Threats Associated with the Potential Spread of XDR Typhoid Fever in Pakistan: Strategies to Tackle the Alarming Situation of Antibiotic Resistance

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Abstract

Antibiotic resistance due to typhoid fever presents serious public health consequences due to the advent of extensively drug-resistant (XDR) *Salmonella enterica* serovar Typhi, leading to treatment failure and further complications. Of all the serotypes of *S.* Typhi is the most prevalent serotype and is capable of developing resistance. A worrying trend is the appearance of XDR *S.* Typhi in many parts of the world, especially Pakistan. An updated summary of the current XDR *Salmonella* Typhi outbreaks in endemic and epidemic areas is being described due to reports of treatment failure in both humans and animals when treating XDR *Salmonella* Typhi infections. However, strict preventative measures can be put in place until the discovery of novel and alternative treatment options. Quick surveillance of pathogenic microorganisms and an emphasis on antimicrobial stewardship are necessary to monitor the potential spread of epidemics in human and animal populations alike. Despite the fact that certain areas are making headway against XDR *Salmonella* Typhi, a concerted and effective global effort is needed to stop the XDR outbreak before it worsens and sends us back to the era before antibiotics.

Keywords: Typhoid, Antibiotic, *Salmonella,* Drug resistance, XDR Typhoid

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Introduction

Salmonella enterica serovar Typhi is a gram-negative bacterial gut pathogen that is limited to humans and causes severe bloodstream infections, even sepsis, which are all referred to as enteric fever (Crump et al., 2015). Enteric fever is particularly common in low and middle-income countries (LMICs) and is spread by tainted food or water (Parry et al., 2002; Crump et al., 2015). In South Asia, Southeast Asia, and sub-Saharan Africa, it is a leading cause of feverish illnesses. A total of 14.3 million cases of enteric fever with 135000 mortalities were reported in 2017 globally (Stanaway et al., 2019).

This bacterium is of great concern for public health in spite of the fact a number of efforts have been done in order to control the spread of *S.* typhi, but it still cause's public health. This hazardous effect is correlated with the resistance to the first-line and second-line drugs. Multidrug-resistant (MDR) *S.* Typhi has rendered ampicillin, co-trimoxazole, and chloramphenicol ineffective. On the other hand, extensively drug-resistant (XDR) *S.* Typhi do not respond to ampicillin, co-trimoxazole, chloramphenicol, fluoroquinolones, and third-generation cephalosporins except azithromycin and carbapenems. The appearance of resistance to these antibiotics has rendered treatment strategies against *S.* Typhi ineffective and created a difficult situation (Chatham-Stephens, 2019). The first sporadic outbreak of typhoid fever in Pakistan was reported in Hyderabad, Sindh, in 2019 (Browne et al., 2024). A large number of population from South Asia contract this bacterium each year, affecting 21 million people globally, causing 200,000 mortalities (War et al., 2022). People from Pakistan and Sindh are more affected by typhoid because of its high endemicity. It is highly endemic in 16 Asian countries (Rasheed et al., 2019; ul Huda et al., 2024). 493 of every 100,000 people are affected by typhoid (Fatima et al., 2021). The incidence rate in Pakistan has increased from 7/100,000 to 15/100,000 in areas of high endemicity (Ahmad et al., 2021; Rasheed et al., 2019). As per the public health authority of Sindh, Pakistan, 15,717/22,354 cases of XDR typhoid fever were reported between 2016-2020 (War et al., 2022).

Farm animals are more vulnerable to *Salmonella* infections from the excrement of infected animals to the healthy ones (Ehuwa et al., 2021). Infection due to *S.* Typhi is due to the consumption of contaminated food and water (Bell et al., 2014; Vt Nair et al., 2018). Tainted food items may also cause the transmission of the bacterium (Abd El-Aziz et al., 2021). The schematic presentation of the transmission of *Salmonella* is given in Fig. 1.

