



Persistence of first-line antibiotic-resistant typhoid fever among Pakistani children: a growing concern for regional antimicrobial stewardship

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The water-borne aerobic, Gram-negative bacterium *Salmonella enterica* subspecies *enterica* serovar Typhi (*S. Typhi*) is the causative agent of typhoid fever (TF). This is a potentially fatal, acute multisystemic infection characterized by fever and abdominal pain that is spread by eating or drinking food or water contaminated with the feces of an infected person (1,2). The annual global incidence of TF exceeds 18 million confirmed cases, resulting in over 200,000 deaths (2). Despite the existence of several efficacious anti-TF vaccines, immunization rates are poor in developing countries, such that TF ranks among the most frequently occurring infectious diseases, particularly in South Asia (2-4).

As the dissemination of *S. Typhi* is associated with poor hygiene and inadequate sewage systems infection is far more likely to affect people in low-income nations. While people of any age may contract TF the disproportionately high incidence in children suggests active community transmission. The actual burden of disease by country remains uncertain because many cases are unrecognized, particularly in young children who may present symptoms of a non-specific illness (2,5).

In recent years there has been an alarming rise in

worldwide rates of antimicrobial resistance by pathogenic enteric bacteria, largely attributed to poor stewardship leading to the misuse of once highly-effective drugs. Multidrug-resistant (MDR) *S. Typhi*, defined as resistance to the three first-line antibiotics used to treat TF – ampicillin, chloramphenicol and cotrimoxazole, appeared in the 1970s and is now widespread globally. This is becoming extensively drug-resistant (XDR) *S. Typhi* (defined as MDR plus resistance to fluoroquinolones and third-generation cephalosporins), mainly through acquiring plasmids conferring antibiotic resistance via bacterial conjugation (commonly associated with the H-58 haplotype) (6,7). When an *S. Typhi* strain develops resistance by acquiring a promiscuous plasmid or undergoing genetic mutation consistent changes occur in the reported incidence of susceptibility to that antibiotic. Hence, thorough and continuous surveillance is a prerequisite to tracking the extent of resistance among *S. Typhi* strains and to gaining a better understanding of the factors involved in disease severity (8).

In Pakistan, the southeast province of Sindh is one of two, along with Punjab, that is most affected by TF. Approximately 1,000 TF cases per 100,000 children have been reported annually over several years in Karachi, the country's most populous city and provincial capital of Sindh, located on the Arabian Sea coast (9). We have recently shown evidence of multidrug resistance in *S. Typhi* isolated from children living in a poverty-stricken slum district of Karachi where water quality and standards of sanitation are both unsatisfactory (7). This first report of the emergence of confirmed cases of MDR *S. Typhi* from the only public hospital in its largest neighborhood identifies a grave public health concern. The rise in prevalence of MDR and, in some instances, XDR, *S. Typhi* that has been observed not only in Karachi but also in Hyderabad (6,9), the second-largest city in Sindh and situated 160 Km to the northeast of Karachi, constitutes a major humanitarian crisis. In 2018, of nearly 8,200 confirmed cases of TF in Sindh two-thirds were XDR, of which Karachi accounted for 69% (10).

Addressing ways to arrest the progressive development of antimicrobial drug resistance in Sindh is a public health challenge that should be prioritized if it is to both be contained locally and thus not to become established in other urban centers in other provinces of Pakistan. An elementary first step is the implementation of a regular and effective nationwide surveillance mechanism to enable clinical cases caused by MDR/XDR *S. Typhi* to be detected with reasonable accuracy. Moreover, a concerted and consolidated effort should be made to restrict ready access to non-prescribed antibiotics among the

general public in South Asian and South East Asian countries through unregulated 'over the counter' pharmacy sales and black market trade (6,7). Not only does this widespread availability provide a natural selection pressure for antimicrobial resistance by *S. Typhi* and other bacterial pathogens it is evident that a suboptimal dose of antibiotics can reduce the severity of TF symptoms sufficiently to obfuscate or delay a confirmatory diagnosis of infection. Physicians also have a responsibility to limit the inefficient prescription of drugs to treat TF (6).

Since the outbreak of the COVID-19 pandemic at the end of 2019 low-income countries have justifiably refocused already strained public health services resources to the testing and treatment of patients with SARS-CoV-2. As an unfortunate consequence, initiatives to tackle neglected tropical diseases have suffered from reallocation of funds (11). Reviving these programs in Pakistan, including TF surveillance, diagnosis and vaccination, will require industrialized nations to commit generous and sustained aid. Pausing to digest the implications of COVID-19 could exacerbate the problem (12).

The growing resistance of *S. Typhi* strains to front-line antibiotics severely limits treatment options. In parallel with this challenge to effective therapy, however, a recent advancement in the control of TF is the roll out of a large-scale global vaccination program. This was initiated by the World Health Organization among children starting from six months of age in developing countries, of which Pakistan is at the forefront (13). In order to achieve equity in TF vaccination coverage nationwide, vaccine acceptance and participation of whole communities are needed, as are free-of-cost immunization and blood testing. In parallel to these interventions, another sustainable long-term solution is to take steps towards disease prevention by enhancing sanitation practices and providing clean, filtered water to the public.

