Editorial

Typhoid Fever: An Enduring Public Health Challenge in Pakistan

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Typhoid fever remains an important public health challenge in Pakistan, particularly amid antimicrobial resistance and persistent transmission. It is caused by *Salmonella enterica* serotype Typhi (commonly known as *Salmonella* Typhi, or *S* Typhi), a Gram-negative bacterium in the family Enterobacteriaceae.[1] Untreated typhoid fever is a life-threatening bacterial infection that can cause prolonged fever, fatigue, headache, abdominal pain, and digestive symptoms, with severe complications including intestinal bleeding or perforation.[2] Humans are the only known reservoir of *S* Typhi, and transmission occurs through the fecal–oral route, particularly where water, sanitation, and hygiene are inadequate.[1] Water shortages, reliance on unsafe or unreliable drinking-water sources, and displacement following natural calamities such as flooding can further increase the risk of transmission.

Though typhoid has declined sharply in settings with sustained improvements in water, sanitation, and living conditions, it remains a major public health problem in South Asia. According to 2019 estimates approximately 9 million typhoid cases and 110,000 deaths each year.[3] Earlier population-based estimates placed Pakistan among the countries with the highest incidence of typhoid in South Asia, with an estimated incidence of approximately 493.5 cases per 100,000 population per year.[4] However, such estimates should not be interpreted as current national incidence, because population-based surveillance remains limited.

The emergence of XDR typhoid in Hyderabad, Sindh, in 2016 added a new dimension to Pakistan's typhoid problem. XDR *S* Typhi was resistant to chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones, and third-generation cephalosporins, substantially narrowing available treatment options.[2,4] Azithromycin and meropenem therefore have an important role in the treatment of XDR *S* Typhi and should be used judiciously in accordance with current treatment guidance.[2] The laboratory surveillance later reported detection of XDR *S* Typhi in Punjab.[5,6] The international spread of XDR *S* Typhi also illustrates how resistant strains can cross borders through international travel, transforming a local antimicrobial-resistance problem into an international public-health concern. Similarly, XDR typhoid was detected in people travelling back to Canada from Pakistan, prompting the Canadian government to issue a travel advisory for its citizens on how to avoid contracting XDR S Typhi while travelling to Pakistan during monsoon season (June to September).[7] Therefore, the emergence of antimicrobial resistance in typhoid is not only a local problem but also a global public health concern.

A parallel, important gap is typhoid diagnosis. Blood culture is the standard laboratory method for confirming typhoid fever, while bone marrow culture is more sensitive but less routinely feasible.[8] Serological tests such as Widal and Typhidot have limited diagnostic accuracy and should not be considered substitutes for culture where culture is available. *S* Typhi can be isolated from blood, particularly during the first week of illness, while stool and urine cultures may provide additional evidence later in illness.[2] However, culture requires trained staff and laboratory infrastructure that may not be readily available in rural and peri-urban areas. In settings where microbiological confirmation is difficult, clinicians may rely more heavily on empirical antibiotic therapy. This can increase inappropriate antibiotic use and reduce opportunities to identify resistant *S* Typhi, thereby contributing to selection pressure and complicating antimicrobial stewardship. National resistance surveillance data and reports of XDR *S* Typhi underscore the need to strengthen laboratory capacity and antimicrobial stewardship alongside improved access to effective treatment.

The relationship between inadequate diagnosis and antimicrobial resistance is particularly important in settings where typhoid is clinically difficult to distinguish from other febrile illnesses. When reliable microbiological diagnosis is unavailable, empirical antibiotic treatment may be initiated without confirmation of *S* Typhi infection or its antimicrobial susceptibility. Repeated or inappropriate antibiotic exposure can create selection pressure favoring resistant organisms, while the absence of culture and susceptibility testing limits timely recognition of emerging resistance. Strengthening diagnostic capacity is therefore not only important for individual patient management but also for antimicrobial-resistance surveillance and stewardship.

The increasing availability of artificial intelligence and machine learning approaches may provide additional opportunities in the future. Conventional antimicrobial susceptibility testing (AST) requires culture, organism identification, and testing against recommended antibiotics, which can take several days. Research in other Salmonella serotypes has explored machine learning approaches to infer antimicrobial susceptibility from high-resolution imaging. For example, researchers developed a machine

learning tool to identify *S* Typhimurium isolates and infer ciprofloxacin susceptibility from structural changes in pathogen cells.[9]

However, this approach has not been established as a clinical diagnostic method for *S* Typhi and requires further validation. Similarly, the TyphoidRx algorithm has explored machine learning-based prediction of antibiotic resistance using patient profiles.[10] These approaches are promising, but their clinical utility for *S* Typhi diagnosis and resistance-guided treatment remains to be established. AI should therefore be viewed as a potential adjunct to, rather than a replacement for, microbiological diagnosis and antimicrobial susceptibility testing. Further validation in real-world *S* Typhi clinical settings is needed before such approaches can be integrated into routine diagnostic practice.

As XDR *S* Typhi narrows treatment options, prevention has become increasingly important. Vaccination, together with safe drinking water, sanitation, food safety, and hand hygiene, is central to reducing transmission. In Pakistan, the National Institutes of Health (NIH) produces two inactivated bacterial vaccines: the TAB vaccine and the typhoid-cholera mixed (TC) vaccine. TAB vaccine contains an inactivated suspension of *S* Typhi and Paratyphi A and B bacteria, whereas the TC vaccine contains inactivated *S* Typhi and each of *Vibrio cholerae* Inaba and *Vibrio cholerae* Ogawa. The NIH states that protection from these vaccines is relatively short-lived and that a booster dose is required after two years.[11] Both of these vaccines differ from the modern typhoid conjugate vaccine (TCV), which is part of routine childhood immunization.[12]

Pakistan was the first country to introduce TCV into routine immunization, beginning in Sindh in 2019 in response to the XDR outbreak. A study conducted in Pakistan showed 95% effectiveness against culture-confirmed *S* Typhi and 97% against culture-confirmed XDR *S* Typhi in children aged 6–59 months.[13] Thus, TCV demonstrated high effectiveness against culture-confirmed *S* Typhi infections, including XDR infections, in this setting. However, vaccination alone cannot eliminate typhoid transmission. The persistence of transmission in settings with inadequate WASH infrastructure means vaccination must be accompanied by sustained improvements in safe drinking water, sanitation, food safety, and hygiene. Similarly, high vaccination coverage does not remove the need for laboratory diagnosis and surveillance, particularly where antimicrobial resistance is already established. The introduction of TCV should therefore be viewed as an important component of a broader typhoid-control strategy rather than as a standalone solution.

TCV is procured through international vaccine-supply mechanisms. Dependence on external suppliers can create supply-chain vulnerabilities for national immunization programs, particularly during international disruptions. Vaccine financing sustainability therefore warrants continued policy attention, particularly as external support is expected to decline.[14]

Pakistan's experience with XDR typhoid demonstrates that antimicrobial resistance, inadequate diagnostic capacity, and persistent transmission are closely interconnected. The emergence of XDR *S* Typhi has narrowed treatment options and consequently increased the importance of prevention. TCV provides an effective tool for reducing culture-confirmed *S* Typhi infection, including XDR infection, but vaccination must be complemented by improvements in WASH, laboratory diagnosis, surveillance and antimicrobial stewardship. A sustained, evidence-based, and coordinated approach will be essential to reduce the burden of typhoid and limit the further emergence and spread of antimicrobial-resistant *S* Typhi.

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