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ANTIMICROBIAL RESISTANCE IN *SALMONELLA* TYPHI ACROSS ALL DOMAINS

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ABSTRACT

The rise of antimicrobial resistance (AMR) is making it harder to treat infectious diseases. *Salmonella* Typhi, the causative agent of typhoid fever, stands as a noteworthy example, with more than 1,16,000 deaths occurring annually worldwide. Historically, narratives on AMR in *S.* Typhi often focus on microbial adaptation, politics and socio-economic considerations. For instance, economic limitations in endemic Low- and Middle-Income Countries (LMICs), including inadequate Water, Sanitation, and Hygiene (WaSH) infrastructure, have driven the selection for resistant strains, but have also influenced both health policies and the trajectory of scientific research on a global level. *S.* Typhi employs various AMR mechanisms - including drug inactivation, efflux pumps, and structural and metabolic changes - to combat antibiotics and ensure survival. Genetic alterations, conferred through spontaneous mutations and horizontal gene transfer, eventually drive these diverse mechanisms. This narrative review addresses the escalating concern of AMR in *S.* Typhi, including the extensively drug-resistant (XDR) strains. Here, we show that despite the endorsement of typhoid conjugate vaccines (TCVs) and advancements in novel target discoveries, the management of AMR in *S.* Typhi is undermined, not only by epidemiology or genetics but also by behavioural factors of individuals and social structures. In a broader sense, this review will also discuss the interplay between human, animal, and environmental interactions in the spread of XDR *S.* Typhi strains.This is because a holistic perspective that includes but is not limited to, global health strategies that transcend socioeconomic and political barriers, is necessary.

Keywords: Antimicrobial Resistance; Multidrug-resistant; *Salmonella* Typhi; Typhoid Fever; One Health; WaSH

INTRODUCTION

Salmonella enterica serovar Typhi is a facultative anaerobic, gram-negative bacillus responsible for causing typhoid fever in humans. Typhoid fever remains a major public health issue, leading to over11-14 million cases and 116,000 deaths annually (Dougan and Baker, 2014; Antillon *et al.,* 2017; Bisanzio and Shokraneh, 2017; Marchello *et al*., 2019; Qamar *et al.,* 2018). The highest incidence rates are found in South Asia, accounting 70% of the global disease burden, while substantial morbidity and mortality also occur in sub-Saharan Africa, Southeast Asia, and Oceania (Mogasale *et al*., 2014; Stanaway *et al*., 2019). A significant concern with *Salmonella* infections is antimicrobial resistance (AMR). Over the years, *Salmonella* strains have developed resistance to multiple antibiotics, and this has made it more challenging to treat and manage salmonellosis. Resistant strains of *Salmonella*, including those causing typhoid, paratyphoid, and nontyphoidal fevers, impact public health, animal health, and economies at both local and global levels. The U.S. CDC has reported that antibiotic-resistant *Salmonella* infections result in more severe and prolonged illnesses, hospitalisation, and higher mortality rates, especially among vulnerable populations such as children and the immunocompromised (Watkins *et al*., 2018). Antimicrobial resistance often leads to higher healthcare costs due to the need for more expensive treatment options and prolonged medical care. Substantially higher costs and longer stays were associated with Quinolone Resistance (QR) in Hong Kong, for instance. Hence, interventions to decrease the prevalence of QR could result in considerable savings for the public health system (Broughton *et al*., 2010). A recent report from the EcoAMR Series projects that AMR could lead to 38.5 million to 45.2 million cumulative deaths globally from 2025 to 2050, with healthcare costs rising to USD 159-325 billion annually by 2050 (Adamie *et al*., 2024). AMR is particularly concerning in regions where multidrug-resistant (MDR) *Salmonella* strains are prevalent (Grimont and Weill, 2007); however, in recent years, the global prevalence of these strains has also been surging in both human and animal populations (Helms *et al*., 2002; Gould *et al*., 2013) In areas with inadequate WaSH infrastructures, resistant strains can spread more easily and increase the risk of widespread community outbreaks (Plumb *et al.,* 2023). The One Health (OH) approach offers a holistic framework that can integrate global and local perspectives into strategies that address the interconnections across human, animal, and environmental health.

