Received: 31 July 2023 | Revised: 12 November 2023 | Accepted: 27 November 2023

DOI: 10.1111/mmi.15209

REVIEW ARTICLE

WILEY

Defying the odds: Determinants of the antimicrobial response of *Salmonella* Typhi and their interplay

Atish Roy Chowdhury[1] | Debapriya Mukherjee[1] | Ritika Chatterjee[1] | Dipshikha Chakravortty[1,2]

[1]Department of Microbiology and Cell Biology, Division of Biological Sciences, Indian Institute of Science, Bangalore, India

[2]School of Biology, Indian Institute of Science Education and Research, Thiruvananthapuram, India

Correspondence
Dipshikha Chakravortty, Department of Microbiology and Cell Biology, Division of Biological Sciences, Indian Institute of Science, Bangalore, India.
Email: dipa@iisc.ac.in

Funding information
ASTRA Chair Professorship and TATA Innovation fellowship funds; CSIR-SRF fellowship; DBT-IISc Partnership Program; Department of Atomic Energy, Government of India, Grant/Award Number: DAE0195; Department of Biotechnology (DBT); IISc fellowship; Ministry of Science and Technology; Department of Science and Technology (DST)

Abstract

Salmonella Typhi, the invasive serovar of *S. enterica* subspecies *enterica*, causes typhoid fever in healthy human hosts. The emergence of antibiotic-resistant strains has consistently challenged the successful treatment of typhoid fever with conventional antibiotics. Antimicrobial resistance (AMR) in *Salmonella* is acquired either by mutations in the genomic DNA or by acquiring extrachromosomal DNA via horizontal gene transfer. In addition, *Salmonella* can form a subpopulation of antibiotic persistent (AP) cells that can survive at high concentrations of antibiotics. These have reduced the effectiveness of the first and second lines of antibiotics used to treat *Salmonella* infection. The recurrent and chronic carriage of *S.* Typhi in human hosts further complicates the treatment process, as a remarkable shift in the immune response from pro-inflammatory Th1 to anti-inflammatory Th2 is observed. Recent studies have also highlighted the overlap between AP, persistent infection (PI) and AMR. These incidents have revealed several areas of research. In this review, we have put forward a timeline for the evolution of antibiotic resistance in *Salmonella* and discussed the different mechanisms of the same availed by the pathogen at the genotypic and phenotypic levels. Further, we have presented a detailed discussion on *Salmonella* antibiotic persistence (AP), PI, the host and bacterial virulence factors that can influence PI, and how both AP and PI can lead to AMR.

KEYWORDS
MDR, persistence, QRDR, quinolone-resistant, XDR

1 | INTRODUCTION

Salmonella enterica subspecies *enterica* serovar Typhi, the Gram-negative bacterium that causes typhoid fever in humans enters the bodies of healthy human hosts through contaminated food and water. Systemic dissemination of *S.* Typhi in humans results in high fever, nausea, abdominal pain and abnormal bowel movements (Masuet-Aumatell & Atouguia, 2021). Studies from 2017 have shown that *S.* Typhi is the causative agent of 76.3% of the cases of enteric fever, with an estimated mean all-age global case mortality of 0.95%, primarily affecting children and older adults, especially in the low-income countries (Buckle et al., 2012; Crump et al., 2004; Disease et al., 2017; Stanaway et al., 2019).

Over the last century, various treatment strategies have been developed to control *Salmonella* infections. These includes the use of multiple classes of antibiotics targeting cell wall synthesis to protein synthesis to clear *Salmonella* from the host body. However, various strains of *Salmonella* resistant to antibiotics have emerged

Atish Roy Chowdhury, Debapriya Mukherjee and Ritika Chatterjee contributed equally.

in different parts of the world, thereby challenging their efficacy (Masuet-Aumatell & Atouguia, 2021). In addition, *Salmonella* can form a subpopulation of antibiotic-tolerant and antibiotic persistent (AP) populations during antibiotic treatment, which can hamper the complete clearance by antimicrobial agents (Balaban et al., 2004). Another threat posed by *S*. Typhi is its ability to subvert the body's immune response and cause persistent infection (PI), whereby they sustain themselves inside the host's body asymptomatically despite eliciting an adaptive immune response. It has been reported that long-term PI can alter the antimicrobial resistance (AMR) responses of *Salmonella* (Marzel et al., 2016; Sabol et al., 2021). All these factors have highlighted the urgent need for regulated and judicial administration of antibiotics and the development of newer therapeutic strategies. In this review article, we have revisited the history of antibiotic resistance in *S*. Typhi, the different molecular mechanisms behind antibiotic resistance and multidrug resistance, common attributes in *Salmonella* pathogenesis and AMR, AP, PI, the alteration in host immune response during PI, and how both AP and PI can lead to the emergence of AMR.

2 | HISTORY OF ANTIMICROBIAL RESISTANCE IN *SALMONELLA* TYPHI

Typhoid fever in humans and its associated complications can be treated by administering a wide range of antibiotics such as penicillins (ampicillin and amoxicillin), cephalosporins (ceftriaxone and cefuroxime), aminoglycosides (streptomycin and gentamycin), macrolides (erythromycin) and fluoroquinolones (ciprofloxacin, ofloxacin, pefloxacin) (Britto et al., 2018; Dyson et al., 2019; Murti et al., 1962; Nair et al., 2018). Chloramphenicol was the first antibiotic used successfully to treat typhoid fever in 1948 (Butler et al., 1977; Masuet-Aumatell & Atouguia, 2021). It also led to uncontrolled and indiscriminate use of this antibiotic, leading to the development of AMR. The first chloramphenicol-resistant strain of *Salmonella* Typhi was isolated within 2 years in England (1950) (Akram et al., 2020; Anderson & Smith, 1972; Colquhoun & Weetch, 1950). The emergence of plasmid-mediated resistance to chloramphenicol in *S*. Typhi and its rapid spread throughout the world (Mexico, India, Vietnam and Korea) in the early and mid-1970s further increased the need for new antibiotics with greater in vivo efficacy. The use of ampicillin and trimethoprim-sulfamethoxazole (co-trimoxazole) in 1964 has shown limited success in treating typhoid/enteric fever (Akram et al., 2020; Brodie et al., 1970; Pettersson et al., 1964; Whitby, 1964). In combination, chloramphenicol, ampicillin and co-trimoxazole are considered the first-line antibiotics against typhoid fever. The multidrug-resistant (MDR) strain of *Salmonella* Typhi, resistant to all three first-line antibiotics, was isolated in the 1970s and spread rapidly worldwide. The alarming epidemic outbreak of MDR-*S*. Typhi in Mexico, with nearly 10,000 reported cases and other sporadic outbreaks worldwide in the following two decades made the discovery of novel anti-*Salmonella* drugs even more urgent (Akram et al., 2020; Dyson et al., 2019; Feasey et al., 2015; Kumar et al., 2001; Olarte & Galindo, 1973; Wain et al., 1999). In the next few years, clinicians began prescribing fluoroquinolones (ciprofloxacin, ofloxacin, lomefloxacin and pefloxacin) as potential means of controlling typhoid fever (Eykyn & Williams, 1987; Hafiz et al., 1998; Tanphaichitra et al., 1986). Fluoroquinolones inhibit bacterial DNA gyrase, an enzyme responsible for maintaining the supercoiled state of bacterial genomic DNA (division, coiling and supercoiling) during replication (Cheng et al., 2020; Yu et al., 2020). The emergence of MDR-*Salmonella* Typhi, which is also resistant to fluoroquinolones, was first reported in England in 1992 (Threlfall, 2000; Threlfall et al., 1997). In subsequent years, massive outbreaks of quinolone-resistant MDR *S*. Typhi were reported in several Southern Asia countries, including India and Pakistan. From 2001 to 2006, the multidrug and quinolone resistance of *S*. Typhi increased from 34.2% to 48.5% and 1.6% to 64.1%, respectively (Akram et al., 2020; Britto et al., 2018; Hasan et al., 2008). The emergence and overwhelming spread of fluoroquinolone-resistant *S*. Typhi has become a serious threat to global health.

Initially, cephalosporin and azithromycin were very effective in reducing the severity of typhoid fever caused by quinolone-resistant MDR-*S*. Typhi. Fluoroquinolones, third-generation cephalosporins and azithromycin are collectively referred to as the second line of antibiotics for the treatment of typhoid fever (Jabeen et al., 2023; Laghari et al., 2019; Rathod et al., 2016). Prudent administration of azithromycin with ceftriaxone allowed some cure for the infection caused by MDR *Salmonella* (Girgis et al., 1999; Parry, 2004; Parry et al., 2023; Veeraraghavan et al., 2021). The first occurrence of the ceftriaxone-resistant MDR *S*. Typhi, also called extensively drug-resistant (XDR) *S*. Typhi, was reported in Sindh, Pakistan, in November 2016 (Akram et al., 2020; Hussain et al., 2019; Klemm et al., 2018; Sah et al., 2019). The quinolone-resistant MDR *S*. Typhi had an IncY plasmid that provided protection against fluoroquinolones. Furthermore, it acquired resistance to ceftriaxone by acquisition of the CTX-M-15 gene *bla* and was thus converted into an XDR strain (Djeghout et al., 2018; Jacob et al., 2021). Recent reports from the WHO documented the first major outbreak of XDR typhoid infection, with 5274 cases from 8188 patients contracting typhoid fever in Hyderabad, Sindh, Pakistan, from November 2016 to December 2018 (WHO, 2018). Between late 2018 and early 2019, international transmission of XDR-related typhoid infections occurred in the United States, the United Kingdom and Canada from Pakistan (Akram et al., 2020; Chirico et al., 2020; Godbole et al., 2018; Wong, Rawahi, et al., 2019). As an alarming decline in the anti-*Salmonella* activity of azithromycin has been noticed recently, clinicians have been prescribing tigecycline, carbapenems and azithromycin (the newest line of antibiotics) to treat the critical infections caused by XDR *S*. Typhi since 2019 (Capoor et al., 2009; Kleine et al., 2017; Tang et al., 2016). A brief timeline of antibiotic resistance is shown in Figure 1.

The origin of antibiotic resistance in *S*. Typhi is still not clear. Instead, most scientific studies focus on the epidemiology of MDR and XDR typhoid fever. The mechanisms underlying the development of the multidrug resistance phenotype in *S*. Typhi are poorly

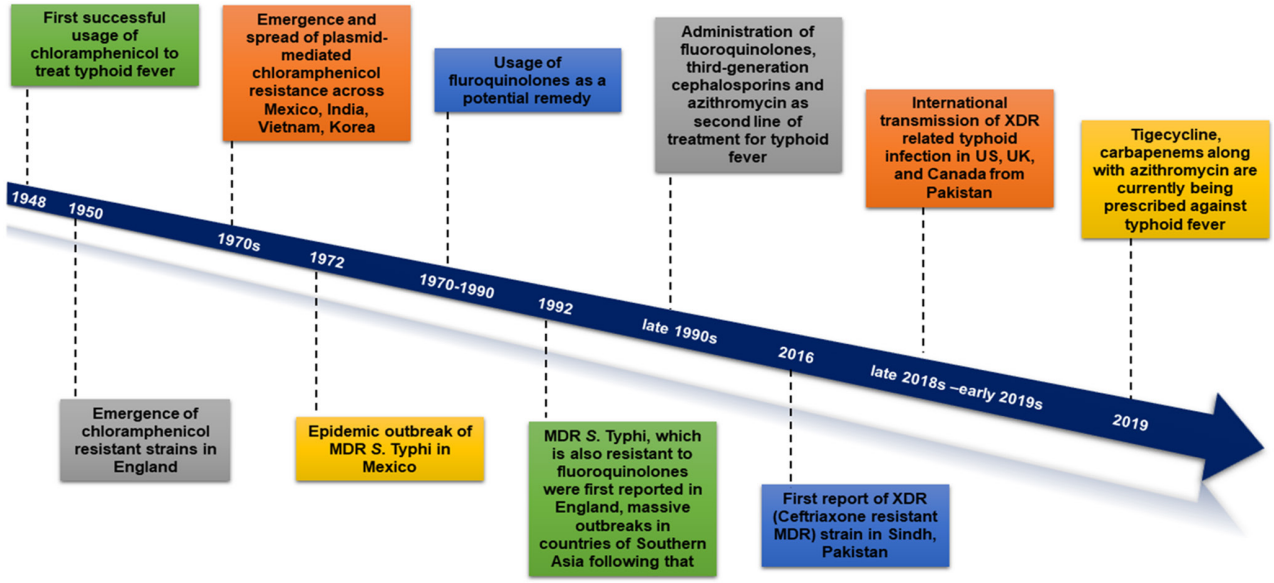

FIGURE 1 A brief timeline of antibiotic administration and resistance generation in *Salmonella* Typhi.

understood, leaving ample scope for future drug development research.

3 | MECHANISMS OF DRUG RESISTANCE IN *SALMONELLA*

3.1 | Genome encoded

Salmonella Typhi has achieved resistance against antimicrobials by acquiring single or multiple foreign DNA elements, gene segments or plasmids encoding antibiotic-modifying enzymes or by inducing specific mutations in different loci of its chromosomal genes. *S.* Typhi can acquire foreign DNA elements, gene segments or plasmids by horizontal gene transfer (HGT), transformation, conjugation or mobilization of transposons (Arnold et al., 2022; Burmeister, 2015). Insertion elements (IS) on both sides of the resistance gene cassette facilitate its transport from the donor to the recipient bacterium. The incorporation of resistance gene cassette into the bacterial chromosome occurs by recombination, which provides protection against antibiotics (Barquist et al., 2013; Doublet et al., 2008). Resistant bacteria can overcome the antibiotics in the following ways: modifying the antibiotic both structurally and functionally, altering the target site of the antibiotic, extruding the antibiotic from its cytoplasm by using an efflux pump, and restricting the entry of the drug by changing the permeability of the outer membrane (Reygaert, 2018).

3.1.1 | Mechanisms of multidrug resistance (MDR)

The MDR isolates of *S.* Typhi show reduced susceptibility to all first-line antibiotics, such as ampicillin, chloramphenicol and co-trimoxazole.

