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# Resistance in Enteric *Shigella* and nontyphoidal *Salmonella*: emerging concepts

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**Purpose of review**
The emergence of globally resistant enteric *Shigella* and nontyphoidal *Salmonella* strains (NTS) has limited the selection of effective drugs, which has become a major challenge for the treatment of infections. The purpose of this review is to provide the current opinion on the antimicrobial-resistant enteric *Shigella* and nontyphoidal *Salmonella*.

**Recent findings**
Enteric *Shigella* and NTS are resistant to almost all classes of antimicrobials in recent years. Those with co-resistance to ciprofloxacin, azithromycin and ceftriaxone, the first-line antibiotics for the treatment of infectious diarrhoea have emerged worldwide. Some of them have caused interregional and international spread by travel, trade, MSM, and polluted water sources. Several strains have even developed resistance to colistin, the last-resort antibiotic used for treatment of multidrug-resistant Gram-negative bacteria infections.

**Summary**
The drug resistance of enteric *Shigella* and NTS is largely driven by the use of antibiotics and horizontal gene transfer of mobile genetic elements. These two species show various drug resistance patterns in different regions and serotypes. Hence treatment decisions for *Shigella* and *Salmonella* infections need to take into consideration prevalent antimicrobial drug resistance patterns. It is worth noting that the resistance genes such as $bla_{CTX}$, *mph*, *ermB*, *qnr* and *mcr*, which can cause resistance to ciprofloxacin, cephalosporin, azithromycin and colistin are widespread because of transmission by IncFII, IncI1, IncI2 and IncB/O/K/Z plasmids. Therefore, continuous global monitoring of resistance in *Shigella* and *Salmonella* is imperative.

**Keywords**
antibiotic, drug resistance, nontyphoidal *Salmonella*, outbreak, *Shigella*

## INTRODUCTION

Enteric *Shigella* and nontyphoidal *Salmonella* (NTS) are widely recognized as predominant bacterial pathogens responsible for foodborne illnesses and are regarded as a significant public health concern globally [1,2]. Although acute diarrhoea caused by *Shigella* and NTS can be unpleasant, these diseases are usually self-limiting, and symptoms usually resolve within a few days with appropriate fluid and electrolyte management. However, in vulnerable populations, including children under 5 years of age, elderly, malnourished and immunocompromised individuals, these diseases can be life threatening. The use of antibiotics is an important means to shorten duration of illness and reduce infectivity [1]. However, with the increasing use of antibiotics, resistance of *Shigella* and NTS to different antibiotics continues to emerge, and these bacteria show high rates of multidrug resistance globally [2,3].

## DRIVERS OF BACTERIAL RESISTANCE

The development of bacterial resistance can occur in certain bacterial strains, and the utilization of antibiotics in medical and veterinary practice exerts selective pressure that expedites this phenomenon

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## KEY POINTS

- The drug resistance of enteric *Shigella* and nontyphoidal *Salmonella* is largely driven by the use of antibiotics and horizontal gene transfer of mobile genetic elements.
- The antimicrobial resistance patterns of enteric *Shigella* and nontyphoidal *Salmonella* tend to be associated with certain serovars and regions.
- Ongoing surveillance of the new antimicrobial resistance patterns is imperative for appropriate clinical management of infections caused by enteric *Shigella* and nontyphoidal *Salmonella*.

[3]. The transmission of resistance to humans can occur through the consumption of meat products from treated animals or food that has been cross-contaminated during processing or retail [4,5]. It has been confirmed that *Salmonella* drug resistance is largely driven by the use of antibiotics in food-producing animals in developed countries [6,7]. Additionally, the spread of resistance can occur through direct contact with animals or environmental pathways, such as water or wildlife [8,9].

In *Shigella* spp., drug resistance is mainly because of0 their adeptness to survive and replicate in the human gastrointestinal tract while incorporating exogenous genetic material, including antimicrobial resistance (AMR) genes on mobile genetic elements, from other Gram-negative bacteria [3,10]. In recent years, multiple reports have demonstrated the isolation of multidrug-resistant (MDR) *Shigella* spp. from untreated sewage or well water, indicating that they are likely to easily obtain various drug-resistant genes or plasmids from the environment [11–13]. In China, one distinct MDR clone of *Shigella sonnei* with multiple resistant plasmids caused six waterborne shigellosis outbreaks from 2015 to 2020 [14▪]. Fang *et al.* [15▪] conducted genomic and equation model analysis of *Shigella flexneri* from 1920 to 2020 worldwide, showing that the consumption of antibiotics promoted drug resistance and that mobile genetic elements were important contributors to antibiotic resistance genes in *S. flexneri* isolates.

