



## REVIEW

### INTRODUCTION OF TYPHOID EXTENSIVELY DRUG-RESISTANT (XDR)

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#### ABSTRACT

*Salmonella typhi* is a major infection problem in Pakistan. This disease affects middle-income countries but antimicrobial resistance and international travel. Decades of indiscriminate antibiotic use have led to the evolution of multidrug-resistant strains (MDR) and more ultimately, extensively drug-resistant (XDR). The outbreak of XDR typhoid fever cases from 2016 to 2018 in the province of Sindh, WHO records that there are 5274 cases of XDR typhoid out of a total 8,188 cases of typhoid fever reported in Pakistan. Since 12 September 2020, XDR typhoid 2883 cases reported in Pakistan. MDR strains are antibiotic first-generation antibiotic drugs such as chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole and second-generation drugs, such as fluoroquinolones, part of Asia and Africa. In Pakistan, all recommended antibiotics for typhoid fever are extensive drug-resistant (XDR) *S. Typhi* strain, include the first-generation, second-generation drugs, and third generation cephalosporins, Meropenem or Azithromycin, and tigecycline. This review paper tries to increase the issue of XDR typhoid concerning its epidemiology, prevention, management, and Vision of future and stresses a better understanding of antimicrobial stewardship and general surveillance of the disease.

## 1. INTRODUCTION

Decades of indiscriminate antibiotic use have led to the evolution of multidrug-resistant strains and more ultimately, extensively drug-resistant (XDR) (Extensively Drug-Resistant (XDR) Typhoid: Evolution, Prevention, and Its Management, (Arsalan *et al.*)<sup>[1]</sup>. Salmonellosis is a bacterium that cause the disorder in both humans and animals (Ashley *et al.*)<sup>[2]</sup>.

*Salmonella* does not retain the crystal violet stain used in the staining method i.e. they are considered as Gram-negative, rod-shaped bacteria, and they have a property to grow in both presence and absence of oxygen that's why they are considered as facultative anaerobes that belong to the family Enterobacteriaceae.

*Salmonella enteric* and *Salmonella bongori* are two genus species of *Salmonella* (Isolation and molecular characterization of *Salmonella enterica* serovar Enteritidis from poultry house and clinical samples. (Brenner and Swaminathan)<sup>[3]</sup>.

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The monophyletic structure of *Salmonella typhi* suggests that create the new disease and conception have evolved 50,000 years ago. The first type of

typhoid fever was in the 1800s, the causative pathogen discovery of the *Salmonella typhi*, was created in 1880 by Karl Eberth. Some years later, Marwat smith developed a vaccine for the disease. (Barnett, 2016). Millions of lives universal in the past discovery of antibiotics against typhoid fever. The evolution of multidrug-resistant and extensively drug-resistant strains of typhoid fever. Unfortunately, decades of antibiotic usage. (Extensively Drug-Resistant (XDR) Typhoid: Evolution, Prevention, and Its Management, 2020. MDR described resistance to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, and third-generation fluoroquinolones, as well as third-generation Cephalosporins, Meropenem or Azithromycin and Tigecycline. (Qamar) [4].

## 2. EPIDEMIOLOGY

Pakistani health authorities began reporting cases of extensively drug-resistant (XDR) typhoid fever, originating in Hyderabad, Sindh in November 2016 according to WHO records (Yousafzai) [5]. A total report records of 5274 cases of XDR typhoid fever, out of a total of 8188 cases of typhoid fever in November 2016 up to December 2018. All cases of XDR the capital city of Sindh and Karachi accounted for 69%. These cases in Hyderabad district recorded 27% while the remaining cases 4% were distributed amongst other provincial districts of Sindh (Field Epidemiology & Disease Surveillance Division (Geneva) [6]. These cases were distributed from 1 November 2016, to 09 December 2018 is shown in Figure 1. Pakistan reported a total of 22,571 typhoid cases from the province of Sindh in Pakistan, from 1 November 2016 to 16 February 2020.

The international transmission of XDR strains of *Salmonella typhi* associated with travelers to Pakistan reports from January to October 2018, of the six total cases, one was reported in the United Kingdom of Great Britain and Northern Ireland was one case reported and remaining five were reported in the United States of America. Residents of Sindh (Karachi), Punjab (Lahore), or Islamabad reported four of six cases. In Canada successfully treated the case of XDR typhoid fever. (Geneva) [6].

## 3. ETIOLOGY

Serologically positive is the bacterium for lipopolysaccharide antigens O9 and O12 as well as the polysaccharide capsular antigen VI. Those strains that are VI positive compared to VI-negative strains antigen appear to be less infectious and less virulent. (Andrews) [7, 8].