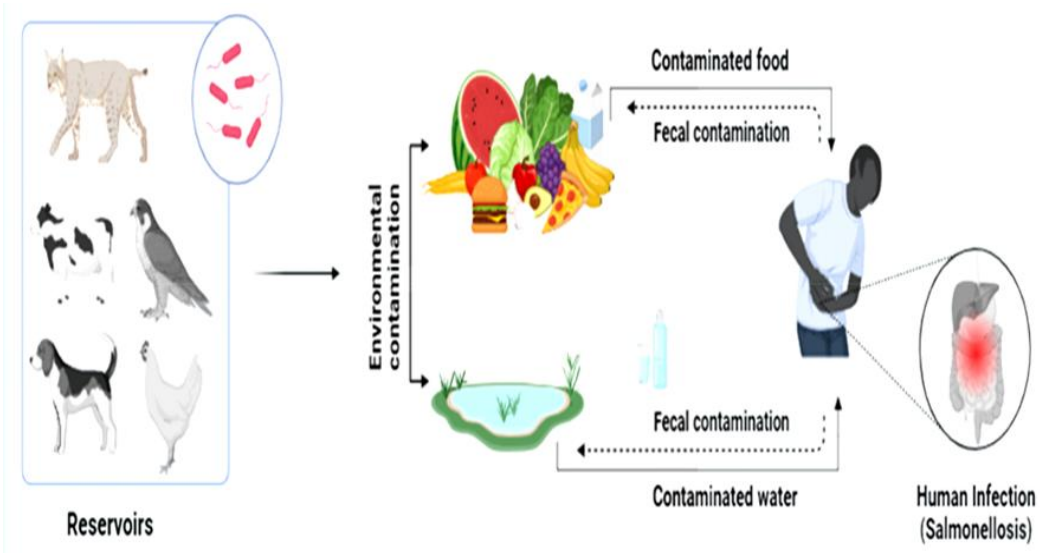

Fig. 1: The Schematic Representation of *Salmonella* Transmission

Typhoid fever is characterized by abdominal pain, vomiting, high-grade fever, and diarrhea, Complications may sometimes lead to death in immuno-compromised persons (Bell et al., 2014; Vt Nair et al., 2018). The current chapter emphasizes the threats linked with the emergence of XDR typhoid fever, which render the available treatment options ineffective.

Furthermore, this chapter will highlight the alternative strategies to combat the rise of resistance to the available regimen and surveillance programmes to address the challenges causing hurdles in the effective treatment of the resistant strains.

Progression of Typhoid Fever

Virulence in *Salmonella* is due to its pathogenicity islands (SPIs). Virulence factors associated with SPIs are capsule, flagella, adhesins, invasions, fimbriae, haemagglutinins, exotoxins, endotoxins, plasmids, biofilm formation, and Type three secretion system (T3SS) (Sabbagh et al., 2010; Chong et al., 2021). Through horizontal gene transfer, the bacteria also pick up virulent genes found on the SPI (Marcus et al., 2000; Kombade & Kaur, 2021; Naushad et al., 2023). Bacteria escape the immunity barrier of the host, colonize, persist in host tissue, and induce inflammation and tissue damage due to proteins generated by invA, sopE, sseL, and spvC proteins and other virulence determinants (Chami & Bao, 2012; Dos Santos et al., 2019; Jajere, 2019). *S.* Typhi acquires resistant genes because of its high adaptability, which may lead to frequent episodes of foodborne illnesses.

It has been proposed that MDR *Salmonella* develop resistant plasmids, changing into XDR *Salmonella* and gaining resistance to all prescribed antibiotics. The H58 clade of *Salmonella* Typhi, a common serotype in South and Southeast Asia as well as areas of Africa and Oceania, has been linked in reports to several local typhoid epidemics and is also the cause of the XDR *Salmonella* outbreak (Costa et al., 2012; Feasey et al., 2015; Hendriksen et al., 2015; Klemm et al., 2018). The emergence of resistant strains of *Salmonella* in both humans and animals should emphasize the urgent need for the development of novel strategies in order to treat these resistant strains and to prevent further spread of these resistant strains (Sajid et al., 2025). The enormous number of data is available on the resistance of *Salmonella* to available antibiotics. It is essential to understand different facets of transmission of S. Typhi from direct exposure to farm animals to the supply chain in order to develop effective control strategies to tackle its further spread and safeguard Public health (Iqbal et al., 2025).

Impact of XDR *S.* Typhi on Public Health

Other than causing increased morbidity and mortality due to low efficacy and availability of limited treatment options, it has long-lasting consequences on human health, especially those with weakened immune systems (Popa & Papa, 2021). It may disseminate to the bloodstream, bones, joints, brain, and sometimes other organs when invasive and can cause potentially life-threatening infections (CDC, 2023; Li et al., 2023). One such consequences is the colonization of the organism which causes the shedding into the stool, hence causing risk to the community and the individual itself (Wang et al., 2022).

People who have XDR *S.* Typhi infections are more likely to develop sepsis or other secondary infections, such as urinary tract infections. These side effects can be serious and necessitate further medical care, increasing the initial *Salmonella* infection's health impact (Saeed et al., 2019). The introduction of XDR *S.* Typhi has led to a substantial socioeconomic burden, especially for those from low-income families who are more likely to contract typhoid fever, and the cost of treatment has increased (Mumtaz et al., 2024). Travelers from endemic to non-endemic areas are subject to restrictions in order to stop the outbreak. According to the CDC, families are more likely to get infected with XDR *S.* Typhi species when traveling to Pakistan. Additionally, a level 2 notice for the outbreak is issued by the CDC, requiring heightened precautions (Akram et al., 2020). According to reports, this pathogen has an impact on diagnosis, treatment, and cost. There have been reports of both the concerning rate of azithromycin resistance and clinical treatment failures. Consequently, this has caused a delay in the creation of new antibiotics for medical use (Hooda et al., 2019; Jabeen et al., 2023). Zakir et al. (2021) reported notable resistance among *S.* Typhi isolates. He reported half of the blood culture-positive isolates in one of the tertiary care hospitals in Lahore.

