A systematic review of antimicrobial resistance of typhoidal Salmonella in India

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**Background & objectives:** The temporal trends in the development of antimicrobial resistance (AMR) among Salmonella Typhi and Salmonella Paratyphi in India have not been systematically reported. We aimed to systematically review the temporal AMR trends (phenotypic and molecular mechanisms) in bacterial isolates from patients with enteric fever over two decades in India.

**Methods:** To identify trends in AMR in India, resistance patterns among 4611 individual S. Typhi isolates and 800 S. Paratyphi A isolates, reported from 1992 to 2017 in 40 publications, were analysed. Molecular resistance determinants were extracted from 22 publications and also reviewed in accordance with the PRISMA guidelines. Articles were sourced using a predefined search strategy from different databases.

**Results:** The analyses suggested that multidrug-resistant (MDR) enteric fever was declining in India and being replaced by fluoroquinolone (FQ) resistance. Mutations in gyrA and parC were key mechanisms responsible for FQ resistance, whereas MDR was largely driven by resistance determinants encoded on mobile genetic elements (plasmids, transposons).

**Interpretation & conclusions:** The results reflect the effect of antimicrobial pressure which has been driving AMR in typhoidal Salmonella in India. Understanding these trends is important in planning future approaches to therapy, which serve as a baseline for assessment of the impact of new typhoid conjugate vaccines against these resistant organisms.

**Key words** Antimicrobial resistance - enteric fever - India - paratyphoid - prevention - typhoid
The chronological trends in AMR among isolates of *Salmonella* Typhi and *S. Paratyphi* A in India have not been systematically reviewed. The WHO strategic group of experts committee, which makes global vaccine policy recommendations, emphasized the need for countries to strengthen the surveillance of typhoid fever and to monitor the occurrence of AMR strains before and after the programmatic implementation of the typhoid conjugate vaccines (TCVs). India has a unique advantage in that the tetanus-toxoid TCVs has already been licensed, and over five million doses have already been sold within the country. It is, however, yet to be used programatically, and one of the postulated uses of TCV is its direct and indirect effects in decreasing AMR.

This study was aimed to systematically review the temporal trends of antimicrobial resistance (AMR) in India. The objectives were two-fold: (i) to systematically delineate the historical trend of the proportion of expressed phenotypic resistance among typhoidal *Salmonella* to first-line antimicrobials, nalidixic acid, ciprofloxacin and cephalosporins; and (ii) to describe the molecular mechanisms of AMR in both serovars.

**Material & Methods**

**Search strategy:** The key words and search strategy for objectives one and two included [(antibiotic susceptibility OR antibiotic sensitivity) OR (antimicrobial susceptibility OR antimicrobial sensitivity)] AND (typhoid OR paratyphoid OR enteric fever) and (fluoroquinolones OR ciprofloxacin OR nalidixic acid OR ofloxacin OR amoxicillin OR ampicillin OR co-trimoxazole OR chloramphenicol) AND (resistance) AND (typhoid OR paratyphoid OR enteric fever), respectively (Fig. 1). Databases searched included PubMed, Google Scholar, EMBASE, MEDLINE and SCOPUS. Filters such as time of publication, study design and language were not applied to ensure complete data collection.

**Phenotypic trends in antimicrobial resistance (AMR):** For the purpose of this systematic review, an isolate was described as resistant to an antimicrobial if it was reported as ‘resistant’, ‘intermediately susceptible’, ‘intermediately resistant’ or ‘non-susceptible’ based on minimum inhibitory concentration (MIC) values or diameters of zones of inhibition *via* disc diffusion using customary interpretive criteria such as the Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards. For uniformity, studies prior to 2000 that reported sensitivities of at least the first-line antimicrobials were included, whereas studies conducted after 2000 which did not report antimicrobial sensitivities of chloramphenicol, co-trimoxazole, ampicillin/amoxicillin, nalidixic acid, ciprofloxacin or at least one cephalosporin were excluded. Studies that reported antibiograms collectively and had not stratified these into intervals shorter than five years were also excluded. These criteria were used to establish the validity of individual studies.