- *Resistance to chloramphenicol*—Resistance to chloramphenicol in *S.*Typhimurium DT104 and other Gram-negative *Enterobacteriaceae* is mediated by the chloramphenicol acetyltransferase (CAT) type I encoded by the *cat* gene (Arcangioli et al., 2000).
- *Resistance to ampicillin*—The bla_{PSE} and bla_{TEM} genes of *S.* Typhi are associated with the synthesis of β-lactamase enzymes that structurally alter and inactivate ampicillin (Boyd et al., 2002; Crump et al., 2015).
- *Resistance to sulfamethoxazole and trimethoprim*—The other two first-line drugs, sulfamethoxazole and trimethoprim, exert their effects by inhibiting the folate biosynthetic pathway, which blocks DNA synthesis in bacteria. In Gram-negative bacilli, *sul1* and *sul2* encode forms of dihydropteroate synthase that are not inhibited by sulfamethoxazole (Antunes et al., 2005). *S.* Typhi uses Sul1 and Sul2 to antagonize the action of sulfamethoxazole (Crump et al., 2015). MDR *Salmonella* can bypass the inhibitory effect of trimethoprim using the *dfr* family genes, which encode the dihydrofolate reductases. In addition, the resistance against trimethoprim is conferred by the presence of conjugative or non-conjugative incompatibility plasmids (termed IncHI1/non-IncHI1). Such plasmids possess a complete transposon that harbours multiple resistance genes such as bla_{TEM-1} (ampicillin resistance), *sul1*, *sul2*, *dfrA7* (trimethoprim-sulfamethaxazole resistance), *strAB* (streptomycin resistance) and *catA1* (chloramphenicol resistance) (Klemm et al., 2018; Pham Thanh, Thompson, et al., 2016; Wong et al., 2015). These plasmids are responsible for the occurrence of multidrug resistance in the H58 haplotype of *S.* Typhi (Wong et al., 2015). This complete transposon has also been integrated into the chromosome of some *S.* Typhi H58 lines (Pham Thanh, Thompson, et al., 2016; Wong et al., 2015). IncHI1 plasmids have also been associated with ESBLs and *qnr* genes (fluoroquinolone resistance) (Chen et al., 2016; McMillan et al., 2020). In Bangladesh,

only 15% of clinical *S*. Typhi isolates with MDR phenotype were attributed to the presence of the IncHI1 plasmid, and the remainder, 85% of the MDR phenotype, arose from the accumulation of mutations in the bacterial chromosome (Chiou et al., 2014). The IncQ1 plasmid was detected in the clinical isolates of MDR-*S*. Typhi (QS468) found in Baluchistan (Fatima et al., 2023). The IncQ1 plasmids are small (10–12 kb), well-conserved and have a broad host range. They are generally associated with *tetAR*, *strAB* and *sul2*, although other antibiotic-resistance genes have been identified (McMillan et al., 2020; Oliva et al., 2017; Poirel et al., 2010). In Bangladesh, recently reported clinical isolates of MDR *S*. Typhi showed higher resistance to nalidixic acid compared to other antibiotics (Mina et al., 2023). Reports from 2014 to 2018 showed that MDR *S*. Typhi and Paratyphi A possessed non-conjugative non-IncHI1 plasmids and multiple gene markers of AMR such as bla_{TEM-1}, *catA*, *sul1*, *sul2*, *dfrA15* (Dutta et al., 2014; Samajpati et al., 2020). These studies strongly suggest that non-conjugative non-IncHI1 plasmids play a role in the emergence of the MDR phenotype in *S*. Typhi and Paratyphi A. Moreover, it can be concluded that in addition to the plasmids, resistance gene cassettes located in the bacterial chromosome such as bla_{TEM-1}, *catA1*, *sul1*, *sul2*, *strA*, *strB* and a class 1 integron possessing the *dfrA7*, gene can lead to MDR phenotypes in *S*. Typhi (Das et al., 2017; Samajpati et al., 2020). Investigation of gene interaction networks using clustering analysis and functional enrichment process provided substantial evidence of the involvement of three chromosomally encoded efflux pumps, namely MacAB-TolC, AcrAB-TolC and major facilitator superfamily (MFS), in the development of the MDR phenotype in *S*. Typhi CT18. We have summarized the functions and localizations of the above genes in Table 1.

3.1.2 | Mechanisms of extensively drug-resistance (XDR)

Cephalosporins such as ceftriaxone and cefixime, which belong to the category of β-lactam antibiotics, inhibit bacterial cell wall synthesis by interacting with penicillin-binding proteins (PBPs) and peptidoglycan cross-links. *S*. Typhi can build resistance to cephalosporins by degrading the β-lactam ring of antibiotics with β-lactamase enzymes (Crump et al., 2015). The MDR-*S*. Typhi that exhibit resistance to fluoroquinolones and third-generation cephalosporins are termed extensively drug-resistant (XDR) (Akram et al., 2020; Bhatti et al., 2019; Khurshid et al., 2019; Pereira & Shah, 2020).

- *Quinolone resistance*—The MDR *S*. Typhi develops resistance to fluoroquinolone drugs (ciprofloxacin and nalidixic acid) using the quinolone resistance determining region (QRDR), plasmid-mediated quinolone resistance (PMQR) and efflux pumps (Crump et al., 2015; Parry et al., 1998; Pham Thanh, Karkey, et al., 2016). The *S*. Typhi genes encoding topoisomerase II (*gyrA* and *gyrB*) and topoisomerase IV (*parC* and *parE*), which help in bacterial DNA replication, are referred to as QRDR (Chang et al., 2021; Ferrari et al., 2013). The introduction of mutations in this QRDR region makes the bacteria resistant to quinolones. One of the most common mutations found in the QRDR region of fluoroquinolone-resistant *S*. Typhi and Paratyphi A isolates was GyrA_Ser83Phe (Okanda et al., 2018). Other major mutations in the QRDR associated with fluoroquinolone resistance include GyrA_Ser83Tyr, GyrA_Ser83Phe, GyrA_Asp87Asn, GyrA_Asp87Tyr, GyrA_Asp87Gly, GyrA_Ala131Gly, ParC_Glu80Gly and ParC_Ser80Ile (Akshay et al., 2023; Britto et al., 2018; Ferrari et al., 2013; Qian et al., 2020; Shariati et al., 2022). A steady decline in the percentage of MDR *S*. Typhi clinical isolates (46.4%–15.6%) was compensated by a parallel increase in the percentage of nalidixic acid-resistant isolates (60.7%–93.8%) and ciprofloxacin-resistant isolates (0%–25%) (Das et al., 2017). Mutations in *gyrA*, the presence of QnrS and the overexpression of efflux pumps were thought to be responsible for this fluoroquinolone resistance phenotype in MDR *S*. Typhi (H58) (Chiou et al., 2014). The IncFIB(K) plasmid carrying the $bla_{CTX-M-15}$ and *qnrS1* genes has been associated with the emergence of quinolone resistance in *Salmonella* Paratyphi A (Irfan et al., 2023). Identification of molecular determinants of AMR in blood isolates of *S*. Typhi from 337 patients between January 2005 and December 2009 in Pondicherry, India, revealed a prominent occurrence of quinolone resistance (78% of the 337 samples) with a concomitant loss of MDR phenotype (only 22% of 337 samples) (Menezes et al., 2012). In addition to inducing mutations in the QRDR, the MDR-*S*. Typhi can achieve quinolone resistance by acquiring an extrachromosomal plasmid. This process is referred to as plasmid-mediated quinolone resistance (PMQR), which facilitates horizontal gene transfer and a high level of resistance (Geetha et al., 2014; Lin et al., 2015). In contrast to QRDR isolates of *S*. Typhi, which exhibit low susceptibility to ciprofloxacin and nalidixic acid, the PMQR genes, such as the *qnr* family genes, *aac(6′)-Ib-cr*, *qepA* and *oqxAB*, are known to confer resistance to ciprofloxacin (Campbell et al., 2018; Tanmoy et al., 2018). The PMQR *qnrA* gene encodes a protein that protects bacterial DNA gyrase and topoisomerase IV by inhibiting the activity of ciprofloxacin (Tran et al., 2005). The PMQR *aac(6′)-Ib* gene encodes for an enzyme, aminoglycoside acetyltransferase, which reduces the antimicrobial potential of ciprofloxacin and norfloxacin by adding N-acetyl groups to piperazinyl substituents (Ferrari et al., 2013). QepA is an MFS-type efflux pump encoded by the PMQR gene *qepA* that pumps quinolones out of the bacteria (Yamane et al., 2007). OqxAB encoded by the PMQR *oqxAB* gene is a novel transmissible resistance-nodulation-division (RND) efflux pump that can remove a wide range of antibiotics from bacterial cells (Wong et al., 2014). Whole-genome sequencing revealed that in addition to QRDR and PMQR, the quinolone-resistant *Salmonella* Typhi had mutations in an additional 19 genes, including *tet*, *sul*, *aad*, *aac-*, *ant-*, *aph-*, *floR* and *cmlA* (Piekarska et al., 2023). The AcrAB-TolC efflux pump was an important resistance factor to levofloxacin in the fluoroquinolone-resistant MDR isolates of *S*. Typhi and Paratyphi A (Okanda et al., 2018). Efflux

TABLE 1 Mechanism of drug resistance in *Salmonella* Typhi.

Types of antibiotic resistance	Appearance (year)	Development of resistance against the antibiotics	Genes involved	Reference
Multidrug resistance (MDR)	1973	First line of antibiotics—chloramphenicol, ampicillin, co-trimoxazole	1. Chromosomal and plasmid-borne bla_{PSE} and bla_{TEM} coding for β-lactamase enzymes to inactivate ampicillin. 2. Chromosomal and plasmid-borne *cat* gene coding for chloramphenicol acetyltransferase. 3. Chromosomal and plasmid-borne *dfr* gene codes for dihydrofolate reductase to modify trimethoprim. 4. Chromosomal and plasmid-borne *sul1* and *sul2* genes confer resistance against sulfamethoxazole by encoding types of dihydropteroate synthase that are not inhibited by the drug. 5. Chromosome-encoded efflux pumps, namely MacAB-TolC, AcrAB-TolC and MFS. 6. *Salmonella* Genomic Island-1 (SGI-1) for the development of MDR in non-typhoidal serovars of *Salmonella*.	Antunes et al. (2005); Crump et al. (2015); Debroy et al. (2020); Doublet et al. (2005); Ingle et al. (2019); Lian et al. (2019); Shaheen et al. (2015); Wain et al. (2003); Wong et al. (2015)
Quinolone resistance	1992	All first line of antibiotics, fluoroquinolones (ciprofloxacin, ofloxacin and perfloxacin)	1. Introducing mutations in the quinolone resistance determining region (QRDR) of the bacterial genome, which consists of genes associated with the biogenesis of topoisomerase II (*gyrA* and *gyrB*) and IV (*parC* and *parE*). 2. Plasmid-mediated quinolone resistance (PMQR) genes such as *qnr* family genes, namely *aac(6′)-Ib-cr coding for aminoglycoside acetyltransferase* to build up resistance against ciprofloxacin. 3. Plasmid-mediated quinolone resistance (PMQR) genes such as *qnr* family genes such as *qepA* and *oqxAB coding for efflux pump to render protection against ciprofloxacin*.	Campbell et al. (2018); Ferrari et al. (2013); Okanda et al. (2018); Wong et al. (2014); Yamane et al. (2007)
Extensively drug resistance	2016	First-generation anti-*Salmonella* antibiotics, fluoroquinolones, third-generation cephalosporins	1. Mainly plasmid-borne extended-spectrum β-lactamase (ESBL): $bla_{CTX\text{-}M\text{-}15}$, $bla_{CTX\text{-}M\text{-}14}$ and $bla_{CTX\text{-}M\text{-}2}$ genes coding for β-lactamase. 2. Plasmid-borne $bla_{NDM\text{-}5}$ gene coding for Carbapenemase. 3. Plasmid-borne $bla_{CMY\text{-}42}$ gene coding for AmpC-type-β-lactamase	Accogli et al. (2013); Ahamed Riyaaz et al. (2018); Ben Sallem et al. (2014); Cao et al. (2018); Foley et al. (2021); Folster et al. (2014); Gao et al. (2020); Ingti et al. (2018); Myat et al. (2020); Sellera et al. (2018); Sidjabat et al. (2014); Smith et al. (2015); Tagg et al. (2014); Tiba-Casas et al. (2019); Walther-Rasmussen and Hoiby (2004); Yassine et al. (2015)

pump inhibition was responsible for the increased susceptibility of MDR-*S*. Typhi to fluoroquinolones such as ciprofloxacin (Tariq et al., 2019). The emergence of MDR strains of *Salmonella* is on the rise, and the field requires a deep understanding of how these mechanisms evolve and are acquired. Table 1 summarizes the locations and mode of action of the genes.

- *Cephalosporin resistance*—The β-lactamase dependent resistance to cephalosporins in Gram-negative bacteria can be divided into three major groups: Extended-Spectrum β-Lactamase (ESBL), carbapenemase and AmpC-type-β-lactamase (Crump et al., 2015). TEM, SHV and CTX-M are the three major ESBLs found in *Enterobacteriaceae* that build resistance to the third-generation cephalosporins. The clinical isolate of XDR *S*. Typhi reported in Pakistan exhibits an abundance of a plethora of resistance genes for the first (bla_{TEM-1}, *sul*1, *cat*A1 and *dhfR7*) and second line (*gyrB*, *gyrA*, *parC*, *parE* and *qnrS*) antibiotics as well as the derivatives of CTX-M ESBLs such as $bla_{CTX-M-U}$, $bla_{CTX-M-1}$, $bla_{CTX-M-15}$, $bla_{CTX-M-2}$, $bla_{CTX-M-8}$ and $bla_{CTX-M-9}$ (Jabeen et al., 2023). The experimental evidences showed the presence of two other ESBLs (SHV and TEM) in the clinical isolates of *S*. Typhi (purified from blood), which are associated with resistance to ceftriaxone, cefixime and ceftazidime (Ahamed Riyaaz et al., 2018). In 2016, for the first time, nearly 300 XDR *S*. Typhi infection cases were reported in Sindh, Pakistan. Whole-genome sequencing of the XDR *S*. Typhi isolates revealed the presence of an additional resistance plasmid element carrying the $bla_{CTX-M-15}$ gene within the bacterial chromosome encoding an extended-spectrum β-lactamase (ESBL), along with a mutated *qnrS* gene. The resistance plasmid carrying the $bla_{CTX-M-15}$ gene and the *qnrS* gene belonged to the IncY category and was named p60006 in this study (Klemm et al., 2018). In China, the MDR strains of *Salmonella* isolated from fattening pigs showed the presence of the IncHI2 plasmid harbouring the ESBLs gene $bla_{CTX-M-14}$ and the colistin resistance gene *mcr-1* (Zhou et al., 2023). A ceftriaxone-resistant isolate of *S*. Typhi from Bangladesh harboured an incompatibility plasmid I1 (IncI1-ST31) carrying an ESBL encoding $bla_{CTX-M-15}$ gene associated with *ISEcp-1* (Djeghout et al., 2018). Because cephalosporins are inadequate in the treatment of XDR typhoid fever, azithromycin, erythromycin and clindamycin are used as potential therapeutic agents.

3.1.3 | Emerging mechanisms of resistance to macrolides and carbapenems

Macrolides can inhibit bacterial protein synthesis by binding to the 50S subunit of the bacterial ribosome (Crump et al., 2015).