Fatima et al. (2023) stated that veterinary medicine encounters multiple challenges as a result of the rising incidence of XDR *Salmonella* in animals, such as higher rates of morbidity and mortality in impacted livestock populations, more difficult infection diagnosis and treatment

because antimicrobials are less effective, and a higher risk of zoonotic transmission. In addition to having an impact on the health of individual animals, XDR *Salmonella* can also pose financial difficulties for agricultural practices by lowering overall animal productivity, decreasing the market value of animal products, and causing financial losses due to higher treatment and prevention costs. It may also contribute to environmental contamination and the ensuing risks to human health (Teklemariam et al., 2023).

Furthermore, International cooperation is required to cope with the spread of the infection from Pakistan to other countries, as shown in Table 1. Keeping in view the threats associated with the spread of XDR typhoid fever, WHO has initiated different surveillance programmes, mitigation strategies of *Salmonella*, traveler advisories highlighting the impacts of vaccination in order to cope with the spread of these resistant strains (Nadeem et al., 2025).

Despite collaborative efforts and immediate needs to develop effective treatment strategies to combat resistance and control measures, there is still lack of comprehensive data on the dynamics of XDR *S*. Typhi outbreaks. This chapter focuses the ongoing outbreaks of the XDR *S*. Typhi in Pakistan and trends to overcome the resistance.

Table 1: Drugs specified for the treatment of multi drug resistant (MDR) and extensively drug resistant (XDR) strains causing typhoid fever in Pakistan

Antibiotic	Route of Administration	Effective Against MDR Typhoid	Effective Against XDR Typhoid	References
Chloramphenicol	Oral, intravenous	No	No	(Walker et al., 2023)
Co-trimoxazole	Oral, intravenous	No	No	(Walker et al., 2023)
Ampicillin	Oral, intramuscular, intravenous	No	No	(Nadeem et al., 2025)
Ciprofloxacin	Oral, intravenous	Yes	No	(Nadeem et al., 2025)
Ceftriaxone	Intramuscular, intravenous	Yes	No	(Hooda et al., 2019)
Azithromycin	Oral	Yes	Yes	(Hooda et al., 2019)
Meropenem	Intravenous	Yes	Yes	(Hooda et al., 2019)
Tigecycline	Intravenous	Yes	Yes	(Hooda et al., 2019)

Challenges

There are significant challenges in the way of diagnosis, treatment, and prevention of XDR *S*. Typhi, which pose serious threats to public health globally. A number of variables are complicating the diagnosis of the infection. Conventional culture-based techniques are more laborious, time-consuming, and have reduced sensitivity and specificity and more chances of false negative results, which may delay treatment (Neupane et al., 2021). Expertise in the study of resistance profiles is required, and these working facilities should be readily available in healthcare settings (Memon et al., 2022). Due to the overlapping clinical presentation of *Salmonella* with other pathogens, it is sometimes difficult to diagnose it, resulting in false diagnoses and antimicrobial therapy (Neupane et al., 2021). Symptoms of many diseases are comparable to each other as salmonellosis and enteric fever. When antimalarial medications no longer work, the disease is sometimes diagnosed as enteric fever or Salmonellosis (Antillón et al., 2017; Bashir et al., 2024). Limited treatment choices have made the treatment of XDR typhoid fever a challenge for health professionals, which has led to the use of last resort antibiotics, rendering them ineffective (Hughes et al., 2021). As in the case of azithromycin, becoming challenge because of acquiring resistance (Butt et al., 2022). Furthermore, self-medication and over the counter medication in the endemic areas has also made the management of typhoid fever more difficult thereby making antimicrobial resistance more prevalent (Butt et al., 2020; Butt et al., 2022).

Another factor contributing to the spread of XDR typhoid fever is the lack of funding in endemic nations like Pakistan to construct basic healthcare facilities for their populace, the majority of whom live in overcrowded areas and below the poverty line (Tharwani et al., 2022). Finally, because XDR *S*. Typhi is a novel disease, there are few existing treatments and no information on how well XDR Typhoid treatments work. Health officials worldwide should be aware that the XDR H58 strain of *S*. Typhi, which is found in Sindh, has the ability to invade, disseminate, and possibly displace native strains in other areas (Akram et al., 2020). Given the likelihood of the disease spreading quickly on a worldwide scale, the WHO has designated the pathogen as a target for the development of novel drugs (Andrews et al., 2018; Akram et al., 2020).

Prevention and Control

Salmonella infection must be prevented and controlled using a variety of methods, such as vaccination, better hygiene, the use of bacteriophages, preserving the safety of human consumables, addressing environmental deficiencies, identifying and treating chronic carriers of the infection, making sure that food safety measures are adequate, protecting drinking and treated water, removing antibiotics from food animals, and the One Health approach. The following provides a sufficient summary of each tactic (Walker et al., 2023).

Food Hygiene

In wealthy nations, preventing salmonellosis requires strict adherence to food hygiene from farm to plate. Implementing evidence-based prevention strategies requires an understanding of the causes and processes of *Salmonella* transmission in low- and middle-income nations (Yesigat et al., 2020). Foodborne outbreaks are uneasy to manage. Reducing the number of people without access to clean drinking water is a consistent goal of Millennium Development Goal 7 (Riahi et al., 2018). The relevant government officials in developing nations should make sure that the infrastructure required to remove human waste from water supplies is put in place and that the general public is taught the need to practice good hygiene (Khan, 2019; Akram et al., 2020).

