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Review Article

Public Health Implications of XDR Typhoid Spread in Pakistan and Roadmap for Resistance Mitigation

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Abstract

Due to the advent of XDR *Salmonella* Typhi, antibiotic resistance in typhoid fever presents a serious public health concern, leading to treatment failure and extended illness. Of all the serotypes of *Salmonella enterica,* serovar Typhi is the most prevalent serotypes and is capable of developing resistance. A worrying trend is the appearance of extensively drug resistant (XDR) *S.* Typhi in many parts of the world, especially Pakistan. However, a thorough understanding of the epidemics and the creation of immediate responses are hampered by the lack of data. 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, treating XDR *Salmonella* Typhi infections is difficult. However, strict preventative measures can be put in place until the discovery of novel and alternative treatment options. Quick surveillance of pathogenic micro-organisms and an emphasis on antimicrobial stewardship are necessary to monitor potential spread of the 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

XDR, MDR, AMP, CHL, CRO

1. Introduction

Salmonella enterica serovar Typhi is a Gram-negative bacterial gut pathogen that is limited to humans and causes severe bloodstream infections leading even to sepsis, which are all referred to as enteric fever [1]. Enteric fever is particularly common in low and middle income countries (LMICs), and is spread by tainted food or water [1, 2]. In South Asia, Southeast Asia, and sub-Saharan Africa, it is a leading cause of feverish illnesses. According to global data, there were 135 000 associated deaths and 14.3 million cases of enteric fever worldwide [3].

In spite of the continuous efforts to control, *S.* Typhi, the causative agent of typhoid fever, remains a hazard to public health. Since multidrug resistance (MDR) of *Salmonella* Typhi to the three first-line therapies ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol and XDR *Salmonella* Typhi (first line drugs, fluoroquinolones and third generation cephalosporins) has emerged, the continuous battle against *Salmonella* Typhi has grown more complicated

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[4]. With reports of resistance to ampicillin, trimethoprim sulfamethoxazole, chloramphenicol, fluoroquinolones and third generation cephalosporins, the advent of XDR *Salmonella* Typhi has more worrisome and left only few alternatives for treatment. In recent years, there has been a noticeable increase in XDR *Salmonella* Typhi outbreaks worldwide, particularly in places like Pakistan, where these strains have led to protracted infections and unsuccessful treatments [5-7]. The first XDR *S.* Typhi resistant strain was observed in Pakistan in November, 2016 in Hyderabad, Karachi [8]. Nearly 21 million individuals worldwide are afflicted by this disease each year, with South Asians making up the bulk. The World Health Organization (WHO) estimates that between 11 and 21 million cases of typhoid fever and 200,000 fatalities have been reported worldwide [9]. Typhoid is endemic in 16 Asian countries, with residents of the Punjab and Sindh provinces most at risk of getting it [10, 11]. A study published in 2018 estimated that, out of all the South East Asian nations, Pakistanis had the highest risk of *S.* Typhi infection. Nearly 493 instances were reported for every 100,000 people [12]. Sindh, a province in Pakistan's Southeast, reported the first widespread outbreak in 2016 [13]. The prevalence of XDR typhoid has risen from 7/100,000 to 15/100,000 in certain areas of Pakistan where certain circumstances are present [11, 14]. According to Pakistani health authorities, there were around 22,354 cases of typhoid fever reported between 2016 and 2020, with 15,717 of those cases being extensive drug-resistant typhoid fever from various Sindh locations [9]. There have been 2,883 cases reported in Pakistan since September 2020, and all of them were isolates with high levels of resistance. By 2019, almost 10,365 cases of XDR *S.* Typhi were reported, according to a WHO estimate [15, 16]. The XDR strain of typhoid fever is extremely resistant to the antibiotic, a condition known as extensive drug resistance. The illness rate, as determined by these estimates, is approximately 15.5/1,000 [91].

A comprehensive analysis of prevalence of XDR *S.* Typhi infections in different continents of the world is given in Figure 1.