Isolates identified from reports were stratified based on year of isolation, geographic location and resistance phenotypes. Stratified isolates that were resistant to each antimicrobial were expressed as a proportion of all the isolates reported. The trends of antimicrobial resistance were expressed in five-year intervals as represented in Table I.

| Year      | Total number | Proportion of *Salmonella* Typhi-resistant isolates | Proportion of *Salmonella* Paratyphi A-resistant isolates |
|-----------|--------------|----------------------------------------------------|---------------------------------------------------------|
|           |              | CH        | AM   | TMX | NA | FQ | CEPH | CH | AM | TMX | NA | FQ | CEPH |
| Pre-2001  | 854          | 0.51      | 0.56  | 0.58 | -  | -  | -     | 0.22 | 0.21 | 0.26 | -  | -  | -      |
| 2001-2005 | 1259         | 0.28      | 0.44  | 0.41 | 0.63 | 0.08 | 0.03 |
| 2006-2010 | 902          | 0.09      | 0.35  | 0.06 | 0.76 | 0.15 | 0.01 |
| 2011-2015 | 1596         | 0.07      | 0.17  | 0.13 | 0.82 | 0.63 | 0.04 |
| Pre-2001  | 179          | 0.22      | 0.21  | 0.26 | -  | -  | -     | 0.29 | 0.43 | 0.21 | 0.59 | 0.03 | 0.00 |
| 2001-2005 | 261          | 0.00      | 0.04  | 0.00 | 0.77 | 0.58 | 0.04 |
| 2006-2010 | 26           | 0.01      | 0.05  | 0.01 | 0.91 | 0.60 | 0.05 |
| 2011-2015 | 329          | 0.01      | 0.05  | 0.01 | 0.91 | 0.60 | 0.05 |

CH, chloramphenicol; AM, ampicillin; TXM, co-trimoxazole; NA, nalidixic acid; FQ, fluoroquinolone; CEPH, cephalosporin
Fig. 1. Search Strategy and PRISMA flow diagram. "The eligibility of these excluded articles were screened for inclusion under objective 2, and non-duplicate articles were included. "The eligibility of these excluded articles were screened for inclusion under objective 1, and non-duplicate articles were included.

Molecular determinants of AMR: For the second objective, molecular mechanisms of AMR of isolates reported in studies either collectively or individually were included. These were only stratified based on the country of isolation and type of mechanism reported as methods used to study these mechanisms were heterogeneous over the years and techniques employed were also changed, thus making temporal comparisons challenging.

Data extraction & risk of bias (RoB): Data from the respective studies were extracted under the following: (i) study identifier including first author, year of publication, year of study commencement, duration of study, country, study design and sampling population (hospital-based/community and travel-associated/endemic or outbreak); (ii) methodology: sample size, site of isolation and antimicrobial susceptibility testing and interpretive criteria. For the studies included to evaluate molecular determinants, the technique of molecular detection was also recorded; and (iii) results: number of *S. Typhi* and *S. Paratyphi* A isolates, frequency of MDR, nalidixic acid-resistant, FQ-resistant and cephalosporin-resistant strains. In addition, data pertaining to the molecular mechanisms of MDR, FQ and cephalosporin resistance were also extracted. Study-specific data extraction was done twice - overall for objectives 1 and 2 separately.

Risk of bias (RoB) was assessed using two tools (Table II). The first classifies studies based on low-, moderate- or high-RoB and is known as the Quality in Prognosis Studies tool. The second is known as the Joanna Briggs Institute (JBI) tool and reports RoB dichotomously. The JBI was adapted for use in this study similar to the adaptations used by Tadesse et al. These RoB analyses were performed separately on studies selected to meet the first and second objectives. The isolates derived from these studies were used for
the frequency analysis. Parameters assessed for bias across the two tools included (i) population description, i.e. whether community or hospital setting; (ii) study design, sample size and sampling techniques; (iii) use of appropriate performance standards and quality control in microbiologic techniques such as bacteriologic culture and antimicrobial sensitivity; and (iv) the statistical analysis used for reporting summary measures.