Prebiotics, Probiotics, Synbiotics, and Postbiotics

Synbiotics are a combination of probiotics and prebiotics. The combined benefits of probiotics and prebiotics prevent or lessen the

symptoms of *Salmonella* via altering gut microbiota, reducing pathogen count, inducing immune system synergistic activities, and other mechanisms. Prebiotics are utilized by the host microorganisms as a food substrate. Prebiotics cause the formation of biofilm on the epithelium of the intestine, thereby preventing the pathogen from causing adhesion (Fatima et al.). When administered in the recommended dosage, probiotics are advantageous microorganisms that improve the host's health. *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Enterococcus*, and *Pediococcus* species are among the probiotics (Kwoji et al., 2021). Because they increase the host immune system, compete with infections for resources, and suppress them by secreting lactic acid, probiotics are good for your health (Latif et al., 2023).

Another recently developed idea is "postbiotics." Non-viable bacteria, their cell fragments, and health-promoting metabolites are the ingredients of postbiotic treatments (Salminen et al., 2021). Postbiotic preparations can make use of a variety of bacterial metabolites, such as peptides, organic acids, short-chain fatty acids, exopolysaccharides, enzymes, and plasmalogens. Postbiotic-treated animals exhibited improved nutritional absorption and decreased *Salmonella* counts (Humam et al., 2019).

Bacteriophages

These are the viruses that infect bacteria. Phages may be able to stop the emergence of resistant *Salmonella* because of their bacteriolytic activity, stability throughout a wider range of salt concentrations, pH, temperature, ability to self-limit, environmental friendliness, genetic amenability, etc. (Khan & Rahman, 2022). They attack multiple strains rather than a single one; phage mixtures with restricted host ranges are better at reducing germs in different foods. SalmoLyseR, PhageGuardS, Salmo Fresh, SalmonFREER, and other phages are examples of those used in the food business to combat *Salmonella* (Mkangara, 2023).

The peptidoglycan layer inside and outside of pathogenic bacteria is hydrolyzed by virion-associated peptidoglycan hydrolases and endolysins derived from bacteriophages, which are produced following lytic cycles. Because of their great efficacy, quick action, specificity, and low likelihood of resistance development, they are a promising alternative therapy against multidrug-resistant bacteria in a variety of disciplines, including food safety and medicine (Lin et al., 2017).

One Health Approach

This method is transdisciplinary, multisectoral, and collaborative. Optimal local, regional, national, and global health outcomes are attained by acknowledging the connections among humans, animals, plants, and their shared environment (CDC, 2024). Fighting drug-resistant *Salmonella* requires a multipronged approach on several fronts. To lessen antibiotic dependency, especially in cattle production, alternative, non-antibiotic techniques must be employed. Further research on the existing alternative control measures, as well as newer strategies, is required. The One Health paradigm must be the foundation for interdisciplinary and global collaborative initiatives since *Salmonella's* growing antibiotic resistance impacts not only human health but also animal and environmental health (McEwen & Collignon, 2018).

One approach to health is to increase funding for vaccines and non-antimicrobial-based interventions. Use multiomics (metagenomics, transcriptomics, proteomics, etc) as a surveillance tool to determine the origin, pattern, and epidemiology of antimicrobial resistance genes. Take part in antimicrobial stewardship programs to ensure that antibiotics are used responsibly in both humans and animals to improve sanitation and infection prevention measures (Chernov et al., 2019).

Vaccination

Immunization is a crucial technique for preventing typhoid fever infections and is crucial for protecting both human and animal populations. Typhoid conjugate vaccines (TCVs) licensed by the WHO for humans include Typbar TCVTM, which uses tetanus toxoid as a carrier, and Vi CMR197, which uses CMR197, a non-toxic mutant of diphtheria toxin as a carrier (WHO, 2019). These vaccines provide sufficient protection against typhoid fever and have decreased the prevalence of XDR *Salmonella* in both endemic and epidemic areas (Sirima et al., 2021).

Because TCVs enhance immunological qualities, are safe for kids, and offer a long-lasting period of protection, they are given to people of all ages. In national vaccination regimens, the vaccine has demonstrated negligible immune interference and is well tolerated, particularly in endemic nations (Sirima et al., 2021). Everyone traveling to areas of the world where typhoid is endemic should get vaccinated against the disease, according to the most recent CDC recommendations (WHO, 2019; Akram et al., 2020; CDC, 2021a). The CDC advises individuals visiting endemic regions to get either the Ty21a or ViPS vaccines (Appiah, 2019). Because vaccine efficacy varies, further precautions, including better cleanliness and food safety procedures, may be required (Vanderslott et al., 2023).

In addition, current research and development initiatives to create vaccines against typhoid fever infections (Hanumunthadu et al., 2023; Smith et al., 2023) have the potential to slow the spread of these diseases and lower the morbidity and fatality rates that go along with them. Vaccines are also being administered to animals and poultry (Li et al., 2020). Immunization against typhoid fever is necessary in order to prevent typhoid fever.