One area of AMR research in *S.* Typhi is directed toward identifying and exploiting novel drug targets. These include, for instance, virulence factors such as the Type III secretion system (T3SS), which is involved in effector protein delivery and intracellular survival. Additionally, targeting resistance enzymes, including extended-spectrum beta-lactamases (ESBLs) and carbapenemases, could restore the efficacy of existing antibiotics. Disrupting vital metabolic pathways like the shikimate pathway (e.g., targeting shikimate dehydrogenase), which is absent in humans but present in *S.* Typhi and other bacteria, is a promising approach for developing antimicrobials with minimal host toxicity (Jalal *et al*., 2021).

This article provides an overview of AMR in *S.* Typhi: its history, contributing factors, mechanisms, epidemiology, and interactions across health domains. The current approaches to managing AMR and potential novel targets for addressing extensively drug-resistant (XDR) *S.* Typhi are briefly discussed. The focus on *S.* Typhi here is owing to its significant impact on children and underprivileged communities, as well as its unique role in causing typhoid fever.

Antimicrobial Therapy and Resistance: A Historical Overview

The history of AMR in *Salmonella* Typhi is a complex narrative shaped by genetic adaptations, socio-economic factors, policy-making, and scientific advances. The disease presents clinical symptoms including high and sustained fever, severe fatigue, abdominal discomfort, headaches, and a characteristic rash known as "rose spots". During the Great Irish Famine of 1847, it is believed that infectious diseases like typhoid fever, typhus, and dysentery were responsible for most deaths as malnutrition and poor living conditions exacerbated their spread (Grada, 2008). Although typhoid-like illnesses have been recorded throughout history, the scientific understanding of *S.* Typhi began in the late 19th century when it was first identified and isolated, and by the early 20th century, typhoid fever had gained public recognition in the United States and other countries (Marineli *et al*., 2013). Historical records describe large outbreaks in overcrowded cities like London and New York, where rapid urbanisation outpaced the development of proper sanitation systems (Kirchman and Kirchman, 2021). The identification of *Salmonella* that paved the way for targeted control measures that have since reduced the incidence of typhoid in high-income countries (Hardy, 2015; Kirchhelle *et al*., 2019). Then, as now, the response to infectious diseases, including those complicated by AMR,

often reflects broader social inequalities, disproportionately impacting marginalised communities that lack access to effective treatment and prevention measures. One notable case is that of Mary Mallon who was an asymptomatic carrier and unknowingly transmitted the infection to many while working as a cook in New York between 1900 and 1907. Despite the identification of hundreds of healthy typhoid carriers in New York City, predominantly men who were less likely to be from impoverished backgrounds, Mallon, a low-wage immigrant woman, was singularly targeted for prolonged isolation and confinement(Desai and Sklar, 2021).

The 1950s marked a breakthrough with the introduction of chloramphenicol, which quickly became the gold standard for treating *S. Typhi* infections. However, resistance was reported as early as two years after its initial use (Murti *et al*., 1962). By the late 1960s, resistance to chloramphenicol became more pronounced, and reports of resistant *S.* Typhi strains increased globally. This resistance prompted the use of alternative antibiotics, including ampicillin and trimethoprim-sulfamethoxazole (co-trimoxazole), which initially proved effective. Nonetheless, transferable resistance mechanisms, particularly plasmid-mediated resistance, lead eventually tothe rapid spread of strains resistant to these drugs. Such developments ultimately validated early warnings about the risks of antibiotic overuse.

In the 1960s and 1970s, high-income countries took individual steps to regulate antibiotic misuse (Orlate and Galindo, 1973). Nonetheless, these efforts were not part of a coordinated global initiative, leaving typhoid to persist in low- and middle-income countries (LMICs) with limited healthcare infrastructure. High-income countries focused on national biosecurity and traveller vaccination rather than addressing the root causes of AMR in typhoid (Taylor *et al*., 1983; Waldvogel and Pitton, 1973). Similar to other trends in emerging resistance, socioeconomic disparities and regional instabilityexacerbated the spread of AMR in*S.* Typhi (Mermin *et al*., 1999; Crump *et al.,* 2004; Fica *et al*., 1996). At a later stage, the emergence of MDR typhoid outbreaks in LMICs drew global attention back due to fears of resistant strains spreading beyond borders (Orlate and Galindo, 1973).

