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Antimicrobial-resistant *Shigella*: where do we go next?

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Shigella spp. that are resistant to almost all antimicrobial classes are increasing in prevalence and becoming globally dominant. The situation is critical and highlights a trend that is mirrored by other enteric bacterial pathogens. New interventions to prevent and treat these infections are essential to tackle a potential public health catastrophe.

Shigella are a genus of Gram-negative bacteria that induce an aggressive inflammatory response in the gastrointestinal tract. Shigellosis, which is characterized by abdominal pain with blood and mucous in watery stools, is the result of ingesting a small number of organisms either by contact with an infected person or via contaminated food or water[1]. The greatest burden of disease is in low- and middle-income countries (LMICs) with poor sanitation, resulting in approximately 200,000 deaths annually[2]. However, intercontinental spread of *Shigella* spp. is also common, and travel-associated cases and outbreaks are regularly reported in higher-income settings. In recent decades, specific *Shigella* clones have emerged as an important cause of sexually transmitted infections that circulate in communities of men who have sex with men in the USA, Europe and Australia[3]. Although unpleasant, the disease is often self-limiting, and by maintaining fluid and electrolytes the symptoms usually subside within a few days. However, in vulnerable populations, including children under 5 years of age, malnourished individuals, elderly individuals and immunocompromised individuals, the disease can be life threatening. In such cases, antimicrobials have a critical role in lowering the risk of severe disease and death, limiting the production of dysenteric diarrhoea and preventing onward transmission. In the absence of a licensed *Shigella* vaccine, antimicrobials are important tools for disease control and can be used to reduce the impact of small outbreaks in nurseries or even larger epidemics occurring during natural disasters and other scenarios characterized by a breakdown in the provision of clean water.

The *Shigella* genus comprises only four species: *Shigella dysenteriae*, *Shigella boydii*, *Shigella flexneri* and *Shigella sonnei*[4]. The current global landscape of *Shigella* disease is dominated by *S. flexneri* and *S. sonnei*, with *S. sonnei* clearly in the ascendency in many LMICs. The insights permitted by genome sequencing technologies and analyses have elegantly described the evolution and geographical spread of these two species[5].

Many bacterial pathogens have been in an 'arms race' with antimicrobials since their use became commonplace, and *Shigella* spp. are no exception. The shigellae are adept at surviving and replicating in the human gastrointestinal tract, and incorporating exogenous genetic material, including antimicrobial resistance (AMR) genes on mobile genetic elements from other Gram-negative bacteria. This ability is arguably one of the most predominant features of the recent phylogenetic structure of *S. flexneri* and *S. sonnei*[6]. The gastrointestinal tract of those living in LMICs is known to be a large biorepository of AMR genes accumulated on large plasmids, where unregulated or unfettered exposure to broad classes of antimicrobials may encourage their maintenance, reassortment and dissemination. Therefore, it is not surprising that shigellae gain resistance genes by interacting with bacteria found within a typical gut microbiome. Furthermore, like *Escherichia coli*, *Salmonella* and many other bacteria, *Shigella* spp. inherit single base-pair mutations in key genes encoding targets for antimicrobials, making multidrug-resistant (MDR; non-susceptibility to three or more classes) and extensively drug-resistant (XDR; non-susceptibility to at least one agent in all but one or two antimicrobial classes) variants an inevitability[7]. We can understand this process more clearly in *S. sonnei*, as this pathogen comprises a single serotype and can be easily segregated into distinct geographical lineages. These signatures present a beautiful case study of how a human pathogen can evolve, spread and trade genetic material to become successful. Indeed, a specific lineage of *S. sonnei* became resistant to all first-line therapies in the 1970s and 1980s, which seems to have driven its dominance as it spread internationally from Asia[5]. Subsequently, a more recent worrying pattern that has emerged is that use of a certain class of antimicrobials may accelerate the development of resistance against other drug classes. Indeed, it was demonstrated that mutations associated with resistance to fluoroquinolones in *S. sonnei* may also actively encourage resistance to other antimicrobials[6]. This necessitates the use of alternative classes of antimicrobials and the cycle is perpetuated.