Conclusion

XDR *Salmonella* poses serious and constantly changing challenges to public health and animal health globally. There is a dire need to initiate certain surveillance programmes, immunization, one health programmes, environmentally friendly agriculture techniques, and the development of different technological advancements in combating the disease.

Furthermore, interdisciplinary research, public awareness programmes, and strong policies are the need of the time to create a *Salmonella*-free, healthier, and resilient future for the healthcare department. Coordinated international approaches are necessary to protect human and animal health and to mitigate hazards caused by XDR *Salmonella*.

References

Abd El-Aziz, N. K., Tartor, Y. H., Gharieb, R. M. A., Erfan, A. M., Khalifa, E., Said, M. A., Ammar, A. M., & Samir, M. (2021). Extensive drug-

resistant Salmonella enterica isolated from poultry and humans: prevalence and molecular determinants behind the co-resistance to ciprofloxacin and tigecycline. *Frontiers in Microbiology*, *12*, 738784.

Ahmad, S., Tsagkaris, C., Aborode, A. T., Haque, M. T. U., Khan, S. I., Khawaja, U. A., dos Santos Costa, A. C., Essar, M. Y., & Lucero-Prisno Iii, D. E. (2021). A skeleton in the closet: the implications of COVID-19 on XDR strain of typhoid in Pakistan. *Public Health in Practice*, *2*, 100084.

Akram, J., Khan, A. S., Khan, H. A., Gilani, S. A., Akram, S. J., Ahmad, F. J., & Mehboob, R. (2020). Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. *BioMed Research International*, *2020*(1), 6432580.

Andrews, J. R., Qamar, F. N., Charles, R. C., & Ryan, E. T. (2018). Extensively drug-resistant typhoid—are conjugate vaccines arriving just in time? *New England Journal of Medicine*, *379*(16), 1493-1495.

Antillón, M., Warren, J. L., Crawford, F. W., Weinberger, D. M., Kürüm, E., Pak, G. D., Marks, F., & Pitzer, V. E. (2017). The burden of typhoid fever in low-and middle-income countries: a meta-regression approach. *PLoS Neglected Tropical Diseases*, *11*(2), e0005376.

Appiah, G. D., M.J. Hughes and K. Chatham-Stephens, 2019. (2019). *Chapter 4: Travel-related infectious diseases: Typhoid and paratyphoid fever*. Centers for Disease Control and Prevention (CDC).

Bashir, I., Muhammad, A., Rasool, A. G., Bashir, G. K., Tahir, U., Noor, A., & Karamat, S. (2024). Toxicity Induced by Commonly used Antimalarial agents. *Complementary and Alternative Medicine: Non–Conventional*, 130.

Bashir, I., Rasool, M. H., Shafique, M., Jabeen, K., & Qamar, M. U. (2024). Exploring the antimicrobial efficacy of Manuka honey against multidrug-resistant and extensively drug-resistant Salmonella Typhi causing septicemia in Pakistan. *Future Microbiology*, *19*(16), 1377-1387.

Bell, B. G., Schellevis, F., Stobberingh, E., Goossens, H., & Pringle, M. (2014). A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infectious Diseases*, *14*, 1-25.

Browne, A. J., Chipeta, M. G., Fell, F. J., Haines-Woodhouse, G., Hamadani, B. H. K., Kumaran, E. A. P., Aguilar, G. R., McManigal, B., Andrews, J. R., & Ashley, E. A. (2024). Estimating the subnational prevalence of antimicrobial resistant Salmonella enterica serovars Typhi and Paratyphi A infections in 75 endemic countries, 1990–2019: a modelling study. *The Lancet Global Health*, *12*(3), e406-e418.

Butt, M., Mohammed, R., Butt, E., Butt, S., & Xiang, J. (2020). Why have immunization efforts in Pakistan failed to achieve global standards of vaccination uptake and infectious disease control? *Risk Management and Healthcare Policy*, 111-124.

Butt, M. H., Saleem, A., Javed, S. O., Ullah, I., Rehman, M. U., Islam, N., Tahir, M. A., Malik, T., Hafeez, S., & Misbah, S. (2022). Rising XDR-typhoid fever cases in Pakistan: are we heading back to the pre-antibiotic era? *Frontiers in Public Health*, *9*, 794868.

CDC (2021a). *Typhoid vaccine information statement*.

CDC (2021b). *Typhoid fever and paratyphoid fever*.

CDC (2023). *Information for healthcare professionals and laboratories*.

CDC (2024). *Drug-Resistant Salmonella*

Serotype Typhi. n.d [cited 2024 Feb 23].from http://www.cdc.gov/DrugResistance/Biggest-Threats.html. Centre dor Disease Control.

Chami, B., & Bao, S. (2012). Salmonella: Invasion, Evasion & Persistence. In *Salmonella-Distribution, Adaptation, Control Measures and Molecular Technologies*. IntechOpen.

Chatham-Stephens, K. (2019). Emergence of extensively drug-resistant Salmonella Typhi infections among travelers to or from Pakistan—United States, 2016–2018. *Morbidity and Mortality Weekly Report*, *68*.