In the 1980s, fluoroquinolones such as ciprofloxacin became the treatment of choice for MDR *S.* Typhi. However, by the 1990s, the emergence of *S.* Typhi strains with reduced susceptibility to fluoroquinolones led to the use of third-generation cephalosporins, such as ceftriaxone and cefotaxime, as alternative

treatments for resistant typhoid (Adachi *et al*., 2005).

Advances in molecular tools in the 1990s and early 2000s enabled detailed phylogenetic analyses which facilitatedtracking the spread and evolution of resistant strains (Roumagnac *et al*., 2006). Epidemiological studies during this period revealed the rise of the H58 haplotype as a dominant MDR lineage (Wong *et al*., 2016). Despite these improved typing techniques, surveillance gaps persisted, and resistance to fluoroquinolone and third-generation cephalosporins became more notable by the 2010s in South Asia (Silva *et al*., 2021). The contemporary narrative of *S.* Typhi resistance is defined by the recent emergence of extensively drug-resistant (XDR) H58 strains. In response, the World Health Organization endorsed typhoid conjugate vaccines (TCVs) in 2018, with subsequent studies affirming their effectiveness (Saha *et al*., 2020). It is the extensive genotypic diversity of *S.* Typhi in South Asia, especially within the H58 lineage, that has contributed to the development of resistance, but major drivers like international travel and trade, have further accelerated the global spread of resistant genes (Silva *et al*., 2021; Bhutta, 2021).

Epidemiology of AMR S. Typhi and One Health

The epidemiology of drug-resistant typhoid fever has shown significant changes over time. International movement, environmental changes, and socio-economic shifts have shaped the geographic patterns of resistance in S. Typhi. A study aimed to investigate global phenotypic and genetic determinants of AMR in the period 1972-2018 found that over 55,000 S. Typhi isolates were AMR with high prevalence in Asia (Marchello *et al.*, 2020). Among the isolates, alarming levels of MDR were observed with chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, ciprofloxacin and ceftriaxone. There is evidence in the literature that suggests the introduction of AMR strains from South Asia to Africa (Britto *et al.*, 2018; Browne *et al.,* 2020) MDR S. Typhi in Africa is becoming more prevalent, and resistance to fluoroquinolones (Fluoroquinolone Non-Susceptible Strains, FQNS) is complicating treatment approaches in resource-limited settings where treatment alternatives such as azithromycin and ceftriaxone are costly and less accessible (Britto *et al.*, 2018).

The prevalence of MDR S. Typhi varies globally, yet it is particularly widespread in LMICs. In South Asia, MDR prevalence has shown a downward trend from 1990 to 2018, while in Southeast Asia, it remains high, with a prevalence exceeding 60% among *S.* Typhi isolates

during most years in that period (Browne *et al.,* 2020). In addition, FQNS prevalence in South Asia increased significantly from 2% in 1990–1994 to 81% in 2010–2014 (Browne *et al.,* 2020). Fluoroquinolone resistance increased following widespread use, especially after the dominance of the H58 clade, and with the advent of resistance to cephalosporins and azithromycin, third-generation cephalosporins have become the main treatment for typhoid in South Asia (Britto *et al.*, 2018). Resistance to traditional first-line drugs like chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole has also risen over time. A notable outbreak of XDR *S.* Typhi, resistant to multiple antibiotics including fluoroquinolones and third-generation cephalosporins, emerged in Pakistan in 2016 (Nde and Logue, 2008). This was followed by the detection of a mutation conferring azithromycin resistance in multiple lineages detected in 2021. The outbreak resulted in 14,360 confirmed cases in Karachi from January 2017 to June 2021 (Butt *et al*., 2022). Nonetheless, third-generation cephalosporin resistance remains relatively low in Africa (Marchello *et al.*, 2020).

Recent efforts in surveillance, more sophisticated modeling approaches, better geographic representation, and high-quality incidence studies have expanded the understanding of typhoid fever's global burden. For example, limitations associated with earlier estimates (e.g., limited population-based data) in Africa suggested that typhoid was less common in Africa than in Asia. However, recent studies revealed that certain regions in sub-Saharan Africa exhibit typhoid incidences comparable to or even exceeding those in Asia (Crump, 2019). Furthermore, trends in typhoid incidence have shown variability across different regions. While some areas have experienced a measurable decline due to improvements in water and sanitation, such as in South and Southeast Asia (e.g., Nepal), other countries (Pacific Island Countries) made little progress and currently face high incidence rates. Observing such changes with continuous surveillance and reliable data is therefore necessary to address the shifting epidemiological landscape of typhoid fever.

