

CORRECTIVE MEASURES OF THE PAKISTAN GOVERNMENT AGAINST AN INVINCIBLE XDR TYPHOID FEVER INFILTRATING THE SOUTHERN PAKISTAN

SUMAIRA KHADIM¹, SHAMA ABIDI², AQSA JAVED³,
FILZA KHAN³, HAFSA RAEES³, IQRA NASIR³,
JAVERIA SHAHID³ AND SHAZIA SYED¹

¹Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan

²Department of Pharmacy, Liaquat National Hospital, Karachi, Pakistan

³Faculty of Pharmacy, Jinnah University for Women, Karachi, Pakistan

ABSTRACT

Salmonella typhi a typhoid causing organism, has developed resistance to oral first line (Ampicillin and Flouroquinolones) and oral third line antibiotics (Chloramphenicol) due to enzymatic and genetic changes. As a result XDR Fever as an epidemic has taken the world by storm with its vivid target of engulfing the mortals and resist towards countless medical therapies. Here, a set of medical regime with precautions are being posed to let the steam out and control the disease. Diverse variety of journal with articles over the subject disease has been scrutinized to get a clear picture of the epidemic from year 2007 till 2020. Following credible databases have been probed: Pub med, ASM Journal, NEJM organization, Oxford Academy, Cidrap, ReAct, Sciencemeg, New England Journal of Medicine. On the basis of literature evaluation, up till now 17756 cases have been observed in Southern part of Pakistan regarding XDR typhoid among which 2000 cases are reported to be fatal. The frequently prescribed treatment against XDR are Azithromycin and/or Carbapenam, while many other drugs with increased immunity and better treatment are available which are unaffordable for Pakistan. To avoid antibiotic resistance, Pakistan should start Anti-microbial resistance program (AMR program) as well as Anti-microbial stewardship program (ASP).

Keywords: XDR typhoid fever, Pakistan, Antibiotic resistance, AMR program, AMS programs

INTRODUCTION

Salmonella typhi, a causative organism of typhoid, is a rod-shaped flagellated bacteria belonging to gram-negative class is a human restricted pathogen, having the ability to efficiently transmit and persist within the human population inside the human genome via contaminated water and food (Qamar *et al.*, 2018; Rasheed *et al.*, 2019; Dyson *et al.*, 2019; Khan, 2019). Its characteristic of a polysaccharide capsule saves it from the phagocytosis process (Lindberg, 1999). The antigens O9 and O12 were found in

lipopolysaccharide and capsule polysaccharide of *S. typhi* after serological tests (John and Ashurst, 2018). *S. typhi* affects only humans causing severe clinical symptoms and high-grade fever. The newer problem is the resistant strains of *S. typhi* to various antibiotics (Crump, 2019). Due to the mutation in *S. typhi* structure and developed resistance against antibiotics, this strain is posing itself as a massive annoyance (Qamar *et al.*, 2018; Rasheed *et al.*, 2019; Dyson *et al.*, 2019; Khan, 2019). Non-resistant typhoid fever is considered to be sensitive from first and second-line treatment but it could be resistant

*Corresponding author: e-mail: sumairakhadim01@gmail.com

to the fluoroquinolone class of antibiotics. Generally two new terminologies MDR and XDR were introduced. The former is used for strain resistant to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole while later one is used for those resistant against the above-mentioned antibiotics with the addition of fluoroquinolones and 3rd generation cephalosporin (FDSRU, 2020). This extreme resistant bacterium strain *Salmonella entericaserovar Typhi* has become a wide disaster for Pakistan especially for two big cities of Sindh province i.e. Karachi and Hyderabad due to irrational prescribing practice.

Universal epidemiology of typhoid infection

Typhoid fever is still a momentous health threat for third world country's people with up to 20 million cases and 0.1-0.2 million deaths each year (WHO, 2018; Antillon *et al.*, 2017; Mogasale, 2014; Radhakrishnan, 2018). Pakistan is also affected similarly to being a lower-middle-income country and the severity is more among children aging between 2-15 years (Qamar *et al.*, 2014; Qamar *et al.*, 2018). Considering the whole world, nearly seventeen million cases were found in 2015 much of them were from South and South-East Asia and Northern Africa. Many cases were untreated which resulted in a death toll of 0.18 million in 2015 (Radhakrishnan *et al.*, 2018). Around three hundred and fifty XDR cases are reported to CDC in the United States each year (Akram *et al.*, 2020).

Spread of XDR by international travelers

The whole world is being charged with pathogens that portray resistance against antibiotics. Due to threatening storm typhoid in Pakistan, the US center of disease control and prevention (CDC) has issued a health warning that travelers to Pakistan are at high risk of XDR typhoid, so they should be properly vaccinated before traveling to Pakistan (WHO, 2019). To boost the epidemic, six international cases have been documented with strains of *Salmonella enteric serovar*

Typhi strain, which traveled to Pakistan (WHO, 2019; FDSRU, 2020).

