

EDITORIAL

XDR TYPHOID: THE PROBLEM AND ITS SOLUTION

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Today I am writing to highlight a new Pakistani health crisis - The rise of typhoid "superbug"! Typhoid fever remains a significant public health threat in low- and middle-income countries, with an estimated 11–20 million cases and between 128 000 and 161 000 typhoid-associated deaths each year.^{1–4} Pakistan has been a high burden country for typhoid with severe disease, very high incidence especially among 2–15 year-olds, and more importantly a high resistance pattern.^{5,6} As a clinician, managing typhoid was easy in days gone by but not anymore. Simple first line oral antibiotics lost efficacy in 1980s as management became more complicated by increasing rates of multi-drug resistance (MDR) strains of *Salmonella* (*S*) species (*Typhi* and *paratyphi A, B and C*). Increasingly high fluoroquinolone resistance rates (>90%) has been observed in these *Salmonella* species probably because of its widespread misuse.^{5,6}

The emergence of cephalosporin resistance in *S. typhi*, documented first in 2014 in Pakistan (0.08% isolates to ceftriaxone), and has caused considerable alarm.⁶ Unfortunately this has now become a reality with the evolution of the "superbug" called extensively drug resistant (XDR) typhoid.⁷ These XDR forms of *Salmonella* isolates are found to be resistant to not only first line antibiotics (ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole) but also to ciprofloxacin and third-generation cephalosporins! The resistant form of pathogen is thus resistant to five types of antibiotics, more than seen in any outbreaks before! The resistant haplotype of *S. typhi* called H58 has been spreading globally including South and Southeast Asia.⁸ Pakistan is already reporting a staggering number of cases associated with this haplotype of *S. typhi*.^{7,9,10}

The large-scale epidemic of the novel *S. typhi* XDR clone was first isolated from Hyderabad, Sindh.⁷ This *S. typhi* clone encodes a chromosomally located resistance region and harbors the IncY plasmid encoding additional resistance elements, including the *bla*_{CTX-M-15} extended-spectrum β -lactamase mediating resistance to ceftriaxone, and carrying the *qnrS* fluoroquinolone resistance gene as well. According to the latest report by WHO since November 2016 to December 2018, an extraordinary 5, 274 cases of XDR typhoid out of 8,188 typhoid fever cases were reported by the Provincial Disease Surveillance and Response Unit (PDSRU) from 14 districts in Sindh Province, Pakistan (76% from Karachi, 27% from Hyderabad District, 4% from other districts).^{10,11} Most (~80%) of these are documented in children. Reports of XDR typhoid cases occurring in other parts of Pakistan are now being informally reported as well as in individuals travelling to UK and USA.¹²

This typhoid epidemic has created a new public health concern as now there are fewer antibiotic options for treatment with poor outcome.^{13–15} *S. typhi* has ability to transform from MDR to XDR in a single step by acquisition of a plasmid with a potential for the XDR clone to spread globally. It is time we take prompt actions to cater to this new typhoid resistant crisis! Diagnostics and therapeutic options must be aimed to curtail this problem as well. These include rapid reliable diagnosis for typhoid fever in every clinical setting. We must do away with unreliable and obsolete serological tests such as the Widal and Typhidot tests.¹⁶ More informative, acceptable and "gold standard" blood culture must be encouraged with emphasis on development of more rapid, reliable and cheap tests.^{17,18}

For the proper management of typhoid fever blood cultures in suspects is a foremost step. We must also avoid the empiric use of quinolones as >90% resistance to quinolones has been documented in many studies in Pakistan.¹⁹ For empiric therapy we have to use 3rd generation cephalosporins and for severe cases IV ceftriaxone. Oral cefixime (high dose) should be used in outpatient settings in less severe cases and even in MDR typhoid cases. Oral Amoxicillin or trimethoprim-sulfamethoxazole can also be given safely if susceptible strains are isolated. Treatment must be long enough (10–14 days) or until afebrile ≥ 5 days whichever is longer. With XDR typhoid the fear of the dreaded "untreatable typhoid" has become a grim reality now. Currently, azithromycin is the only reliable first-line oral treatment option to treat uncomplicated XDR typhoid. For suspected severe or complicated XDR typhoid fever patients carbapenems are the only IV option available.^{18,20} Other treatment options are unfortunately few.

Immediate preventive and control measures should be instituted by the government at all levels and every sector to control typhoid and especially XDR typhoid strains from spreading. Measures aimed at health education of the public, vaccination and emphasis on hygiene and food safety is of paramount importance.^{21,22} Specific measures include: 1) Supply of clean, safe drinking water, 2) Effective and sanitary disposal of human feces and urine, 3) Careful attention to cleanliness and hygiene during food preparation, 4) Provision of adequate hand washing facilities wherever food is handled, 5) Education in personal hygiene procedures and public health measures, 6) Enforced regulations governing manufacture of food and drink.

A mass vaccination campaign is also required at this point in time. We need to meet the changing needs of our population that protects, transforms and strengthens

the health care to all Pakistanis. After the recent outbreak in Sindh the Provincial government took some preventive steps (including vaccination, community awareness on hand washing/proper sewage disposal, etc).²³ Also at the national level there was approval of first new conjugate typhoid vaccine (TCV) by the Federal EPI/ Ministry of NHR & C for routine EPI schedule. WHO prequalified the vaccine (Typbar-TCV®)²⁴ has many advantages such as being administered beginning at the age of 6 months, 87% protected efficacy and providing longer protection of >5 years. More than 116,000 children between 6 months to 10 years age in Hyderabad high-risk areas have been vaccinated against typhoid so far.

In conclusion XDR typhoid has emerged as a major infectious disease crisis. It has taught us, albeit late, that major national public health related preventive measures such as hygiene, sanitation and vaccination must be taken to control epidemics such as XDR typhoid into making it a major catastrophe.

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