apoptosis and allows for escape into tissue. This is followed by basolateral entrance into epithelial cells and cell-to-cell spread.[90] Invasion is aided by effector proteins that are delivered into the host cell cytoplasm via a type III secretion system (T3SS), which is encoded on a virulence plasmid.[83,84] Effector proteins, many of which are also encoded on a virulence plasmid and secreted via T3SS, can regulate gene expression, and manipulate host cell death and survival signal pathways, thereby promoting bacterial colonisation and survival.[84,91] *S sonnei* differs from *S flexneri* in its ability to compete with gut- colonising bacteria through use of colistins and a type VI secretion system, which provides an advantage over other gut colonisers.[31]

Bacteria replicate within epithelial cells and spread to neighbouring cells via actin-based motility. Class II PIK3C2A is required for intercellular spread of *S flexneri* bacteria.[92] Time-lapse microscopy revealed that PIK3C2A is required for the resolution of protrusions into vacuoles through the formation of an intermediate membrane-bound compartment known as a vacuole-like protrusion.

Innate immunity

When it first encounters the intestinal epithelium, *Shigella* spp are confronted by the host innate antimicrobial effectors, such as the constitutively secreted antimicrobial peptides (also known as host defence peptides), which are produced by mucosal epithelial cells to recruit and regulate immune cell activities.[93] *Shigella* spp have evolved an immune escape strategy to circumvent the host defence by downregulating the transcription of endogenous antimicrobial peptide. Pathogen-mediated downregulation of antimicrobial peptides is a phenomenon seen in other infectious diseases;[94–96] blocking these is a strategy that has been explored to combat infection.[97] Experimental and human studies have shown that using diverse small molecular compounds known to induce antimicrobial peptides (short chain fatty acids, phenylbutyrate, etc) could counteract the suppression of endogenous antimicrobial peptides, thereby reducing inflammation and promoting earlier tissue healing.[94,98–100]

The early host immune response generated from *Shigella*-infected macrophages is marked by an intense inflammatory reaction mediated by IL-1β and IL-18. This reaction triggers an influx of neutrophils, leading to epithelial barrier damage, bacterial invasion, and inflammation.[90,101–103] Stool cytokine levels are elevated at disease onset, substantially higher than in serum, and correlate with disease severity.[104] Persistent inflammation, including increased immune-cell trafficking, larger numbers of apoptotic cells, and upregulation of proinflammatory cytokines in the lamina propria and epithelial lining, can occur in the rectal tissue of patients with *Shigella* infection for over a month after the onset of infection.[104–109] Prolonged inflammation occurs most notably in children compared with adult populations.[107]

IFN-γ is a key cytokine that plays a role in susceptibility to and recovery from shigellosis. Analysis of peripheral blood mononuclear cells from patients with *Shigella* infection revealed downregulation of IFN-γ mRNA-expressing cells during acute infection, whereas healthy controls living in *Shigella* endemic areas had elevated levels of stool IFN-γ.[104,110,111]

Adaptive immunity

Shigellosis generates a mucosal immune response to infection, which includes stool secretory IgA, *Shigella*-specifc serum bactericidal antibody (SBA), and serotype-specific lipopolysaccharide O-antigen IgG.[112–114] The onset of this adaptive immune response is delayed and lower in magnitude in children compared with adults.[5,115–117] Effective antibody-mediated immunity requires multiple infections, is short-lived, and correlates with disease severity.[118] No systematic large-scale seroepidemiological studies across ascending age groups (eg, infants, children, and adults) have been conducted in endemic countries. Shigella-specific antibodies identified from a small number of patients during shigellosis outbreaks in the late 1970s to 1990s are used as correlates of protection in vaccine studies[5,105,114,116,117,119–121] (appendix pp 4, 5).