Chernov, V. M., Chernova, O. A., Mouzykantov, A. A., Lopukhov, L. L., & Aminov, R. I. (2019). Omics of antimicrobials and antimicrobial resistance. *Expert Opinion on Drug Discovery*, *14*(5), 455-468.

Chong, A., Cooper, K. G., Kari, L., Nilsson, O. R., Hillman, C., Fleming, B. A., Wang, Q., Nair, V., & Steele-Mortimer, O. (2021). Cytosolic replication in epithelial cells fuels intestinal expansion and chronic fecal shedding of Salmonella Typhimurium. *Cell Host & Microbe*, *29*(7), 1177-1185.

Costa, M. M., Penido, M., Dos Santos, M. S., Doro, D., de Freitas, E., Michalick, M. S. M., Grimaldi, G., Gazzinelli, R. T., & Fernandes, A. P. (2012). Improved canine and human visceral leishmaniasis immunodiagnosis using combinations of synthetic peptides in enzyme-linked immunosorbent assay. *PLoS Neglected Tropical Diseases*, *6*(5), e1622.

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.

Dos Santos, A. M. P., Ferrari, R. G., & Conte-Junior, C. A. (2019). Virulence factors in Salmonella Typhimurium: the sagacity of a bacterium. *Current Microbiology*, *76*, 762-773.

Ehuwa, O., Jaiswal, A. K., & Jaiswal, S. (2021). Salmonella, food safety and food handling practices. *Foods*, *10*(5), 907.

Fatima, A., Saleem, M., Nawaz, S., Khalid, L., Riaz, S., & Sajid, I. (2023). Prevalence and antibiotics resistance status of Salmonella in raw meat consumed in various areas of Lahore, Pakistan. *Scientific Reports*, *13*(1), 22205.

Fatima, M., Kumar, S., Hussain, M., Memon, N. M., Vighio, A., Syed, M. A., Chaudhry, A., Hussain, Z., Baig, Z. I., & Baig, M. A. (2021). Morbidity and mortality associated with typhoid fever among hospitalized patients in Hyderabad district, Pakistan, 2017-2018: retrospective record review. *JMIR Public Health and Surveillance*, *7*(5), e27268.

Fatima, R., Sadia, B., Parveen, Z., & Khan, A. M. A. Advancements in Understanding Auxin's Role in Starch Production.

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

Hanumunthadu, B., Kanji, N., Owino, N., Da Silva, C. F., Robinson, H., White, R., Ferruzzi, P., Nakakana, U., Canals, R., & Pollard, A. J. (2023). Salmonella Vaccine Study in Oxford (SALVO) trial: protocol for an observer-participant blind randomised placebo-controlled trial of the iNTS-GMMA vaccine within a European cohort. *BMJ Open*, *13*(11), e072938.

Hendriksen, R. S., Leekitcharoenphon, P., Lukjancenko, O., Lukwesa-Musyani, C., Tambatamba, B., Mwaba, J., Kalonda, A., Nakazwe, R., Kwenda, G., & Jensen, J. D. (2015). Genomic signature of multidrug-resistant Salmonella enterica serovar Typhi isolates related to a massive outbreak in Zambia between 2010 and 2012. *Journal of Clinical Microbiology*, *53*(1), 262-272.

Hooda, Y., Sajib, M. S. I., Rahman, H., Luby, S. P., Bondy-Denomy, J., Santosham, M., Andrews, J. R., Saha, S. K., & Saha, S. (2019). Molecular mechanism of azithromycin resistance among typhoidal Salmonella strains in Bangladesh identified through passive pediatric surveillance. *PLoS Neglected Tropical Diseases*, *13*(11), e0007868.

Hughes, M. J., Birhane, M. G., Dorough, L., Reynolds, J. L., Caidi, H., Tagg, K. A., Snyder, C. M., Yu, A. T., Altman, S. M., & Boyle, M. M. (2021). Extensively drug-resistant typhoid fever in the United States.

Humam, A. M., Loh, T. C., Foo, H. L., Samsudin, A. A., Mustapha, N. M., Zulkifli, I., & Izuddin, W. I. (2019). Effects of feeding different postbiotics produced by Lactobacillus plantarum on growth performance, carcass yield, intestinal morphology, gut microbiota composition, immune status, and growth gene expression in broilers under heat stress. *Animals*, *9*(9), 644.

Iqbal, U. Z., Riaz, A., Sheraz, M., Imran, F., Arfa, A., Nadeem, M., Zafar, S., Shehzadi, I., Ahmad, A., & Ambrose, S. (2025). Role of metallic nanoparticles in the control of hazardous insects affecting plants and animals: Nanoparticles against Insects. *Letters In Animal Biology*, *5*(2), 27-40.

Jabeen, K., Saleem, S., Jahan, S., Nizamudin, S., Arshad, F., Huma, Z.-e., Raza, S. M., Mehmood, M., Roman, M., & Haq, F. U. (2023). Molecular characterization of extensively drug resistant Salmonella enterica Serovar Typhi clinical isolates from Lahore, Pakistan. *Infection and Drug Resistance*, 2987-3001.

Jajere, S. M. (2019). A review of Salmonella enterica with particular focus on the pathogenicity and virulence factors, host specificity and antimicrobial resistance including multidrug resistance. *Veterinary World*, *12*(4), 504.