	Prevalence of resistance, 1990	Number of drug resistant infections, 1990	Prevalence of resistance, 2019	Number of drug resistant infections, 2019
MDR S Typhi				
North Africa and Middle East	19·4 (14·4–25·1)	68 016 (40 140–109 703)	19·5 (14·5–25·1)	36 817 (21 892–59 214)
South Asia	55·4 (49·3–61·0)	7 817 806 (4 861 263–12 593 675)	21·9 (19·5–24·9)	1 522 393 (935 142–2 321 547)
Southeast Asia, east Asia, and Oceania	19 (16·1–22·4)	485 102 (312 259–728 403)	4·7 (3·2–6·7)	56 866 (31 990–95 564)
Sub-Saharan Africa	6·0 (4·3–8·0)	100 903 (57 291–169 368)	72·7 (67·7–77·3)	922 302 (583 673–1 379 446)
Total (endemic area)	45·2 (40·4–49·6]	8 471 828 (5 289 599–13 542 673]	26·4 (24·4–28·8)	2 538 377 (1 574 044–3 822 395)
FQNS S Typhi				
North Africa and Middle East	1·1 (0·3–2·6)	3923 (1049–10 096)	35·0 (22·0–48·6)	65 954 (35 678–108 716)
South Asia	0·9 (0·3–2·0)	130 215 (41 712–315 435)	95·2 (91·4–97·7)	6 621 091 (4 162 818–10 210 827)
Southeast Asia, east Asia, and Oceania	1·9 (0·7–3·8)	49 421 (17 211–108 206)	36·4 (28·7–44·8)	434 937 (278 341–661 753)
Sub-Saharan Africa	1·3 (0·4–2·8)	21 762 (6495–52 313)	19·7 (10·9–30·6)	249 612 (116 502–437 343)
Total (endemic area)	1·1 (0·5–2·2)	205 322 (71 483–452 201)	76·6 (71·9–80·8)	7 371 594 (4 696 598–11 304 962)
Third-generation cephalosporin-resistant S Typhi				
North Africa and Middle East	0·7 (0·3–1·4)	2383 (881–5 341)	1·6 (0·8–3·1)	3078 (1249–6537)
South Asia	2·0 (1·3–3·0)	284 292 (146 848–535 314)	17·9 (15·7–20·7)	1 247 042 (782 227–1 918 397)
Southeast Asia, east Asia, and Oceania	0·7 (0·3–1·4)	16 714 (6 247–40 367)	1·5 (0·7–3)	17 970 (7 348–40 443)
Sub-Saharan Africa	1·6 (0·7–3·1)	26 762 (10 562–62 792)	3·6 (1·9–6·2)	45 378 (21 060–95 222)
Total (endemic area)	1·8 (1·1–2·6)	330 150 (173 586–604 776)	13·7 (11·9–15·7)	1 313 468 (820 108–2 048 670)

Figure 1. *A Comprehensive view of prevalence of XDR S. Typhi in different Continents of the world [8].*

Salmonella infections are a direct risk, especially on farms, as the disease can spread from the excrement of infected animals or humans to healthy ones [17]. *Salmonella* Typhi infections has been connected to the contamination of a number of food sources, including fruits, vegetables, poultry, fresh produce, and ready-to-eat items, according to investigations into these outbreaks [18, 19]. Furthermore, consuming tainted food items might result in indirect infections, increasing the likelihood of *Salmonella* transmission [20]. A synopsis of *Salmonella* infections in humans and animals is presented in Figure 2.