## STUDY SETTING AND POPULATION

The second-largest city is Hyderabad of Sindh Province in Pakistan. 2.2 million Population in this area Qasimabad, Latifabad, Hyderabad urban and Hyderabad rural divided into four administrative units was Hyderabad city. Spread to the rest of the country and November 2016 outbreak of XDR typhoid in two areas Qasimabad and Latifabad. (Sonia) [9].

Aga Khan University in Karachi (AKUH) and Aga Khan Maternal and Child Centre (AKMCC) in Hyderabad oversee the XDR Typhoid cases in two hospitals. AKUH is a 740-bed private teaching care hospital. It located in the metropolitan city of Karachi. AKMCC is a Private secondary care hospital develop only for mothers and children. It located in the city of Hyderabad. Many patients identified the XDR Typhi and registry of both hospitals. According to Hospital records of typhoid patients treated as either inpatient 1<sup>st</sup> April 2017 to 30<sup>th</sup> June 2018.

The five classes of antibiotics (ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, fluoroquinolone, and 3rd generation cephalosporin (ceftriaxone or cefixime) were eligible to be included in this study the Typhoid patients with blood culture confirmation for *S. Typhi* and resistance.

The eligibility criteria were included in this study a total of 142 records with the diagnosis of typhoid were screened and only 81 records which fulfilled. (Sonia) [9].

## 4. PREVENTION

*Salmonella typhi* infections are small size only present in human hosts and passed on through water supplies and bad hygiene practices, such as fecal contamination. (Ajibola) [10]. If certain practical prevention measures maybe considered the pathogen possession of a host and resulting infection maybe prevent.

### 4.1 Immunization

The destruction of contamination from water supplies, immunization against typhoid provides the best route of protection from typhoid the processes of rapid urbanization in developing countries.

The process usage of such a vaccine in counties where typhoid is endemic and exhibits antimicrobial resistance the WHO has not only prequalified a tetanus-toxoid conjugated VI polysaccharide typhoid vaccine developed in India (Typbar TVC). (World Health Organization, "Typhoid vaccines: WHO

position paper, March 2018 - Recommendations,” (WHO) <sup>[11]</sup>. Gavi, has committed \$85 million towards the production of conjugate vaccines in poverty-stricken countries the vaccine alliance (WHO) <sup>[12]</sup> Vi-polysaccharide typhoid vaccine since 2017, Hyderabad has received the WHO approximated 250,000 children. (Rasheed) <sup>[13]</sup>.

#### **4.2. Hygiene and Water Supply**

Before the 20<sup>th</sup> century the case with North America and Europe, the distribution of treated water was employed, and typhoid remained an epidemic concern until measures ensuring adequate sanitation. The government authority’s developing countries should be public about good hygiene practices of the education. The elimination of human waste from water supplies as well as the infrastructural operations.

### **5. FOOD SAFETY**

Food safe is generally cooked because high temperatures lowering the survivability of microbes. The risk of becoming contaminated again that if the same food is allowed to sit food extended periods of at room temperature it should be warned. Any microorganisms present would need for their survival, Dry food packages in factories with good hygiene practices, may also be regarded as safe for consumption. The risk of contamination is high street food should be avoided the raw foods, including meats, fruits, and, vegetables. These may have come to be products of a contaminated water supply as well as similarly tap water, fresh juices, fountain drinks, and ice from unknown sources in developing countries are best to avoid. (WHO) <sup>[11, 12, 14]</sup>.

### **6. HEALTH CARE MANAGEMENT**

The two things should be noted in typhoid cases from Pakistan during the course study. First things that the Pakistani strain of XDR typhoid exhibits susceptibility to azithromycin and carbapenems. Secondly, Pakistan have low susceptibility to or exhibit resistance against fluoroquinolones, including ciprofloxacin and 90% of *Salmonella typhi* isolated from Pakistan.

XDR typhoid present themselves serious infection before it becomes a global health concern and serious attention and decreasing the treatment options for typhoid fever (Hassing) <sup>[15]</sup>. Azithromycin sensitivity decreased designate reports, which clinicians are using as a utilized the treatment for XDR typhoid fever, along with tigecycline and carbapenems (Dyson) <sup>[16]</sup>.

Typhoid is most common, and their mainstream use is unfavorable given the resource-stricken environment because Carbapenems are expensive.

Typhoid against azithromycin highlights an additional need to develop orally administered antibiotics concurrently rising resistance and both tigecycline and carbapenems are administered parenterally. Typhoid patients are treated as outpatients total 90%. A limited number of oral antibiotic options would involve treating such cases as inpatients, at the chances of over burdening hospitals improving where nosocomial infections associated with drug-resistant pathogens are prevalent.

