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COVID-19 and XDR Typhoid Co-epidemic in Pakistan

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A B S T R A C T

Typhoid fever is a major public health problem since November 2016 in developing countries, which also includes Pakistan. During the COVID-19 pandemic, a surge has been seen in the expression of extensively drug-resistant (XDR) typhoid due to poor sanitary disposal in hospitals and at other public places. The XDR strain of *Salmonella typhi* is still vulnerable to azithromycin, but its extensive use for the treatment might impede its effectiveness against XDR soon. And if azithromycin does develop resistance it will lead to life-threatening issues in more than 15% of untreated patients and the death toll will increase. Fighting COVID-19 and XDR simultaneously is a huge burden on the health system of Pakistan and can crush its backbone if the issue is not addressed properly at the national level thus awareness about the severity of the issue along with its management needs to reach the masses.

Keywords: COVID-19; XDR Typhoid; *Salmonella Typhi*

Introduction

Typhoid fever is an acute illness caused by the gram-negative bacteria *Salmonella enterica* serovar Typhi. Its antibiotic-resistant S Typhi strains' appearance has increased across the world. The XDR strain of S Typhi is resistant to most medications used for the treatment of typhoid fever.¹ It originates from the *Salmonella enterica* taxonomic subspecies, enterica serovar Typhi. In recent years, more accurate data and knowledge has helped better understand typhoid fever, along with a rise within the geographic representation and variety of Typhoid incidence studies, and modern and sophisticated modeling approaches.² Typhoid fever may be a common disease, however, it has serious effects on adolescents and children of developing countries. Bacteria *Salmonella enterica* is responsible for the majority of cases of typhoid fever; but, *S. Paratyphi A* has also been seen and reported as an emerging threat and a growing concern.³

Typhoid fever is contracted through contaminated food or water, particularly in regions where there are unhygienic practices. In such regions, water is most susceptible to fecal contamination, resulting in increased transmission of Enterobacteriaceae (S) Typhi and Paratyphi, the causative agents. Typhoid fever is a major threat to public health in low resource and developing countries, with millions of cases reported annually, and between 128,000 and 161,000 typhoid-associated deaths every year.⁴ There are multiple signs which are associated with clinical findings in typhoid fever, including slow defervescence, eosinopenia, febrile temperatures with relative cardiac arrhythmia, and other manifestations like hepatitis. Positive blood cultures are used in diagnosing the disease.⁵ Fever is presented in most of the patients with Typhoid (>90 %) regardless of their age bracket, and mortality is considerably higher in adolescents and children.⁶ Antibiotic resistance to *Salmonella enterica* serovar Typhi is a major public health concern S Typhi is spreading at a very fast pace and infecting bigger regions as it progresses. Its strains are resistant to three first-line drugs, including, trimethoprim sulfamethoxazole, ampicillin, chloramphenicol, along with third generation cephalosporins and fluoroquinolones in Sindh, a province in Pakistan, thus making it a highly drug-resistant strain.⁷ Decades of antibiotics have driven the development of multidrug-resistant and largely resistant strains of typhoid fever. In recent years, a multidrug-resistant (MDR) haplotype of *Salmonella typhi*, H58, was found and is widespread in parts of Asia and Africa. Conventionally Typhoid MDR is resistant to all first-line antibiotics as said by the World Health Organization (WHO): It is also believed that *Salmonella typhi* can be converted from MDR to XDR by acquiring plasmid.⁸

In Pakistan, a wide range of resistant typhi has developed and is a drug-resistant *Salmonella typhi* (XDR) strain resistant to all recommended antibiotics. Another possible reason for Pakistan's resistance to antibiotics can be the lack of well-equipped standardized laboratories in rural areas. These laboratories lack the resources to process blood cultures and cannot accurately report the susceptibility and resistance of *Salmonella typhi*, resulting in ineffective treatment options.⁹ During the 9 COVID-19 pandemic, poor hygiene and sanitation practices have contributed to the increase of typhoid fever. Overdose of azithromycin in the treatment of COVID-19 may affect one of the few XDR regimens. Most of these cases are treated with carbapenem and azithromycin. With the outbreak of this pandemic, azithromycin has been commonly used as a treatment for COVID-19. Although serology tests are the most reliable diagnostic tool to detect typhoid fever, existing laboratories have been saturated in COVID-19 testing, making it unrealistic to test for typhoid fever with such methods.¹⁰

The typhoid strain is resistant to all available antibiotics, making it extremely expensive and difficult to treat. The typhoid outbreak in Pakistan is currently classified as XDR. Moreover, the high burden of COVID 19 on the - already fragile health care system and infrastructure in underdeveloped countries can result in devastating consequences.¹¹ Clinical diagnosis of typhoid that is extensively resistant to drugs now requires competent laboratories, which is a big challenge for developing countries dealing with the COVID-19 pandemic. Nonspecific signs and symptoms of typhoid resemble much like illnesses such as malaria, dengue, and COVID 19. Due to the similarities of symptoms of those - illnesses, it's difficult to discover the true underlying causes of the patient's condition without proper diagnostic tests. During the COVID 19 pandemic, - healthcare employees are overburdened with the excessive inflow of COVID 19 cases in hospitals. In such - conditions, upward thrust in the figures of cases of typhoid is additionally causing a huge problem that is unhandled. Health care professionals are having a difficult time differentiating illnesses because of symptoms similarities, including fatigue, pain, fever, and diarrhea.

Recent epidemiological research discovered a massive percentage of H58 S. Considering the fact that strains of Typhi in Pakistan's population since 2016 are XDR, isolates have been resistant to chloramphenicol, ampicillin, TMP-SMZ, fluoroquinolones, and third-era cephalosporins, leaving a very little alternative option for the treatment of patients. Alarming, a recently performed observation confirmed that XDR S. Typhi underwent speedy clonal growth and sickened multiple people endemically, in addition to worldwide travelers.¹²

In the short and medium terms, new typhoid control strategies in the form of typhoid conjugate vaccine (TCV) have emerged, which provides hope for disease control in the near future. Immunization by WHO Strategic Advisory Group of Experts (SAGE) recommends that TCV be used programmatically in countries with a high burden of disease.¹³ Sometimes combined antibiotic therapy is used to treat intestinal fever, especially in the slow response of treatment. Access to safe, pure, clean drinking water and investment in sanitation and personal hygiene will be the key to reducing the global typhoid burden.

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