Emergence of Novel Mutations in Extensively Drug-Resistant *Salmonella enterica* Serovar Typhi from Pakistan

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In response to the recent discussion on extensively drug-resistant (XDR) typhoid in Pakistan (1), we would like to draw attention to the critical genotypic evolution in *Salmonella enterica* serovar Typhi strains from Pakistan that would be of interest to the health care community. In 2016, a large outbreak of XDR *S. Typhi* emerged in Pakistan in the Sindh province (2). From November 2016 until now, >21,000 cases of typhoid were reported from Sindh, among which 70.8% were XDR typhoid. A study in 2017 genetically characterized the linkage of emerged XDR strains with the H58 haplotype and suggested that strains acquired an extended-spectrum β -lactamase-encoding antibiotic-resistant plasmid from *Escherichia coli* (3). Since then, quite a few cases have been reported from other parts of the country. We characterized *S. Typhi* strains isolated from Punjab province in 2018 through whole-genome sequencing in collaboration with the CDC and noted certain mutations (3). The sequence of one of the strains (GenBank accession no. CP044007 [chromosome] and CP044008 [plasmid]) carries *catA1*, *dfrA7*, and *sul1* in a chromosomally integrated IS1-mediated composite transposon at the same location as in Pak60006_2016 (4) but lacks a 7,857-bp internal region containing the partial *IncQ1* replicon, *aph(3'')-Ib*, *aph(6)-Id*, *bla*_{TEM-1B'}, and *sul2*. It may be a single nucleotide polymorphism event mediated by a promiscuous insertion sequence. The partial copy of the *IncQ* plasmid is embedded in the chromosome. The finding suggests that more stable inheritance for antibiotic resistance genes can be expected from *S. Typhi* strains over time. There is a dire need to keep track of ongoing deletion events in XDR *S. Typhi* strains. Routine surveillance of *S. Typhi* infection is recommended in areas of endemicity to ensure its detection before it is widely spread (5). The rapidly emerging patterns in XDR *S. Typhi* strains have led to a challenging situation in the region (6). The current ongoing epidemic has led to development of a nationwide action plan developed through national (NIH Pakistan) and international (WHO and CDC) collaboration. The plan is in effect across the country and includes surveillance at the genomic level; selected sites have been sharing the XDR strains with a national reference laboratory for sequence analysis. The joint efforts by different stakeholders are imperative contain the rapidly increasing and evolving *S. Typhi* strains in Pakistan.

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A.A. conceptualized the idea and wrote the manuscript. A.I. and M.S. provided critical review.

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