Results

Phenotypic trends of AMR

Thirty two (Fig. 1) studies (Table II)9-36 satisfied the inclusion criteria from which 49 yr-stratified summaries of S. Typhi antimicrobial-resistant isolates were obtained. For instance, Gautam et al.15 reported the isolates of their study in a year-stratified manner for five years, therefore providing five serial year-stratified summaries. Of these 49 yr-stratified summaries, 27 were undertaken prior to the year 2005 and over 80 per cent were retrospective in study design. The summaries obtained from each report were pooled into the following temporal intervals: pre-2001, 2001-2005, 2006-2010 and 2011-2015 and expressed as a proportion of resistant isolates for each antimicrobial (Table I). 19 yr-stratified summaries of antimicrobial-resistant S. Paratyphi A were obtained, of which 11 were prior

| Year of study | Year of publication | Author & Reference | No. of isolates | Study Design | Risk of Bias |
|---------------|---------------------|--------------------|----------------|--------------|--------------|
| 2012          | 2017                | Harichandran & Dinesh19 | 79             | Retrospective | Low No |
| 2016          | 2016                | Sharvani et al20     | 167            | Retrospective | Low No |
| 2013-2014     | 2015                | Misra et al21        | 50             | Retrospective | Low No |
| 2015          | 2015                | Narain & Gupta22     | 220            | Prospective   | Low No |
| 2012          | 2014                | Srirangaraj et al23  | 16             | Retrospective | Low No |
| 2014          | 2017                | Dahiya et al24       | 380            | Retrospective | Low No |
| 2010          | 2013                | Choudhary et al25    | 322            | Retrospective | Low No |
| 2012          | 2013                | Venkatesh et al26    | 251            | Retrospective | Low No |
| 2008-2010     | 2013                | Gupta et al27        | 257            | Retrospective | Low No |
| 2010-2012     | 2013                | Jain & Chugh28       | 266            | Retrospective | Low No |
| 2008          | 2011                | Kumar et al29        | 128            | Retrospective | Low No |
| 2011          | 2011                | Adhikary et al30     | 2              | Case Report   | Low Yes |
| 2000-2006     | 2010                | Verma et al31        | 159            | Retrospective | Low No |
| 2008          | 2009                | Kumar et al32        | 50             | Retrospective | Low No |
| 1990          | 1992                | Rodrigues et al33    | 74             | Retrospective | Low No |
| 2004          | 2007                | Joshi & Amarnath34   | 25             | Retrospective | Low No |
| 2002          | 2007                | Capoor et al35       | 178            | Retrospective | Low No |
| 2003          | 2007                | Banerjee et al36     | 60             | Retrospective | Low No |
| 2004-2005     | 2006                | Manchanda et al37    | 56             | Retrospective | Low No |
| 2006          | 2006                | Ray et al38          | 70             | Cross-sectional | Low No |
| 1999-2004     | 2006                | Mohanty et al39      | 629            | Retrospective | Low No |
| 2001-2004     | 2006                | Lakshmi et al40      | 60             | Retrospective | Low No |
| 2003-2004     | 2005                | Dutta et al41        | 379            | Retrospective | Low No |
| 2004          | 2005                | Senthilkumar et al42 | 6              | Retrospective | Low No |
| 2002          | 2004                | Madhulika et al43    | 157            | Cross-sectional | Low No |
| 1997-2001     | 2002                | Gautam et al44       | 436            | Retrospective | Low No |
| 2001-2003     | 2005                | Kadhiravan et al45   | 50             | Retrospective | Low No |
| 2006-2007     | 2010                | Nagshetty et al46    | 84             | Retrospective | Low No |

QUIPS, Quality in Prognosis Studies tool; JBI, Joanna Briggs Institute
to the year 2005. The various studies included in this systematic review were found in the medium-to-low spectrum in the RoB assessment (Table III)\(^{37-39}\).