- *Macrolide resistance*—The efficacy of azithromycin in curing XDR *S*. Typhi has been reduced due to its indiscriminate use. Gram-negative bacteria belonging to the *Enterobacteriaceae* family also possess several genes (*erm* genes encoding methylases to modify target sites; *ere* genes and *mph* genes encoding esterases and phosphorus transferases, respectively, to alter the structure of the antibiotics) to fight against macrolides (Phuc Nguyen et al., 2009). A recent study by Ahsan et al. found that out of 40 clinical isolates of *S*. Typhi (n = 33) and Paratyphi A (n = 7), 95% showed resistance to azithromycin, while 100% of the isolates were resistant to clindamycin. The absence of the *mefA* gene, which encodes for macrolide-resistant efflux pumps, in any of these resistant isolates suggests the role of another independent protein in the development of macrolide resistance phenotype (Ahsan & Rahman, 2019). *S*. Typhi, which had a single mutation R717Q in the AcrB efflux pump, showed a higher MIC (≥32 μg/mL) for azithromycin (Iqbal et al., 2020). The recent development of azithromycin resistance in *S*. Typhi has raised concerns among clinicians regarding the antimicrobial treatment needed to manage typhoid fever successfully.
- *Carbapenem resistance*—The carbapenems are a potent class of β-lactam antibiotics that are considered as the last resort for curing life-threatening bacterial infections. XDR typhoid can be treated with carbapenems such as imipenem and meropenem (Al-Rashdi et al., 2021; Capoor et al., 2009; Eshaghi et al., 2020; Mylona et al., 2021; Petrin et al., 2020; Pokharel et al., 2006). Carbapenem resistance is not uncommon. *E. coli* and *K. pneumoniae*, two bacterial pathogens responsible for causing nosocomial infections, have been shown to exhibit carbapenem resistance through plasmid-borne carbapenemases and the modifications of outer membrane influx proteins (Aubron et al., 2005; Mathers et al., 2015; Wong, Romano, et al., 2019). To date, there are few reports of carbapenem resistance in *S*. Typhi. Studies conducted in Pakistan in 2000 identified emerging resistance to carbapenems as a new threat in the treatment of *S*. Typhi. They found meropenem resistance in 47.7% of the *S*. Typhi isolates and 11.3% of the isolates were partially sensitive. However, 100% of the isolates were sensitive to imipenem (Ali Shah et al., 2020). Studies conducted in Faisalabad, Pakistan, have identified VIM (Verona integron-encoded metallo-β-lactamase) and GES (Guiana extended-spectrum β-lactamase) as two carbapenemase genes in *S*. Typhi (Ain et al., 2022; Huang et al., 2023).

With the emergence of numerous drug-resistant strains, it is a challenge for researchers worldwide to develop new generations of antibiotics. Perhaps a different approach to modify mammalian targets instead of bacterial targets can serve the purpose. We have listed the mechanisms of drug resistance in *Salmonella* in Table 1 and Figure 2.

3.1.4 | *S*. Typhi virulence overlaps with AMR

In a bacterium, the resistome refers to all the resistance-associated genes (Wright, 2007). It includes the proto-resistance genes (which have the potential to develop a resistance function) and cryptic resistance genes (a resistance gene that is distributed in the chromosome of the bacterium but not necessarily expressed) (Kumar & Kumar, 2021; Wright, 2007). Although the proteins

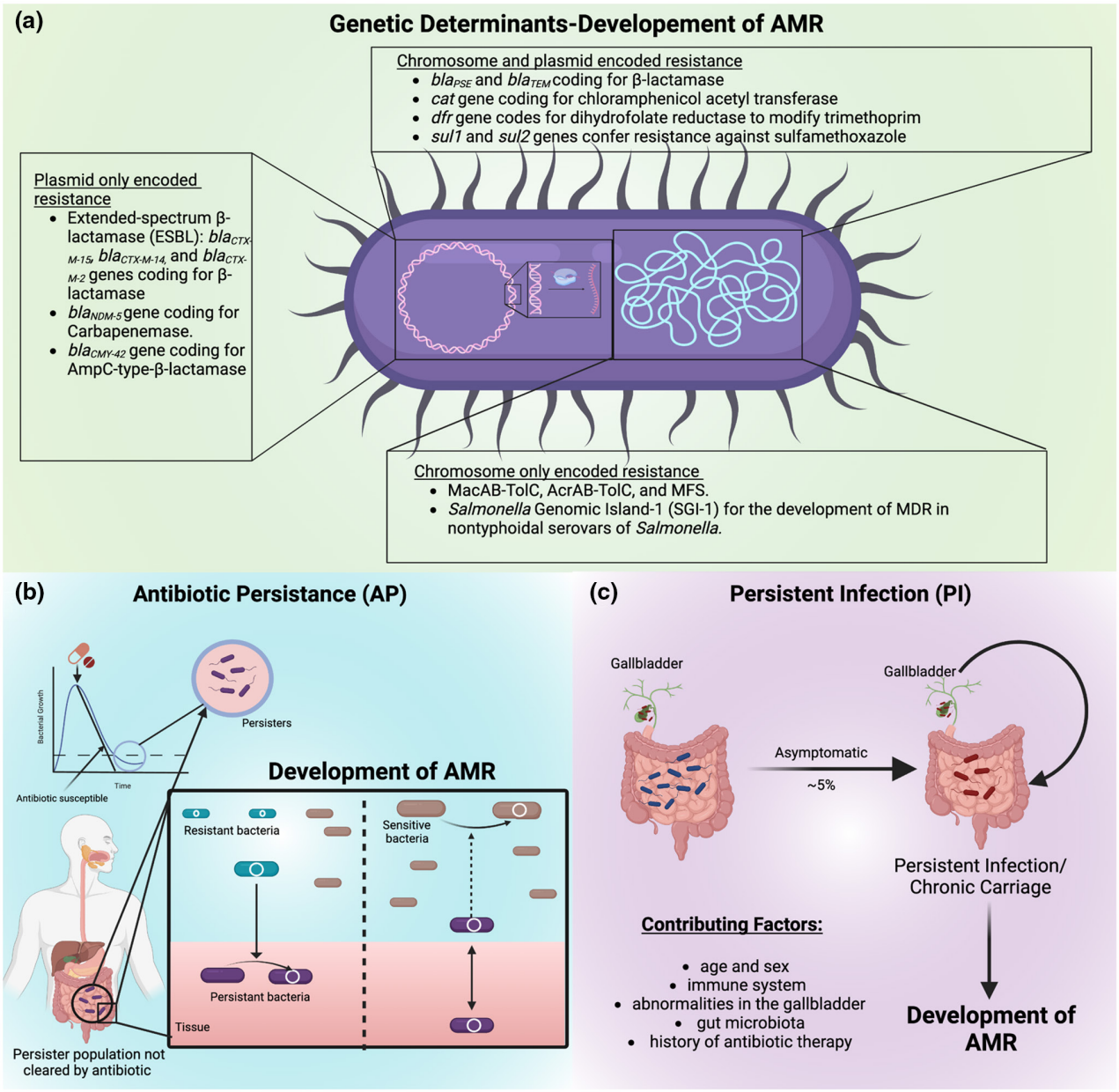

FIGURE 2 Determinant factors of antimicrobial response in *Salmonella* Typhi. Created by Biorender.com.

specific to AMR are largely different from those responsible for virulence in *S*. Typhi, there are several attributes in the bacterium that support both functions. In Gram-negative bacteria, the cell envelope is the front line of this system. It consists of an asymmetric lipopolysaccharide-phospholipid bilayer that serves as a physical barrier to the entry of molecules (including many antimicrobial agents) into the cells. An array of proteins spanning the outer membrane facilitates the entry of small molecules into the cell and passively precludes the entry of many antibiotics (Akshay et al., 2022). Sigma factors can initiate bacterial gene expression and are controlled by various regulators (activators and inhibitors). They are important means by which bacteria can adapt to different conditions (Baruzzo et al., 2023; Mascher, 2013; Missiakas & Raina, 1998; Qin et al., 2020). RpoE has been reported to promote the expression of flagellar genes under hyperosmotic stress, and a strong cross-talk between the two sigma factors RpoE and RpoS was observed (Du et al., 2011). Xie et al. identified RpoE as a putative regulator of antimicrobial response in *S*. Typhi. It has been reported that the RpoE mutant of *S*. Typhi exhibits resistance to multiple antimicrobial agents, including aminoglycosides, quinolones and β-lactams. This is caused by the upregulation of RamA, a member of the efflux pump AraC/XylS family, and the downregulated expression of two prominent outer membrane proteins, OmpC and OmpF (Xie et al., 2016). The role of OmpC and OmpF in the survival to the bile salt sodium deoxycholate was previously reported in *S*. Typhi (Villarreal et al., 2014). Our laboratory has extensively characterized the role of outer membrane protein A (OmpA) in combating innate immune responses and

AMR in *S*. Typhimurium (Chowdhury et al., 2022; Roy Chowdhury et al., 2022).

During infection in macrophages, *Salmonella* encounters oxidative stress mounted in the form of a respiratory burst. Phagocytes sequentially employ specific oxygen-derived antimicrobial effectors to clear off the infection. ROS can pervade through the bacterial membrane and cause damage to proteins and nucleic acids (Chanana et al., 2006; Hajra et al., 2022; van der Heijden et al., 2016). This stimulates a change in the membrane permeability so that the antimicrobial agents cannot penetrate the bacterial cell. This, in turn, leads to resistance to cefotaxime (van der Heijden et al., 2016). This study was performed in Typhimurium serovar and a similar incidence may occur with Typhi serovar as well. Castanheira et al. have shown that the major penicillin-binding proteins or PBPs (PBP2 and PBP3) involved in cell elongation and division in *Salmonella* under extracellular conditions are replaced by other PBPs ($PBP2_{SAL}$ and $PBP3_{SAL}$) during their intracellular life in a phagosome. This replacement helps *Salmonella* survive in the face of acidic pH and nutrient limitation in the phagosome. These modifications also protect against the currently available beta-lactam antibiotics. The development of novel drugs targeting the modified PBPs could help eliminate intracellular and intraphagosomal *Salmonella* (Castanheira et al., 2020; Thilliez & Kingsley, 2020). Thus, the properties of the bacterial cell that protect the pathogen from the innate immune response also provide protection against antimicrobial agents. Although there are not multiple reports of this intersection, preliminary studies do indicate more such overlaps and open a new domain for future research.

3.2 | Antibiotic persistence mediated

Resistance mechanisms facilitate bacterial growth in elevated drug concentrations. This may be considered a major cause of treatment failure. In addition, population-wide tolerance mechanisms, shielding effects of the physical niches in vivo and the emergence of AP populations are also considered important factors in treatment failure (Windels et al., 2019). Tolerance refers to the ability of genetically susceptible bacteria to survive bactericidal antibiotics at concentrations above the minimum inhibitory concentration (MIC). Unlike resistant bacteria, tolerant populations cannot proliferate in the presence of antimicrobials, but they are killed at a slower rate. AP cells refer to genetically identical bacteria that tend to form smaller or larger subpopulations that exhibit transient tolerance (Bakkeren et al., 2020; Pontes & Groisman, 2019). Extensive phenotypic variation in the intracellular *Salmonella* species may influence the treatment efficacy. Eradication of *S*. Typhimurium in host cells is delayed primarily by the abundant subset of moderately growing bacterial cells with partial tolerance. Slow-growing *Salmonella* survived the best after each dose (Claudi et al., 2014). Furthermore, it has been shown that in a population of *E. coli* cells, increased persistence has been shown to promote more cells in the reservoir of viable cells and increase the likelihood of resistance-conferring mutations (Windels et al., 2019).

S. enterica and *E. coli* harbour multiple resistance plasmids and different strains are often observed to colonize the same host (Apperloo-Renkema et al., 1990; Coque et al., 2008; Crump et al., 2015; San Román et al., 2018; Tenaillon et al., 2010; Wilcock et al., 1976; Wood et al., 1989). High cell densities in the intestinal lumen favour high rates of plasmid transfer between and within species (Diard et al., 2017; Moor et al., 2017; Stecher et al., 2012). Bakkeren et al. have shown that *S*. Typhimurium APs can promote the spread of resistance plasmids. In their study, they showed that tissue-associated *S*. Typhimurium are long-lived reservoirs of resistance plasmid donors or recipients. Re-seeding of these persister bacterial cells into the intestinal lumen allows for the co-occurrence of donors and recipients in the gut. This promotes the plasmid transfer between different species of *Enterobacteriaceae*. Their study has shown that bacterial persistence can promote the spread of antibiotic resistance along with disease relapse in chronic infections (Bakkeren et al., 2019). Induction of an SOS response by bactericidal antibiotics such as β-lactams and fluroquinolones can induce the expression of genes responsible for conjugative transfer in suitable donor bacteria such as *S. enterica*, *V. cholerae* and *S. aureus*. This increases the frequency of transfer of plasmids, transposons, integrons and lysogenic phages harbouring the antibiotic resistance genes between the donor and recipient bacteria (Bearson & Brunelle, 2015; Blazquez et al., 2018; Eisenreich et al., 2022; Hebrard et al., 2009; Liu et al., 2017; Maiques et al., 2006). From these studies, we can infer that bacterial antibiotic persistence may be an understudied and unexplored cause of AMR. We have summarized these literature studies in Figure 2.

Although these studies have been strictly limited to the non-typhoidal serovar of *Salmonella*, it would be very interesting to extend the same in the Typhi serovar. Over the years, *S*. Typhi has undergone pseudogenization to optimize host specificity (Chatterjee et al., 2023). Elucidating specific similarities or differences in AP mechanisms due to pseudogenization will indeed open a fascinating area for future research.

3.3 | Persistent infection and its role in AMR

In addition to the development of resistant strains in the form of MDR and XDR, the intra-host PI of *Salmonella* leads to chronic infection. The presence of asymptomatic and chronic typhoid carriers has been documented for more than a century, with the case of Mary Mallom or Typhoid Mary being the best example. The ability of bacterial pathogens to cause long-lasting infection despite host immune surveillance is referred to as intra-host PI. It should be noted that AP and PI are two distinct phenomena. In the following sections, we will focus exclusively on PI, unless stated otherwise. PI is also a major obstacle to the elimination of *Salmonella* by antibiotics. Approximately 3%–5% of the individuals infected with *S*. Typhi become chronic carriers of the pathogen. They are asymptomatic and may transmit the disease through fecal excretions (Schioler et al., 1983). Although typhoid infections in humans are temporary and efficiently cleared by the human immune system, there is always a subset of pathogens

that can stealthily evade the strict host immune surveillance and colonize one or more niches to cause long-lasting infections. The PI of *S*. Typhi in the human host may be asymptomatic when the infected person shows no sign of pathology (carriage), or it may be symptomatic, characterized by repetitive typhoid fever (recurrence). Depending upon the shedding time of the bacteria through the stools of infected individuals, the carriage of the persistent *S*. Typhi can further be categorized into two groups: temporary carriage (when the bacterial shedding lasts up to 12 months) and chronic carriage (bacterial shedding lasts beyond 12 months) (Gal-Mor, 2019; Ruby et al., 2012; Vogelsang & Boe, 1948). Although typhoid fever carriers are asymptomatic, they are highly contagious.