*Salmonella typhi* may not be too slow to acquire such resistance and evolution predicts additionally carbapenems resistance has already been witnessed in nontyphoidal *salmonella* serovars. The WHO identifies *Salmonellae* as a target for the development of novel antibiotics and Since the global-scale dissemination of such a resistant microorganism would be swift (Andrews) <sup>[7, 8]</sup>.

### **7. VISION OF THE FUTURE**

The capacity to invade and spread to regions beyond Pakistan, with the potential to replace native strains has a densely populated area in Asia, and health authorities across the globe should be warned that the XDR H58 haplotype of *Salmonella typhi* originating in Sindh (WHO) <sup>[14]</sup>. The first Canadian pediatric case of XDR typhoid, well demonstrate its ability to spread intercontinentally, XDR typhoid to the United States and the United Kingdom of international transmission associated with the 6 travel reports.

XDR typhoid presents a single step that leaves them with a pathogen that is practically untreatable in a developing country the prospective acquisition of resistance to azithromycin such as Pakistan provide the local health fact. Typhoid cases 15% of developing countries end in fatality (Levine and Simon) <sup>[17]</sup>.

Fortunately, no zoonotic reservoirs exist humans are the only long-term reservoir for *Salmonella typhi* and the bacterium only persists in the environment for as long as the carrier sheds it into the surroundings by fecal material which may last from months to years.

Environmental adaptations, such as spore-formation, are absent in the bacteria, and so, it possesses only a limited capacity to survive long-term Bacteria absent in spore-formation, such as environmental adaptations, it possesses a limited capacity to survive long-term.

Informal settlement areas lacking proper sanitation and adequate water infrastructure facilitate the transmission and international migration of XDR typhoid strain from Pakistan across the rest of the globe.

Thus, local government continues to be taking adequate sanitation measures and practical recommendations to stop this local outbreak. Wide spread immunization by the typebar TVC vaccine is also included. The provincial government has set aside 399 million Pakistani rupees for the rehabilitation of water supply system and for re-establishment of sewage system in Hyderabad 414 million Pakistani rupees set aside by government of Pakistan, according to news reporter.

Informal settlement areas lacking proper sanitation and adequate water infrastructure facilitate the transmission and international migration of XDR typhoid strain from Pakistan across the rest of the globe.

Salmonella enterica (S. enterica) is a Gram-negative facultative intra-cellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of S. enterica have been identified belonging to six subspecies Salmonella enterica (S. enterica) is a Gram-negative facultative intra-cellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of S. enterica have been identified belonging to six subspecies Salmonella enterica (S. enterica) is a Gram-negative facultative intra-cellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of S. enterica have been identified belonging to six subspecies Salmonella enterica (S. enterica) is a Gram-negative facultative intra-cellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of S. enterica have been identified belonging to six subspecies Salmonella enterica (S. enterica) is a Gram-negative facultative intra-cellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of S. enterica have been identified belonging to six subspecies Salmonella enterica (S. enterica) is a Gram-negative facultative intra-cellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of S. enterica have been identified belonging to six subspecies Salmonella enterica (S. enterica) is a Gram-negative facultative intra-cellular anaerobe of worldwide importance causing as many as 1.3 billion cases of disease annually. Over 2500 serovars of S. enterica have been identified belonging to six subspecies

have been identified belonging to six subspecies.1, 2 Subspecies are further Subdivided into serovars that are differentiated by their flagellar, carbohydrate and lipopolysaccharide (LPS) structures. S. enterica species are typically orally acquired pathogens that cause one of four major syndromes: enteric fever (typhoid), enterocolitis/diarrhea, bac-teremia and chronic asymptomatic carriage. The disease manifestation depends on both host susceptibility and the infectious S. enterica serovar *Salmonella enterica* serovar (Sertype) typhi (*Salmonella typhi*) exists as a gram-negative, rod-shaped, and flagellated bacterium.

## 8. CONFLICT OF INTEREST

All authors have declared that there is no conflict of interests regarding the publication of this article.

