Systematic Review

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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

Enteric fever caused by serovars Typhi and Paratyphi A, B and C of the *Salmonella enterica* species accounts for over 25 million cases of febrile illness globally, with children being affected disproportionally[1-3]. India is endemic for enteric fever, where it is one of the main differential diagnoses for fever of unknown origin. In addition to the morbidity and mortality associated with enteric fever, the empiric and appropriate treatment of this disease continues to drive antimicrobial resistance (AMR). Multidrug-resistant (MDR) enteric fever isolates, defined as combined resistance to chloramphenicol, ampicillin and co-trimoxazole, were a common occurrence in the 1990s that necessitated the use of fluoroquinolones (FQs), subsequently cephalosporins and most recently azithromycin[2].

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)[2,3]. 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[4]. It is, however, yet to be used programmatically, 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[5] . 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.

Table I. Enteric fever pathogen isolates derived from reports systematically reviewed in this study

Year	Total number	Proportion of *Salmonella* Typhi-resistant isolates					
		CH	AM	TMX	NA	FQ	CEPH
Pre-2001	854	0.51	0.56	0.58	-	-	-
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
		Proportion of *Salmonella* Paratyphi A-resistant isolates					
Pre-2001	179	0.22	0.21	0.26	-	-	-
2001-2005	261	0.29	0.43	0.21	0.59	0.03	0.00
2006-2010	26	0.00	0.04	0.00	0.77	0.58	0.04
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

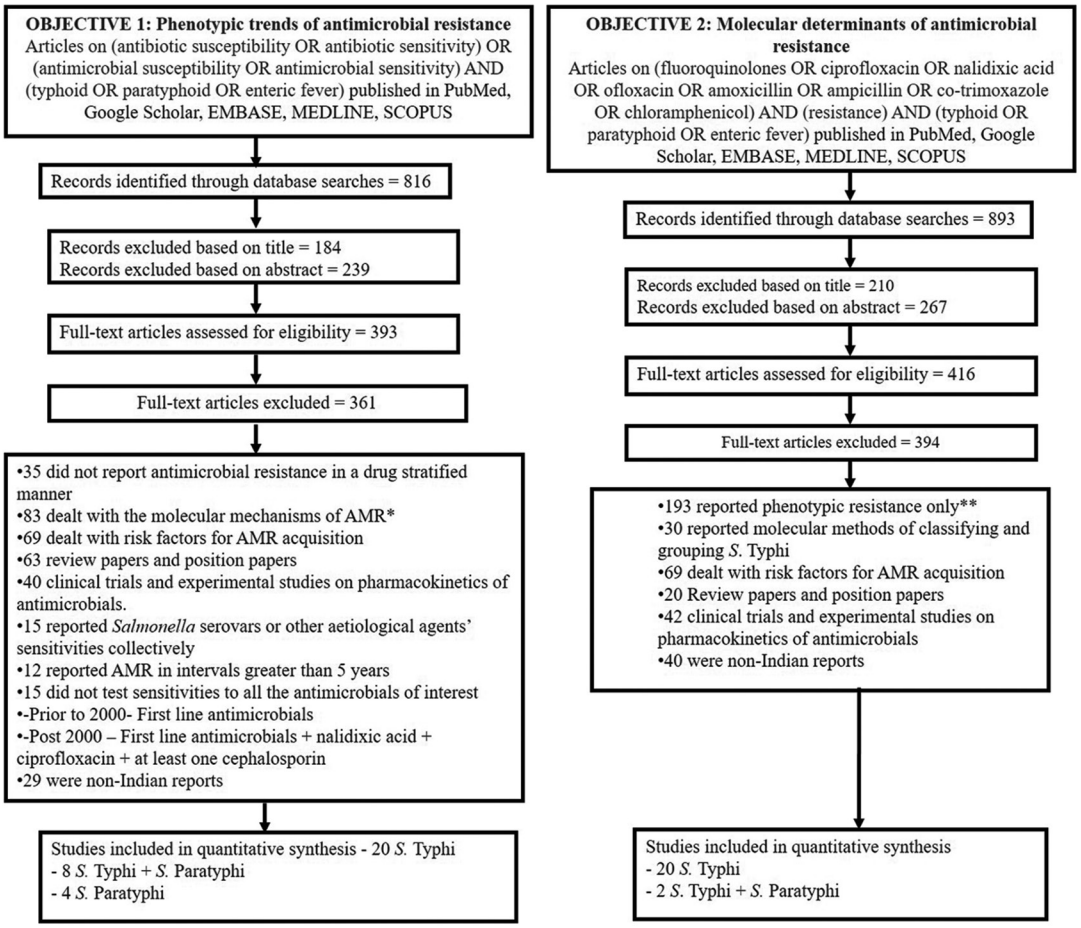


Fig. 1. Search Strategy and PRISMA flow diagram. *The eligibility of these excluded articles were screened for inclusion under objective 2, and non-duplicate articles were included. **The eligibility of these excluded articles were screened for inclusion under objective 1, and non-duplicate articles 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[6]. The second is known as the Joanna Briggs Institute (JBI) tool[7] and reports RoB dichotomously. The JBI was adapted for use in this study similar to the adaptations used by Tadesse *et al*[8]. 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