The gallbladder and the biliary tract are the primary sites in the human body for the chronic carriage of typhoidal serovars of *S. enterica* (Hoffman et al., 2023). The diagnosis of the majority of the individuals with chronic carriage of persistent *S*. Typhi with gallstones and cholecystitis (chronic inflammation of the gallbladder) showed that individuals with pre-existing complications in the gallbladder tend to become a reservoir for PI (Lai et al., 1992; Schioler et al., 1983). There are multiple studies that have investigated the intra-gallbladder niche of *S*. Typhi during PI and its release from the gallbladder for excretion in the feces (Crawford et al., 2010). PI bacteria either grow freely in the lumen of the gallbladder or invade the epithelial lining of the gallbladder and multiply there without migrating into the mucosa (Menendez et al., 2009).

There is more than one mechanism of bile resistance present in *S. enterica*. However, several reports suggest that the initial resistance is mediated by the envelope structure of the lipopolysaccharide (Crawford et al., 2012; Hernandez et al., 2012; May & Groisman, 2013; Murata et al., 2007; Picken & Beacham, 1977; van Velkinburgh & Gunn, 1999) and the common enterobacterial antigen (Ramos-Morales et al., 2003). This surface protection reduces the overall uptake of bile salts inside the bacterial cell. Several studies have also shown that *S*. Typhi can form a biofilm on cholesterol-coated gallstones in the gallbladder. The capsular Vi antigen of the bacteria and the extracellular polymeric substances (EPS) of the biofilm protect the bacteria from the bactericidal action of bile salts in the gallbladder (Di Domenico et al., 2017; Prouty et al., 2002; Tsai et al., 2019). The Vi capsule of *S*. Typhi also protects the biofilm resident bacteria from the bactericidal innate immune response of macrophages and neutrophils by reducing their ability to generate RNS and ROS, respectively (Hahn & Gunn, 2020). The reduction of porins in the bacteria also limits the uptake of bile salts (Hernandez et al., 2012). Another prominent resistance mechanism is efflux pumps, which efficiently inhibit bile salt accumulation. RND efflux systems are among the most studied and can transport bile salts outside the cell (Lyu et al., 2022; Murakami et al., 2002; Nikaido, 1996; Williams et al., 1984).

In the case of PI, a staggered or continuous manifestation of disease pathology in the symptomatic carrier of typhoid occurs, and the recurrence of the disease generally occurs in episodes linked to a single infection event. However, it is well-differentiated from re-infection in which the host becomes infected with the same pathogen in multiple independent cases (Gal-Mor, 2019). Even after acute *S*. Typhi infection has resolved, approximately 10% of the convalescent untreated infected patients excrete the bacteria in their feces for up to 3 months. The asymptomatic carrier usually excretes 10^4–10^{10} *S*. Typhi bacteria per gram of stool for more than 12 months (Levine et al., 1982; Musher & Rubenstein, 1973). Even without clinical symptoms, they may periodically excrete considerable number of bacteria in their stool for decades (Levine et al., 1982; Vogelsang & Boe, 1948). The chronic carrier of *S*. Typhi is always human, as the pathogen is human-restricted and only humans provide a natural reservoir for this pathogen in the population (Bhan et al., 2005; Kidgell et al., 2002). There is a largely unexplored area of asymptomatic carriage of *S*. Paratyphi A, B and C. However, one of the recent reports from Nepal showed a similar incidence of PI and carriage of *S*. Typhi and Paratyphi A in endemic areas (Dongol et al., 2012). A similar finding suggests that 11% of the reported *S*. Paratyphi B PI cases are temporary carriage and 2% are chronic carriage (Vogelsang & Boe, 1948).

The PI of typhoidal and NTS *Salmonella* in human hosts depends on many physiological factors such as the age and sex of the infected individuals, their immune system, gallbladder abnormalities, the health of the gut microbiota and history of antibiotic therapy. The healthy gut microbiota of individuals can limit the colonization of invading pathogens by nutrient deprivation, activating the innate and adaptive immune response, and secreting antimicrobial substances (Endt et al., 2010; Fabich et al., 2008; Macpherson & Uhr, 2004; Salzman et al., 2003, 2010; Slack et al., 2009; Stecher & Hardt, 2011). Prolonged antibiotic therapy can cause dysbiosis of the gut microflora and promote chronic PI of *S*. Typhi in the human host by delaying their clearance by the immune system (Endt et al., 2010; Lawley et al., 2008). In addition to the gallbladder and biliary tract, the PI population of *S*. Typhi can invade various other organs of the human body, such as the MLN, liver, bone marrow, kidney, urinary tract, etc. (Gal-Mor, 2019).

3.3.1 | Models to study *S*. Typhimurium PI

Since *S*. Typhi infection is restricted to humans, the investigation of *S*. Typhi PI is challenging. Nowadays, 129X1/SvJ mice carrying a wild-type allele of *Nramp1* are used to study *S*. Typhimurium PI in the host (Gonzalez et al., 2018). These mice can survive for 1 year even after oral infection with a lethal dose of 10^8 CFU of wild-type *S*. Typhimurium (Monack et al., 2004). 129X1/SvJ mice fed with a lithogenic diet form gallstones that support bacterial biofilm formation, which may be an excellent model for studying *S*. Typhimurium PI (Crawford et al., 2010). Studies on *S*. Typhi persisters are incredibly sparse and thus, the scope of exploration is vast.

3.3.2 | Host immune responses during *Salmonella* PI

Despite being unique in their virulence, *S*. Typhi and Typhimurium share about 89% of the genes (McClelland et al., 2001; Sabbagh

et al., 2010). The lack a suitable infection model for *S*. Typhi made persister-related in vivo studies extremely difficult. The high genetic homology between the two serovars and the availability of several in vivo infection models (including C57BL/6, BALB/c and 129X1/SvJ) made *S*. Typhimurium an excellent candidate for studying *Salmonella* PI. During acute infection and the early stages of systemic spread in mice, when *S*. Typhimurium is phagocytosed by the macrophages and remains in the SCV (Chaudhuri et al., 2018; Majee et al., 2021), they are strongly challenged by a strong Th1 and a weak Th2 response of the host. The Th1 response is characterized by increased expression and secretion of pro-inflammatory cytokines like IFN-ɣ, TNF-α, IL-12, generation of bactericidal ROS and RNS, etc. (Gal-Mor, 2019; Sashinami et al., 2006; Mastroeni, 2002). *Salmonella* use their SPI-2 encoded virulent factors to survive in the hostile environment of the host (Chakravortty et al., 2002; Roy Chowdhury et al., 2022). In the chronic stage of *Salmonella* infection, the Th1 response is diminished by the enhanced Th2 response, leading to increased expression of the anti-inflammatory cytokine IL-10. Overexpression of IL-10 attenuates the secretion of IFN-ɣ, TNF-α and IL-12 from macrophages and reduces the biogenesis of ROS and RNS, which eventually promotes the intracellular proliferation of the bacteria (Chausse et al., 2014; Ruby et al., 2012). During the first PI phase of *Salmonella* infection in the mouse model (129CvJ X C57BL/6) (21–28 dpi), the effector T cell population outnumbered the $FOXP3^+$ T_{reg} population, which promoted the growth of persisters in mice. Subsequently, the $FOXP3^+$ T_{reg} population decreases, and the increasing effector T cell population regulates the bacteria growth in vivo (Johanns et al., 2010). The documentation of a distinct switch from the pro-inflammatory Th1 response (observed on day 7 post-infection, i.e. the early stage of infection) to the anti-inflammatory Th2 response (found on day 21 post-infection, i.e. of chronic infection) in the transcriptomic analysis of the gallbladder of 129X1/SvJ mice fed with a lithogenic diet and infected with *S*. Typhimurium 14028S also confirmed the authenticity of the above system for the in vivo model host of *S*. Typhimurium PI (Gonzalez et al., 2019). The anti-inflammatory Th2 response in the infected gallbladder was characterized by the ameliorated expression of the Th2 master regulator GATA3, the Th2 marker IL-4 and STAT-6 (Gonzalez et al., 2019).

3.3.3 | Bacterial effector proteins required for PI of *S*. Typhimurium

S. Typhimurium uses several genes to promote PI in response to the host signaling and immune attacks in the organs or the body fluids. Several genes belonging to the virulence determining major pathogenicity islands of the bacterium, such as *sipB*, *sipC*, *sipD* of SPI-1 and *sseK2*, *sseJ* of SPI-2, play an active role in the long-term systemic infection of mice (Lawley et al., 2006). During macrophage infection, antibiotic-resistant *S*. Typhimurium persisters can transform the pro-inflammatory cytokine profile into an infection-permissive anti-inflammatory state with the help of the virulence factor SteE encoded by the SPI-2 (Stapels et al., 2018). SteE can promote the M2 polarization state of granuloma macrophages by antagonizing the action of TNF signaling, which further facilitates the survival of *S*. Typhimurium persisters in the spleen of 129X1/SvJ mice (Pham et al., 2020). The phosphorylated form of SteE makes mammalian serine/threonine kinase GSK3 to phosphorylate STAT3 specifically at the 705th residue, which eventually activates the M2 macrophage marker IL-4Rα and promotes bacterial PI (Panagi et al., 2020). In addition to the virulence factors encoded by SPI, other bacterial genes play equally important role in promoting and establishing chronic infection in vivo. The fimbrial operon genes *lpf*, *bcf*, *stb*, *stc*, *std* and *sth* of *S*. Typhimurium play a critical role in long-term intestinal carriage in a genetically resistant CBA/J mouse model (Weening et al., 2005). Mig-14, an inner membrane protein of *S*. Typhimurium, associated with its resistance to the cathelin-related antimicrobial peptide (CRAMP) in macrophages, also promotes the PI in mesenteric lymph nodes and spleen of chronically infected 129X1/SvJ mice (Brodsky et al., 2005). The two outer membrane proteins, namely ShdA and RatB of *S*. Typhimurium, play a critical role in bacterial shedding in the CBA/J mouse model (Kingsley et al., 2003). Previous reports suggest that *Salmonella* genes such as *virK*, *rcsC* and *somA*, which are transcriptionally co-activated with SPI-2, play an important role in long-term infection in the mouse model (Detweiler et al., 2003).

The unique ability of the APs to initiate infection relapse in the face of macrophage-induced dsDNA breaks has been demonstrated by Hill et al. They have shown that this AP-specific ability is largely due to RecA-mediated DNA repair as the few *ΔrecA* bacteria that were able to resist antibiotic treatment were unable to initiate infection relapse, quite in contrast to the wild-type strain (Hill et al., 2021). It has also been demonstrated that acidification and most likely starvation inside the macrophages play key roles in the generation of AP cells (Helaine et al., 2014). A clear connection, if any, between AP and PI has not been established till date. However, it is very likely that the environment of the host cell leads to the formation of APs and selects them specifically, leading to PI in the long term.

3.3.4 | PI and its role in AMR

Preliminary studies have shown that PI leads to an altered antimicrobial response in *S*.Typhimurium. Profiling of antibiograms of early and later isolates from patients who had PI of *S*. Typhimurium revealed MDR responses to piperacillin, ceftriaxone, trimethoprim-sulfamethaxazole, in one of the later isolates. This phenotype was associated with the acquisition of a large plasmid conferring ESBL activity. Thus, the resistance profile of *Salmonella* may change during the course of infection which could have different implications for the treatment methods (Marzel et al., 2016). However, this study did not address the source of the plasmid in *Salmonella* PI. We have summarized this section in Figure 2.

These studies show that there are many unexplored areas of *Salmonella* pathogenesis and antibiotic resistance development. An important approach to combat these phenomena may be to alter the host immune responses and prevent any chance of PI.

4 | CONCLUSION

Over the years, there have been significant scientific advances in the development of therapeutic interventions to combat *S*. Typhi infections. However, in the race against drug-resistant *S*. Typhi, there is still a continuous need to develop newer therapeutics. The recent insights into the role of AP and PI populations of *Salmonella* have opened new areas for comprehensive exploration of alternative antimicrobial strategies. The interplay of multiple mechanisms in persister populations leads to heterogenous phenotypes and the emergence of highly drug-resistant variants. This prolongs the treatment time for the patients and greatly increases the economic burden on the healthcare infrastructure. In such cases, comprehensive high-end research to study single-cell and population dynamics would help us identify new targets in host and bacterial cells. This will enable us to successfully target the drug-resistant, PI and AP populations that cause recurrent and deadly infections.

AUTHOR CONTRIBUTIONS

Dipshikha Chakravortty: Conceptualization; investigation; funding acquisition; writing – original draft; validation; visualization; writing – review and editing; project administration; supervision; resources. **Atish Roy Chowdhury:** Writing – original draft; conceptualization; writing – review and editing. **Debapriya Mukherjee:** Writing – original draft; conceptualization; validation; writing – review and editing. **Ritika Chatterjee:** Conceptualization; investigation; writing – original draft; writing – review and editing; supervision.

ACKNOWLEDGEMENTS

We thank the financial support from Department of Biotechnology (DBT), Ministry of Science and Technology; Department of Science and Technology (DST), Ministry of Science and Technology. DC acknowledges DAE for the SRC outstanding investigator award and funds, ASTRA Chair Professorship and TATA Innovation fellowship funds. The authors jointly acknowledge the DBT-IISc Partnership Program. Infrastructure support from ICMR (Center for Advanced Study in Molecular Medicine), DST (FIST) and UGC-CAS (special assistance) is acknowledged. ARC acknowledges Shamrao M. Kaikini and Krishna S. Kaikini fellowship. DM acknowledges IISc fellowship. RC duly acknowledges CSIR-SRF fellowship.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ETHICS STATEMENT

No human or animal subjects or material were used in this review.

ORCID

Ritika Chatterjee https://orcid.org/0000-0003-3432-9245
Dipshikha Chakravortty https://orcid.org/0000-0002-7838-5145

REFERENCES

Accogli, M., Fortini, D., Giufrè, M., Graziani, C., Dolejska, M., Carattoli, A. et al. (2013) IncI1 plasmids associated with the spread of CMY-2, CTX-M-1 and SHV-12 in *Escherichia coli* of animal and human origin. *Clinical Microbiology and Infection*, 19(5), E238–E240.

Ahamed Riyaaz, A.A., Perera, V., Sivakumaran, S. & de Silva, N. (2018) Typhoid fever due to extended spectrum beta-lactamase-producing *Salmonella enterica* Serovar Typhi: a case report and literature review. *Case Reports in Infectious Diseases*, 2018, 4610246.

Ahsan, S. & Rahman, S. (2019) Azithromycin resistance in clinical isolates of *Salmonella enterica* serovars Typhi and Paratyphi in Bangladesh. *Microbial Drug Resistance*, 25(1), 8–13.

Ain, Q., Tahir, M., Sadaqat, A., Ayub, A., Awan, A.B., Wajid, M. et al. (2022) First detection of extensively drug-resistant *Salmonella* Typhi isolates harboring VIM and GES genes for Carbapenem resistance from Faisalabad, *Pakistan*. *Microbial Drug Resistance*, 28(12), 1087–1098.