The global incidence of typhoid fever in 2017 was estimated at 10.9 million cases (Stanaway *et al.*, 2019). Incidence rates were highest among children, especially in the five-to-nine-year age group. About 12.6% of cases were in children under five years, and 55.9% of cases occurred in children under 15. The burden of typhoid and paratyphoid fever in terms of years of life lost (YLLs) and years lived with disability (YLDs) was significant, and these collectively resulted in a total of 9.8 million disability-adjusted

life years (DALYs) (Stanaway *et al*., 2019).

Typhoid fever and other waterborne diseases pose severe consequences in regions with poor water and sanitation infrastructures (Ziraba *et al.,* 2016; Araya *et al*., 2016). Alarming cases of ceftriaxone-resistant typhoid were reported in Pakistan (Qamar *et al*., 2018), and a severe outbreak in Tajikistan resulted in nearly 9000 patients and 100 deaths (Mermin *et al.*, 1999). Recognising the environmental context associated with these incidents is crucial. The extensive use of antimicrobials and the improper disposal of untreated human waste can contribute to the proliferation of AMR bacteria like MDR *S.* Typhi (Araya *et al*., 2016). As illustrated previously, the environmental presence of such bacteria is exacerbated by horizontal gene transfer among different bacterial species (Alcock *et al*., 2017). Moreover, climate change may further complicate control efforts and increase the incidence of typhoid fever (O'Neill, 2016; Ayukekbong *et al*., 2017; Charani *et al*., 2019; Douesnard-Malo and Daigle, 2011). Surveys in regions like Fiji have indicated potential links between climate events, such as cyclones and the incidence of typhoid fever (Martinez-Urtaza *et al*., 2004). Yet, it is estimated that antimicrobial use could be reduced by 60% if there was universal access to appropriate WASH services in LMICs (Araya *et al.,* 2016; O' Neill, 2016).

The survival and transmission of *S.* Typhi can be influenced by environmental niches that contribute also to AMR. For instance, the coexistence between *S.* Typhi and protozoans like *Acanthamoeba castellanii* may enhance its survival and spread (Douesnard-Malo and Daigle, 2011). Co-cultivation of *S.* Typhi with *A. castellanii* lead to a prolonged survival period of at least three weeks, compared to less than ten days when cultured alone. Growth rates of amoebae showed similarity after 14 days, suggesting no cytotoxic properties towards *A. castellanii*. Co-cultured bacteria were extracellular and did not depend on physical contact. Seafood, often considered safe from Salmonella contamination, can become a vehicle for *S.* Typhi through anthropogenic activities that lead to cross-contamination (Martinez-Urtaza *et al*., 2004). The growth of the bacterium in seafood is temperature-dependent, with room temperature being conducive to proliferation (Kumar *et al.,* 2015). *Salmonella* ability to survive in contaminated shellfish poses a risk of human infection when the seafood is consumed raw or undercooked (Bundesen, 1925). Interestingly, historical outbreaks of typhoid fever linked to contaminated mollusks led to the establishment of the National Shellfish Sanitation Program in the United States (Iwamoto *et al*., 2010). Finally, the

genetic adaptability of *S.* Typhi enables it to acquire resistance traits from other serovars through horizontal gene transfer (Toro *et al.*, 1998). Integrons, particularly class I integrons, can disseminate AMR genes among *Salmonella* species. Agricultural sectors, such as poultry, which serve as reservoirs for ESBL-producing Salmonella, can facilitate the transmission of resistant strains to humans (Orabi *et al.*, 2022).

Socio-economic and community-level factors are known to contribute to typhoid risk and AMR spread. In England, analysis of typhoid fever cases from 2015 to 2019 found higher rates and hospitalisation among Pakistani, Indian, and Bangladeshi individuals -despite lower symptom severity reported- when compared to White populations (Buczkowska *et al.,* 2023). Higher rates in deprived areas may be partly explained by the fact that these areas have a larger proportion of people from ethnic groups who are at a higher risk of typhoid due to travel behaviors, but also due to other social determinants. Both socioeconomic and ethnic factors should inform health interventions in areas where this context is relevant. Similarly, a study in two slums of Kolkata, India, suggests a correlation between socioeconomic indicators (ownership of refrigerators, accommodation, etc.) and higher risk for typhoid fever (Sur *et al*., 2007). This study has also shown the importance of proper WaSH infrastructure; higher-risk areas had limited access to tap water and latrines compared to lower-risk zones.

