Extensively Drug-Resistant Typhoid Fever: A Call to Action

Sir,

Salmonella typhi infection is more prevalent in South Asian countries because of poor hygiene practices, fecal contamination of water bodies, water scarcity, poverty, and overcrowding. According to recent reports, around 21 million people contract typhoid each year, causing 161,000 deaths.[1] The incidence of multidrug-resistant (MDR) typhoid cases in a recently reported study in India was 7%.[2] Ceftriaxone-resistant strains have been reported sporadically in India.[3] Decades of empiric antibiotic use have resulted in the development of MDR organisms (resistant to ampicillin, co-trimoxazole, and chloramphenicol) followed by extensively drug-resistant (XDR) *S. typhi* strains (resistant to chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones, and third-generation cephalosporin). Patients with resistant infections have a twofold higher mortality risk and financial burden than patients with infections with sensitive strains. The existence of drug target modification and three separate multidrug efflux pumps in the bacterium is hypothesized as a mechanism for resistance to these antibiotics.

Currently, the health risk posed by XDR strains in the region of South Asia is important. Figure 1 shows the proportion of resistant strains of *S. typhi* in Asia. Although MDR *S. typhi* is on the decline, quinolone-resistant strains have become extremely prevalent in India.[4,5] In recent studies in Pakistan, it has been found that MDR has risen from 34.2% to 64.1%, while extensive drug resistance has risen from 1.6% to 64.1% over the same period.[6] Although the first outbreak of XDR typhoid (third-generation cephalosporin resistance) was identified in Sindh (Pakistan), cephalosporin-resistant *S. typhi* strains have also been reported from India, Bangladesh, Philippines, Iraq, Guatemala, and Italy, so it is not just a problem of a single country. Even though very few ceftriaxone-resistant cases have been reported in India to date, in clinical practice, we have encountered numerous ceftriaxone unresponsive cases. Such cases go unreported due to insufficient workup, patients' financial constraints, and a lack of proper enforcement of national surveillance policies.

A study by Klemm *et al*. foreshadows potentially disastrous scenarios for typhoid fever management if the XDR strain of *Salmonella enterica serovar typhi,* namely the XDR strain, spreads globally. This is understandable considering that the outbreak strain is of the H58 haplotype, which is well-known for its capacity to spread globally and displace endemic *S. typhi*. It warns the global community to approach typhoid fever control more effectively through prevention if therapeutic options become unavailable.[7]

The Indian Society of Critical Care Medicine guidelines for treatment of typhoid fever recommend ceftriaxone as a first-line antibiotic to cover the MDR variant and suggest azithromycin and ciprofloxacin as an alternative therapy. Chloramphenicol, co-trimoxazole, ampicillin, ciprofloxacin, ceftriaxone, azithromycin, meropenem, and tigecycline are the antibiotics with activity against *S. typhi*. The latter three medications are generally reserved for XDR cases. Resistance to azithromycin has also been recently emerged, which leaves meropenem and tigecycline as the only alternatives, posing a significant threat to the outpatient management of the disease. Both being parenteral antibiotic preparations increase the cost of therapy beyond the reach of many patients, particularly in developing countries like India.

Blood culture is the gold standard for diagnosis with very high specificity but less sensitivity (40–80%), however, practically Typhidot rapid diagnostic test is the only sensitive (95%–97%) and specific (89%) way for the diagnosis of typhoid fever. General practitioners often prefer the Widal test, but it is neither specific nor sensitive. Blood culture for every febrile illness is not feasible in low- and middle-income countries such as India because it is costly and not possible in remote areas. Because of costlier diagnostic methods, it is now common practice to administer wide-spectrum antibiotics such as ceftriaxone empirically to any patient who has a nonlocalized fever (other than pneumonia, meningitis or urinary tract infection, etc.) without first doing a culture or understanding the sensitivity patterns of the organism. Clinical practitioners often lack the critical knowledge required to treat these infections. As a result, 30%–60% of antibiotics recommended in the inpatient settings are not suggested (either too broad or too narrow). This rampant use of broad-spectrum antibiotics is resulting in the development of resistance to antibiotics. Hence, efforts are required to reduce inappropriate antibiotic use. Sharvani *et al*. underlined the need of utilizing antibiotics judiciously, particularly fluoroquinolones and cephalosporins, and have suggested using the older first-line

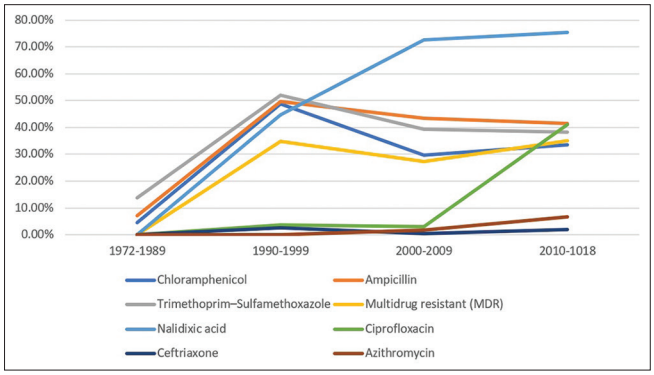

Figure 1: Proportion of *Salmonella typhi* isolates resistant to antimicrobials in Asia over the last four decades (Marchello *et al*., 2000)

medicines for the treatment of typhoid fever.[4] Srirangaraj *et al*. in their study also have suggested salvaging the first-line antibiotics for the management of cases of typhoid fever presently.[4,8] They also concluded that standardized laboratory testing recommendations for ciprofloxacin and azithromycin susceptibility testing for *S. typhi* isolates are much required for improving this condition of menace of rampantly prescribing higher antibiotics. In another recently done multicentric study across India, researchers found the proportion of MDR was 3%, and XDR strain was not seen in any isolate.[5]

All of this suggests a need for the strict implementation of programs like the antibiotic stewardship program (ASP) in the country. The adoption of such a program has proven difficult in India because of the obstacle-limited specialized pharmacy staff, physicians' resistance to change, ineffective electronic medical records, insufficient physical visibility of stewardship practices, limited microbiology staff, and high antibiotic usage in the population. As a result, hospital antibiotic utilization and practitioner prescription habits are important foci for antibiotic stewardship initiatives. Furthermore, antibiotic time-outs, a key component of ASP, must be implemented in India.

Finally, community hygiene, strict sanitary protocols, vaccination, carrier surveillance and treatment, effective oral antibiotics for disease control, as well as the methods suggested above, are needed to reduce the public health burden of MDR and XDR typhoid. Furthermore, in order to enact effective countermeasures, health-care agencies must consider the scope of the danger ahead of time. To alleviate the disease's health and financial burden, it is vital to find an effective oral antibiotic against XDR typhoid and to undertake preventative measures on a war footing, especially in developing countries like India, where the disease is endemic.

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Conflicts of interest

There are no conflicts of interest.

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