Akram, J., Khan, A.S., Khan, H.A., Gilani, S.A., Akram, S.J., Ahmad, F.J. et al. (2020) Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. *BioMed Research International*, 2020, 6432580.

Akshay, S.D., Anupama, K.P., Deekshit, V.K., Rohit, A. & Maiti, B. (2022) Effect of sub-minimum inhibitory concentration of ceftriaxone on the expression of outer membrane proteins in *Salmonella enterica* serovar Typhi. *World Journal of Microbiology and Biotechnology*, 38(11), 190.

Akshay, S.D., Nayak, S., Deekshit, V.K., Rohit, A. & Maiti, B. (2023) Differential expression of outer membrane proteins and quinolone resistance determining region mutations can lead to ciprofloxacin resistance in *Salmonella* Typhi. *Archives of Microbiology*, 205(4), 136.

Ali Shah, S.A., Nadeem, M., Syed, S.A., Fatima Abidi, S.T., Khan, N. & Bano, N. (2020) Antimicrobial sensitivity pattern of *Salmonella* Typhi: emergence of resistant strains. *Cureus*, 12(11), e11778.

Al-Rashdi, A., Kumar, R., Al-Bulushi, M., Al Abri, S. & Al-Jardani, A. (2021) Genomic analysis of the first cases of extensively drug-resistant, travel-related *Salmonella enterica* serovar Typhi in Oman. *IJID Regions*, 1, 135–141.

Anderson, E.S. & Smith, H.R. (1972) Chloramphenicol resistance in the typhoid bacillus. *British Medical Journal*, 3(5822), 329–331.

Antunes, P., Machado, J., Sousa, J.C. & Peixe, L. (2005) Dissemination of sulfonamide resistance genes (sul1, sul2, and sul3) in Portuguese *Salmonella enterica* strains and relation with integrons. *Antimicrobial Agents and Chemotherapy*, 49(2), 836–839.

Apperloo-Renkema, H., Van der Waaij, B. & Van der Waaij, D. (1990) Determination of colonization resistance of the digestive tract by biotyping of Enterobacteriaceae. *Epidemiology & Infection*, 105(2), 355–361.

Arcangioli, M.A., Leroy-Setrin, S., Martel, J.-L. & Chaslus-Dancla, E. (2000) Evolution of chloramphenicol resistance, with emergence of cross-resistance to florfenicol, in bovine *Salmonella* Typhimurium strains implicates definitive phage type (DT) 104. *Journal of Medical Microbiology*, 49(1), 103–110.

Arnold, B.J., Huang, I.T. & Hanage, W.P. (2022) Horizontal gene transfer and adaptive evolution in bacteria. *Nature Reviews. Microbiology*, 20(4), 206–218.

Aubron, C., Poirel, L., Ash, R.J. & Nordmann, P. (2005) Carbapenemase-producing *Enterobacteriaceae*, U.S. Rivers. *Emerging Infectious Disease Journal*, 11(2), 260–264.

Bakkeren, E., Diard, M. & Hardt, W.-D. (2020) Evolutionary causes and consequences of bacterial antibiotic persistence. *Nature Reviews Microbiology*, 18(9), 479–490.

Bakkeren, E., Huisman, J.S., Fattinger, S.A., Hausmann, A., Furter, M., Egli, A. et al. (2019) *Salmonella* persisters promote the spread of antibiotic resistance plasmids in the gut. *Nature*, 573(7773), 276–280.

Balaban, N.Q., Merrin, J., Chait, R., Kowalik, L. & Leibler, S. (2004) Bacterial persistence as a phenotypic switch. *Science*, 305(5690), 1622–1625.

Barquist, L., Langridge, G.C., Turner, D.J., Phan, M.D., Turner, A.K., Bateman, A. et al. (2013) A comparison of dense transposon insertion libraries in the *Salmonella* serovars Typhi and Typhimurium. *Nucleic Acids Research*, 41(8), 4549–4564.

Baruzzo, G., Serafini, A., Finotello, F., Sanavia, T., Cioetto-Mazzabò, L., Boldrin, F. et al. (2023) Role of the extracytoplasmic function sigma factor SigE in the stringent response of *Mycobacterium tuberculosis*. *Microbiology Spectrum*, 11(2), e0294422.

Bearson, B.L. & Brunelle, B.W. (2015) Fluoroquinolone induction of phage-mediated gene transfer in multidrug-resistant *Salmonella*. *International Journal of Antimicrobial Agents*, 46(2), 201–204.

Ben Sallem, R., Ben Slama, K., Rojo-Bezares, B., Porres-Osante, N., Jouini, A., Klibi, N. et al. (2014) IncI1 plasmids carrying Bla(CTX-M-1) or Bla(CMY-2) genes in *Escherichia coli* from healthy humans and animals in Tunisia. *Microbial Drug Resistance*, 20(5), 495–500.

Bhan, M.K., Bahl, R. & Bhatnagar, S. (2005) Typhoid and paratyphoid fever. *The Lancet*, 366(9487), 749–762.

Bhatti, J.M., Memon, Y., Sarfaraz, S. & Salahuddin, N. (2019) An unusual case of extensively drug resistant typhoid fever. *Cureus*, 11(5), e4664.

Blazquez, J., Rodriguez-Beltran, J. & Matic, I. (2018) Antibiotic-induced genetic variation: how it arises and how it can be prevented. *Annual Review of Microbiology*, 72, 209–230.

Boyd, D., Cloeckaert, A., Chaslus-Dancla, E. & Mulvey, M.R. (2002) Characterization of variant *Salmonella* genomic Island 1 multidrug resistance regions from serovars Typhimurium DT104 and Agona. *Antimicrobial Agents and Chemotherapy*, 46(6), 1714–1722.

Britto, C.D., Wong, V.K., Dougan, G. & Pollard, A.J. (2018) A systematic review of antimicrobial resistance in *Salmonella enterica* serovar Typhi, the etiological agent of typhoid. *PLoS Neglected Tropical Diseases*, 12(10), e0006779.

Brodie, J., Macqueen, I.A. & Livingstone, D. (1970) Effect of trimethoprim-sulphamethoxazole on typhoid and salmonella carriers. *British Medical Journal*, 3(5718), 318–319.

Brodsky, I.E., Ghori, N., Falkow, S. & Monack, D. (2005) Mig-14 is an inner membrane-associated protein that promotes *Salmonella* typhimurium resistance to CRAMP, survival within activated macrophages and persistent infection. *Molecular Microbiology*, 55(3), 954–972.

Buckle, G.C., Walker, C.L. & Black, R.E. (2012) Typhoid fever and paratyphoid fever: systematic review to estimate global morbidity and mortality for 2010. *Journal of Global Health*, 2(1), 010401.

Burmeister, A.R. (2015) Horizontal gene transfer. *Evolution, Medicine, and Public Health*, 2015(1), 193–194.

Butler, T., Linh, N.N., Arnold, K., Adickman, M.D., Chau, D.M. & Muoi, M.M. (1977) Therapy of antimicrobial-resistant typhoid fever. *Antimicrobial Agents and Chemotherapy*, 11(4), 645–650.

Campbell, D., Tagg, K., Bicknese, A., McCullough, A., Chen, J., Karp, B.E. et al. (2018) Identification and characterization of *Salmonella enterica* serotype Newport isolates with decreased susceptibility to ciprofloxacin in the United States. *Antimicrobial Agents and Chemotherapy*, 62(7), e00653-18.

Cao, G., Allard, M., Hoffmann, M., Muruvanda, T., Luo, Y., Payne, J. et al. (2018) Sequence analysis of IncA/C and IncI1 plasmids isolated from multidrug-resistant *Salmonella* Newport using single-molecule real-time sequencing. *Foodborne Pathogens and Disease*, 15(6), 361–371.

Capoor, M.R., Nair, D., Posti, J., Singhal, S., Deb, M., Aggarwal, P. et al. (2009) Minimum inhibitory concentration of carbapenems and tigecycline against *Salmonella* spp. *Journal of Medical Microbiology*, 58(Pt 3), 337–341.

Castanheira, S., López-Escarpa, D., Pucciarelli, M.G., Cestero, J.J., Baquero, F. & García-del Portillo, F. (2020) An alternative penicillin-binding protein involved in *Salmonella* relapses following ceftriaxone therapy. *eBioMedicine*, 55, 102771.

Chakravortty, D., Hansen-Wester, I. & Hensel, M. (2002) *Salmonella* pathogenicity Island 2 mediates protection of intracellular *Salmonella* from reactive nitrogen intermediates. *The Journal of Experimental Medicine*, 195(9), 1155–1166.

Chanana, V., Majumdar, S. & Rishi, P. (2006) Tumour necrosis factor alpha mediated apoptosis in murine macrophages by *Salmonella enterica* serovar Typhi under oxidative stress. *FEMS Immunology and Medical Microbiology*, 47(2), 278–286.

Chang, M.X., Zhang, J.F., Sun, Y.H., Li, R.S., Lin, X.L., Yang, L. et al. (2021) Contribution of different mechanisms to ciprofloxacin resistance in *Salmonella* spp. *Frontiers in Microbiology*, 12, 663731.

Chatterjee, R., Chowdhury, A.R., Mukherjee, D. & Chakravortty, D. (2023) From Eberthella typhi to *Salmonella* Typhi: the fascinating journey of the virulence and pathogenicity of *Salmonella* Typhi. *ACS Omega*, 8(29), 25674–25697.

Chaudhuri, D., Roy Chowdhury, A., Biswas, B. & Chakravortty, D. (2018) *Salmonella* Typhimurium infection leads to colonization of the mouse brain and is not completely cured with antibiotics. *Frontiers in Microbiology*, 9, 1632.

Chausse, A.M., Grépinet, O., Bottreau, E., Robert, V., Hennequet-Antier, C., Lalmanach, A. et al. (2014) Susceptibility to *Salmonella* carrier-state: a possible Th2 response in susceptible chicks. *Veterinary Immunology and Immunopathology*, 159(1–2), 16–28.

Chen, W., Fang, T., Zhou, X., Zhang, D., Shi, X. & Shi, C. (2016) IncHI2 plasmids are predominant in antibiotic-resistant *Salmonella* isolates. *Frontiers in Microbiology*, 7, 1566.

Cheng, P., Yang, Y., Li, F., Li, X., Liu, H., Fazilani, S.A. et al. (2020) The prevalence and mechanism of fluoroquinolone resistance in *Escherichia coli* isolated from swine farms in China. *BMC Veterinary Research*, 16(1), 258.

Chiou, C.S., Lauderdale, T.L., Phung, D.C., Watanabe, H., Kuo, J.C., Wang, P.J. et al. (2014) Antimicrobial resistance in *Salmonella enterica* Serovar Typhi isolates from Bangladesh, Indonesia, Taiwan, and Vietnam. *Antimicrobial Agents and Chemotherapy*, 58(11), 6501–6507.

Chirico, C., Tomasoni, L.R., Corbellini, S., de Francesco, M.A., Caruso, A., Scaltriti, E. et al. (2020) The first Italian case of XDR *Salmonella* Typhi in a traveler returning from Pakistan, 2019: an alert for increased surveillance also in European countries? *Travel Medicine and Infectious Disease*, 36, 101610.

Chowdhury, A.R., Mukherjee, D., Singh, A.K. & Chakravortty, D. (2022) Loss of outer membrane protein a (OmpA) impairs the survival of *Salmonella* Typhimurium by inducing membrane damage in the presence of ceftazidime and meropenem. *The Journal of Antimicrobial Chemotherapy*, 77(12), 3376–3389.

Claudi, B., Spröte, P., Chirkova, A., Personnic, N., Zankl, J., Schürmann, N. et al. (2014) Phenotypic variation of *Salmonella* in host tissues delays eradication by antimicrobial chemotherapy. *Cell*, 158(4), 722–733.

Colquhoun, J. & Weetch, R.S. (1950) Resistance to chloramphenicol developing during treatment of typhoid fever. *Lancet*, 2(6639), 621–623.

Coque, T.M., Baquero, F. & Cantón, R. (2008) Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. *Eurosurveillance*, 13(47). Available from: https://doi.org/10.2807/ese.13.47.19044-en

Crawford, R.W., Keestra, A.M., Winter, S.E., Xavier, M.N., Tsolis, R.M., Tolstikov, V. et al. (2012) Very long O-antigen chains enhance fitness during *Salmonella*-induced colitis by increasing bile resistance. *PLoS Pathogens*, 8(9), e1002918.

Crawford, R.W., Rosales-Reyes, R., Ramírez-Aguilar, M.L., Chapa-Azuela, O., Alpuche-Aranda, C. & Gunn, J.S. (2010) Gallstones play a significant role in *Salmonella* spp. gallbladder colonization and carriage.

Proceedings of the National Academy of Sciences of the United States of America, 107(9), 4353–4358.

Crump, J.A., Luby, S.P. & Mintz, E.D. (2004) The global burden of typhoid fever. *Bulletin of the World Health Organization*, 82(5), 346–353.

Crump, J.A., Sjölund-Karlsson, M., Gordon, M.A. & Parry, C.M. (2015) Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial Management of Invasive *Salmonella* infections. *Clinical Microbiology Reviews*, 28(4), 901–937.

Das, S., Samajpati, S., Ray, U., Roy, I. & Dutta, S. (2017) Antimicrobial resistance and molecular subtypes of *Salmonella enterica* serovar Typhi isolates from Kolkata, India over a 15 years period 1998-2012. *International Journal of Medical Microbiology*, 307(1), 28–36.

Debroy, R., Miryala, S.K., Naha, A., Anbarasu, A. & Ramaiah, S. (2020) Gene interaction network studies to decipher the multi-drug resistance mechanism in *Salmonella enterica* serovar Typhi CT18 reveal potential drug targets. *Microbial Pathogenesis*, 142, 104096.

Detweiler, C.S., Monack, D.M., Brodsky, I.E., Mathew, H. & Falkow, S. (2003) virK, somA and rcsC are important for systemic *Salmonella enterica* serovar Typhimurium infection and cationic peptide resistance. *Molecular Microbiology*, 48(2), 385–400.

Di Domenico, E.G., Cavallo, I., Pontone, M., Toma, L. & Ensoli, F. (2017) Biofilm producing *Salmonella* Typhi: chronic colonization and development of gallbladder cancer. *International Journal of Molecular Sciences*, 18(9), 1887.

Diard, M., Bakkeren, E., Cornuault, J.K., Moor, K., Hausmann, A., Sellin, M.E. et al. (2017) Inflammation boosts bacteriophage transfer between *Salmonella* spp. *Science*, 355(6330), 1211–1215.

Disease, G.B.D., Injury, I. & Prevalence, C. (2017) Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease study 2016. *Lancet*, 390(10100), 1211–1259.

Djeghout, B., Saha, S., Sajib, M.S.I., Tanmoy, A.M., Islam, M., Kay, G.L. et al. (2018) Ceftriaxone-resistant *Salmonella* Typhi carries an IncI1-ST31 plasmid encoding CTX-M-15. *Journal of Medical Microbiology*, 67(5), 620–627.