A question we have not asked successfully and have fundamentally largely ignored is what happens when we run out of antimicrobials to which the pathogens are susceptible. Historically, this question has never been an issue as we had a sequential abundance of chemicals to work through, which bought us time to think (or not) about alternatives. But now we face this question directly; we have had the stepwise acquisition of resistance to all alternative antimicrobials in a dramatically short time frame, rendering us short of any real alternative drugs. Since the first report in Vietnam in 2014, XDR *S. sonnei* has spread rapidly and internationally, following the same pattern of fluoroquinolone resistance as several years previously[6]. Consequently, a search for alternatives using compound libraries led to the identification of an oral carbapenem (notably, no novel mode-of-action antimicrobials were identified), which was highly efficacious in cells and animals[8] but has not yet been suitably tested in humans. Additionally, the use of oral carbapenems will, somewhat inevitably, lead to resistance to the last real weapon we have in our antimicrobial arsenal for treating not only *Shigella* spp., but all highly resistance bacterial infections. The situation we find ourselves in with AMR in *Shigella* spp. is not unique, but it has occurred more rapidly and in a more chronological fashion than with many other Gram-negative pathogens. So now, as we face the *Shigella*

antimicrobial endgame, we do have to confront the existential question that we never wanted to ask: where do we go next with antimicrobial treatment for *Shigella* spp. now that we have exhausted our resources?

Finding ourselves in a situation where successive generations of antimicrobials have become, or are becoming, ineffective against *Shigella* spp., and lacking a pipeline of effective small-molecule drugs, there is a clear need for alternative treatments and/or prophylactics against shigellosis. Vaccines are an obvious solution, as they not only prevent morbidity but reduce disease incidence and spread. Vaccines have the potential to greatly reduce the use of antimicrobials and slow the development of resistance. Suitable technologies to make effective *Shigella* vaccines have existed for decades, but limited progress has been made until recently due to substantial knowledge gaps in both epidemiology and immunological protection. Multiple serotypes (>50) and a poor understanding of the important circulating serotypes, as well as the lack of a clear correlate of protection and suboptimal animal models, have severely restricted progress. However, we now know that protection is serotype specific, with O-antigen being the key target antigen and serum IgG correlating with protective efficacy[9]. In addition, the funding for clinical trials has been limited and inadequate; however, in the past decade or so, this has changed. Major funders have a renewed interest in neglected bacterial diseases like shigellosis, and recent success with the typhoid conjugate vaccine has demonstrated that vaccine development and implementation can be both economical and impactful. There are now clear goal posts: the World Health Organization has a detailed 'wish list' for a *Shigella* vaccine, requesting a cost-effective formulation to prevent moderate-to-severe diarrhoea in children under the age of 5 years[10].

There are multiple current efforts to produce prototype *Shigella* vaccines using several different approaches, including live-attenuated, glycoconjugate (traditional, bioconjugate and synthetic), outer membrane vesicles and protein subunit designs. Several have reached clinical trial with mixed success (reviewed in ref. 9). Of particular interest for *Shigella* spp., given the large number of serotypes, is the development of subunit vaccines utilizing proteins conserved across *Shigella* serotypes and species, which would enable the multivalent protection at potentially reduced manufacturing complexity and cost. Controlled human infection models, which were key for accelerating the typhoid conjugate vaccine clinical phase forward to large trials in endemic regions, are being developed for *Shigella* spp. Additionally, we now have more sensitive and quantitative PCR assays to reliably measure vaccine performance in the field. Monoclonal antibodies (mAbs) are another promising alternative to small-molecule antimicrobials. Widely used against cancer and some viral diseases, their use against bacterial infections is presently limited, but there are reasons to be optimistic that cost-effective mAbs can have an important role in prophylactic or even perhaps therapeutic treatment of *Shigella* infections.

Sustained control of shigellosis over extended time frames realistically requires several simultaneous interventions. Investing in the development and refinement of antimicrobials, mAbs and vaccines offers the most realistic hope of tackling the ongoing *Shigella* predicament and avoiding the coming global health crisis for all infections impacted by antimicrobial resistance.

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Competing interests

The authors declare no competing interests.