Table II. Studies included in the systematic review in which phenotypic AMR trends of *S.* Typhi isolates were analysed

Year of study	Year of publication	Author & Reference	No. of isolates	Study Design	Risk of Bias	
					QUIPS	JBI
2012	2017	Harichandran & Dinesh[17]	79	Retrospective	Low	No
2016	2016	Sharvani *et al*[33]	167	Retrospective	Low	No
2013-2014	2015	Misra *et al*[26]	50	Retrospective	Low	No
2015	2015	Narain & Gupta[29]	220	Prospective	Low	No
2012	2014	Srirangaraj *et al*[34]	16	Retrospective	Low	No
2014	2017	Dahiya *et al*[13]	380	Retrospective	Low	No
2010	2013	Choudhary *et al*[12]	322	Retrospective	Low	No
2012	2013	Venkatesh *et al*[35]	251	Retrospective	Low	No
2008-2010	2013	Gupta *et al*[16]	257	Retrospective	Low	No
2010-2012	2013	Jain & Chugh[18]	266	Retrospective	Low	No
2008	2011	Kumar *et al*[22]	128	Retrospective	Low	No
2011	2011	Adhikary *et al*[9]	2	Case Report	Low	Yes
2000-2006	2010	Verma *et al*[36]	159	Retrospective	Low	No
2008	2009	Kumar *et al*[21]	50	Retrospective	Low	No
1990	1992	Rodrigues *et al*[31]	74	Retrospective	Low	No
2004	2007	Joshi & Amarnath[19]	25	Retrospective	Low	No
2002	2007	Capoor *et al*[11]	178	Retrospective	Low	No
2003	2007	Banerjee *et al*[10]	60	Retrospective	Low	No
2004-2005	2006	Manchanda *et al*[25]	56	Retrospective	Low	No
2006	2006	Ray *et al*[30]	70	Cross-sectional	Low	No
1999-2004	2006	Mohanty *et al*[27]	629	Retrospective	Low	No
2001-2004	2006	Lakshmi *et al*[23]	60	Retrospective	Low	No
2003-2004	2005	Dutta *et al*[14]	379	Retrospective	Low	No
2004	2005	Senthilkumar *et al*[32]	6	Retrospective	Low	No
2002	2004	Madhulika *et al*[24]	157	Cross-sectional	Low	No
1997-2001	2002	Gautam *et al*[15]	436	Retrospective	Low	No
2001-2003	2005	Kadhiravan *et al*[20]	50	Retrospective	Low	No
2006-2007	2010	Nagshetty *et al*[28]	84	Retrospective	Low	No

QUIPS, Quality in Prognosis Studies tool[6]; JBI, Joanna Briggs Institute[7]

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

Year of study	Year of publication	Author & Reference	No. of isolates	Study design	Risk of Bias	
					QUIPS	JBI
1996-2001	2000	Chandel *et al*[37]	83	Retrospective	Low	No
1997-2001	2002	Gautam *et al*[15]	94	Retrospective	Low	No
2012-2014	2017	Harichandran & Dinesh[17]	22	Retrospective	Low	No
2004	2004	Harish *et al*[38]	1	NA	Low	No
2010-2011	2013	Jain & Chugh[18]	75	Retrospective	Low	No
2012	2013	Venkatesh *et al*[35]	92	Cross-sectional	Low	No
2004	2007	Joshi[19]	25	Cross-sectional	Low	No
2014-2015	2015	Misra *et al*[26]	14	Case Report	Low	No
1999-2000	2006	Mohanty *et al*[27]	198	Retrospective	Low	No
2014	2015	Narain & Gupta[29]	5	unknown	Low	No
2013	2016	Sharvani *et al*[33]	152	Cross-sectional	Low	No
2001-2002	2003	Tankhiwale *et al*[39]	39	Retrospective	Low	No

QUIPS, Quality in Prognosis Studies tool[6]; JBI, Joanna Briggs Institute[7]