## REGIONAL DIFFERENCES IN BACTERIAL RESISTANCE

Antibiotic resistance rates in *Salmonella* vary by country and are affected by antimicrobial usage practices among humans and animals, and geographical regional differences in *Salmonella* epidemiology and *Salmonella* serovars. Over the past few years, surveillance data have indicated a rise in the resistance rates in *Salmonella* isolates from poultry in the United States and Brazil and a decline in Canada and eastern Spain [8,16–18]. In contrast to other countries, including the United States, China exhibits a notably elevated incidence of MDR *Salmonella* Enteritidis (*S.* Enteritidis) [19]. The proportions of MDR *Salmonella* significantly vary among different countries and sources. In Bangladesh, 94% of *Salmonella* strains isolated from broiler chickens exhibited multidrug resistance [20]. Drug sensitivity testing showed that 47.3% of NTS strains in Taiwan were MDR between 2017 and 2018 [21]. Furthermore, the emergence and widespread dissemination of a novel *Salmonella* Typhimurium (*S.* Typhimurium) sequence type (ST) 313 in sub-Saharan Africa has resulted in sepsis without accompanying gastroenteritis. Additionally, a highly drug-resistant sublineage of ST313 has been identified, characterized by a combination of multidrug resistance, extended-spectrum β-lactamase (ESBL) production, and resistance to azithromycin [22]. The rise in drug-resistant *S.* Typhimurium ST313 isolates can be attributed to the sustained use of antibiotics [23].

Antimicrobial resistance (AMR) patterns in *Shigella* spp. are varied in different regions of the world, which is closely related to the frequency of antibiotic use and the development level (Table 1). *Shigella* isolates from Africa have high resistance to trimethoprim/sulfamethoxazole, tetracycline and ampicillin, while their resistance to ciprofloxacin, azithromycin and third-generation cephalosporin antibiotics is low [24–26]. In addition to the high resistance of *Shigella* isolates in Asia to tetracycline, ampicillin and other older antibiotics, it is concerning that the resistance to azithromycin, ciprofloxacin and ceftriaxone is already at a high level or shows an upward trend [2,27,28]. Whereas shigellosis is endemic in Asia and Africa, burdening mostly children younger than 5 years, in developed regions, such as Europe, the Americas and Australia, *Shigella* infections are more common among gay or bisexual men, people with HIV, and homeless people or travellers. Moreover, the proportion of sexually transmitted *Shigella* infections is very high. Their rates of multidrug resistance are higher than those of *Shigella* isolates with other modes of transmission, with gradually increasing resistance trends, mainly to ampicillin and trimethoprim, azithromycin, ceftriaxone and ciprofloxacin [29,30,31▪▪,32▪▪].

Although resistance of *Shigella* spp. has certain regional differences, the spatiotemporal change in resistance is of a major concern. Initially, *S. sonnei* only developed resistance to some old antibiotics (such as tetracycline and ampicillin); however, a ciprofloxacin-resistant clone has later emerged in

**Table 1.** Resistance patterns of *Shigella* spp. and *Salmonella* spp. in different regions or serovar

| Species | Region or serovar | Antibiotic with resistance | Reference |
|---|---|---|---|
| *Shigella* spp. | Africa | Trimethoprim/sulfamethoxazole, Tetracycline, Ampicillin | [24–26] |
| | Asia | Tetracycline, Ampicillin, Chloramphenicol, Azithromycin, Ciprofloxacin, Ceftriaxone | [2,27,28] |
| | Europe, Americas, Australia | Tetracycline, Ampicillin, Trimethoprim, Azithromycin, Ceftriaxone, Ciprofloxacin | [29,30,31▪▪,32▪▪] |
| *Salmonella* spp. | Typhimurium | Ampicillin, Chloramphenicol, Streptomycin, Sulfonamides, Tetracycline | [35] |
| | Enteritidis | Nalidixic acid, Ampicillin, Streptomyces, Cefoperazone | [8,37,40] |
| | 1,4,[5],12:i:- | Ampicillin, Streptomycin, Sulphamethoxazole, Tetracycline Sulfaoxazole, Doxycycline | [41▪,42] |
| | Infantis | Nalidixic acid, Trimethoprim, Tetracycline, Ampicillin, Ciprofloxacin | [5] |
| | Albany | Ampicillin, Chloramphenicol, Streptomycin, Sulfisoxazole, Tetracycline, Nalidixic acid | [40] |