Of the 4611 \textit{S.} Typhi isolates obtained from the various studies, 41 per cent (1936 \textit{S.} Typhi isolates) were from the 2011-2015 time period, although the time period between 2000 and 2004 had 21 yr-stratified summaries, making up 43 per cent of the total year-wise summaries in this study. Nalidixic acid, ciprofloxacin and cephalosporin trends were only analysed from the year 2000 as these drugs were not routinely tested as part of antimicrobial sensitivity studies prior to this period, although preliminary reports of ciprofloxacin resistance surfaced as early as 1992\(^{40}\). Fig. 2 summarises the pan-Indian AMR trends, which indicate a decline in MDR and a high level of FQ resistance.

The temporal trends of AMR showed a steady decline in the proportion of MDR isolates and

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**Table III.** Studies included in the systematic review in which phenotypic AMR trends of \textit{S.} Paratyphi isolates were analysed

| Year of study | Year of publication | Author & Reference | No. of isolates | Study design | Risk of Bias |
|---------------|---------------------|--------------------|----------------|-------------|-------------|
| 1996-2001     | 2000                | Chandel \textit{et al}\(^{37}\) | 83             | Retrospective | Low         | No          |
| 1997-2001     | 2002                | Gautam \textit{et al}\(^{13}\) | 94             | Retrospective | Low         | No          |
| 2012-2014     | 2017                | Harichandran \& Dinesh\(^{17}\) | 22             | Retrospective | Low         | No          |
| 2004          | 2004                | Harish \textit{et al}\(^{18}\) | 1              | NA           | Low         | No          |
| 2010-2011     | 2013                | Jain \& Chugh\(^{18}\) | 75             | Retrospective | Low         | No          |
| 2012          | 2013                | Venkatesh \textit{et al}\(^{15}\) | 92             | Cross-sectional | Low         | No          |
| 2004          | 2007                | Joshi\(^{19}\) | 25             | Cross-sectional | Low         | No          |
| 2014-2015     | 2015                | Misra \textit{et al}\(^{26}\) | 14             | Case Report | Low         | No          |
| 1999-2000     | 2006                | Mohanty \textit{et al}\(^{27}\) | 198            | Retrospective | Low         | No          |
| 2014          | 2015                | Narain \& Gupta\(^{29}\) | 5              | unknown      | Low         | No          |
| 2013          | 2016                | Sharvani \textit{et al}\(^{33}\) | 152            | Cross-sectional | Low         | No          |
| 2001-2002     | 2003                | Tankhiwale \textit{et al}\(^{39}\) | 39             | Retrospective | Low         | No          |

QUIPS, Quality in Prognosis Studies tool\(^6\); JBI, Joanna Briggs Institute\(^7\)

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**Fig. 2.** Temporal representation of AMR trends of enteric fever isolates from Indian reports. (A and B) graphical representations of the proportion of \textit{Salmonella} Typhi and \textit{Salmonella} Paratyphi A isolates obtained from various Indian reports that were resistant to antimicrobials (indicated by coloured lines). Isolates represented in this graph were consolidated from published reports between the 1990s and 2017 from endemic and epidemic sources, assembled systematically. \textit{Source:} Refs 9-39.
Table IV. Studies included in the systematic review in which molecular characteristics of AMR in S. Typhi and Paratyphi A were analysed