Epidemiology of typhoid infection in southern Pakistan

In Pakistan, the population of Sindh and Punjab were at higher risk taking into account all sixteen typhoid-struck countries (Rasheed *et al.*, 2019). PDSRU report in collaboration with WHO from a period between 2016 to 2018 shows emerging cases of XDR typhoid in 14 districts of Sindh out of which most cases (about three-fourth approx.) were from Karachi and Hyderabad (one-fourth approx.) and only 4% were from other districts (WHO, 2018; MNHS, 2018). The problem arises when most of these people travel abroad carrying the disease (Chatham- Stephens *et al.*, 2019). Table1 manifests the origination of strain from Hyderabad and with a succession of years, Karachi renders the highest number of cases in 2019.

Emergence of resistance against antibiotics by S. Typhi strain

Chloramphenicol was the first drug proven to be effective in Typhoid in 1948. Just after 2 years, *Salmonella typhi* acquired R factor Plasmid, its resistant strains become responsible for the resistance to chloramphenicol which became widespread in 1970 (Levine and Simon, 2018). In the same year, the MDR epidemic hit Mexico (Olarde and Galindo, 1973). Ampicillin efficacy was reported in 1964 and that of trimethoprim-sulfamethoxazole was reported in 1968. In 1973 MDR strains emerged which were resistant to multiple antibiotics, which become widespread in the early 80s. In 1985 Fluoroquinolone efficacy was reported which was also turned down by resistant strain in 1997 because of mutations in chromosomal *gyr* loci (Levine and Simon, 2018) and up to 2015, almost 90% of strains were resistant to this antibiotic. In 2014 Ceftriaxone become more effective than Fluoroquinolone. But within a short period i.e. in November 2016 an *S. typhi* strain resistant to Ceftriaxone was spread in Pakistan. This resistant strain H58 was reported against

chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole antibiotics due to a plasmid IncY. This plasmid is not only resistant to fluoroquinolones (via gene *qnrS*) but also to ceftriaxone (via gene CTX-M-15 *bla*) (Klemm *et al.*, 2018). This dangerous strain was transmitted through passengers going to Europe and America from Pakistan in 2018 and 2019. The efficacy of Azithromycin was reported in 1995 (Tribble *et al.*, 1995). Although there are some cases of resistance to Azithromycin discovered in 2018, still it is prescribed (Andrews *et al.*, 2018). Now only available drugs for XDR are Azithromycin, tigecycline and carbapenems (imipenem-cilastatin combination, meropenem, ertapenem) (Javed *et al.*, 2020). In these the cost of carbapenems and tigecycline is very high so could be used in industrialized countries but it will not be a better option as a first-line treatment in developing country economically (Levine and Simon, 2018). This is why still Azithromycin and Imipenem are prescribed in Pakistan.

Prevalence & precautions of XDR typhoid

A novel XDR typhoid i.e. extensively-drug resistant typhoid is named as untreatable typhoid fever by some scholars. It proves to be quite a nuisance, especially in third world countries where the recipe of negligence is very much prevalent and includes: Poor sanitation, insufficient water, hygienic issues, low vaccination coverage, inappropriate use of antibiotics, awareness deficiency, poor surveillance system and many other factors (WHO, 2019 and Dall, 2018). So this is an alarming situation for the people living in these areas. It is necessary to stop the chain of this XDR typhoid which can only be possible by taking strict precautions towards it.

Appropriate hygiene & sanitation

XDR typhoid is a life-threatening condition that has affected more than 21 million of the population. *Salmonella entericaserovar Typhi* is rapidly transmitted by contaminated water and unhygienic food which spreads in areas with poor sanitation. Pakistan Government realizes the need for an awareness campaign

related to XDR cases and started the purification & sanitation activities as well as created a National XDR Typhoid task force (Dall, 2018). Awareness campaigns on sanitation practices and safe hygiene including the use of safe and purified drinking water, health education on hand hygiene and environmental sanitation were carried out. Chlorine tablets were distributed among the population of such areas.

Provision of vaccination coverage

For the people traveling abroad from Pakistan, two types of vaccination are in practice. (Vivotif, an oral vaccine & Typhim Vi, an intramuscular vaccine). Both vaccines have an efficacy of up to 50-80%. For the local inhabitants of Pakistan, in 2017 Typhoid vaccination of Vi-polysaccharide was conducted in Hyderabad and recently another campaign of Typhoid Conjugate vaccine is launched. This vaccine can be given to children aged 6 months and has durable effects than other vaccines (WHO, 2019; Septimus, 2018; Zikria *et al.*, 2019).