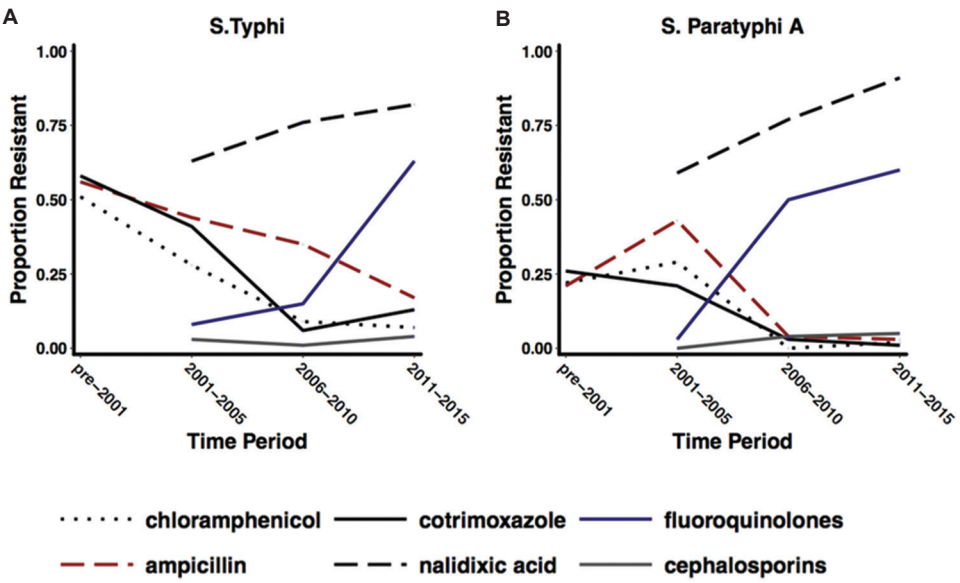


Fig. 2. Temporal representation of AMR trends of enteric fever isolates from Indian reports. (**A** and **B**) graphical representations of the proportion of *Salmonella* Typhi and *Salmonella* Paratyphi A isolates obtained from various Indian reports that were resistant to antimicrobials (indicated 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. *Source*: Refs 9-39.

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 *S.* Typhi isolates obtained from the various studies, 41 per cent (1936 *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

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	
				QUIPS	JBI
Capoor *et al*[44]	2009	14	-		
Capoor[11]	2007	12	-	Low	No
Chau *et al*[54]	2007	23	-	Low	No
Dahiya *et al*[57]	2014	18	-	Low	No
Das *et al*[58]	2017	165	-	Low	No
Devanga Ragupathi *et al*[59]	2016	1	-	Low	No
Dutta *et al*[60]	2008	2	-	Low	Yes
Dutta *et al*[61]	2014	18	-	Low	No
Elumalai *et al*[62]	2016	1	-	Low	Yes
Gaind *et al*[63]	2006	8	7	Low	No
Geetha *et al*[45]	2014	36	-	Low	No
Gopal *et al*[46]	2016	131	-	Low	No
Jain and Chugh[18]	2013	266	-	Low	No
Kumarasamy *et al*[47]	2012	1	-	Low	No
Misra *et al*[48]	2016	100	-	Low	No
Mohanty *et al*[49]	2010	1	-	Low	Yes
Nath & Maurya[50]	2010	1	-	Low	No
Ramachandran *et al*[51]	2017	2	-	Low	No
Renuka *et al*[52]	2004	52	4	Low	No
Shanahan *et al*[55]	2000	2	-	Low	No
Shanahan *et al*[53]	1998	20	-	Low	No
Thamizhmani *et al*[56]	2012	6	-	Low	No

QUIPS, Quality in Prognosis Studies tool[6]; JBI, Joanna Briggs Institute[7]

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[41-43]. 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)[11,18,44-63] 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[46] which looked at the mechanisms of FQ resistance other than single-nucleotide polymorphisms (SNPs) in quinolone resistance-determining region (QRDR) (*qnr* 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 *qnrS1* genes, were reported[64]. 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 *gyrA* D87N, further underpinning the importance of *gyrA*-associated SNPs, likely in response to antimicrobial selection pressure. Isolates harbouring combinations of three SNPs in *gyrA*, at codons 83 and 87 as well as mutations at codon 80 in *parC,* are associated with a high level of ciprofloxacin resistance and designated as 'triple mutants'[64]. SNPs in *parE* and *gyrB* were also observed but to a much lower extent (three and seven isolates, respectively). The *qnrB2*, *qnrB4* and *qnrS1* resistance determinants were found in *S*. Typhi but are still rare when compared with QRDR mutations.

The recent decline in MDR *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 *catA, sul1, sul2, dfrA, bla*$_{TEM-1}$, *strA*, *strB, tetA, tetB, tetC* and *tetD*. These MDR-associated genes can also be found integrated on the chromosome of H58 *S*. Typhi in isolates from countries including India and Bangladesh[64,65] Other plasmids identified in *S*. Typhi included R27-like, B7-like and those falling into IncH and IncN, but these are relatively uncommon. Extended-spectrum β-lactamase (ESBL)-producing *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 bla$_{SHV-12}$ and bla$_{CMY-2}$ determinants[66], as well as bla$_{TEM-1B}$ and bla$_{DHA-1}$, probably on an IncN plasmid[59].