Poor household hygiene and food practices can contribute to the transmission of typhoid fever. A meta-analysis found that protective 'individual-level' practices such as following the WHO-recommended food safety practices, good hygiene, and water treatment, all lowered typhoid odds (Brockett *et al.*, 2020). Certain foods, like dairy, ice cream, and fruits, were linked to elevated risk. Therefore, household-focused interventions can be a crucial part of a comprehensive strategy to reduce exposure to contaminated food and water, though sustaining these practices may require long-term behavioral change efforts and broader systemic support.

Factors Contributing to AMR in *Salmonella* Typhi

A. Environmental and Behavioural Drivers of AMR

Behavioural factors, including the actions of healthcare providers, pharmacists, patients, farmers, and government bodies, are major contributors to AMR (Nambiar and Asha, 2023). Key among these is the misuse and overuse of antibiotics. In India and Pakistan, for instance, there has been an increase in the use of third-generation cephalosporins for febrile illnesses and

fluoroquinolones for diarrhoea (Shaikh *et al*., 2023). In many regions where typhoid fever is endemic, self-medication is not uncommon with readily available over-the-counter antibiotics. A study in Karachi -across 1,342 households- reported self-medication with antibiotic by 6.3% of individuals within the previous four weeks (Sturm *et al*., 1997). Such patterns were found to increase with socio-economic status (11.1% in affluent areas compared to 2.8% in disadvantagedcommunities). Self-medicating individuals may lack the knowledge or resources to complete a full course of antibiotics, which can result in incomplete pathogen eradication and increased chances of resistance development. Self-medication is influenced by a variety of factors including the ease of obtaining over-the-counter drugs, cost of medical care, limited access to healthcare, and other individual reasons (Ali *et al*., 2016). In Pakistan, the high accessibility to antibiotics without prescriptions has contributed to a significant burden of MDR and fluoroquinolone-resistant typhoid strains (Britto *et al*., 2019).

Systemic inefficiencies such as inadequate clinical guidelines, the lack of reliable and timely diagnostics, and financial pressures further influence prescribing practices (Kasse *et al*., 2024). Hospitals, for instance, are many times described as‘incubators’ for resistant strains due to empirical treatment or insensitive diagnostic methods (e.g., the Widal test) (Olusegun and Olusegun, 2017). With limited diagnostic capabilities, physicians may prescribe broad-spectrum antibiotics empirically to cover multiple suspected pathogens, including *S.* Typhi. Healthcare facilities may lack infection control practices and proper surveillance protocols under which conditions resistant strains may spread among typhoid fever patients and other vulnerable populations in hospitals and clinics. Indeed, non-compliance and weak regulations, inadequate training for healthcare workers, limitedaccess to diagnostics and healthcareare all systemic issues that accelerate the emergence and spread of resistant strains (Batool *et al.*, 2022).

The environmental context is highly relevant too. *S.* Typhi is primarily transmitted through the faecal-oral route, often via contaminated food and water. Poor sanitation and hygiene practices, such as inadequate handwashing, open defecation, and unsafe food handling, are often linked to insufficient WaSH infrastructure. A widespread exposure in such conditions does not only sustain transmission but also promotes the selection of AMR strains. The cycle of resistance is perpetuated as individuals, having previously used antibiotics, shed resistant bacteria back into the environment and possibly contaminate

water sources. Repeated exposure to these contaminated sources reintroduces resistant strains into the community, making the cycle difficult to break (Fletcher, 2015). This "community-level amplification" is usually accompanied by an increase in the use of antibiotics.

While *S.* Typhi is primarily a human pathogen, there is evidence to suggest that the use of antibiotics in agriculture has broad implications for AMR *S.* Typhi in human populations (See the section below). This intensive use of antibiotics in livestock farming and poultry production can promote the selection of resistant bacterial strains, including *Salmonella* spp., which can transfer resistance genes to *S.* Typhi through horizontal gene transfer (Vijayamohan *et al*., 2022).