Asia [33]. Subsequently, a clone with multiresistance to azithromycin, ciprofloxacin, and third-generation cephalosporin emerged in 2014 and was transmitted among MSM in Europe and America during 2015 and 2022 [31▪▪,32▪▪,34]. In recent years, clones with multiresistance to azithromycin and ceftriaxone that frequently cause waterborne outbreaks have been found in Asia, some of which were even resistant to colistin [14▪].

## SEROVAR DIFFERENCES OF BACTERIAL RESISTANCE

The AMR surveillance data for *Salmonella* show that serovar differences have the most impact on overall resistance trends [35] (Table 1). The predominant antibiotic resistance pattern observed in *S.* Typhimurium is ACSSuT (ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline), which is attributed to the prevalence of phage type DT104 in *S.* Typhimurium [36]. Compared with other serovars, *S.* Enteritidis exhibited elevated resistance to nalidixic acid, with reported rates as high as 94.5% [37]. Medalla *et al.* [38] conducted a comparative analysis of the incidence of antimicrobial-resistant NTS infections in the United States during two distinct periods, 2004–2008 and 2015–2016, utilizing a Bayesian hierarchical model. The results of their study indicated a significant increase of 40% in the annual incidence of *Salmonella* infections with clinically important resistance, specifically to ampicillin or ceftriaxone, or insensitivity to ciprofloxacin. This increase is primarily attributed to a surge in reports of serotype 1,4,[5],12:i:- and serovar Enteritidis [38]. The variation in the resistance observed among poultry isolates from East Asia and the European Union could be primarily attributed to dissimilarities in the serovar profiles of the respective isolates [20,39,40]. Most recently, *Salmonella* 1,4,[5],12:i:- has emerged as a significant etiological agent of the NTS disease in both animals and humans on a global scale. Additionally, this serotype exhibited the highest prevalence of multidrug resistance among all *Salmonella* serotypes, with 89.6% reported in Guizhou, China [41▪,42].

There are also differences in drug resistance among *Shigella* serotypes. The F2a, F3a and F4s serotypes of *S. flexneri* have higher multidrug resistance rates than other serotypes [43–45]. In addition, as *S. sonnei* is more easily spread than *S. flexneri*, the transmission rate of drug resistance gene elements is higher. Therefore, the multidrug resistance rate of *S. sonnei* is higher than that of *S. flexneri*, especially for antibiotics such as fluoroquinolones and trimethoprim/sulfamethoxazole [31▪▪,46].

## MOLECULAR MECHANISMS OF BACTERIAL RESISTANCE

Resistance of *Shigella* spp. and Salmonella spp. to first-line and second-line antibiotics used in clinical treatment is of particular concern. Ceftriaxone and ciprofloxacin resistance has been increasingly reported in *Shigella* spp. and *Salmonella* spp. and multiple molecular mechanisms have already been described. Genes encoding ESBL such as $bla_{\text{TEM}}$, $bla_{\text{SHV}}$, $bla_{\text{CMY}}$, $bla_{\text{CTX-M}}$ and $bla_{\text{OXA}}$ contribute to ceftriaxone resistance in *Shigella* spp. and *Salmonella* spp. [47–49]. Ciprofloxacin resistance in these bacteria is primarily attributed to dual mutations in the *gyrA* gene and a singular mutation in the *parC* gene,