Discussion

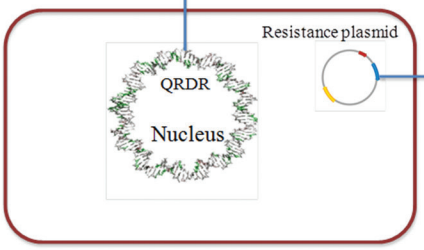
The rapidly changing antimicrobial pressure in India has selected certain clones of *S.* Typhi which continue to adapt to changing pressures. The dominant clone currently circulating is known as H58 and has constantly evolved over the last 15 yr as evidenced by Bayesian estimates[64]. These H58 strains 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 *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 *S.* Typhi and *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 Tn*6029* (*sul2*, *strA, strAB* and *bla*$_{TEM-1}$) and Tn*21* (*dfrA7, sul1*) inserted within Tn*9* (*catA*)*,* which is often carried on the IncHI1 group of plasmids[64]. This plasmid possesses genes which confer resistance to sulphonamides (*sul1, sul2*), ampicillin (*bla*$_{TEM-1}$), trimethoprim (*dfrA7*), chloramphenicol (*catA*) and streptomycin (*strAB*). The horizontal transfer of these plasmids to *S.* Typhi and *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 *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 *S.* Typhi and *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 *gyrA*, *parC*, *parE* and *gyrB*, with *gyrA* SNPs correlating strongly with treatment failure[69]. Accumulating mutations in the QRDR cause *S.* Typhi to gradually increase the MIC values of ciprofloxacin. Ciprofloxacin-susceptible strains (MIC - 0.06 µg ml) are known to acquire a *gyrA* S83F single mutation with a subsequent increase in MIC values (0.12-0.5 µg ml), and additional *gyrA* and

SNPs conferring fluoroquinolone resistance

Gene	*gyrA*		*parC*	*gyrA* + *parC*	Others
SNP	S83F/Y	D87N/V/G/Y	S80I	S83+D87+S80	-
Number	273	29	24	5	9



Plasmids conferring MDR

Plasmid type	Number
IncHI1	24
Other Inc type	38
Non-Inc	2

MDR genes carried on plasmids or within the genome

Gene	*catA*	*strA & strB*	bla_{TEM-1}	*dfrA*	*sul1 & sul2*	Others
Antimicrobial	chloramphenicol	streptomycin	β-lactams	trimethoprim	sulfonamides	-
Number	113	3	118	110	236	45

Fig. 3. Molecular determinants of AMR in enteric fever isolates from India. Fluoroquinolone resistance occurs through mutational DNA gyrase enzyme of the bacteria which is encoded by *gyrA*, *gyrB*, *parC* and *parE* genes (quinolone resistance-determining region). Number refers to the number of isolates harbouring the respective determinant of antimicrobial resistance as identified through the review. Amino acids: S, serine; F, phenylalanine; Y, tyrosine; D, asparagine; N, aspartic acid; I, isoleucine.

parC mutations continue to cause an increase in MICs up to 4 µg ml[71].

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 IncY 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[79]. 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[80]. 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[78]. The strongest factor attributed to this trend was an increase in the use of cephalosporins[81], 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[81]. Cephalosporins replaced penicillins and quinolones for infection management in both empirical and definitive treatment[78]. Antimicrobials available to the community from both private and public sector pharmacies included FQs, cephalosporins, macrolides and co-trimoxazole[82], 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[83] as well as respiratory tract infections[84] and the inappropriate usage of FQs for diarrhoea[82,85] 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[86]. 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[87].

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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References