| Author & Reference     | Year of publication | No. of S. Typhi analysed | No. of S. Paratyphi analysed | Risk of Bias |
|------------------------|---------------------|--------------------------|-----------------------------|--------------|
| Capoor et al44         | 2009                | 14                       | -                           | Low, No      |
| Capoor41               | 2007                | 12                       | -                           | Low, No      |
| Chau et al42           | 2007                | 23                       | -                           | Low, No      |
| Dahiya et al47         | 2014                | 18                       | -                           | Low, No      |
| Das et al48            | 2017                | 165                      | -                           | Low, No      |
| Devanga Ragupathi et al59 | 2016        | 1                        | -                           | Low, No      |
| Dutta et al40          | 2008                | 2                        | -                           | Low, Yes     |
| Dutta et al41          | 2014                | 18                       | -                           | Low, No      |
| Elumalai et al42       | 2016                | 1                        | -                           | Low, Yes     |
| Gaind et al43          | 2006                | 8                        | 7                           | Low, No      |
| Geetha et al45         | 2014                | 36                       | -                           | Low, No      |
| Gopal et al46          | 2016                | 131                      | -                           | Low, No      |
| Jain and Chugh18       | 2013                | 266                      | -                           | Low, No      |
| Kumarasamy et al47     | 2012                | 1                        | -                           | Low, No      |
| Misra et al48          | 2016                | 100                      | -                           | Low, No      |
| Mohanty et al49        | 2010                | 1                        | -                           | Low, Yes     |
| Nath & Maurya50        | 2010                | 1                        | -                           | Low, No      |
| Ramachandran et al41   | 2017                | 2                        | -                           | Low, No      |
| Renuka et al42         | 2004                | 52                       | 4                           | Low, No      |
| Shanahan et al45       | 2000                | 2                        | -                           | Low, No      |
| Shanahan et al46       | 1998                | 20                       | -                           | Low, No      |
| Thamizhmani et al46    | 2012                | 6                        | -                           | Low, No      |

QUIPS, Quality in Prognosis Studies tool; JBI, Joanna Briggs Institute

accounted for less than 20 per cent of isolates obtained between 2011 and 2015, whereas resistance to FQs continued to increase during this period (from 10% in 2001-2005 to 66% in 2011-2015), necessitating the use of third-generation cephalosporins in the treatment of enteric fever. Third-generation cephalosporin resistance remained constant across all time periods (Table I and Fig. 2). Azithromycin is often used for the treatment of enteric fever, but the number of reports on the susceptibility was too few to be presented in this study although there are sporadic reports of phenotypic resistance. The scenario was similar with the S. Paratyphi A isolates (Table I).

Molecular determinants of AMR

A total of 880 S. Typhi and 11 S. Paratyphi A isolates spanning 22 studies (Table IV) were included for the analysis of molecular mechanisms. Most studies (76%) incorporated the polymerase chain reaction method using specific probes of interest to study the molecular determinants of AMR. There was only one study which looked at the mechanisms of FQ resistance other than single-nucleotide polymorphisms (SNPs) in quinolone resistance-determining region (QRDR) genes, the aac(6\')-lb-cr gene, oqxAB and qepA genes. All other studies only looked at QRDR SNPs.

Genetic signatures implicated in FQ resistance were very distinct amongst the identified Indian isolates. SNPs in gyrA, gyrB, parC and parE, which include the QRDR in the S. Typhi genome, as well as FQ resistance conferring plasmids containing qnrB2, qnrB4 and qnrSI genes, were reported. It was apparent that FQ resistance in S. Typhi was frequently linked to mutations with gyrA (Fig. 3). A frequent position for SNPs in gyrA is codon 83, with the S83F being the most common occurring in 244 isolates. S80I was the most common SNP in the parC gene, detected in 24 isolates, together with a concordant SNP in S83F. The S83Y mutation was detected in 29 isolates, while...
18 isolates harboured the mutation \(\text{gyrA}\) D87N, further underpinning the importance of \(\text{gyrA}\)-associated SNPs, likely in response to antimicrobial selection pressure. Isolates harbouring combinations of three SNPs in \(\text{gyrA}\), at codons 83 and 87 as well as mutations at codon 80 in \(\text{parC}\), are associated with a high level of ciprofloxacin resistance and designated as ‘triple mutants’.\(^{64}\) SNPs in \(\text{parE}\) and \(\text{gyrB}\) were also observed but to a much lower extent (three and seven isolates, respectively). The \(\text{qnrB2}\), \(\text{qnrB4}\) and \(\text{qnrS1}\) resistance determinants were found in \(\text{S. Typhi}\) but are still rare when compared with QRDR mutations.