Provoking surveillance system

Updated surveillance tools are provided to overcome the spread of XDR typhoid to other parts of Pakistan. XDR National Taskforce was launched in July 2018 and a joint WHO and US Centers for Disease Control and Prevention mission were established. Currently, these collaborations are transformed into a national action plan in Pakistan. Another campaign was started on 7th September 2018 whose purpose was to collect additional data and further enhance inspection about XDR typhoid (WHO, 2019; Septimus, 2018; Zikria *et al.*, 2019).

Implementation of antimicrobial stewardship programs

Antimicrobial stewardship programs are intended to ameliorate patients' health outcomes by reducing the unplanned implications of antimicrobial use.

The motives of antimicrobial stewardship programs include attenuating antimicrobial

Table 1: Total Registered XDR Typhoid Cases in Sindh, Pakistan during 2016-2020.

Period	Karachi District	Hyderabad District	Other Districts	Total Reg. Cases
2016(Jan - Dec)	Nil	12	Nil	12
2017(Jan - Dec)	175	485	04	664
2018(Jan - Dec)	3712	891	207	4810
2019 (Jan - Dec)	7088	1645	998	9731
2020 (Jan1-July 19)	1801	448	290	2539
Total	12776	3481	1499	17756

When we look at data from January 2017 to July 2020, it is surprising that only in Karachi city 12776 cases of XDR typhoid were recorded. More surprising is the fact that maximum cases (7799) were reported in the ages of zero to four years, then in five to nine years. It was also evident that more cases were reported in females as compared to males (FDSRU, 2020). Looking at the data of approximately similar periods of Sindh province without including Karachi city, it was found that only 4980 cases were reported among which 70% were of Hyderabad district. It manifests how the epidemic that initiated from Hyderabad, later got favored by the aura of Karachi and affected >7000 people in 2019 and >1800 in the early seven months of 2020.

resistance, preventing antimicrobial related toxicity and minimizing health care infections and cost of inappropriate antimicrobial use. Infectious Disease Society of America, Society for Healthcare Epidemiology of America, WHO and other organizations explain an evidence-based approach to antimicrobial stewardship in health systems (Parente, 2018; Raviglione, 2007). Antimicrobial programs have been introduced in Pakistan to ameliorate patients' health and subside the antimicrobial related toxicity.

Proposed diagnosis, treatment & deterrents of XDR typhoid:

It is recommended that serological tests like Widal test and Typhidot Tests are obsolete now and proper management requires advanced techniques like Gold Standard blood culture which is reliable and cost-effective (Ajibola *et al.*, 2018; Veeraraghavan *et al.*, 2018). Concerning the treatment, Quinolones should be avoided as 90% of cases are resistant to this drug in Pakistan (Khan, 2018). We can replace quinolones with 3rd generation cephalosporins and ceftriaxone intravenously to hospitalized patients. When the patients are discharged they may continue oral dosage forms of cefixime (high dose) instead of IV even in cases of multi-drug resistance typhoid.

In some susceptible cases, amoxicillin and trimethoprim-sulfamethoxazole were prescribed as reported in two different studies conducted about antibiotic prescription in Karachi and Sialkot (Laghari *et al.*, 2019; Sattar *et al.*, 2020). The recommended treatment period for XDR Typhoid fever is ten to fourteen days. As the XDR typhoid is increasing, the only choice of the drug becomes azithromycin as 1st line oral treatment for uncomplicated cases and for severe ones, carbapenem IV is the only option (Veeraraghavan, 2018; Ryan and Jason, 2019).

CONCLUSION

After viewing and going through various researches and reports, it can be concluded that XDR typhoid is controllable only if the residents tend to guard themselves against all the causative agents that pave the way for the strain to color the picture. As drug susceptibility testing is a luxury for developing countries and new medications will take several years to strike the market, the aforementioned measures must be taken into consideration to avoid contact with the disease. Moreover, the imperative to preserve the effectiveness of current drugs can only be made sure if no second-line drugs are used without proper supervision.

Future perspective

Typhoid is not given weightage like Big 3 diseases (AIDS, TB and Malaria) by funding agencies and global health officials, though it is an emerging problem. This may be because it has struck developing countries and not developed countries. More focus should be done on enhancing stewardship programs and reducing antibiotic usage as we have seen in some Asian countries where after taking correct measures, MDR strain was diminished. If proper funding and care won't be provided to XDR then there is a chance that the infection may spread in the developed world from Pakistan and other sufferers (Levine and Simon, 2018; Maurice, 2012; Bhutta and Threlfall, 2009). A good load of investment is direly needed for research and development concerning the disease for a handful of fine tools to combat and further maintenance of those tools to prolong their efficacy.

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