1. Buckle GC, Walker CL, Black RE. Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. *J Glob Health* 2012; *2* : 010401.
2. Summary of the October 2017 Meeting of the Strategic Advisory Group of Experts on Immunization. Geneva, Switzerland; 17-19 October. 2017.
3. SAGE Working Group on Typhoid Vaccines. Background Paper to SAGE on typhoid Vaccine Policy recommendations; 24 September, 2017.
4. World Health Organization. *Safety of Typhoid Vaccines*. Available from: *http://www.who.int/vaccine_safety/committee/topics/typhoid/Dec_2016/en/*, accessed on April 3, 2018.
5. Britto CD, Wong VK, Dougan G, Pollard AJ. A systematic review of antimicrobial resistance in *Salmonella enterica* serovar Typhi, the etiological agent of typhoid. *PLoS Negl Trop Di* 2018; *12* : e0006779.
6. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; *158* : 280-6.
7. Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H. *Methodology for JBI umbrella reviews*. Joanna Briggs Institute Reviewers' Manual: 2014 edition / Supplement (pp. 1-34). Australia: The Joanna Briggs Institute; 2014.
8. Tadesse G, Tessema TS, Beyene G, Aseffa A. Molecular epidemiology of fluoroquinolone resistant *Salmonella* in Africa: A systematic review and meta-analysis. *PLoS One* 2018; *13*: e0192575.
9. Adhikary R, Joshi S. Dual *Salmonella typhi* Typhi infection. *Indian J Pathol Microbiol* 2011; *54* : 849-50.
10. Banerjee A, Kalghatgi AT, Singh P, Nagendra A, Singh Z, Handa SK. Epidemiological investigation of an outbreak of enteric fever. *Med J Armed Forces India* 2007; *63* : 322-4.
11. Capoor MR, Nair D, Aggarwal P, Mathys V, Dehem M, Bifani PJ. *Salmonella enterica* serovar Typhi: Molecular analysis of strains with decreased susceptibility and resistant to ciprofloxacin in India from 2001-2003. *Braz J Infect Dis* 2007; *11* : 423-5.
12. Choudhary A, Gopalakrishnan R, Nambi PS, Ramasubramanian V, Ghafur KA, Thirunarayan MA. Antimicrobial susceptibility of *Salmonella enterica* serovars in a tertiary care hospital in southern India. *Indian J Med Res* 2013; *137* : 800-2.
13. Dahiya S, Sharma P, Kumari B, Pandey S, Malik R, Manral N, *et al*. Characterisation of antimicrobial resistance in Salmonellae during 2014-2015 from four centres across India: An ICMR antimicrobial resistance surveillance network report. *Indian J Med Microbiol* 2017; *35* : 61-8.
14. Dutta S, Sur D, Manna B, Bhattacharya SK, Deen JL, Clemens JD. Rollback of Salmonella enterica serotype Typhi resistance to chloramphenicol and other antimicrobials in Kolkata, India. *Antimicrob Agents Chemother* 2005; *49* : 1662–3.
15. Gautam V, Gupta NK, Chaudhary U, Arora DR. Sensitivity pattern of *Salmonella* serotypes in Northern India. *Braz J Infect Dis* 2002; *6* : 281-7.
16. Gupta V, Singla N, Bansal N, Kaistha N, Chander J. Trends in the antibiotic resistance patterns of enteric fever isolates - a three year report from a tertiary care centre. *Malays J Med Sci* 2013; *20* : 71-5.
17. Harichandran D, Dinesh KR. Antimicrobial susceptibility profile, treatment outcome and serotype distribution of clinical isolates of *Salmonella enterica* subspecies enterica: A 2-year study from Kerala, South India. *Infect Drug Resist* 2017; *10* : 97-101.
18. Jain S, Chugh TD. Antimicrobial resistance among blood culture isolates of *Salmonella enterica* in New Delhi. *J Infect Dev Ctries* 2013; *7* : 788-95.
19. Joshi S, Amarnath SK. Fluoroquinolone resistance in *Salmonella* Typhi and *S*. Paratyphi A in Bangalore, India. *Trans R Soc Trop Med Hyg* 2007; *101* : 308-10.
20. Kadhiravan T, Wig N, Kapil A, Kabra SK, Renuka K, Misra A. Clinical outcomes in typhoid fever: adverse impact of infection with nalidixic acid-resistant *Salmonella* Typhi. *BMC Infect Dis* 2005; *5* : 37.
21. Kumar Y, Sharma A, Mani KR. High level of resistance to nalidixic acid in *Salmonella enterica* serovar Typhi in Central India. *J Infect Dev Ctries* 2009; *3* : 467-9.
22. Kumar Y, Sharma A, Mani KR. Re-emergence of susceptibility to conventionally used drugs among strains of *Salmonella* Typhi in central west India. *J Infect Dev Ctries* 2011; *5* : 227-30.
23. Lakshmi V, Ashok R, Susmita J, Shailaja VV. Changing trends in the antibiograms of *Salmonella* isolates at a tertiary care hospital in Hyderabad. *Indian J Med Microbiol* 2006; *24* : 45-8.
24. Madhulika U, Harish BN, Parija SC. Current pattern in antimicrobial susceptibility of *Salmonella* Typhi isolates in Pondicherry. *Indian J Med Res* 2004; *120* : 111-4.
25. Manchanda V, Bhalla P, Sethi M, Sharma VK. Treatment of enteric fever in children on the basis of current trends of antimicrobial susceptibility of *Salmonella enterica* serovar typhi and paratyphi A. *Indian J Med Microbiol* 2006; *24* : 101-6.
26. Misra R, Prasad KN, Amrin N, Kapoor P, Singh S, Ghar M. Absence of multidrug resistance in *Salmonella enterica* serotypes Typhi and Paratyphi A isolates with intermediate susceptibility to ciprofloxacin. *Trans R Soc Trop Med Hyg* 2015; *109* : 538-40.
27. Mohanty S, Renuka K, Sood S, DAS BK, Kapil A. Antibiogram pattern and seasonality of *Salmonella* serotypes in a North Indian tertiary care hospital. *Epidemiol Infect* 2006; *134* : 961-6.
28. Nagshetty K, Channappa ST, Gaddad SM. Antimicrobial susceptibility of *Salmonella* Typhi in India. *J Infect Dev Ctries* 2010; *4* : 70-3.