Khan, E. A. (2019). XDR Typhoid: The problem and its solution. *Journal of Ayub Medical College Abbottabad*, *31*(2), 139-140.

Khan, M. A. S., & Rahman, S. R. (2022). Use of phages to treat antimicrobial-resistant Salmonella infections in poultry. *Veterinary Sciences*, *9*(8), 438.

Klemm, E. J., Shakoor, S., Page, A. J., Qamar, F. N., Judge, K., Saeed, D. K., Wong, V. K., Dallman, T. J., Nair, S., & Baker, S. (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), 10-1128.

Kombade, S., & Kaur, N. (2021). Pathogenicity island in Salmonella. In *Salmonella spp.-A Global Challenge*. IntechOpen.

Kwoji, I. D., Aiyegoro, O. A., Okpeku, M., & Adeleke, M. A. (2021). Multi-strain probiotics: synergy among isolates enhances biological activities. *Biology*, *10*(4), 322.

Latif, A., Shehzad, A., Niazi, S., Zahid, A., Ashraf, W., Iqbal, M. W., Rehman, A., Riaz, T., Aadil, R. M., & Khan, I. M. (2023). Probiotics: Mechanism of action, health benefits and their application in food industries. *Frontiers in Microbiology*, *14*, 1216674.

Li, Q., Ren, J., Xian, H., Yin, C., Yuan, Y., Li, Y., Ji, R., Chu, C., Qiao, Z., & Jiao, X. (2020). rOmpF and OMVs as efficient subunit vaccines against Salmonella enterica serovar Enteritidis infections in poultry farms. *Vaccine*, *38*(45), 7094-7099.

Li, X., Cao, H., Chen, J. H.-K., Ng, Y.-Z., Fung, K.-K., Cheng, V. C.-C., & Ho, P.-L. (2023). Genomic investigation of Salmonella Typhi in Hong Kong revealing the predominance of genotype 3.2. 2 and the first case of an extensively drug-resistant H58 genotype. *Microorganisms*, *11*(3), 667.

Lin, D. M., Koskella, B., & Lin, H. C. (2017). Phage therapy: An alternative to antibiotics in the age of multi-drug resistance. *World journal of gastrointestinal pharmacology and therapeutics*, *8*(3), 162.

Marcus, S. L., Brumell, J. H., Pfeifer, C. G., & Finlay, B. B. (2000). Salmonella pathogenicity islands: big virulence in small packages. *Microbes and infection*, *2*(2), 145-156.

McEwen, S. A., & Collignon, P. J. (2018). Antimicrobial resistance: a one health perspective. *Antimicrobial resistance in bacteria from livestock and companion animals*, 521-547.

Memon, H., Saeed, F., Iqbal, M., Saboohi, E., Hanif, S., & Mallick, A. H. H. (2022). Association of extensively drug resistant salmonella infection in children with typhoid fever. *Pakistan Journal of Medical Sciences*, *38*(7), 1864.

Mkangara, M. (2023). Prevention and control of human Salmonella enterica infections: An implication in food safety. *International Journal of Food Science*, *2023*(1), 8899596.

Mumtaz, M. N., Irfan, M., Siraj, S., Khan, A., Khan, H., Imran, M., Khan, I. A., & Khan, A. (2024). Whole-genome sequencing of extensively drug-resistant Salmonella enterica serovar Typhi clinical isolates from the Peshawar region of Pakistan. *Journal of Infection and Public Health*, *17*(2), 271-282.

Nadeem, M., Shahbaz, M., Ahmad, F., & Waraich, E. A. (2025). Enhancing wheat resistance to salinity: The role of gibberellic acid and β-Carotene in morphological, yielding and ionic adaptations. *Journal of Ecological Engineering*, *26*(6), 76-94.

Naushad, S., Ogunremi, D., & Huang, H. (2023). Salmonella: A Brief Review. *Salmonella-Perspectives for Low-Cost Prevention, Control and Treatment*.

Neupane, D. P., Dulal, H. P., & Song, J. (2021). Enteric fever diagnosis: current challenges and future directions. *Pathogens*, *10*(4), 410.

NIH. (2021). *Weekly field epidemiology*. https://
www.nih.org.pk/wpcontent/uploads/2021/06/25-
FELTP-Pakistan-Weekly-Epidemiological-Report-June13-19-2021: report

Parry, C. M., Hien, T. T., Dougan, G., White, N. J., & Fever, J. J. F. T. (2002). 347. *DOI: https://doi. org/10.1056/NEJMra020201*, 1770-1782.

Popa, G. L., & Papa, M. I. (2021). Salmonella spp. infection-a continuous threat worldwide. *Germs*, *11*(1), 88.

Rasheed, M., Hasan, S. S., & Ahmed, S. I. (2019). Extensively drug-resistant typhoid fever in Pakistan. *The Lancet Infectious Diseases*, *19*(3), 242-243.

Riahi, M., Mohammadi, A. A., Moghadam, V. K., Robati, Z. S., & Bidkhori, M. (2018). Diarrhea deaths in children among countries with different levels of the human development index. *Data in brief*, *17*, 954.