Natural shigellosis shows activation of T lymphocytes and B lymphocytes, NK cells, increased memory T cells in circulation, and expansion of $CD8^+$T cells and γδ-T cells in the rectal mucosa.[109,112,122] Again, the pathogen applies diverse mechanisms to elude the host adaptive immune responses and manipulate it to its advantage. Without invading the cells, *Shigella* spp induce TLR2-dependent apoptosis of B lymphocytes through binding of IpaD, a virulence protein, to the T3SS.[123] *Shigella* spp impair the migration of $CD4^+$T cells while invading activated $CD4^+$T cells and dendritic cells, inducing

	Composition	Serotype, serogroup, or strain	Most recent clinical studies and findings
Attenuated			
WRSs2 and WRSs3[128,129]	Δ*virG*, *senA*, and *senB* genes	*S sonnei* Moseley	Completed phase 1 trial in healthy adult participants in the USA (no safety concerns, induced robust and functional serotype-specific anti-LPS antibodies, response correlated with faecal shedding)
ShigETEC[130,131]	Δ*rfbF*, *ipaBC*, and *setBA* expressing fusion protein B subunit of ETEC	*S flexneri 2a* 2457T	Completed phase 1 trial in healthy adults in Hungary (no safety concerns, induced robust and functional serotype-specific anti-ShigETEC and anti-LTB antibodies, response correlated with faecal shedding)
Subunit			
S4V-EPA[127]	OAg-EPA conjugate	*S sonnei*; *S flexneri* 2a; *S flexneri* 3a; *S flexneri* 6	Monovalent version (Flexyn2a-EPA) completed phase 1 and 2b (CHIM) in healthy adults in the USA (no safety concerns, robust and functional anti-2a serum IgG response); quadrivalent S4V currently undergoing phase 2 study in Kenya and CHIM study in the USA
SF2a-TT15[132–134]	OAg-TT conjugate	*S flexneri* 2a	Completed phase 1 study in Israeli healthy adults (no safety concerns, induced high titre of anti-SF2a LPS IgG antibodies); currently undergoing a dose-finding study in Kenya and CHIM study in the USA
ZF0901[135,136]	OAg-TT conjugate	*S sonnei*; *S flexneri* 2a	Completed preliminary phase 1 study in an age-descending order from adults to infants aged 3 months (no safety concerns); completed phase 2 safety and immunogenicity RCT in children aged 3 months to 5 years (robust serotype-specific anti-LPS IgG levels); currently undergoing phase 3 trial in China and Bangladesh
altSonflex1–2-3[135,136]	OAg in GMMA	*S sonnei*; *S flexneri* 2a; *S flexneri* 3a; *S flexneri* 1b	Completed phase 1 of a two-stage phase 1/2 RCT in European healthy adults (no safety concerns, induced robust and functional serotype-specific anti-LPS antibodies)
Invaplex$_{AR\text{-}Detox}$[119,137]	Ipp proteins and LPS with artificial InvaPlex	Conserved IpaB and IpaC; *S flexneri 2a* 2457T	Completed phase 1 trial in adult participants in the USA (no safety concerns; high anti-LPS, anti-IpaB, and anti-IpaC antibody IgG titres); currently recruiting for phase 1a/1b dose-escalation RCT trial using vaccine adjuvanted with dmLT in healthy Dutch and Zambian adults

S=*Shigella*. ETEC=enterotoxigenic *Escherichia coli*. OAg=O antigen. EPA=exotoxin A of *Pseudomonas aeruginosa*. TT=tetanus toxoid. CDC=Centers for Disease Control and Prevention. GMMA=generalised modules for membrane antigens. Ipa=invasion plasmid antigen. LPS=lipopolysaccharide. RCT=randomised controlled trial. dmLT=double mutant enterotoxigenic *Escherichia coli* heat-labile toxin. CHIM=controlled human infection model. Δ=deletion. LTB=heat-labile toxin B subunit.