29. Narain U, Gupta R. Emergence of resistance in community-acquired enteric fever. *Indian Pediatr* 2015; *52* : 709.
30. Ray P, Sharma J, Marak RSK, Garg RK. Predictive efficacy of nalidixic acid resistance as a marker of fluoroquinolone resistance in *Salmonella enterica* var Typhi. *Indian J Med Res* 2006; *124* : 105-8.
31. Rodrigues C, Mehta A, Mehtar S, Blackmore PH, Hakimiyan A, Fazalbhoy N, *et al*. Chloramphenicol resistance in *Salmonella* typhi. Report from Bombay. *J Assoc Physicians India* 1992; *40* : 729-32.
32. Senthilkumar B, Prabakaran G. Multidrug resistant *Salmonella* typhi in asymptomatic typhoid carriers among food handlers in Namakkal district, Tamil Nadu. *Indian J Med Microbiol* 2005; *23* : 92-4.
33. Sharvani R, Hemavathi, Dayanand DK, Shenoy P, Sarmah P. Antibiogram of *Salmonella* Isolates: Time to consider antibiotic salvage. *J Clin Diagn Res* 2016; *10* : DC06-8.
34. Srirangaraj S, Kali A, Charles MV. A study of antibiogram of *Salmonella enterica* serovar Typhi isolates from Pondicherry, India. *Australas Med J* 2014; *7* : 185-90.
35. Venkatesh BM, Joshi S, Adhikary R, Bhaskar BH. Antibiogram of *Salmonella* typhii and *Salmonella* paratyphi A in a tertiary care hospital in 2012. *Indian J Pathol Microbiol* 2013; *56* : 484-5.
36. Verma S, Thakur S, Kanga A, Singh G, Gupta P. Emerging *Salmonella* Paratyphi A enteric fever and changing trends in antimicrobial resistance pattern of salmonella in Shimla. *Indian J Med Microbiol* 2010; *28* : 51-3.
37. Chandel DS, Chaudhry R, Dhawan B, Pandey A, Dey AB. Drug-resistant *Salmonella enterica* serotype paratyphi A in India. *Emerg Infect Dis* 2000; *6* : 420-1.
38. Harish BN, Madhulika U, Parija SC. Isolated high-level ciprofloxacin resistance in *Salmonella enterica* subsp. enterica serotype Paratyphi A. *J Med Microbiol* 2004; *53* (Pt 8) : 819.
39. Tankhiwale SS, Agrawal G, Jalgaonkar SV. An unusually high occurrence of *Salmonella enterica* serotype Paratyphi A in patients with enteric fever. *Indian J Med Res* 2003; *117* : 10-2.
40. Ugboko H, De N. Mechanisms of antibiotic resistance in *Salmonella* typhi. *Int J Curr Microbiol App Sci* 2014; *3* : 461-76.
41. Rai S, Jain S, Prasad KN, Ghoshal U, Dhole TN. Rationale of azithromycin prescribing practices for enteric fever in India. *Indian J Med Microbiol* 2012; *30* : 30-3.
42. Kumar VA, Kumar A, Khan S, Dinesh KR, Karim S. Revised ciprofloxacin breakpoints for *Salmonella*: Is it time to write an obituary? *J Clin Diagn Res* 2013; *7* : 2467-9.
43. Patel SR, Bharti S, Pratap CB, Nath G. Drug resistance pattern in the recent isolates of *Salmonella* Typhi with special reference to cephalosporins and azithromycin in the gangetic plain. *J Clin Diagn Res* 2017; *11* : DM01-DM03.
44. Capoor MR, Nair D, Walia NS, Routela RS, Grover SS, Deb M, *et al*. Molecular analysis of high-level ciprofloxacin resistance in *Salmonella enterica* serovar Typhi and *S.* Paratyphi A: need to expand the QRDR regio. *Epidemiol Infect* 2009; *137* : 871-8.
45. Geetha VK, Yugendran T, Srinivasan R, Harish BN. Plasmid-mediated quinolone resistance in typhoidal Salmonellae: a preliminary report from South India. *Indian J Med Microbiol* 2014; *32* : 31-4.
46. Gopal M, Elumalai S, Arumugam S, Durairajpandian V, Kannan MA, Selvam E, *et al*. GyrA ser83 and ParC trp106 mutations in *Salmonella enterica* serovar Typhi isolated from typhoid fever patients in tertiary care hospital. *J Clin Diagn Res* 2016; *10* : DC14-8.
47. Kumarasamy K, Krishnan P. Report of a *Salmonella enterica* serovar Typhi isolate from India producing CMY-2 AmpC beta-lactamase. *J Antimicrob Chemother* 2012; *67* : 775-6.
48. Misra R, Thakare R, Amrin N, Prasad KN, Chopra S, Dhole TN. Antimicrobial susceptibility pattern and sequence analysis of DNA gyrase and DNA topoisomerase IV in *Salmonella enterica* serovars Typhi and Paratyphi A isolates with decreased susceptibility to ciprofloxacin. *Trans R Soc Trop Med Hyg* 2016; *110* : 472-9.
49. Mohanty S, Gaind R, Paglietti B, Paul P, Rubino S, Deb M. Bacteraemia with pleural effusions complicating typhoid fever caused by high-level ciprofloxacin-resistant *Salmonella enterica* serotype Typhi. *Ann Trop Paediatr* 2010; *30* : 233-40.
50. Nath G, Maurya P. Drug resistance patterns in *Salmonella enterica* subspecies enterica serotype Typhi strains isolated over a period of two decades, with special reference to ciprofloxacin and ceftriaxone. *Int J Antimicrob Agents* 2010; *35* : 482-5.
51. Ramachandran A, Shanthi M, Sekar U. Detection of blaCTX-M extended spectrum beta-lactamase producing *Salmonella enterica* Serotype Typhi in a tertiary care centre. *J Clin Diagnostic Res* 2017; *11* : DC21-DC24.
52. Renuka K, Kapil A, Kabra SK, Wig N, Das BK, Prasad VV, *et al*. Reduced susceptibility to ciprofloxacin and gyra gene mutation in North Indian strains of *Salmonella enterica* serotype Typhi and serotype Paratyphi A. *Microb Drug Resist* 2004; *10* : 146-53.
53. Shanahan PM, Jesudason MV, Thomson CJ, Amyes SG. Molecular analysis of and identification of antibiotic resistance genes in clinical isolates of *Salmonella* Typhi from India. *J Clin Microbiol* 1998; *36* : 1595-600.
54. Chau TT, Campbell JI, Galindo CM, Van Minh Hoang N, Diep TS, Nga TT, *et al*. Antimicrobial drug resistance of *Salmonella enterica* serovar typhi in asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. *Antimicrob Agents Chemother* 2007; *51* : 4315-23.
55. Shanahan PM, Karamat KA, Thomson CJ, Amyes SG. Characterization of multi-drug resistant *Salmonella* Typhi isolated from Pakistan. *Epidemiol Infect* 2000; *124* : 9-16.
56. Thamizhmani R, Bhattacharya D, Sayi DS, Bhattacharjee H, Muruganandam N, Ghosal SR, *et al*. Emergence of fluoroquinolone resistance in *Salmonella*