The recent decline in MDR \(\text{S. Typhi}\) across South and South-East Asia has been accompanied by a decrease in the proportion of isolates carrying IncHI1 plasmids\(^{64,65}\), which often harbour the resistance genes responsible for MDR typhoid (Fig. 3). Such resistance genes are clustered on composite transposons and include \(\text{catA}\), \(\text{sul1}\), \(\text{sul2}\), \(\text{dfrA}\), \(\text{bla}_{\text{TEM-1}}\), \(\text{strA}\), \(\text{strB}\), \(\text{tetA}\), \(\text{tetB}\), \(\text{tetC}\) and \(\text{tetD}\). These MDR-associated genes can also be found integrated on the chromosome of H58 \(\text{S. Typhi}\) in isolates from countries including India and Bangladesh\(^{64,65}\). Other plasmids identified in \(\text{S. Typhi}\) included R27-like, B7-like and those falling into IncH and IncN, but these are relatively uncommon. Extended-spectrum \(\beta\)-lactamase (ESBL)-producing \(\text{S. Typhi}\) isolates, which confer resistance to third-generation cephalosporins, have been reported in India and Pakistan\(^{66,67}\). The Indian isolates carried IncX3 and IncA plasmids which encoded \(\text{bla}_{\text{SHV-12}}\) and \(\text{bla}_{\text{CMY-2}}\) determinants\(^{68}\), as well as \(\text{bla}_{\text{TEM-1B}}\) and \(\text{bla}_{\text{DHA-1}}\), probably on an IncN plasmid\(^{69}\).

**Discussion**

The rapidly changing antimicrobial pressure in India has selected certain clones of \(\text{S. Typhi}\) which continue to adapt to changing pressures. The dominant clone currently circulating is known as H58 and has constantly evolved over the last 15 yr as evidenced by Bayesian estimates\(^{64}\). These H58 strains comprise two main lineages namely lineage I and lineage II\(^{68}\). Analysis of enteric fever isolates from Nepal suggested that lineage I strains were dominant in the 1990s and were gradually replaced by lineage II strains which are now the most prevalent. The distinction of lineages is important due to their varying capacities in carrying AMR-determining genes. While lineage I is more strongly associated with MDR, lineage II strains favour FQ resistance\(^{68}\) with a rapidly expanding highly FQ-resistant sub-population known as ‘triple mutants’.\(^{64}\) These triple mutations are most commonly identified in \(\text{S. Typhi}\) isolates from South Asia, often as a distinct sub-group within the main H58 clonal population\(^{64}\).

The decline in MDR typhoid as seen in the results is likely due to the infrequent use of chloramphenicol and co-trimoxazole in India and in the Indian subcontinent in general. The first-line antimicrobials namely chloramphenicol, co-trimoxazole and ampicillin were widely used in the 1990s which prompted both \(\text{S. Typhi}\) and \(\text{S. Paratyphi A}\) to adapt to this antimicrobial pressure. Both organisms subsequently acquired resistance to these antimicrobials via acquisition of the full suite of seven acquired AMR genes that are typically located within a composite transposon, comprising Tn6029 (\(\text{sul2}\), \(\text{strA}\), \(\text{strAB}\) and \(\text{bla}_{\text{TEM-1}}\)) and Tn21 (\(\text{dfrA7}\), \(\text{sul1}\)) inserted within Tn9 (\(\text{catA}\)), which is often carried on the IncHI1 group of plasmids\(^{64}\). This plasmid possesses genes which confer resistance to sulphonamides (\(\text{sul1}\), \(\text{sul2}\)), ampicillin (\(\text{bla}_{\text{TEM-1}}\)), trimethoprim (\(\text{dfrA7}\)), chloramphenicol (\(\text{catA}\)) and streptomycin (\(\text{strAB}\)). The horizontal transfer of these plasmids to \(\text{S. Typhi}\) and \(\text{S. Paratyphi A}\) also meant that these plasmids could be lost in the absence of such antimicrobial pressure, as was seen at the turn of the century when FQs became the drug of choice and the first-line antimicrobials fell out of favour among clinicians due to widespread resistance.