Table 2: **Shigella vaccine candidates furthest along in development**

apoptosis, thereby downregulating the antigen-presenting function of dendritic cells.[124–126]

Vaccine development

There are no licensed *Shigella* vaccines. However, with increasing knowledge of *Shigella*'s immunopathogenesis, continued widespread disease impact, rising antimicrobial resistance, and the advent of new technologies, there have been renewed efforts to develop vaccines against shigellosis.[127] We discuss only *Shigella* vaccine candidates that are furthest along in development and are undergoing clinical trials (table 2). Most of the candidate vaccines currently being studied can be broadly grouped as live attenuated or subunit vaccines, which can be either serotype or antigen based.[127–142]

Attenuated vaccines

A series of live attenuated vaccine candidates (WRSs1, WRSs2, WRSs3, WRSf3, WRSf2G12, WRSf2G15, WRSd1, SC602, and SC599), mostly developed at the Walter Reed Army Institute of Research, involve a mutation in the virulence plasmid-encoded *virG* (also known as *icsA*), which is essential for *Shigella* adherence and actin-based motility.[135,143] Some of these candidates have been evaluated in phase 1 or 2 clinical trials with variable success.[135] The phase 1 trial of the oral vaccine WRSs1 (*S sonnei*, deletion in *icsA*) in Bangladesh reported vaccine shedding in 50% of the adult recipients and in 0% of children at the highest dose[144] (three doses of 3×10^6 colony-forming units). At this dose, 63% of adults and 70% of children seroconverted with IgA directed to lipopolysaccharides. Children exhibited increased SBA titres compared with baseline after the second and third doses of WRSS1 vaccine, unlike adults who did not show any increase after vaccination.[145] Next-generation candidates, WRSs2 and WRSs3, are similar in their deletion of *icsA* in *S sonnei* strains with additional deletions of enterotoxin (*senA* and *senB*) and acyl transferase (*msbB*, only WRSs3) genes for better tolerability. High levels of SBA and opsonophagocytic killing antibodies were detected in serum and faecal extracts from phase 1 trial participants after single doses of both WRSs2 and WRSs3.[128,129]

A newer approach used elimination of the *Shigella* lipopolysaccharide O-antigen (ΔrfbF), disruption of the invasion complex (T3SS), and addition of detoxified toxin antigens (heat-labile toxin and heat-stable toxin) of ETEC to develop a combined oral vaccine for *Shigella* and ETEC infection (ShigETEC). These modifications allow for the recognition of conserved cell surface antigens shared across multiple *Shigella* serotypes and the closely related ETEC.[130] In mouse models,[138] the vaccine generated robust humoral responses and serotype-independent protection against *Shigella* challenge. A phase 1 trial of the vaccine in Hungary, a non-endemic country, has been completed showing safety and immunogenicity.[131] Additional trials are in progress in endemic settings in Bangladesh.

Subunit vaccines

Shigella glycoconjugate vaccine candidates have included recombinant, synthetic, and semi-synthetic

glycoconjugate or O-polysaccharide covalently linked to immunogenic carrier proteins. The early carbohydrate–protein conjugate vaccines conceptualised and developed by Robbins and Schneerson, consisted of detoxified lipopolysaccharides from *S flexneri* 2a (SF2a), S *sonnei*, and Sd1, conjugated to carrier proteins,[145] albeit with expensive manufacturing challenges.[135] Although a *S sonnei* detoxified lipopolysaccharides conjugate vaccine showed type-specific protective efficacy in 74% of young adult military recruits[146] and in 71% of children aged 3–4 years, the protective efficacy was not seen in children younger than 3 years.[147] These results led to the development of newer monovalent and multivalent bioconjugate vaccines.

The Flexyn2a vaccine (*S flexneri* 2a bioconjugate vaccine consisting of *S flexneri* 2a O-antigen conjugated to the EPA of *Pseudomonas aeruginosa*) showed safety and robust immunogenicity in a phase 1 trial.[132] In a subsequent controlled human infection model study, Flexyn2a showed partial protection against severe SF2a infection,[133] which paved the way for the development of a tetravalent version of the vaccine, S4V-EPA, which targets *S sonnei*, *flexneri* 3a, *flexneri* 6, and *flexneri* 2a and is currently undergoing a phase 2 trial in Kenya and a controlled human infection model study in the USA.[127] The SF2a vaccine, SF2a-TT15, is a synthetic glycoconjugate vaccine candidate that is linked to a tetanus toxoid protein carrier. In the first-in-human trial, the SF2a-TT15 vaccine generated a strong memory B-cell response and functional anti-SF2a lipopolysaccharide IgG, which was sustained in most participants up to 3 years post vaccination.[119,134–140] Additionally, an SF2a and S *sonnei* O-antigen-tetanus toxoid linked bivalent vaccine (ZF0901) is currently undergoing a phase 3 clinical trial in China and Bangladesh, after showing safety and immunogenicity in a phase 2 trial.[135,137]