Finally, regional movements (e.g., international travel) are known to facilitate the global spread of AMR *S.* Typhi (Muresu *et al*., 2020). Travellers visiting endemic areas may acquire resistant strains and introduce them to new regions upon their return. It is important to note here that individuals infected with *S.* Typhi can become asymptomatic carriers in which the pathogencan persist in the gallbladder and be shed intermittently. Consequently, carriers may unknowingly continue to spread resistant strains within their communities and beyond. Approximately 84% of typhoid and paratyphoid fever cases in the European Union are travel-associated, with reports also noting the presence of multidrug-resistant (MDR) *S.* Typhi isolates (European Centre for Disease Prevention and Control, 2023). As international movements become increasingly common, surveillance at international borders and within communities is needed to monitor and control the spread of resistant strains.

B. Genetic Basis of AMR

Antimicrobial resistance in *S.* Typhi involves both plasmid-mediated and chromosomal mechanisms. Resistance is acquired through horizontal gene transfer of resistance genes, which can be facilitated by insertion sequences, transposons, and conjugative plasmids, or via chromosomal mutations at various loci. The mechanisms of AMR in *S.* Typhi is typically achieved through the following strategies (Kumar and Kumar, 2021):

- Enzymatic Inactivation: Carb-like genes (*tem*, *oxa-1*, and *blaTEM-1, catA1*) produce enzymes that degrade or inactivate antibiotics (beta-lactams and chloramphenicol).

- Efflux Pumps: Efflux-related genes such as *tetA*, *tetG*, *tetB*, *floR*, *cmlA* encode efflux pumps (e.g. AcrAB-TolC*)* that expel antibiotics (tetracycline, doxycycline, florfenicol, and chloramphenicol) from

the cell to lower intracellular drug concentrations.

• Altering target sites: Modifying antibiotic binding sites through mutations in genes like *gyrA*, *gyrB* (with Ser464Phe mutation), *parC*, *parE*, *topoisomerase IV*, *dfrA1*, *dfrA14*, and *dfrB*can prevent antibiotics (fluoroquinolones and trimethoprim) from binding effectively.

• Reducing cell permeability: Mutations or downregulation in porin genes, or regulatory gene activation that suppresses porin expression, can decrease cell permeability and limit antibiotic entry into the bacterial cell (*marA* and *soxS* can decrease the expression of porins).

IncHI1 plasmids played a significant role in spreading antibiotic resistance. This was the case during the 1972 Mexico City outbreak, where an*IncHI1* plasmid carrying resistance genes was isolated from *S.* Typhi strains. This plasmid subsequently contributed to the global spread of chloramphenicol resistance (Wain *et al.*, 2001). Furthermore, class 1 integrons detected in MDR S. Typhi isolates from Vietnam and India between 1999 and 2000 carried gene cassettes conferring resistance to trimethoprim (*dfrVII* gene) and spectinomycin/streptomycin (*aadA1* cassette) (Ploy *et al.*, 2003). The presence of these integrons suggests a potential association with *IncHI1* plasmids, which could facilitate horizontal gene transfer and promote the spread of MDR within *S.* Typhi populations.

Although less frequent, chromosomal resistance is essential, especially with the rise of fluoroquinolone resistance (Kumar, 2021). Mutations in the *gyrA, gyrB,* and *ParC* genes of *S.* Typhi have been linked to fluoroquinolone resistance, along with plasmid-mediated quinolone-resistant (PMQR) genes (Pfeifer *et al*., 2021). Single point chromosomal mutations in the Quinolone Resistance-Determining Region (QRDR) of the topoisomerase gene *gyrA* are exacerbated by the indiscriminate use of antibiotics like nalidixic acid and ciprofloxacin (Kumar and Kumar, 2021). The presence of plasmid-encoded *qnr* genes has also been implicated in fluoroquinolone resistance.

Interestingly, a study has shown that taking antibiotics during hospitalization did not influence the difference in lengths of stay between quinolone-resistant (QR) and quinolone-susceptible (QS) groups (Broghton *et al*., 2010). This may indicate that longer stays in QR infections are likely attributed to the AMR-associated *Salmonella* virulence rather than antibiotic treatment failure. This is consistent with *in vitro*, animal, and human studies linking *Salmonella* virulence and AMR (Weir *et al*.,

2008; Sharma *et al*., 2013; Nde and Logue, 2008; Molback, 2005). The *ArcAB-TolC* efflux system is one of the pumps for which a role in virulence and quinolone resistance is observed in *Salmonella* (Buckley *et al.,* 2006; Virlogeux-Payant *et al.,* 2008)

Resistance mechanisms may cause *S.* Typhi to be better at causing disease through enhanced immune evasion and increased virulence. The relationship between AMR and virulence in bacteria is complicated. Specific virulence gene clusters are strongly associated with drug-resistant phenotypes of Salmonella isolates. *SodC1*, *gipA*, and integron-associated integrase class I gene (*IntI1*) are found alongside resistance genes in *Salmonella* isolates (Higgins *et al.,* 2020).