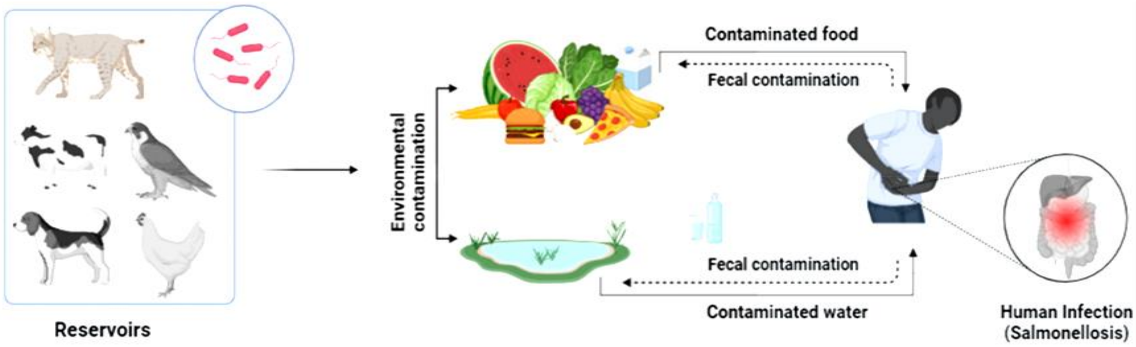

Figure 2. *A synopsis of Salmonella infections in humans and animals [21].*

Symptoms include vomiting, fever, cramping in the abdomen, and diarrhea; severe instances can result in complications or even death, particularly in susceptible populations. Safe handling of animals and their surroundings, good hygiene, and careful cooking are all essential preventive steps for reducing the risk of *Salmonella* transmission [18, 19].

Salmonella pathogenicity is linked to a number of virulence factors. Included in the *Salmonella* pathogenicity islands (SPI) are virulence features such as flagella, capsules, plasmids, adhesion systems such as adhesins, invasins, fimbriae, hemagglutinins, exotoxins, endotoxins, biofilm development, and type 3 secretion systems (T3SS) [22, 23]. Through horizontal gene transfer, the bacteria also picks up virulence genes found on the SPI [24-26]. Together with other virulence determinants, these genes (invA, spvC, sopE, and sseL) generate proteins that help bacteria elude the host's immune system, colonize and persist in host tissues, and induce tissue damage and inflammation [27-29].

Because *Salmonella* Typhi is so adaptable, it can acquire resistance genes and is frequently linked to foodborne illnesses, which contributes to its widespread existence. 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 [13, 30-32]. It contains the *Inc*Y plasmid, which confers ceftriaxone and fluoroquinolone resistance via the bla$_{CTX\text{-}M\text{-}15}$ gene [33]. It was discovered that the *H58 S*. Typhi clonal population carried a plasmid that may have been obtained from *E. coli* and carried a gene for both *qnr* fluoroquinolone resistance and extended-spectrum β-lactamase (ESBL). But it is susceptible to carbapenems and macrolides [13, 34].

According to multiple research, XDR *Salmonella* has been isolated from animals, their feces, and the caregivers. A study conducted by Abd El-Aziz, Tartor [20], 82.8% of poultry farms had XDR *Salmonella* (24/29), of which 41.38% were caused by XDR *Salmonella Typhimurium*, which was found in 33.3% of fowl and 66.67% of poultry workers.

According to another study by Joaquim, Herrera [35], the greatest XDR index is found in *S. Typhimurium* and swine *Salmonella*.

Due to the spread of XDR *Salmonella* in both humans and animals, the introduction of this strain emphasizes the urgent need to stop more resistance and the creation of *Salmonella* infections that are challenging to treat with current medications. There is a lot of information on *Salmonella's* resistance to different antibiotics, but not much on XDR *Salmonella*.

It is essential to comprehend the different aspects of *S. Typhi* transmission, from direct exposure on farms to indirect dispersion across the food supply chain, in order to put effective control measures in place and protect public health.

2. Global Distribution of XDR Salmonella in Human Population

As per World Health Organization (WHO) reports, *Salmonella* is one of the main causes of diarrheal illness [36]. Every year, more than 2 billion people are impacted [37]. Around 22 million cases of typhoidal Salmonella resulted in 210,000 deaths and 5.4 million cases of paratyphoid fever worldwide [38-40].