Health literacy is relatively underexplored as a concept in Pakistan, and evidence from Karachi suggests that levels are low (14). Even where knowledge of risks is adequate, behavioral responses may fall short. A high prevalence of self-medication with antibiotics in the relatively unregulated Pakistani pharmaceutical market, including by sectors of the Karachi population with proficient health literacy (15), is extremely troubling.

Keywords

Typhoid fever, *Salmonella Typhi*, antimicrobial resistance, antibiotic, Pakistan.

Conflict of interest

The authors declare that there is no conflict of interest.

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Authors' contributions

Both authors have made substantial contributions to the conception of the article, contributed significantly to writing

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References

- Mohsin S, Taylor-Robinson AW. Improved vaccine design and delivery as part of an integrated approach to meet the public health challenge of typhoid fever in developing countries. *Curr Trends Vaccine Vaccinol*. 2018; 1(1): 103. doi: 10.31021/ctvv.20181103.
- Antillón M, Warren JL, Crawford FW, Weinberger DM, Kürüm E, Pak GD, et al. The burden of typhoid fever in low- and middle-income countries: a meta-regression approach. *PLoS Negl Trop Dis*. 2017; 11(2): e0005376. doi: 10.1371/journal.pntd.0005376.
- Shakya M, Voysey M, Theiss-Nyland K, Colin-Jones R, Pant D, Adhikari A, et al. Efficacy of typhoid conjugate vaccine in Nepal: final results of a phase 3, randomised, controlled trial. *Lancet Glob Health*. 2021; 9(11): e1561-8. doi: 10.1016/S2214-109X(21)00346-6.
- Meiring JE, Shakya M, Khanam F, Voysey M, Phillips MT, Tonks S, et al. Burden of enteric fever at three urban sites in Africa and Asia: a multicentre population-based study. *Lancet Glob Health*. 2021; 9(12): e1688-96. doi: 10.1016/S2214-109X(21)00370-3.
- Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. *Lancet*. 2015; 21(385): 1136-45. doi: 10.1016/S0140-6736(13)62708-7.
- Qamar FN, Yousafzai MT, Dehraj IF, Shakoos S, Irfan S, Hotwani A, et al. Antimicrobial resistance in typhoidal salmonella: Surveillance for Enteric Fever in Asia Project, 2016–2019. *Clin Infect Dis*. 2020; 71(Suppl. 3): S276-84. doi.org/10.1093/cid/ciaa1323.
- Mohsin S, Aziz Q, Muurlink OT, Taylor-Robinson AW. Burden of antibiotic resistance among children with typhoid in Gadap Town, Karachi, Pakistan. *Microbes Infect Dis*. 2022; in press. doi: 10.21608/mid.2021.87000.1174.
- Katiyar A, Sharma P, Dahiya S, Singh H, Kapil A, Kaur P. Genomic profiling of antimicrobial resistance genes in clinical isolates of *Salmonella Typhi* from patients infected with typhoid fever in India. *Sci Rep*. 2020; 10(1): 8299. doi: 10.1038/s41598-020-64934-0.
- Yousafzai MT, Irfan S, Thobani RS, Kazi AM, Hotwani A, Memon AM, et al. Burden of culture confirmed enteric fever cases in Karachi, Pakistan: surveillance for Enteric Fever in Asia Project (SEAP), 2016–2019. *Clin Infect Dis*. 2020; 71(Suppl. 3): S214-21. doi: 10.1093/cid/ciaa1308.
- Akram J, Khan AS, Khan HA, Gilani SA, Akram SJ, Ahmad FJ, et al. Extensively drug-resistant (XDR) typhoid: evolution, prevention, and its management. *Biomed Res Int*. 2020; 2020: 6432580. doi: 10.1155/2020/6432580.
- Haqqi A, Khurram M, Din MSU, Aftab MN, Ali M, Ahmed H, et al. COVID-19 and *Salmonella Typhi* co-epidemics in Pakistan: a real problem. *J Med Virol*. 2021; 93(1): 184-6. doi: 10.1002/jmv.26293.
- Ehrenberg JP, Utzinger J, Fontes G, da Rocha EMM, Ehrenberg N, Zhou XN, et al. Efforts to mitigate the economic impact of the COVID-19 pandemic: potential entry points for neglected tropical diseases. *Infect Dis*

- Poverty. 2021; 10(1):1-10. doi: 10.1186/s40249-020-00790-4.
13. World Health Organization. Pakistan first country to introduce new typhoid vaccine into routine immunization programme. 15 November 2019. Available at: <http://www.emro.who.int/pak/pakistan-news/pakistan-first-country-to-introduce-new-typhoid-vaccine-into-routine-immunization-programme.html>.
 14. Ahmed W, Shaikh ZN, Soomro JA, Qazi HA, Soomro AK. Assessment of health literacy in adult population of Karachi: a preliminary investigation for concept-based evidence. *Int J Health Promot Educ*. 2018; 56(2): 95-104. doi: 10.1080/14635240.2017.1421866.
 15. Shah SJ, Ahmad H, Rehan RB, Najeeb S, Mumtaz M, Jilani MH, et al. Self-medication with antibiotics among non-medical university students of Karachi: a cross-sectional study. *BMC Pharmacol Toxicol*. 2014; 15: 74. doi: 10.1186/2050-6511-15-74.