The vaccine candidate Invaplex$_{AR\text{-}Detox}$ uses a high molecular mass complex (artificial Invaplex) to deliver IpaB and IpaC proteins along with purified *Shigella* lipopolysaccharide. This vaccine has shown protection against both homologous and heterologous *Shigella* serogroup infections in animal models, which has led to phase 1 studies that showed safety and immunogenicity.[139,140] Generalised modules for membrane antigens, modified outer membrane particles that are generated with an altered OAg:protein ratio, have been used to deliver a *S sonnei* vaccine (1790GAHB).[148] Phase 1 clinical trials of 1790GAHB have shown vaccine tolerability and robust anti-O-antigen antibody production in participants from both endemic and non-endemic settings but did not show clinical efficacy in a subsequent controlled human infection model study.[149,150] These results led to the formulation of altSonflex1–2–3, a new construct with 10-fold higher OAg per generalised modules for membrane antigen protein and the addition of three *S flexneri* serotypes.[149,150] Phase 3 trial planning for this formulation is currently underway in India.[151]

Controversies and outstanding research questions

The increased sensitivity of qPCR-based multipathogen diagnostic panels for diarrhoeal illness has revealed a larger burden of disease than previously recognised, as well as identifying asymptomatic qPCR-positive infections and co-infections. The clinical significance of these findings needs to be better understood and their existence considered in the design of vaccine and surveillance trials for shigellosis.[61,148]

With the rise of multidrug-resistant strains of *Shigella* limiting the ability to treat infection, particularly with oral antibiotics in low-resource settings, there is an even greater demand to develop preventive strategies for infection. Improved access to clean water, sanitation, and hygiene can substantially reduce morbidity and mortality due to diarrhoeal diseases, particularly in LMICs; however, developing the associated infrastructure is costly and can be difficult to achieve, being closely linked to the economic growth of the country itself. Vaccination remains the most promising approach for a practical, cost-effective, sustainable, and long-lasting means to prevent these diseases.

Vaccine development against *Shigella* spp has proven to be challenging for several reasons: observational and experimental studies have shown that immunity to shigellosis is serotype specific (based on the O polysaccharide antigen of lipopolysaccharides in the outer membrane) and there are about 50 distinct serotypes. Therefore, exposure to one serotype does not protect against another serotype. A desirable balance between reactogenicity and immunogenicity is difficult to achieve, particularly in young children (aged <5 years) living in *Shigella*-endemic countries.

The majority of the live attenuated *Shigella* vaccines tested to date have been designed to induce serotype-dependent immune response. Thus, to generate protection against commonly circulating strains globally, multiple strains would be required in single-dose vaccines, which can be a major challenge.[12,152,153] Based on the GEMS, a multivalent vaccine including *S flexneri* 2a, 3a, and 6, in addition to *S sonnei*, would provide direct protection against at least 72% of circulating strains and cross protection for up to 89% of strains.[154] Other challenges include, but are not limited to, the minimal amount of suitable small animal models, little understanding of host protection mechanisms, and the ability of *Shigella* to subvert the host innate and adaptive immune responses.[124] Lastly, although there are observational and clinical trial studies that show correlates of protection against shigellosis, particularly with regard to serum IgG anti-lipopolysaccharide,[133,155–157] there is little consensus on the crucial immunological correlates of protection, which reduces comparisons across studies.[141,158]

Contributors

All authors contributed to the literature review, writing, reviewing, and editing of this Seminar.

Declaration of interests
JH was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1TR003015/KL2TR003016) and is currently supported by a Mentored Patient-Oriented Research Career Development Award (K23) from the National Institutes of Allergy and Infectious Diseases (K23AI187708). RR, ZN, ASGF, RH, and WAP declare no competing interests.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps.

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