Additionally, recent estimates indicated that each year, roughly 6 million cases and 54,000 fatalities are attributed to paratyphoid, whereas approximately 11-21 million cases and 128,000-161,000 deaths are attributed to typhoid fever worldwide [41, 42]. Typhoid fever is claimed to affect 17.8 million people annually in low and middle income nations. MDR and XDR *S.* Typhi are the are prevalent in these regions due to lack of antibiotic stewardship programmes. The first outbreak of XDR typhoid fever was held in Pakistan in 2016 in Hyderabad, Sindh. According to reports, the strain known as S. Typhi 4.3.1 (*H58*) clade possesses a *bla*$_{CTX\text{-}M\text{-}15}$ ESBL gene that confers resistance to ceftriaxone and is resistant to trimethoprim-sulfamethoxazole, ampicillin, fluoroquinolones, and third-generation cephalosporins [13, 34]. But they were susceptible to meropenem, imipenem, and azithromycin roughly 27% and 69% of XDR *S.* Typhi were found in Hyderabad and Karachi, respectively [43]. Between January 2017 and June 2021, 14,360 cases of XDR-Typhoid Fever (XDR-TF) were reported in Karachi, 5,741 confirmed cases were reported in Sindh province between November 2016 and June 2021, and 69.5% of cases were recorded in Hyderabad, according to weekly field epidemiological reports published by the NIH Isl since 2016 [44]. As advised by the WHO, Pakistan was the first nation to incorporate a typhoid conjugated vaccine into its regular immunization schedule in 2019 [33]. The CDC received reports of XDR S. Typhi cases in the US in 2018 that were connected to travel to Pakistan [45].

Additionally, Canada documented its first case involving a 3-year-old and travel to Pakistan in 2018 [46]. The first XDR *S.* Typhi case was reported in 2019 by Australia, Spain, and Denmark; all of the cases included travel to Pakistan [47-49]. An unvaccinated 4 year old child with XDR-TF was reported to have had the disease in the United Arab Emirates in 2019. The girl was vaccinated and showed full recovery after receiving intravenous meropenem and oral azithromycin [50]. 71 cases of XDR *S.* Typhi infections in the US were reported to the CDC in 2021. Of the 67 patients, 87% had visited Pakistan, according to the records published by CDC [51].

3. Impact of XDR *S.* Typhi on Public Health

Other than causing increased morbidity and mortalities due to low efficacy and availability of limited treatment options, it has long lasting consequences on human health especially those with weekend immune system [52]. It may disseminate to blood stream, bones, joints, brain and sometime to other other organs when become invasive and can cause potentially life threatening infections [53, 54]. 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 [7].

People who have XDR *S.* Typhi infections are more likely to develop sepsis or other secondary infections such urinary tract infections. These side effects can be serious and necessitate further medical care, increasing the initial Salmonella infection's health impact [55]. 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 [56]. 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 [33]. According to reports, this pathogen has an impact on diagnosis, treatment, and cost. There have been reports of both a concerning rate of azithromycin resistance and clinical treatment failures. Using whole genome sequencing to determine the genetic basis of the resistance has become difficult as a result. Consequently, this has caused a delay in the creation of new antibiotics for medical use [16, 57]. Zakir, Khan [58] reported notable resistance among *S.* Typhi isolates. He reported half of the blood culture positive isolates in one of the tertiary care hospital in Lahore.

Fatima, Saleem [59] 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 [60]. It may also contribute to environmental contamination and the ensuing risks to human health.

Furthermore, the transmission of XDR *S.* Typhi from Pakistan to nearby nations via air travel emphasizes how urgently international cooperation is needed to stop the spread of this infection. In response to the growing threat, public health organizations around the world have started surveillance and mitigation measures, such as issuing traveler advisories stressing the value of vaccination prior to departure in order to guard against this extremely resistant strain. Additionally, a study of air travel trends has been used to determine which nations are most likely to see outbreaks of XDR *S.* Typhi. This is accomplished by looking at air travel ties to Pakistan, evaluating these nations' capacity to maintain local pathogen transmission, and determining how well public health officials can target preventive efforts [6].

Despite the urgent need, a crucial gap still exists since there is a lack of comprehensive data, which makes it difficult to comprehend the dynamics of XDR *S.* Typhi outbreaks and to develop practical, real time remedies. This chapter offers a current analysis of the ongoing outbreaks of XDR *S.* Typhi and trends to combat XDR resistance.