The AMR mechanisms, particularly those involving altered cell wall components, can enhance biofilm formation. The *Mig-14* gene is necessary for resistance to polymyxin B (PB) by regulating the expression of genes related to antimicrobial resistance, including outer membrane proteins (*ompF* and *ompC*) and biofilm formation genes (*csgD*) (Brodsky *et al.,* 2002). *Mig-14* contributes to PB resistance by reducing outer membrane permeability. In *S.* Typhi, deletion of this gene reduced biofilm formation and increased the mRNA levels of the porin proteins ompF and ompC, which regulate small molecule permeability (Sheng *et al.*, 2019).

Some AMR mechanisms involve changes in bacterial metabolism, which can also affect the bacteria's ability to utilize host nutrients and survive within host tissues. The metabolic profiles of *Salmonella* Derby are linked to its susceptibility to ceftriaxone (CRO)(Ji *et al.*, 2023). Specifically, CRO-resistant *S.* Derby exhibits a different metabolic status with changes in glutathione biosynthesis, with lower levels of glutathione oxidized (GSSG) and citrulline. Glutathione metabolism is closely related to the drug resistance of foodborne *Salmonella* Derby to cephalosporins. Specifically, the abundance of GSSG and citrulline were found to be greatly suppressed in CRO-resistant *S.* Derby, whereas glutathione reduced (GSH) levels remained unaffected. In other words, changes in glutathione metabolism in CRO-resistant *S.* Derby, linked to its AMR profile, may enable the pathogen to better manage stress and survive longer in hostile environments.

Efflux pumps work by expelling antibiotics from the cell and reducing their intracellular concentration. This is illustrated with the AcrAB-TolC efflux system in *Salmonella enterica* serovar Typhimurium DT104 strains, which contributes to resistance against

various classes of antibiotics, including quinolones, chloramphenicol-florfenicol, and tetracyclines, as well as contributes to decreased susceptibility to other classes such as fluoroquinolones (Baucheron *et al.,* 2004). Mutations in regulatory genes or in the promoter region of the AcrAB-TolC operon can result in overexpression of the efflux pump (Tatavarthy *et al.,* 2014; Sharma *et al.*, 2013). The activation of *MarA* genes, for instance, leads to increased expression of the AcrAB-TolC operon and subsequent enhancement of drug efflux (Weston *et al.*, 2018). Moreover, *S.* Typhi can become resistant by reducing membrane permeability to prevent drug entry through, for example, the alteration of membrane transport proteins or porin channels. *S. Typhi* has demonstrated the ability to adjust its outer membrane (OM) permeability in response to oxidative stress, enhancing its survival against reactive oxygen species (Hebrard *et al.,* 2009; Du *et al.,* 2011).

Resistance mechanisms involving drug inactivation are primarily mediated by enzymes. For example, β-lactamases hydrolyse the β-lactam ring in penicillins and some cephalosporins, rendering them ineffective. Genes encoding certain β-lactamases, such as AmpC β-lactamases (e.g., *blaCMY-2*) and some Class A β-lactamases (e.g. *TEM-1*, *PSE-1*), confer resistance to a range of cephalosporins (e.g., cefalotin, cefuroxime, and cefuroxime axetil), penicillins, and β-lactam/β-lactamase inhibitor combinations like ampicillin/sulbactam and piperacillin/tazobactam (El-Tayeb *et al.*, 2017; Frye and Jackson, 2013). Extended-spectrum β-lactamases (ESBLs) are a subset of β-lactamases that can target an even broader range of β-lactam antibiotics, such as third-generation cephalosporins and penicillins.

Another example is acetyltransferases, which inactivate drugs like chloramphenicol and aminoglycosides by acetylation. The genes *aadA*, *strA*, and *strB* are responsible for resistance to streptomycin by adenylylation and phosphorylation, respectively (El-Tayeb *et al.*, 2017; Frye and Jackson, 2013). These modifications prevent streptomycin from binding to the 30S ribosomal subunit, thus inhibiting its ability to disrupt protein synthesis.