Ciprofloxacin and ofloxacin were the choices for both empirical therapy and treatment of culture-proven enteric fever, resulting in FQ-associated antimicrobial pressure. The spread of FQ resistance across India was enhanced by the emergence of the H58 clade, which dominated circulating \(\text{S. Typhi}\) populations in India by the late 1990s, with an apparent increased fitness advantage and enhanced transmission success\(^{69,70,71}\). These clones of \(\text{S. Typhi}\) and \(\text{S. Paratyphi A}\) accumulated non-synonymous SNPs in the genome inducing conformational changes in DNA gyrase and topoisomerase IV, the main sites of FQ action\(^{64,72}\). The genes in which SNPs occur include \(\text{gyrA}\), \(\text{parC}\), \(\text{parE}\) and \(\text{gyrB}\), with \(\text{gyrA}\) SNPs correlating strongly with treatment failure\(^{69}\). Accumulating mutations in the QRDR cause \(\text{S. Typhi}\) to gradually increase the MIC values of ciprofloxacin. Ciprofloxacin-susceptible strains (MIC - 0.06 \(\mu\)g ml) are known to acquire a \(\text{gyrA}\) S83F single mutation with a subsequent increase in MIC values (0.12-0.5 \(\mu\)g ml), and additional \(\text{gyrA}\) and
parC mutations continue to cause an increase in MICs up to 4 µg ml\(^{-1}\).

The standard method of antimicrobial sensitivity testing, i.e. disc diffusion, suggested that S. Typhi was still relatively sensitive to ciprofloxacin despite ongoing treatment failure and relapse\(^{73,74}\). A WHO report comprising an antimicrobial surveillance study of enteric fever isolates from 15 sites across India between 2008 and 2010 revealed that sensitivity of nalidixic acid was a good indicator of FQ sensitivity, but nalidixic acid resistance correlated poorly with ciprofloxacin resistance\(^{74}\). The fact that nalidixic acid breakpoints on disc diffusion correlated more accurately with ciprofloxacin-related treatment outcomes prompted a revision in the CLSI-recommended breakpoints for ciprofloxacin. A report from Veeraraghavan et al\(^{75}\) compared breakpoints for ciprofloxacin using the CLSI guidelines before and after the 2012 revision and also with the EUCAST guidelines and found that only three per cent of isolates were sensitive using the revised guidelines versus 95 per cent of isolates that were sensitive using the older guidelines. The sensitivities of isolates reported using EUCAST breakpoints were comparable to the revised CLSI breakpoints\(^{75}\). In our analysis, the trend lines of changing nalidixic acid and ciprofloxacin resistance over time seem to converge from 2011, which may in large part be due to revisions in the CLSI guidelines.