4. Challenges

Significant obstacles exist in the diagnosis, treatment, and prevention of XDR *S.* Typhi infections, which pose a serious risk to global human health. Numerous factors can confound the diagnosis of infections. Conventional culture based *Salmonella* testing techniques can be laborious, postpone starting treatment, and sometimes make the infection worse [61]. Furthermore, certain testing facilities and knowledge are needed to identify the antibiotic resistance profile of XDR *S.* Typhi strains, and these resources could only be easily accessible in certain healthcare environments [62]. Additionally, it can be difficult to differentiate XDR *S.* Typhi from other pathogens exhibiting comparable symptoms because of their overlapping clinical presentations, which could result in incorrect diagnosis and therapy [61]. The symptoms of EF and salmonellosis, for example, are similar to those of several other conditions [63]. When antimalarial medication fails to alleviate the illness or when malaria cannot be verified, enteric fever and salmonellosis are considered.

It typically leads to typhoid fever and malaria co-infection. The limited treatment options for XDR *Salmonella* infections have made treating them a therapeutic challenge for medical professionals worldwide, making the therapeutic approach more difficult and requiring the use of antibiotics as a last resort, which may have negative side effects and be less effective [64]. Since azithromycin is the only oral medication available among the three regularly used treatments for XDR typhoid fever, it is the last choice for treating XDR *S.* Typhi patients in an outpatient setting. Nevertheless, new research indicates that the XDR typhoid is becoming increasingly resistant to azithromycin, which further reduces the range of available treatments [65].

Furthermore, even with relatively few treatment choices, the majority of sick patients in endemic areas self-medicate with over the counter medications, making the management of XDR typhoid difficult. Antibiotic resistance cases are more prevalent in these locations because of a lack of affordable, high-quality healthcare facilities and medical personnel, as well as a lack of affordable services [65, 66].

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 [67].

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. Given the likelihood of the disease spreading quickly on a worldwide scale, WHO has designated the pathogen as a target for the development of novel drugs [33, 68].

5. 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 tactics:

5.1. 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 [69]. Foodborne outbreaks are complicated, and there are many possible sources of contamination, making this task difficult [6]. Reducing the number of people without access to clean drinking water is a consistent goal of Millennium Development Goal 7 [70]. 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 of practicing good hygiene [33, 71].

5.2. Prebiotics, Probiotics, Synbiotics and Post-biotics

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 micro-organisms as food substrate. Prebiotics causes the formation of biofilm on the epithelium of the intestine thereby preventing the pathogen from causing adhesion (120). 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 [72]. 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 [73].

Another recently developed idea is "postbiotics." Non-viable bacteria, their cell fragments, and health-promoting metabolites are the ingredients of postbiotic treatments [74]. 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 [75].

5.3. Reduced Use of Antibiotics Food Animals

Antibiotic resistance in humans and animals is not the sole effect of the inappropriate use of antibiotics in food animals. Many slaughterhouses in LMIC nations lack a drug monitoring system, which enables farmers to kill food animals on medications without adhering to the manufacturer's recommended withdrawal period. Due to this action, people have been exposed to antibiotics while they are not ill, which has raised the prevalence of antibiotic resistance globally.

According to Dutil, Irwin [76], there is a direct link between the rise in human cases in Canada and chicken samples tainted with *Salmonella* Heidelberg, which is resistant to ceftriaxone. To lessen the rise in XDR *Salmonella* cases, governments and providers of animal healthcare services should use fewer antibiotics on food animals. The use of antibiotics to treat human Salmonella infections ought to be prohibited in the practice of food animal medicine. This will help reduce the spread of resistant *Salmonella* to human populations.

5.4. Bacteriophages

These are the viruses which 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. [77]. 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, SalmoFresh, SalmonFREER and other phages are examples of those used in the food business to combat *Salmonella* [78].

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 [79].

5.5. 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 [80]. 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 are 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 [81].

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; improve sanitation and infection prevention measures; and take part in antimicrobial stewardship programs to ensure that antibiotics are used responsibly in both humans and animals [82].