Dongol, S., Thompson, C.N., Clare, S., Nga, T.V.T., Duy, P.T., Karkey, A. et al. (2012) The microbiological and clinical characteristics of invasive *Salmonella* in gallbladders from cholecystectomy patients in Kathmandu, Nepal. *PLoS One*, 7(10), e47342.

Doublet, B., Boyd, D., Mulvey, M.R. & Cloeckaert, A. (2005) The *Salmonella* genomic Island 1 is an integrative mobilizable element. *Molecular Microbiology*, 55(6), 1911–1924.

Doublet, B., Praud, K., Bertrand, S., Collard, J.-M., Weill, F.-X. & Cloeckaert, A. (2008) Novel insertion sequence- and transposon-mediated genetic rearrangements in genomic Island SGI1 of *Salmonella enterica* serovar Kentucky. *Antimicrobial Agents and Chemotherapy*, 52(10), 3745–3754.

Du, H., Wang, M., Luo, Z., Ni, B., Wang, F., Meng, Y. et al. (2011) Coregulation of gene expression by sigma factors RpoE and RpoS in *Salmonella enterica* serovar Typhi during hyperosmotic stress. *Current Microbiology*, 62(5), 1483–1489.

Dutta, S., das, S., Mitra, U., Jain, P., Roy, I., Ganguly, S.S. et al. (2014) Antimicrobial resistance, virulence profiles and molecular subtypes of *Salmonella enterica* serovars Typhi and Paratyphi a blood isolates from Kolkata, India during 2009-2013. *PLoS One*, 9(8), e101347.

Dyson, Z.A., Klemm, E.J., Palmer, S. & Dougan, G. (2019) Antibiotic resistance and typhoid. *Clinical Infectious Diseases*, 68(Suppl 2), S165–S170.

Eisenreich, W., Rudel, T., Heesemann, J. & Goebel, W. (2022) Link between antibiotic persistence and antibiotic resistance in bacterial pathogens. *Frontiers in Cellular and Infection Microbiology*, 12, 900848.

Endt, K., Stecher, B., Chaffron, S., Slack, E., Tchitchek, N., Benecke, A. et al. (2010) The microbiota mediates pathogen clearance from the gut lumen after non-typhoidal *Salmonella* diarrhea. *PLoS Pathogens*, 6(9), e1001097.

Eshaghi, A., Zittermann, S., Bharat, A., Mulvey, M.R., Allen, V.G. & Patel, S.N. (2020) Importation of extensively drug-resistant *Salmonella enterica* Serovar Typhi cases in Ontario, Canada. *Antimicrobial Agents and Chemotherapy*, 64(5), e02581-19.

Eykyn, S.J. & Williams, H. (1987) Treatment of multiresistant *Salmonella typhi* with oral ciprofloxacin. *Lancet*, 2(8572), 1407–1408.

Fabich, A.J., Jones, S.A., Chowdhury, F.Z., Cernosek, A., Anderson, A., Smalley, D. et al. (2008) Comparison of carbon nutrition for pathogenic and commensal *Escherichia coli* strains in the mouse intestine. *Infection and Immunity*, 76(3), 1143–1152.

Fatima, S., Ishaq, Z., Irfan, M., AlAsmari, A.F., Achakzai, J.K., Zaheer, T. et al. (2023) Whole-genome sequencing of multidrug resistance *Salmonella* Typhi clinical strains isolated from Balochistan, Pakistan. *Frontiers in Public Health*, 11, 1151805.

Feasey, N.A., Gaskell, K., Wong, V., Msefula, C., Selemani, G., Kumwenda, S. et al. (2015) Rapid emergence of multidrug resistant, H58-lineage *Salmonella typhi* in Blantyre, Malawi. *PLoS Neglected Tropical Diseases*, 9(4), e0003748.

Ferrari, R., Galiana, A., Cremades, R., Rodríguez, J.C., Magnani, M., Tognim, M.C. et al. (2013) Plasmid-mediated quinolone resistance (PMQR) and mutations in the topoisomerase genes of *Salmonella enterica* strains from Brazil. *Brazilian Journal of Microbiology*, 44(2), 651–656.

Foley, S.L., Kaldhone, P.R., Ricke, S.C. & Han, J. (2021) Incompatibility group I1 (IncI1) plasmids: their genetics, biology, and public health relevance. *Microbiology and Molecular Biology Reviews*, 85(2), e00031-20.

Folster, J.P., Tolar, B., Pecic, G., Sheehan, D., Rickert, R., Hise, K. et al. (2014) Characterization of blaCMY plasmids and their possible role in source attribution of *Salmonella enterica* serotype Typhimurium infections. *Foodborne Pathogens and Disease*, 11(4), 301–306.

Gal-Mor, O. (2019) Persistent infection and long-term carriage of typhoidal and nontyphoidal *Salmonellae*. *Clinical Microbiology Reviews*, 32(1), e00088-18.

Gao, Y., Wen, J., Wang, S., Xu, X., Zhan, Z., Chen, Z. et al. (2020) Plasmid-encoded Bla(NDM-5) gene that confers high-level carbapenem resistance in *Salmonella* Typhimurium of pork origin. *Infection and Drug Resistance*, 13, 1485–1490.

Geetha, V.K., Yugendran, T., Srinivasan, R. & Harish, B.N. (2014) Plasmid-mediated quinolone resistance in typhoidal *Salmonellae*: a preliminary report from South India. *Indian Journal of Medical Microbiology*, 32(1), 31–34.

Girgis, N.I., Butler, T., Frenck, R.W., Sultan, Y., Brown, F.M., Tribble, D. et al. (1999) Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug resistance. *Antimicrobial Agents and Chemotherapy*, 43(6), 1441–1444.

Godbole, G.S., Day, M.R., Murthy, S., Chattaway, M.A. & Nair, S. (2018) First report of CTX-M-15 *Salmonella* Typhi from England. *Clinical Infectious Diseases*, 66(12), 1976–1977.

Gonzalez, J.F., Alberts, H., Lee, J., Doolittle, L. & Gunn, J.S. (2018) Biofilm formation protects *Salmonella* from the antibiotic ciprofloxacin in vitro and in vivo in the mouse model of chronic carriage. *Scientific Reports*, 8(1), 222.

Gonzalez, J.F., Kurtz, J., Bauer, D.L., Hitt, R., Fitch, J., Wetzel, A. et al. (2019) Establishment of chronic typhoid infection in a mouse carriage model involves a type 2 immune shift and T and B cell recruitment to the gallbladder. *mBio*, 10(5), e02262-19.

Hafiz, S., Habib, F., Ahmad, N., Haq, I. & Husain, R. (1998) Typhoid fevers: treatment with lomefloxacin. *The Journal of the Pakistan Medical Association*, 48(6), 168–170.

Hahn, M.M. & Gunn, J.S. (2020) *Salmonella* extracellular polymeric substances modulate innate phagocyte activity and enhance tolerance of biofilm-associated bacteria to oxidative stress. *Microorganisms*, 8(2), 253.

Hajra, D., Nair, A.V., Roy Chowdhury, A., Mukherjee, S., Chatterjee, R. & Chakravortty, D. (2022) *Salmonella* Typhimurium U32 peptidase, YdcP, promotes bacterial survival by conferring protection against in vitro and in vivo oxidative stress. *Microbial Pathogenesis*, 173(Pt B), 105862.

Hasan, R., Zafar, A., Abbas, Z., Mahraj, V., Malik, F. & Zaidi, A. (2008) Antibiotic resistance among *Salmonella enterica* serovars Typhi and Paratyphi A in Pakistan (2001-2006). *Journal of Infection in Developing Countries*, 2(4), 289–294.

Hebrard, M., Viala, J.P.M., Méresse, S., Barras, F. & Aussel, L. (2009) Redundant hydrogen peroxide scavengers contribute to *Salmonella* virulence and oxidative stress resistance. *Journal of Bacteriology*, 191, 4605–4614, 14.

Helaine, S., Cheverton, A.M., Watson, K.G., Faure, L.M., Matthews, S.A. & Holden, D.W. (2014) Internalization of *Salmonella* by macrophages induces formation of nonreplicating persisters. *Science*, 343(6167), 204–208.

Hernandez, S.B., Cota, I., Ducret, A., Aussel, L. & Casadesús, J. (2012) Adaptation and preadaptation of *Salmonella enterica* to bile. *PLoS Genetics*, 8(1), e1002459.

Hill, P.W.S., Moldoveanu, A.L., Sargen, M., Ronneau, S., Glegola-Madejska, I., Beetham, C. et al. (2021) The vulnerable versatility of *Salmonella* antibiotic persisters during infection. *Cell Host & Microbe*, 29(12), 1757–1773 e10.

Hoffman, S.A., Sikorski, M.J. & Levine, M.M. (2023) Chronic *Salmonella* Typhi carriage at sites other than the gallbladder. *PLoS Neglected Tropical Diseases*, 17(3), e0011168.

Huang, E., Yang, X., Leighton, E. & Li, X. (2023) Carbapenem resistance in the food supply chain. *Journal of Food Protection*, 86(7), 100108.

Hussain, A., Satti, L., Hanif, F., Zehra, N.M., Nadeem, S., Bangash, T.M. et al. (2019) Typhoidal *Salmonella* strains in Pakistan: an impending threat of extensively drug-resistant *Salmonella* Typhi. *European Journal of Clinical Microbiology & Infectious Diseases*, 38(11), 2145–2149.

Ingle, D.J., Nair, S., Hartman, H., Ashton, P.M., Dyson, Z.A., Day, M. et al. (2019) Informal genomic surveillance of regional distribution of *Salmonella* Typhi genotypes and antimicrobial resistance via returning travellers. *PLoS Neglected Tropical Diseases*, 13(9), e0007620.

Ingti, B., Saikia, P., Paul, D., Maurya, A.P., Dhar (Chanda), D., Chakravarty, A. et al. (2018) Occurrence of Bla(CMY-42) on an IncI1 plasmid in multidrug-resistant *Escherichia coli* from a tertiary referral hospital in India. *Journal of Global Antimicrobial Resistance*, 14, 78–82.

Iqbal, J., Dehraj, I.F., Carey, M.E., Dyson, Z.A., Garrett, D., Seidman, J.C. et al. (2020) A race against time: reduced azithromycin susceptibility in *Salmonella enterica* Serovar Typhi in Pakistan. *mSphere*, 5(4), e00215-20.

Irfan, S., Hasan, Z., Qamar, F., Ghanchi, N., Ashraf, J., Kanji, A. et al. (2023) Ceftriaxone resistant *Salmonella enterica* serovar Paratyphi a identified in a case of enteric fever: first case report from Pakistan. *BMC Infectious Diseases*, 23(1), 267.

Jabeen, K., Saleem, S., Jahan, S., Nizamudin, S., Arshad, F., Huma, Z.E. et al. (2023) Molecular characterization of extensively drug resistant *Salmonella enterica* Serovar Typhi clinical isolates from Lahore, Pakistan. *Infection and Drug Resistance*, 16, 2987–3001.

Jacob, J.J., Pragasam, A.K., Vasudevan, K., Veeraraghavan, B., Kang, G., John, J. et al. (2021) *Salmonella* Typhi acquires diverse plasmids from other Enterobacteriaceae to develop cephalosporin resistance. *Genomics*, 113(4), 2171–2176.

Johanns, T.M., Ertelt, J.M., Rowe, J.H. & Way, S.S. (2010) Regulatory T cell suppressive potency dictates the balance between bacterial proliferation and clearance during persistent *Salmonella* infection. *PLoS Pathogens*, 6(8), e1001043.

Khurshid, N., Khan, B.A., Bukhari, S.W., Shahid, A. & Punshi, A. (2019) Extensively drug-resistant *Salmonella* typhi meningitis in a 16-year-old male. *Cureus*, 11(10), e5961.

Kidgell, C., Reichard, U., Wain, J., Linz, B., Torpdahl, M., Dougan, G. et al. (2002) *Salmonella* typhi, the causative agent of typhoid fever, is approximately 50,000 years old. *Infection, Genetics and Evolution*, 2(1), 39–45.

Kingsley, R.A., Humphries, A.D., Weening, E.H., de Zoete, M.R., Winter, S., Papaconstantinopoulou, A. et al. (2003) Molecular and phenotypic analysis of the CS54 Island of *Salmonella enterica* serotype typhimurium: identification of intestinal colonization and persistence determinants. *Infection and Immunity*, 71(2), 629–640.

Kleine, C.E., Schlabe, S., Hischebeth, G.T.R., Molitor, E., Pfeifer, Y., Wasmuth, J.C. et al. (2017) Successful therapy of a multidrug-resistant extended-spectrum beta-lactamase-producing and fluoroquinolone-resistant *Salmonella enterica* subspecies *enterica* Serovar Typhi infection using combination therapy of Meropenem and Fosfomycin. *Clinical Infectious Diseases*, 65(10), 1754–1756.

Klemm, E.J., Shakoor, S., Page, A.J., Qamar, F.N., Judge, K., Saeed, D.K. et al. (2018) Emergence of an extensively drug-resistant *Salmonella enterica* Serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *mBio*, 9(1), e00105-18.

Kumar, A. & Kumar, A. (2021) Antibiotic resistome of *Salmonella typhi*: molecular determinants for the emergence of drug resistance. *Frontiers in Medicine*, 15(5), 693–703.

Kumar, R., Aneja, K.R., Punia, A.K., Roy, P., Sharma, M., Gupta, R. et al. (2001) Changing pattern of biotypes, phage types & drug resistance of *Salmonella typhi* in Ludhiana during 1980-1999. *The Indian Journal of Medical Research*, 113, 175–180.

Laghari, G.S., Hussain, Z., Hussain, S.Z.M., Kumar, H., Uddin, S.M.M. & Haq, A. (2019) Antimicrobial susceptibility patterns of salmonella species in southern Pakistan. *Cureus*, 11(4), e4379.

Lai, C.W., Chan, R.C., Cheng, A.F., Sung, J.Y. & Leung, J.W. (1992) Common bile duct stones: a cause of chronic salmonellosis. *The American Journal of Gastroenterology*, 87(9), 1198–1199.

Lawley, T.D., Bouley, D.M., Hoy, Y.E., Gerke, C., Relman, D.A. & Monack, D.M. (2008) Host transmission of *Salmonella enterica* serovar Typhimurium is controlled by virulence factors and indigenous intestinal microbiota. *Infection and Immunity*, 76(1), 403–416.

Lawley, T.D., Chan, K., Thompson, L.J., Kim, C.C., Govoni, G.R. & Monack, D.M. (2006) Genome-wide screen for *Salmonella* genes required for long-term systemic infection of the mouse. *PLoS Pathogens*, 2(2), e11.

Levine, M.M., Black, R.E. & Lanata, C. (1982) Precise estimation of the numbers of chronic carriers of *Salmonella* typhi in Santiago, Chile, an endemic area. *The Journal of Infectious Diseases*, 146(6), 724–726.