with infrequent identification of mutations in the *gyrB* and *parE* genes [50]. Furthermore, the emergence of plasmid-mediated quinolone resistance and efflux pumps have been identified as contributing factors to the development of low-level resistance to quinolones and fluoroquinolones [51]. The *qnr* genes comprise five distinct families, each possessing a varying number of alleles, namely *qnrA1-7*, *qnrS1-4*, *qnrB1-31*, *qnrC* and *qnrD*. Among these, *qnrA*, *qnrB* and *qnrS* are frequently identified in *Salmonella* [52▪▪,53]. As there is an increasing incidence of resistance to ciprofloxacin and ceftriaxone, azithromycin is regarded as a last resort, Food and Drug Administration (FDA)-approved antimicrobial agent for the treatment of systemic infections, especially those caused by *Shigella* spp. and *Salmonella* spp. The mechanisms of azithromycin resistance vary among bacteria, and carrying macrolide-resistant genes is considered the main mechanism of resistance for *Shigella* spp. and NTS. The azithromycin resistance phenotype is often conferred by the *erm(B)* gene and/or the complete genetic structure *IS26-mph(A)-mrx-mphR-IS6100* in NTS [54]. The genetic structures *IS26-mph(A)-mrx (A)-mph(R)(A)-IS6100* and *mph(E)-msr(E)-IS482-IS6* carrying macrolide-resistant genes were also found in *Shigella* [55]. It is worth noting that in recent years, the emergence of *Shigella* spp. and NTS strains resistant to colistin, mediated by a plasmid-borne colistin resistance gene *mcr*, have become prevalent in many countries [14▪,56–58]. Additionally, Zhai *et al.* [59▪] recently found that AcrB and CpxR could target ATP and reactive oxygen species generation to potentiate antibacterial activity of colistin.

## CARRIERS OF BACTERIAL RESISTANCE

The dissemination of MDR plasmids among Gram-negative bacteria is the major factor in the spread of AMR. Plasmids carrying multiple AMR genes in NTS are mainly of the IncI1 and IncHI2 types [49,60]. A conjugative IncC type plasmid simultaneously encoding resistance to ciprofloxacin, ceftriaxone and azithromycin in NTS was reported in 2021 [51]. A broad-host-range IncC plasmid and its integrative mobilizable *Salmonella* genomic island 1 (SGI1) counterpart contribute to the spread of medically important antibiotic resistance genes among Gram-negative pathogens [61]. The emergence of $bla_{\text{CTX-M}}$-harbouring pESI plasmids was reported in clinical NTS in Germany [62]. A self-transferable IncA/C plasmid and a hybrid IncA/C-FIIs MDR plasmid were found to be the major vehicles for disseminating both *mcr-3* and $bla_{\text{CTX-M55}}$ genes among *Salmonella* strains [61].

Plasmids commonly carrying multiple AMR genes in *Shigella* spp. mainly include IncFII, IncI1, IncI2 and IncB/O/K/Z plasmids, which can carry the $bla_{\text{CTX-M-3}}$, $bla_{\text{CTX-M-14}}$, $bla_{\text{CTX-M-15}}$, $bla_{\text{CTX-M-27}}$, $bla_{\text{CTX-M-55}}$, $bla_{\text{CTX-M-134}}$, *mphA*, *aac(3)-IId*, *dfrA17*, *aadA5*, *sul1* and *mcr-1* genes [14▪,63]. In the last quarter of 2021, an outbreak of *S. sonnei* infection occurred that likely involved multiple European countries [31▪▪]. From this *Shigella* strain, researchers isolated an IncFII plasmid carrying not only the $bla_{\text{CTX-M-27}}$ resistance gene but also multiple other resistance genes, such as *mphA*. Moreover, the *S. sonnei* strain causing waterborne outbreaks in China contains an IncB/O/K/Z plasmid, which carries both $bla_{\text{CTX-M-14}}$ and *mphA*. Analysis shows that these plasmids not only promote the flow of MDR *Shigella* strains but can also spread between *S. sonnei* and *S. flexneri*, indicating a high risk of drug resistance spread [64▪].

## CONCLUSION

In summary, antibiotic resistance exhibited by enteric *Shigella* and NTS presents a significant challenge to the efficacy of treatment. These bacteria are complex pathogens with multifactorial transmission, and significant variations in drug resistance have been observed across different serotypes, isolation sources, or regions. The horizontal transfer of MDR plasmids is a significant contributing factor to the dissemination of drug resistance. Therefore, ongoing global surveillance of enteric *Shigella* and NTS resistance is imperative.

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### Conflicts of interest

*There are no conflicts of interest.*

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