5.6. 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 [83]. These vaccines provide sufficient protection against typhoid fever and have decreased the prevalence of XDR *Salmonella* in both endemic and epidemic areas.

Because the 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 [84]. Everyone traveling to areas of the world where typhoid is endemic should get vaccinated against the disease, according to the most recent CDC recommendations [33, 83, 85]. The CDC advises individuals visiting endemic regions to get either the Ty21a or ViPS vaccines [86]. Because vaccine efficacy varies, further precautions including better cleanliness and food safety procedures may be required [87].

In addition, current research and development initiatives to create vaccines against typhoid fever infections [88, 89] have the potential to slow the spread of these diseases and lower the morbidity and fatality rates that go along with them. Simultaneously, the veterinary or animal health industry uses a variety of vaccines to prevent salmonellosis in animals, especially livestock and poultry [90]. These vaccines prevent human exposure to *Salmonella* through tainted food products, protecting animal health and promoting food safety.

In order to improve public health and lessen the prevalence of these infectious diseases worldwide, immunization against typhoid fever infections is essential.

6. Further Recommendations and Conclusions

Given the emergence of extensively drug-resistant (XDR) strains of *Salmonella*, vaccination is a crucial weapon in the fight against infections. Humans may be able to stop the spread of antibiotic resistance if targeted vaccines are developed against common XDR *Salmonella* serotypes like *Typhimurium* and *Enteritidis*, as well as multivalent alternatives.

The disease burden can be considerably reduced by giving vaccination programs priority to high-risk groups like healthcare workers and food handlers. Vaccines provide promising means of preventing antibiotic resistance and granting herd immunity, protecting unvaccinated members of a human and animal population as a sizable percentage of the population receives vaccinations. Antimicrobial drug abuse is decreased as a result of their ability to target particular infections and guarantee treatment specificity [91-94].

The One Health approach provides a comprehensive framework for tackling the issues raised by XDR *Salmonella* because it acknowledges the interdependence of environmental, animal, and human health. It will be crucial to adopt this strategy in upcoming studies and legislative efforts in order to lessen the effects of these illnesses. To stop the spread of XDR *Salmonella* across the food chain, extensive immunization programs for pigs, poultry, and animals are therefore necessary. It is equally crucial to expand these initiatives to include wildlife and companion animals like dogs and cats that may act as reservoirs for human infection.

Additionally, introducing sustainable farming methods, such probiotics and organic farming, can lessen *Salmonella* contamination in food production systems. Powerful tools for efficient disease control and prevention are provided by technological developments, such as genetic surveillance and artificial intelligence for outbreak prediction.

International cooperation and support for strong policy frameworks that emphasize shared accountability for health protection are essential to our joint effort to ensure that human and animal populations have a healthier, more resilient future.

Furthermore, since it is a necessity for disease prevention, putting water, sanitation, and hygiene (WASH) into practice should have top priority. In addition, a more effective and reasonably priced healthcare system and education should be offered in endemic and epidemic regions to lessen the severity of Salmonella infections.

In conclusion, XDR *Salmonella* species represent a serious and constantly changing risk to the health of people and animals around the world. The significance of immunization programs, the One Health philosophy, environmentally friendly agricultural methods, and technology developments in the fight against these illnesses has been underlined in this revised overview. For a healthier, more resilient future, interdisciplinary research partnerships, public awareness initiatives, and strong policy frameworks are crucial. Our common duty to protect the health of both human and animal populations is highlighted by the need for a coordinated, international effort to address the problems posed by XDR *Salmonella.*

Abbreviations

XDR	Extensively Drug Resistant
WASH	Water, Sanitation, and Hygiene
CDC	Centre for Disease Control and Prevention
WHO	World Health Organization
MDR	Multi Drug Resistant
CRO	Ceftriaxone
T3SS	Type 3 Secretion System
SPI	Salmonella Pathogenecity Island
LMICs	Low and Middle Income Countries
ESBLs	Extended Spectrum Beta Lactamases
CHL	Chloramphenicol
AMP	Ampicillin
TCV	Typhoid Conjugate Vaccine

Conflicts of Interest

The authors declare no conflicts of interest.

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