Lian, X., Wang, X., Liu, X., Xia, J., Fang, L., Sun, J. et al. (2019) oqxAB-positive IncHI2 plasmid pHXY0908 increase *Salmonella enterica* serotype Typhimurium strains tolerance to ciprofloxacin. *Frontiers in Cellular and Infection Microbiology*, 9, 242.

Lin, D., Chen, K., Wai-Chi Chan, E. & Chen, S. (2015) Increasing prevalence of ciprofloxacin-resistant food-borne *Salmonella* strains harboring multiple PMQR elements but not target gene mutations. *Scientific Reports*, 5, 14754.

Liu, P., Wu, Z., Xue, H. & Zhao, X. (2017) Antibiotics trigger initiation of SCCmec transfer by inducing SOS responses. *Nucleic Acids Research*, 45(7), 3944–3952.

Lyu, M., Ayala, J.C., Chirakos, I., Su, C.C., Shafer, W.M., Yu, E.W. et al. (2022) Structural basis of peptide-based antimicrobial inhibition of a resistance-nodulation-cell division multidrug efflux pump. *Microbiology Spectrum*, 10(5), e0299022.

Macpherson, A.J. & Uhr, T. (2004) Induction of protective IgA by intestinal dendritic cells carrying commensal bacteria. *Science*, 303(5664), 1662–1665.

Maiques, E., Úbeda, C., Campoy, S., Salvador, N., Lasa, I., Novick, R.P. et al. (2006) Beta-lactam antibiotics induce the SOS response and horizontal transfer of virulence factors in *Staphylococcus aureus*. *Journal of Bacteriology*, 188(7), 2726–2729.

Majee, S., Chowdhury, A.R., Pinto, R., Chattopadhyay, A., Agharkar, A.N., Chakravortty, D. et al. (2021) Spatiotemporal evaporating droplet dynamics on fomites enhances long term bacterial pathogenesis. *Communications Biology*, 4(1), 1173.

Marzel, A., Desai, P.T., Goren, A., Schorr, Y.I., Nissan, I., Porwollik, S. et al. (2016) Persistent infections by nontyphoidal *Salmonella* in humans: epidemiology and genetics. *Clinical Infectious Diseases*, 62(7), 879–886.

Mascher, T. (2013) Signaling diversity and evolution of extracytoplasmic function (ECF) sigma factors. *Current Opinion in Microbiology*, 16(2), 148–155.

Mastroeni, P. (2002) Immunity to systemic *Salmonella* infections. *Current Molecular Medicine*, 2(4), 393–406.

Masuet-Aumatell, C. & Atouguia, J. (2021) Typhoid fever infection—antibiotic resistance and vaccination strategies: a narrative review. *Travel Medicine and Infectious Disease*, 40, 101946.

Mathers, A.J., Peirano, G. & Pitout, J.D. (2015) The role of epidemic resistance plasmids and international high-risk clones in the spread of multidrug-resistant Enterobacteriaceae. *Clinical Microbiology Reviews*, 28(3), 565–591.

May, J.F. & Groisman, E.A. (2013) Conflicting roles for a cell surface modification in *Salmonella*. *Molecular Microbiology*, 88(5), 970–983.

McClelland, M., Sanderson, K.E., Spieth, J., Clifton, S.W., Latreille, P., Courtney, L. et al. (2001) Complete genome sequence of *Salmonella enterica* serovar Typhimurium LT2. *Nature*, 413(6858), 852–856.

McMillan, E.A., Jackson, C.R. & Frye, J.G. (2020) Transferable plasmids of *Salmonella enterica* associated with antibiotic resistance genes. *Frontiers in Microbiology*, 11, 562181.

Menendez, A., Arena, E.T., Guttman, J.A., Thorson, L., Vallance, B.A., Vogl, W. et al. (2009) *Salmonella* infection of gallbladder epithelial cells drives local inflammation and injury in a model of acute typhoid fever. *The Journal of Infectious Diseases*, 200(11), 1703–1713.

Menezes, G.A., Harish, B.N., Khan, M.A., Goessens, W.H.F. & Hays, J.P. (2012) Antimicrobial resistance trends in blood culture positive *Salmonella* Typhi isolates from Pondicherry, India, 2005-2009. *Clinical Microbiology and Infection*, 18(3), 239–245.

Mina, S.A., Hasan, Z., Zakir Hossain, A.K.M., Barua, A., Mirjada, R. & Masudul Azad Chowdhury, A.M. (2023) The prevalence of multi-drug resistant *Salmonella typhi* isolated from blood sample. *Microbiology Insights*, 16, 11786361221150760.

Missiakas, D. & Raina, S. (1998) The extracytoplasmic function sigma factors: role and regulation. *Molecular Microbiology*, 28(6), 1059–1066.

Monack, D.M., Bouley, D.M. & Falkow, S. (2004) *Salmonella* typhimurium persists within macrophages in the mesenteric lymph nodes of chronically infected Nramp1+/+ mice and can be reactivated by IFNgamma neutralization. *The Journal of Experimental Medicine*, 199(2), 231–241.

Moor, K., Diard, M., Sellin, M.E., Felmy, B., Wotzka, S.Y., Toska, A. et al. (2017) High-avidity IgA protects the intestine by enchaining growing bacteria. *Nature*, 544(7651), 498–502.

Murakami, S., Nakashima, R., Yamashita, E. & Yamaguchi, A. (2002) Crystal structure of bacterial multidrug efflux transporter AcrB. *Nature*, 419(6907), 587–593.

Murata, T., Tseng, W., Guina, T., Miller, S.I. & Nikaido, H. (2007) PhoPQ-mediated regulation produces a more robust permeability barrier in the outer membrane of *Salmonella enterica* Serovar Typhimurium. *Journal of Bacteriology*, 189(20), 7213–7222.

Murti, B.R., Rajyalakshmi, K. & Bhaskaran, C.S. (1962) Resistance of *Salmonella typhi* to chloramphenicol. I. A preliminary report. *Journal of Clinical Pathology*, 15(6), 544–551.

Musher, D.M. & Rubenstein, A.D. (1973) Permanent carriers of nontyphosa *Salmonellae*. *Archives of Internal Medicine*, 132(6), 869–872.

Myat, T.O., Oo, K.M., Mone, H.K., Htike, W.W., Biswas, A., Hannaway, R.F. et al. (2020) A prospective study of bloodstream infections among febrile adolescents and adults attending Yangon General Hospital, Yangon, Myanmar. *PLoS Neglected Tropical Diseases*, 14(4), e0008268.

Mylona, E., Voong Vinh, P., Qureshi, S., Karkey, A., Dongol, S., Ha Thanh, T. et al. (2021) Tebipenem as an oral alternative for the treatment of typhoid caused by XDR *Salmonella* Typhi. *The Journal of Antimicrobial Chemotherapy*, 76(12), 3197–3200.

Nair, D.V.T., Venkitanarayanan, K. & Kollanoor Johny, A. (2018) Antibiotic-resistant *Salmonella* in the food supply and the potential role of antibiotic alternatives for control. *Food*, 7(10), 167.

Nikaido, H. (1996) Multidrug efflux pumps of gram-negative bacteria. *Journal of Bacteriology*, 178(20), 5853–5859.

Okanda, T., Haque, A., Ehara, T., Huda, Q., Ohkusu, K., Miah, R.A. et al. (2018) Characteristics of resistance mechanisms and molecular epidemiology of fluoroquinolone-nonsusceptible *Salmonella enterica* Serovar Typhi and Paratyphi a isolates from a Tertiary Hospital in Dhaka, Bangladesh. *Microbial Drug Resistance*, 24(10), 1460–1465.

Olarte, J. & Galindo, E. (1973) *Salmonella typhi* resistant to chloramphenicol, ampicillin, and other antimicrobial agents: strains isolated during an extensive typhoid fever epidemic in Mexico. *Antimicrobial Agents and Chemotherapy*, 4(6), 597–601.

Oliva, M., Monno, R., D'Addabbo, P., Pesole, G., Dionisi, A.M., Scrascia, M. et al. (2017) A novel group of IncQ1 plasmids conferring multidrug resistance. *Plasmid*, 89, 22–26.

Panagi, I., Jennings, E., Zeng, J., Günster, R.A., Stones, C.D., Mak, H. et al. (2020) *Salmonella* effector SteE converts the mammalian serine/threonine kinase GSK3 into a tyrosine kinase to direct macrophage polarization. *Cell Host & Microbe*, 27(1), 41–53 e6.

Parry, C., Wain, J., Chinh, N.T., Vinh, H. & Farrar, J.J. (1998) Quinolone-resistant *Salmonella* typhi in Vietnam. *Lancet*, 351(9111), 1289.

Parry, C.M. (2004) The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Viet Nam. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 98(7), 413–422.

Parry, C.M., Qamar, F.N., Rijal, S., McCann, N., Baker, S. & Basnyat, B. (2023) What should we Be recommending for the treatment of enteric fever? *Open Forum Infectious Diseases*, 10(Suppl 1), S26–S31.

Pereira, N.M.D. & Shah, I. (2020) Cephalosporin-resistant typhoid. *SAGE Open Medical Case Reports*, 8, 2050313X20917835.

Petrin, C.E., Steele, R.W., Margolis, E.A., Rabon, J.M., Martin, H. & Wright, A. (2020) Drug-resistant *Salmonella typhi* in Pakistan. *Clinical Pediatrics (Phila)*, 59(1), 31–33.

Pettersson, T., Klemola, E. & Wager, O. (1964) Treatment of acute cases of *Salmonella* infection and *Salmonella* carriers with ampicillin and neomycin. *Acta Medica Scandinavica*, 175, 185–190.

Pham, T.H.M., Brewer, S.M., Thurston, T., Massis, L.M., Honeycutt, J., Lugo, K. et al. (2020) *Salmonella*-driven polarization of granuloma macrophages antagonizes TNF-mediated pathogen restriction during persistent infection. *Cell Host & Microbe*, 27(1), 54–67 e5.

Pham Thanh, D., Karkey, A., Dongol, S., Ho Thi, N., Thompson, C.N., Rabaa, M.A. et al. (2016) A novel ciprofloxacin-resistant subclade of H58 *Salmonella* Typhi is associated with fluoroquinolone treatment failure. *eLife*, 5, e14003.

Pham Thanh, D., Thompson, C.N., Rabaa, M.A., Sona, S., Sopheary, S., Kumar, V. et al. (2016) The molecular and spatial epidemiology of typhoid fever in rural Cambodia. *PLoS Neglected Tropical Diseases*, 10(6), e0004785.

Phuc Nguyen, M.C., Woerther, P.L., Bouvet, M., Andremont, A., Leclercq, R. & Canu, A. (2009) *Escherichia coli* as reservoir for macrolide resistance genes. *Emerging Infectious Diseases*, 15(10), 1648–1650.

Picken, R.N. & Beacham, I.R. (1977) Bacteriophage-resistant mutants of *Escherichia coli* K12. Location of receptors within the lipopolysaccharide. *Journal of General Microbiology*, 102(2), 305–318.

Piekarska, K., Wołkowicz, T., Zacharczuk, K., Stepuch, A. & Gierczyński, R. (2023) The mechanisms involved in the fluoroquinolone resistance of *Salmonella enterica* strains isolated from humans in Poland,

2018-2019: the prediction of antimicrobial genes by in silico whole-genome sequencing. *Pathogens*, 12(2), 193.

Poirel, L., Carattoli, A., Bernabeu, S., Bruderer, T., Frei, R. & Nordmann, P. (2010) A novel IncQ plasmid type harbouring a class 3 integron from *Escherichia coli*. *The Journal of Antimicrobial Chemotherapy*, 65(8), 1594–1598.

Pokharel, B.M., Koirala, J., Dahal, R.K., Mishra, S.K., Khadga, P.K. & Tuladhar, N.R. (2006) Multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing *Salmonella enterica* (serotypes Typhi and Paratyphi A) from blood isolates in Nepal: surveillance of resistance and a search for newer alternatives. *International Journal of Infectious Diseases*, 10(6), 434–438.

Pontes, M.H. & Groisman, E.A. (2019) Slow growth determines nonheritable antibiotic resistance in *Salmonella enterica*. *Science Signaling*, 12(592), eaax3938.

Prouty, A.M., Schwesinger, W.H. & Gunn, J.S. (2002) Biofilm formation and interaction with the surfaces of gallstones by *Salmonella* spp. *Infection and Immunity*, 70(5), 2640–2649.

Qian, H., Cheng, S., Liu, G., Tan, Z., Dong, C., Bao, J. et al. (2020) Discovery of seven novel mutations of gyrB, parC and parE in *Salmonella* Typhi and Paratyphi strains from Jiangsu Province of China. *Scientific Reports*, 10(1), 7359.

Qin, H., Liu, Y., Cao, X., Jiang, J., Lian, W., Qiao, D. et al. (2020) RpoS is a pleiotropic regulator of motility, biofilm formation, exoenzymes, siderophore and prodigiosin production, and trade-off during prolonged stationary phase in *Serratia marcescens*. *PLoS One*, 15(6), e0232549.

Ramos-Morales, F., Prieto, A.I., Beuzón, C.R., Holden, D.W. & Casadesús, J. (2003) Role for *Salmonella enterica* enterobacterial common antigen in bile resistance and virulence. *Journal of Bacteriology*, 185(17), 5328–5332.

Rathod, P., Patil, P., Choure, B. & Patil, A. (2016) Study of current prescribing pattern of antimicrobial drugs in indoor cases of enteric fever in a tertiary care hospital. *International Journal of Basic and Clinical Pharmacology*, 5, 159–162.

Reygaert, W.C. (2018) An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiology*, 4(3), 482–501.

Roy Chowdhury, A., Sah, S., Varshney, U. & Chakravortty, D. (2022) *Salmonella* Typhimurium outer membrane protein a (OmpA) renders protection from nitrosative stress of macrophages by maintaining the stability of bacterial outer membrane. *PLoS Pathogens*, 18(8), e1010708.

Ruby, T., McLaughlin, L., Gopinath, S. & Monack, D. (2012) Salmonella's long-term relationship with its host. *FEMS Microbiology Reviews*, 36(3), 600–615.

Sabbagh, S.C., Forest, C.G., Lepage, C., Leclerc, J.M. & Daigle, F. (2010) So similar, yet so different: uncovering distinctive features in the genomes of *Salmonella enterica* serovars Typhimurium and Typhi. *FEMS Microbiology Letters*, 305(1), 1–13.

Sabol, A., Joung, Y.J., VanTubbergen, C., Ale, J., Ribot, E.M. & Trees, E. (2021) Assessment of genetic stability during serial in vitro passage and in vivo carriage. *Foodborne Pathogens and Disease*, 18(12), 894–901.

Sah, R., Donovan, S., Seth-Smith, H.M.B., Bloemberg, G., Wüthrich, D., Stephan, R. et al. (2019) A novel lineage of ceftriaxone-resistant *Salmonella* Typhi from India that is closely related to XDR *S*. Typhi found in Pakistan. *Clinical Infectious Diseases*, 71, 1327–1330.