In the face of FQ resistance, third-generation cephalosporins and azithromycin have become the preferred treatment choices for enteric fever. However, the most contemporary concern stems from the emergence of ESBLs produced by various Gram-negative species, which has originated as a result of the widespread cephalosporin use which has subsequently led to treatment failure with third-generation cephalosporins in India\(^{59,66}\). More worryingly, reports from Pakistan\(^{67,76}\) detailing an extensively drug-resistant typhoid outbreak in populous parts of the Sindh province\(^{76}\) are a cause for concern. These isolates had a composite transposon as described above and an additional Inc\(Y\) plasmid containing \(bla_{CTX-M15}\) and \(qnrS\) genes\(^{77}\), conferring resistance to the first-line antimicrobials, FQs and third-generation cephalosporins. Cephalosporins were the most commonly used antimicrobial in India followed by broad-spectrum penicillins, FQs and macrolides as per a 2014 report\(^{78}\) and more recently by a 2018 report\(^{79}\). This indirectly portrays the antimicrobial pressure exerted by the use of cephalosporins, which has consequently led to the production of ESBLs by Gram-negative bacteria, including S. Typhi\(^{59,66,67}\).
As with most community-acquired infections, single-drug therapy (monotherapy) has been a common practice in the management of enteric fever. Monotherapy with the former first-line antimicrobials may not be an unreasonable option in India as evidenced by the results from this systematic review. A case report from Nepal suggests that treatment with co-trimoxazole results in complete remission of H58-related typhoid which was FQ-resistant but not MDR. However, a more judicious approach might involve combination therapy with a first-line antimicrobial and perhaps azithromycin. This approach could potentially facilitate the conservation of cephalosporins and reduce the antimicrobial pressure currently exerted by the widespread use of this class of drugs. The decrease in MDR as highlighted in these data following the scant use of first-line antibiotics (amoxicillin, chloramphenicol and co-trimoxazole) suggests that an additional option of cycling these antimicrobials potentially exists, on the condition that close monitoring of antimicrobial susceptibility is feasible.

India is not only one of the largest global consumers of antibiotics, but also one of the countries with the highest rates of AMR. Between 2000 and 2015, antimicrobial consumption expressed in defined daily doses increased by 103 per cent (3.2 billion in 2000-6.5 billion in 2015), making it the number one consumer of antimicrobials in low- and middle-income countries. The strongest factor attributed to this trend was an increase in the use of cephalosporins, due to changing prescribing practices for enteric fever and other infections including those of the respiratory tract, skin and soft tissue as well as gonococcal infections. Cephalosporins replaced penicillins and quinolones for infection management in both empirical and definitive treatment. Antimicrobials available to the community from both private and public sector pharmacies included FQs, cephalosporins, macrolides and co-trimoxazole, and more recently carbapenems, with chloramphenicol being rarely prescribed or used over the counter. The excessive use of third-generation cephalosporins for acute febrile illnesses as well as respiratory tract infections and the inappropriate usage of FQs for diarrhoea all contribute to antimicrobial pressure which impacts treatment options for bloodstream infections such as enteric fever. Fixed-drug combinations that are available for use include combinations of FQs with antiprotozoal drugs, FQs with azithromycin or cefixime and cefixime with azithromycin, often licensed for use by State Drug Licensing Authorities without documented central regulatory approval. Social factors that contribute to rising AMR include access to antimicrobials without prescription and the use of pharmacies and informal providers as sources of healthcare by the general public, exposure to antimicrobial residues in animal husbandry (such as ciprofloxacin used for growth promotion in poultry) leading to a general increase in antimicrobial pressure in the environment, plus the lack of established monitored standards for antimicrobial residues in pharmaceutical industry effluents.

This study was limited by the fact that these isolates did not represent the antibiogram of Indian isolates in its entirety. Most isolates in this study were obtained from tertiary care settings, with almost no representation from community settings although it is plausible that the antibiogram of isolates would not be very different between community and hospital settings as far as enteric fever is concerned. Finally, the CLSI breakpoints were significantly revised in 2011, and it was not possible to ascertain how quickly laboratories transitioned to the new breakpoint guidelines which might have a bearing on the estimation of ciprofloxacin resistance around the 2011-2012 period.

The problem of AMR in the pathogens which cause enteric fever underscores the importance of controlling the spread of typhoid through the deployment of vaccines and prudent antimicrobial use in the short term. Immunization could theoretically reduce the number of circulating MDR, FQ- and cephalosporin-resistant strains and, furthermore, decrease the incidence of undifferentiated febrile illness, thereby reducing the need for empirical antimicrobial therapy.

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Conflicts of Interest: The last author (AJP) chairs the UK Department of Health’s (DH) Joint Committee on Vaccination and Immunisation (JCVI) and is a member of the World Health Organization’s (WHO) Strategic Advisory Group of Experts. The views expressed in this manuscript do not necessarily reflect the views of JCVI, DH, or WHO. Other authors have no competing interests to declare.
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