Roper, L. E. (2024). Use of Additional Doses of 2024–2025 COVID-19 Vaccine for Adults Aged≥ 65 Years and Persons Aged≥ 6 Months with Moderate or Severe Immunocompromise: Recommendations of the Advisory Committee on Immunization Practices—United States, 2024. *MMWR. Morbidity and Mortality Weekly Report*, *73*.

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.

Saeed, N., Usman, M., & Khan, E. A. (2019). An overview of extensively drug-resistant Salmonella Typhi from a tertiary care hospital in Pakistan. *Cureus*, *11*(9).

Sajid, M., Fatima, A., Mehmood, T., Sirajvi, M. M. A., Manzoor, M., Zohaib, M., Iqbal, U. Z., & Khan, A. M. A. (2025). Prevalence of nematodes in wildlife and livestock animals and their control by medicinal plants: Prevalence of Nematodes and their control. *Letters In Animal Biology*, *5*(1), 30-41.

Salminen, S., Collado, M. C., Endo, A., Hill, C., Lebeer, S., Quigley, E. M. M., Sanders, M. E., Shamir, R., Swann, J. R., & Szajewska, H. (2021). The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nature Reviews Gastroenterology & Hepatology*, *18*(9), 649-667.

Sirima, S. B., Ouedraogo, A., Barry, N., Siribie, M., Tiono, A. B., Nébié, I., Konaté, A. T., Berges, G. D., Diarra, A., & Ouedraogo, M. (2021). Safety and immunogenicity of co-administration of meningococcal type A and measles–rubella vaccines with typhoid conjugate vaccine in children aged 15–23 months in Burkina Faso. *International Journal of Infectious Diseases*, *102*, 517-523.

Smith, C., Smith, E., Chiu, C., Hinton, J., Sepulveda, B. P., Gordon, M., Choy, R. K. M., Hill, P. W. S., Meiring, J. E., & Darton, T. C. (2023). The challenge non-typhoidal salmonella (CHANTS) consortium: development of a non-typhoidal salmonella controlled human infection model: report from a consultation group workshop, 05 July 2022, London, UK. *Wellcome Open Research*, *8*.

Stanaway, J. D., Reiner, R. C., Blacker, B. F., Goldberg, E. M., Khalil, I. A., Troeger, C. E., Andrews, J. R., Bhutta, Z. A., Crump, J. A., & Im, J. (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.

Teklemariam, A. D., Al-Hindi, R. R., Albiheyri, R. S., Alharbi, M. G., Alghamdi, M. A., Filimban, A. A. R., Al Mutiri, A. S., Al-Alyani, A. M., Alseghayer, M. S., & Almaneea, A. M. (2023). Human salmonellosis: a continuous global threat in the farm-to-fork food safety continuum. *Foods*, *12*(9), 1756.

Tharwani, Z. H., Kumar, P., Salman, Y., Islam, Z., Ahmad, S., & Essar, M. Y. (2022). Typhoid in Pakistan: Challenges, efforts, and recommendations. *Infection and Drug Resistance*, 2523-2527.

ul Huda, N., Sohail, M., Mirani, Z. A., & Khan, S. (2024). Source tracking of extensively drug resistant Salmonella Typhi in food and raw vegetables using molecular approaches. *The Journal of Infection in Developing Countries*, *18*(02), 227-234.

Vanderslott, S., Kumar, S., Adu-Sarkodie, Y., Qadri, F., & Zellweger, R. M. (2023, 2023). Typhoid control in an era of antimicrobial resistance: challenges and opportunities.

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

Walker, J., Chaguza, C., Grubaugh, N. D., Carey, M., Baker, S., Khan, K., Bogoch, I. I., & Pitzer, V. E. (2023). Assessing the global risk of typhoid outbreaks caused by extensively drug resistant Salmonella Typhi. *Nature Communications*, *14*(1), 6502.

Wang, Y., Lu, D., Jin, Y., Wang, H., Lyu, B., Zhang, X., Huang, Y., Shu, G., Liu, B., & Lin, C. (2022). Extensively drug-resistant (XDR) Salmonella typhi outbreak by waterborne infection—Beijing Municipality, China, January–February 2022. *China CDC Weekly*, *4*(12), 254.

War, J. M., Nisa, A. U., Wani, A. H., & Bhat, M. Y. (2022). Microbial food-borne diseases due to Climate Change. In *Climate Change and Microbes* (pp. 187-234). Apple Academic Press.

WHO. (2019). Typhoid vaccines: WHO position paper, March 2018–Recommendations. *Vaccine*, *37*(2), 214-216.

Yesigat, T., Jemal, M., & Birhan, W. (2020). Prevalence and associated risk factors of Salmonella, Shigella, and intestinal parasites among food handlers in Motta town, North West Ethiopia. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *2020*(1), 6425946.

Zakir, M., Khan, M., Umar, M. I., Murtaza, G., Ashraf, M., & Shamim, S. (2021). Emerging trends of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella Typhi in a tertiary care Hospital of Lahore, Pakistan. *Microorganisms*, *9*(12), 2484.