Salzman, N.H., Ghosh, D., Huttner, K.M., Paterson, Y. & Bevins, C.L. (2003) Protection against enteric salmonellosis in transgenic mice expressing a human intestinal defensin. *Nature*, 422(6931), 522–526.

Salzman, N.H., Hung, K., Haribhai, D., Chu, H., Karlsson-Sjöberg, J., Amir, E. et al. (2010) Enteric defensins are essential regulators of intestinal microbial ecology. *Nature Immunology*, 11(1), 76–83.

Samajpati, S., das, S., Jain, P., Ray, U., Mandal, S., Samanta, S. et al. (2020) Changes in antimicrobial resistance and molecular attributes of *Salmonellae* causing enteric fever in Kolkata, India, 2014-2018. *Infection, Genetics and Evolution*, 84, 104478.

San Román, B., Garrido, V., Sánchez, S., Martínez-Ballesteros, I., Garaizar, J., Mainar-Jaime, R.C. et al. (2018) Relationship between *Salmonella* infection, shedding and serology in fattening pigs in low–moderate prevalence areas. *Zoonoses and Public Health*, 65(5), 481–489.

Sashinami, H., Yamamoto, T. & Nakane, A. (2006) The cytokine balance in the maintenance of a persistent infection with *Salmonella enterica* serovar Typhimurium in mice. *Cytokine*, 33(4), 212–218.

Schioler, H., Dyrskjøt Christiansen, E., Høybye, G., Nørby Rasmussen, S., Greibe, J. & The Danish Salca-Group. (1983) Biliary calculi in chronic *Salmonella* carriers and healthy controls: a controlled study. *Scandinavian Journal of Infectious Diseases*, 15(1), 17–19.

Sellera, F.P., Fernandes, M.R., Moura, Q., Lopes, R.B., Souza, T.A., Cerdeira, L. et al. (2018) Draft genome sequence of a Bla(CMY-2)/IncI1-harbouring *Escherichia coli* D:ST457 isolated from coastal benthic organisms. *Journal of Global Antimicrobial Resistance*, 14, 83–84.

Shaheen, A., Ismat, F., Iqbal, M., Haque, A., de Zorzi, R., Mirza, O. et al. (2015) Characterization of putative multidrug resistance transporters of the major facilitator-superfamily expressed in *Salmonella* Typhi. *Journal of Infection and Chemotherapy*, 21(5), 357–362.

Shariati, A., Arshadi, M., Khosrojerdi, M.A., Abedinzadeh, M., Ganjalishahi, M., Maleki, A. et al. (2022) The resistance mechanisms of bacteria against ciprofloxacin and new approaches for enhancing the efficacy of this antibiotic. *Frontiers in Public Health*, 10, 1025633.

Sidjabat, H.E., Seah, K.Y., Coleman, L., Sartor, A., Derrington, P., Heney, C. et al. (2014) Expansive spread of IncI1 plasmids carrying blaCMY-2 amongst *Escherichia coli*. *International Journal of Antimicrobial Agents*, 44(3), 203–208.

Slack, E., Hapfelmeier, S., Stecher, B., Velykoredko, Y., Stoel, M., Lawson, M.A.E. et al. (2009) Innate and adaptive immunity cooperate flexibly to maintain host-microbiota mutualism. *Science*, 325(5940), 617–620.

Smith, H., Bossers, A., Harders, F., Wu, G., Woodford, N., Schwarz, S. et al. (2015) Characterization of epidemic IncI1-Igamma plasmids harboring ambler class a and C genes in *Escherichia coli* and *Salmonella enterica* from animals and humans. *Antimicrobial Agents and Chemotherapy*, 59(9), 5357–5365.

Stanaway, J.D., Reiner, R.C., Blacker, B.F., Goldberg, E.M., Khalil, I.A., Troeger, C.E. et al. (2019) The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Infectious Diseases*, 19(4), 369–381.

Stapels, D.A.C., Hill, P.W.S., Westermann, A.J., Fisher, R.A., Thurston, T.L., Saliba, A.E. et al. (2018) *Salmonella* persisters undermine host immune defenses during antibiotic treatment. *Science*, 362(6419), 1156–1160.

Stecher, B., Denzler, R., Maier, L., Bernet, F., Sanders, M.J., Pickard, D.J. et al. (2012) Gut inflammation can boost horizontal gene transfer between pathogenic and commensal Enterobacteriaceae. *Proceedings of the National Academy of Sciences of the United States of America*, 109(4), 1269–1274.

Stecher, B. & Hardt, W.D. (2011) Mechanisms controlling pathogen colonization of the gut. *Current Opinion in Microbiology*, 14(1), 82–91.

Tagg, K.A., Iredell, J.R. & Partridge, S.R. (2014) Complete sequencing of IncI1 sequence type 2 plasmid pJIE512b indicates mobilization of blaCMY-2 from an IncA/C plasmid. *Antimicrobial Agents and Chemotherapy*, 58(8), 4949–4952.

Tang, H.J., Chen, C.C. & Ko, W.C. (2016) Tigecycline therapy for bacteremia and aortitis caused by *Salmonella enterica* serotype Choleraesuis: a case report. *Journal of Microbiology, Immunology, and Infection*, 49(1), 131–133.

Tanmoy, A.M., Westeel, E., de Bruyne, K., Goris, J., Rajoharison, A., Sajib, M.S.I. et al. (2018) *Salmonella enterica* serovar Typhi in Bangladesh: exploration of genomic diversity and antimicrobial resistance. *mBio*, 9(6), e02112-18.

Tanphaichitra, D., Sahaphong, S. & Srimuang, S. (1986) Ofloxacin, a new quinolone in the treatment of genitourinary and enteric infections. *Infection*, 14(Suppl 4), S321–S323.

Tariq, A., Sana, M., Shaheen, A., Ismat, F., Mahboob, S., Rauf, W. et al. (2019) Restraining the multidrug efflux transporter STY4874 of

Salmonella Typhi by reserpine and plant extracts. *Letters in Applied Microbiology*, 69(3), 161–167.

Tenaillon, O., Skurnik, D., Picard, B. & Denamur, E. (2010) The population genetics of commensal *Escherichia coli*. *Nature Reviews Microbiology*, 8(3), 207–217.

Thilliez, G. & Kingsley, R.A. (2020) *Salmonella* intracellular adaptation is key to understand cephalosporin treatment relapse. *eBioMedicine*, 56, 102802.

Threlfall, E.J. (2000) Epidemic *Salmonella typhimurium* DT 104—a truly international multiresistant clone. *The Journal of Antimicrobial Chemotherapy*, 46(1), 7–10.

Threlfall, E.J., Ward, L.R. & Rowe, B. (1997) Increasing incidence of resistance to trimethoprim and ciprofloxacin in epidemic *Salmonella typhimurium* DT104 in England and Wales. *Euro Surveillance*, 2(11), 81–84.

Tiba-Casas, M.R., Camargo, C.H., Soares, F.B., Doi, Y. & Fernandes, S.A. (2019) Emergence of CMY-2-producing *Salmonella* Heidelberg associated with IncI1 plasmids isolated from poultry in Brazil. *Microbial Drug Resistance*, 25(2), 271–276.

Tran, J.H., Jacoby, G.A. & Hooper, D.C. (2005) Interaction of the plasmid-encoded quinolone resistance protein QnrA with *Escherichia coli* topoisomerase IV. *Antimicrobial Agents and Chemotherapy*, 49(7), 3050–3052.

Tsai, M.H., Liang, Y.H., Chen, C.L. & Chiu, C.H. (2019) Characterization of salmonella resistance to bile during biofilm formation. *Journal of Microbiology, Immunology, and Infection*, 53, 518–524.

van der Heijden, J., Reynolds, L.A., Deng, W., Mills, A., Scholz, R., Imami, K. et al. (2016) *Salmonella* rapidly regulates membrane permeability to survive oxidative stress. *mBio*, 7(4), e01238-16.

van Velkinburgh, J.C. & Gunn, J.S. (1999) PhoP-PhoQ-regulated loci are required for enhanced bile resistance in *Salmonella* spp. *Infection and Immunity*, 67(4), 1614–1622.

Veeraraghavan, B., Pragasam, A.K., Ray, P., Kapil, A., Nagaraj, S., Perumal, S.P.B. et al. (2021) Evaluation of antimicrobial susceptibility profile in *Salmonella* Typhi and *Salmonella* Paratyphi A: Presenting the current scenario in India and strategy for future management. *The Journal of Infectious Diseases*, 224(Supple 5), S502–S516.

Villarreal, J.M., Becerra-Lobato, N., Rebollar-Flores, J.E., Medina-Aparicio, L., Carbajal-Gómez, E., Zavala-García, M.L. et al. (2014) The *Salmonella enterica* serovar Typhi ltrR-ompR-ompC-ompF genes are involved in resistance to the bile salt sodium deoxycholate and in bacterial transformation. *Molecular Microbiology*, 92(5), 1005–1024.

Vogelsang, T.M. & Boe, J. (1948) Temporary and chronic carriers of *Salmonella* typhi and *Salmonella* paratyphi B. *Journal of Hygiene (Lond)*, 46(3), 252–261.

Wain, J., Diem Nga, L.T., Kidgell, C., James, K., Fortune, S., Song Diep, T. et al. (2003) Molecular analysis of incHI1 antimicrobial resistance plasmids from *Salmonella serovar* Typhi strains associated with typhoid fever. *Antimicrobial Agents and Chemotherapy*, 47(9), 2732–2739.

Wain, J., Hien, T.T., Connerton, P., Ali, T., M. Parry, C., Chinh, N.T.T. et al. (1999) Molecular typing of multiple-antibiotic-resistant *Salmonella enterica* serovar Typhi from Vietnam: application to acute and relapse cases of typhoid fever. *Journal of Clinical Microbiology*, 37(8), 2466–2472.

Walther-Rasmussen, J. & Hoiby, N. (2004) Cefotaximases (CTX-M-ases), an expanding family of extended-spectrum beta-lactamases. *Canadian Journal of Microbiology*, 50(3), 137–165.

Weening, E.H., Barker, J.D., Laarakker, M.C., Humphries, A.D., Tsolis, R.̈.M. & Bäumler, A.J. (2005) The *Salmonella enterica* serotype Typhimurium lpf, bcf, stb, stc, std, and sth fimbrial operons are required for intestinal persistence in mice. *Infection and Immunity*, 73(6), 3358–3366.

Whitby, J.M. (1964) Ampicillin in treatment of *Salmonella typhi* carriers. *Lancet*, 2(7350), 71–72.

WHO. (2018) *Typhoid Fever—Islamic Republic of Pakistan*. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/27-december-2018-typhoid-pakistan-en [Accessed 6th December 2023].

Wilcock, B.P., Armstrong, C.H. & Olander, H.J. (1976) The significance of the serotype in the clinical and pathological features of naturally occurring porcine salmonellosis. *Canadian Journal of Comparative Medicine*, 40(1), 80–88.

Williams, R.J., Livermore, D.M., Lindridge, M.A., Said, A.A. & Williams, J.D. (1984) Mechanisms of beta-lactam resistance in British isolates of *Pseudomonas aeruginosa*. *Journal of Medical Microbiology*, 17(3), 283–293.

Windels, E.M., Michiels, J.E., Fauvart, M., Wenseleers, T., van den Bergh, B. & Michiels, J. (2019) Bacterial persistence promotes the evolution of antibiotic resistance by increasing survival and mutation rates. *The ISME Journal*, 13(5), 1239–1251.

Wong, J.L.C., Romano, M., Kerry, L.E., Kwong, H.S., Low, W.W., Brett, S.J. et al. (2019) OmpK36-mediated carbapenem resistance attenuates ST258 Klebsiella pneumoniae in vivo. *Nature Communications*, 10(1), 3957.

Wong, M.H., Chan, E.W., Liu, L.Z. & Chen, S. (2014) PMQR genes oqxAB and aac(6')Ib-cr accelerate the development of fluoroquinolone resistance in *Salmonella typhimurium*. *Frontiers in Microbiology*, 5, 521.

Wong, V.K., Baker, S., Pickard, D.J., Parkhill, J., Page, A.J., Feasey, N.A. et al. (2015) Phylogeographical analysis of the dominant multidrug-resistant H58 clade of *Salmonella* Typhi identifies inter- and intracontinental transmission events. *Nature Genetics*, 47(6), 632–639.

Wong, W., Rawahi, H.A., Patel, S., Yau, Y., Eshaghi, A., Zittermann, S. et al. (2019) The first Canadian pediatric case of extensively drug-resistant *Salmonella* Typhi originating from an outbreak in Pakistan and its implication for empiric antimicrobial choices. *IDCases*, 15, e00492.

Wood, R.L., Pospischil, A. & Rose, R. (1989) Distribution of persistent *Salmonella* typhimurium infection in internal organs of swine. *American Journal of Veterinary Research*, 50(7), 1015–1021.

Wright, G.D. (2007) The antibiotic resistome: the nexus of chemical and genetic diversity. *Nature Reviews Microbiology*, 5(3), 175–186.

Xie, X., Zhang, H., Zheng, Y., Li, A., Wang, M., Zhou, H. et al. (2016) RpoE is a putative antibiotic resistance regulator of *Salmonella enteric* Serovar Typhi. *Current Microbiology*, 72(4), 457–464.

Yamane, K., Wachino, J.I., Suzuki, S., Kimura, K., Shibata, N., Kato, H. et al. (2007) New plasmid-mediated fluoroquinolone efflux pump, QepA, found in an *Escherichia coli* clinical isolate. *Antimicrobial Agents and Chemotherapy*, 51(9), 3354–3360.

Yassine, H., Bientz, L., Cros, J., Goret, J., Bébéar, C., Quentin, C. et al. (2015) Experimental evidence for IS1294b-mediated transposition of the blaCMY-2 cephalosporinase gene in Enterobacteriaceae. *The Journal of Antimicrobial Chemotherapy*, 70(3), 697–700.

Yu, X., Zhang, D. & Song, Q. (2020) Profiles of *gyrA* mutations and plasmid-mediated quinolone resistance genes in *Shigella* isolates with different levels of fluoroquinolone susceptibility. *Infection and Drug Resistance*, 13, 2285–2290.

Zhou, L., Zhang, T.J., Zhang, W., Xie, C., Yang, Y., Chen, X. et al. (2023) Prevalence and genetic diversity of multidrug-resistant *Salmonella* Typhimurium monophasic variant in a swine farm from China. *Frontiers in Microbiology*, 14, 1200088.

How to cite this article: Chowdhury, A.R., Mukherjee, D., Chatterjee, R. & Chakravortty, D. (2023) Defying the odds: Determinants of the antimicrobial response of *Salmonella* Typhi and their interplay. *Molecular Microbiology*, 00, 1–17. Available from: https://doi.org/10.1111/mmi.15209