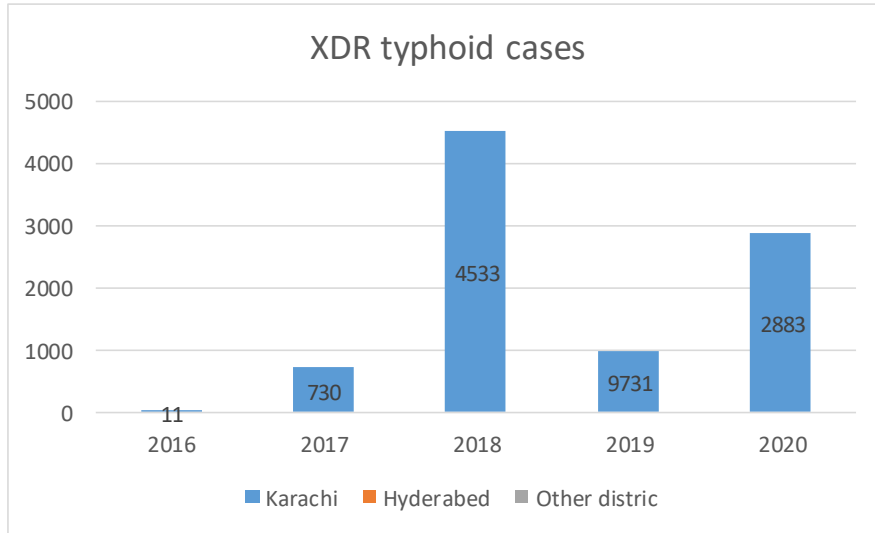
## REFERENCES

- [1] Arsalan , S.K., Hassan, A.K., Syed, A.G., Shehla , J.A. and Fridoon, J.A. (2020). Extensively Drug-Resistant (XDR) Typhoid: Evolution, Prevention, and Its Management. *Hindawi*.
- [2] Ashley, S., Sabool, A., Khan, M., Ali, N., Stefanova, R. and Khan, A. (2014). Isolation and molecular characterization of Salmonella enterica serovar Enteritidis from poultry house and clinical samples during 2010. *Food Microbiology*, 38, 67-74.
- [3] Brenner, F.W. and Swaminathan, B. (2000). Salmonella Nomenclature. *Journal of Clinical Microbiology*, 38, 3.
- [4] Qamar, M. T. (2020). Adverse events following immunization with typhoid conjugate vaccine in an outbreak setting in Hyderabad, Pakistan. *Vaccine*, 38.
- [5] Yousafzai MT. (2019). Clin Infect Dis. *Ceftriaxone-resistant Salmonella Typhi Outbreak in Hyderabad City of Sindh, Pakistan: High Time for the Introduction of Typhoid Conjugate Vaccine*.
- [6] Geneva, (2018). Typhoid fever - Islamic Republic of Pakistan. *World Health Organization*. Geneva. Retrieved from <https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/>

- [7] Andrews, F. N. (2018). “Extensively drug-resistant typhoid—are conjugate vaccines arriving just in time?”. *New England Journal of Medicine*, 16. <https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/>.
- [8] Andrews, F. N. (2018). Extensively drug-resistant typhoid—are conjugate vaccines arriving just in time? *New England Journal of Medicine*, 379, 1493–1495.
- [9] Sonia, Q. (2020). Response of extensively drug resistant Salmonella Typhi to treatment with meropenem and azithromycin, in Pakistan.
- [10] Ajibola, O. (2018). Typhoid fever diagnosis in endemic countries: a clog in the wheel of progress. *Medicin*, 2. Retrieved from <https://doi.org/10.3390/medicina54020023>
- [11] WHO (2018). Tphoid fever – Islamic Republic of Pakistan.
- [12] WHO (2018). *Islamic Republic of Pakistan*,. Retrieved from
- [13] Rasheed, S. S. (2019). Extensively drug-resistant typhoid fever in Pakistan,” *The Lancet Infectious Diseases*, 19, 242-243,.
- [14] WHO (2018). *Islamic Republic of Pakistan*. Retrieved from <https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/>.
- [15] Hasing, W. H. (2014). Salmonella subtypes with increased MICs for azithromycin in travelers returned to the Netherlands,”. *Emerging Infectious Diseases*, 20, 705–708.
- [16] Dyson, Z.A. (2019). “Antibiotic resistance and typhoid,”. *Clinical Infectious Diseases*, 68, S165–S170.
- [17] Levine, M. M. and Simon, R. (2018). The gathering storm: is untreatable typhoid fever on the way? *mBio*, 9, 2.

### Types of resistance and antibiotic Names

No.	Antibiotic generations	Antibiotic drugs Name
1	First-generation drugs (MDR)	Chloramphenicol, Ampicillin, and Trimethoprim-Sulfamethoxazole
2	Second-generation drugs (MDR)	Fluoroquinolones,
3	Third-generation drugs (XDR)	Cephalosporins, Meropenem or Azithromycin and Tigecycline



**Figure 1** XDR typhoid cases in Pakistan. (WHO, 2018, p. 12) (Shoaib Ahmad, 2021, p. 13)