enterica serovar Typhi in Andaman and Nicobar Islands, India. *Indian J Med Res* 2012; *136* : 98-101.

57. Dahiya S, Kapil A, Lodha R, Kumar R, Das BK, Sood S, *et al*. Induction of resistant mutants of *Salmonella enterica* serotype Typhi under ciprofloxacin selective pressure. *Indian J Med Res* 2014; *139* : 746-53.
58. Das S, Samajpati S, Ray U, Roy I, Dutta S. Antimicrobial resistance and molecular subtypes of *Salmonella enterica* serovar Typhi isolates from Kolkata, India over a 15 years period 1998-2012. *Int J Med Microbiol* 2017; *307* : 28-36.
59. Devanga Ragupathi NK, Muthuirulandi Sethuvel DP, Shankar BA, Munusamy E, Anandan S, Veeraraghavan B. Draft genome sequence of blaTEM-1-mediated cephalosporin-resistant *Salmonella enterica s*erovar Typhi from bloodstream infection. *J Glob Antimicrob Resist* 2016; *7* : 11-2.
60. Dutta S, Sur D, Manna B, Sen B, Bhattacharya M, Bhattacharya SK, *et al*. Emergence of highly fluoroquinolone-resistant *Salmonella enterica* serovar Typhi in a community-based fever surveillance from Kolkata, India. *Int J Antimicrob Agents* 2008; *31* : 387-9.
61. Dutta S, Das S, Mitra U, Jain P, Roy I, Ganguly SS, *et al*. Antimicrobial resistance, virulence profiles and molecular subtypes of *Salmonella enterica* serovars Typhi and Paratyphi A blood isolates from Kolkata, India during 2009-2013. *PLoS One* 2014; *9* : e101347.
62. Elumalai S, Seetharaman S. Molecular analysis of fluoroquinolone resistance in *Salmonella enterica* serovar Typhi from a breast abscess case. *Indian J Pathol. Microbiol* 2016; *59* : 261.
63. Gaind R, Paglietti B, Murgia M, Dawar R, Uzzau S, Cappuccinelli P, *et al*. Molecular characterization of ciprofloxacin-resistant *Salmonella enterica* serovar Typhi and Paratyphi A causing enteric fever in India. *J Antimicrob Chemother* 2006; *58* : 1139-44.
64. Wong VK, Baker S, Pickard DJ, Parkhill J, Page AJ, Feasey NA, *et al*. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of *Salmonella* Typhi identifies inter- and intracontinental transmission events. *Nat Genet* 2015; *47* : 632-9.
65. International Typhoid Consortium, Wong VK, Holt KE, Okoro C, Baker S, Pickard DJ, *et al*. Molecular surveillance identifies multiple transmissions of typhoid in west Africa. *PLoS Negl Trop Dis* 2016; *10* : e0004781.
66. Rodrigues C, Kapil A, Sharma A, Devanga Ragupathi NK, Inbanathan FY, Veeraraghavan B, *et al*. Whole-Genome Shotgun Sequencing of cephalosporin-resistant *Salmonella enterica* serovar Typhi. *Genome Announc* 2017; *5*. pii: e01639-16.
67. Munir T, Lodhi M, Ansari JK, Andleeb S, Ahmed M. Extended spectrum beta lactamase producing cephalosporin resistant *Salmonella* Typhi, reported from Rawalpindi, Pakistan. *J Pak Med Assoc* 2016; *66* : 1035-6.
68. Britto CD, Dyson ZA, Duchene S, Carter MJ, Gurung M, Kelly DF, *et al*. Laboratory and molecular surveillance of paediatric typhoidal *Salmonella* in Nepal: Antimicrobial resistance and implications for vaccine policy. *PLoS Negl Trop Dis* 2018; *12* : e0006408.
69. Pham Thanh D, Karkey A, Dongol S, Ho Thi N, Thompson CN, Rabaa MA, *et al*. A novel ciprofloxacin-resistant subclade of H58 *Salmonella* Typhi is associated with fluoroquinolone treatment failure. Elife 2016; *5* : e14003.