Similarly, resistance to carbapenems, a potent broad-spectral class of β-lactams, is mediated by inactivation through carbapenemase enzymes. Carbapenems are currently a last-resort option for extensively drug-resistant (XDR) typhoid. While resistance remains relatively low in *Enterobacteriaceae*, it is being rarely reported, primarily due to the production of carbapenemases (Nizamuddin *et al.,* 2023). Among *Enterobacteriaceae*, it is believed that carbapenem resistance

is reported for the first time in *Salmonella* Typhi (Ain *et al.,* 2022). This is worrying since carbapenems are often the last line of defense against many Gram-negative infections.

Resistance genes that confer antimicrobial resistance - whether through drug-degrading enzymes, efflux pumps, target modifications, or reduced drug uptake - can arise from chromosomal mutations or through the acquisition of external resistance factors via gene transfer mechanisms.

Current Approaches to the Treatment of AMR *S.* Typhi and Novel Targets

Antimicrobial susceptibility testing is essential for diagnosing extensively drug-resistant (XDR) Typhi isolates, and treatment should be adjusted accordingly. Empiric treatment options include carbapenems, azithromycin, or a combination of both while awaiting susceptibility results (CDC, 2021). Severe or complicated cases of typhoid fever can be effectively treated with carbapenems like meropenem or imipenem, despite their high cost. Patients with uncomplicated illness may use oral azithromycin alone, but cost limitations in resource-limited settings should be considered (Effa *et al.,* 2011; Ishaque *et al.,* 2022; Hughes *et al.,* 2021)

Combining more than one antimicrobial agent is suggested for treating enteric fever because it involves a mix of intracellular and extracellular bacteria. Combinations like azithromycin and cefixime or azithromycin and ceftriaxone are recommended. Cefixime and ceftriaxone are more effective against external bacteria, while azithromycin targets intracellular bacteria (Parry *et al*., 2023; Pascual *et al.,* 1995; Matsumoto *et al.,* 2001). Long-term management of chronic carriage lacks precise recommendations due to limited data and clinical trials (McCann *et al*., 2022)

Potential new treatments and drug targets for XDR *S.* Typhi include Colanic acid biosynthesis acetyltransferase (wcaB), which disrupts the synthesis of colanic acid vital for bacterial survival in the stomach's acidic environment. Other potential drug targets include Shikimate dehydrogenase, Pantoate-beta-alanine ligase, and Multidrug efflux RND transporter permease subunit, with various inhibitors developed for each (Jalal *et al.,* 2021). Shikimate dehydrogenase, not present in humans, is a target for disrupting the synthesis of aromatic amino acids (Diaz-Quiroz *et al.*, 2018). Pantothenate synthetase, involved in vitamin B5 production, has inhibitors designed to target it. MdtC, a permease associated with drug efflux,

presents potential blockers for inhibiting antimicrobial resistance (Suresh *et al*., 2020; Nikaido, 2011)

CONCLUSION

The AMR in *S.* Typhi presents a layered challenge that involves genetic, behavioural, and environmental factors. The historical context shows an evolution from early containment successes in high-income nations to the current struggle against MDR and XDR strains. The surge in resistance correlates with socio-economic disparities and is amplified by the misuse of antibiotics and inadequate healthcare systems. Molecular genetics has advanced our understanding of the mechanisms of resistance, but this knowledge alone is insufficient without the implementation of robust surveillance systems, responsible prescribing practices, and global cooperation. The behavioural and individual-level aspects are important too, but they must be tackled with systemic changes, through regulations and infrastructure improvements to curb the misuse of antibiotics. Additionally, recognising the environmental domain of health involves overcoming WaSH deficiencies, contamination of ecosystems, promoting sustainable agricultural practices, and monitoring the spread of resistance genes across environmental reservoirs. As the epidemiology of *S.* Typhi continues to evolve, the role of climate change and human-animal-environment interactions in the spread of AMR becomes increasingly apparent. The AMR typhoid is as much a global and social issue as it is a medical one. Current strategies in managing AMR in *S.* Typhi involve a combination of empirical treatments, vaccination, and, importantly, global public health efforts. Research into novel treatments and drug targets continues, but without addressing the root causes of AMR and the socio-economic factors at play, these solutions may be temporary.

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