70. Saad NJ, Bowles CC, Grenfell BT, Basnyat B, Arjyal A, Dongol S, *et al*. The impact of migration and antimicrobial resistance on the transmission dynamics of typhoid fever in Kathmandu, Nepal: A mathematical modelling study. *PLoS Negl Trop Dis* 2017; *11* : e0005547.
71. Cuypers WL, Jacobs J, Wong V, Klemm EJ, Deborggraeve S, Van Puyvelde S. Fluoroquinolone resistance in *Salmonella*: insights by whole-genome sequencing. *Microb genomics* 2018; *4*.
72. Holt KE, Phan MD, Baker S, Duy PT, Nga TV, Nair S, *et al*. Emergence of a globally dominant inchi1 plasmid type associated with multiple drug resistant typhoid. *PLoS Negl Trop Dis* 2011; *5* : e1245.
73. Parry CM. The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Vietnam. *Trans R Soc Trop Med Hyg* 2004; *98* : 413-22.
74. Rupali P, Abraham OC, Jesudason MV, John TJ, Zachariah A, Sivaram S, *et al*. Treatment failure in typhoid fever with ciprofloxacin susceptible *Salmonella enterica* serotype Typhi. *Diagn Microbiol Infect Dis* 2004; *49* : 1-3.
75. Veeraraghavan B, Sharma A, Ranjan P, Kapil A. Revised ciprofloxacin breakpoints for *Salmonella* Typhi: Its implications in India. *Indian J Med Microbiol* 2014; *32* : 161-3.
76. Qamar FN, Saleem K, Shakoor S, Yousufzai T, Kazi M, Lohana H, *et al*. Proceedings of 10th International Conference on Typhoid and other Invasive Salmonelloses. Kampala, Uganda; 2017. p. 40.
77. Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, *et al*. Emergence of an extensively drug-resistant *Salmonella* enterica serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *MBio* 2018; *9* : e00105-18.
78. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, *et al.* Global antibiotic consumption 2000 to 2010: An analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014; *14* : 742-50.
79. Karki M, Pandit S, Baker S, Basnyat B. Cotrimoxazole treats fluoroquinolone-resistant *Salmonella* Typhi H58 infection. *BMJ Case Rep* 2016; *2016*. pii: bcr2016217223.
80. O'Neill J. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations; 2016. Available from: *https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf*, accessed on April 11, 2018.
81. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, *et al*. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A* 2018 ; *115* : E3463-E3470.

82. Kotwani A, Holloway K. Trends in antibiotic use among outpatients in New Delhi, India. *BMC Infect Dis* 2011; *11* : 99.

83. Robinson ML, Kadam D, Kagal A, Khadse S, Kinikar A, Valvi C, *et al*. Antibiotic utilization and the role of suspected and diagnosed mosquito-borne illness among adults and children with acute Febrile illness in Pune, India. *Clin Infect Dis* 2017; *66* : 1602-9.

84. Gandra S, Singh SK, Jinka DR, Kanithi R, Chikkappa AK, Sharma A, *et al*. Point prevalence surveys of antimicrobial use among hospitalized children in six hospitals in India in 2016. *Antibiotics* (*Basel*) 2017; *6* . pii: E19.

85. Kotwani A, Chaudhury RR, Holloway K. Antibiotic-prescribing practices of primary care prescribers for acute diarrhea in New Delhi, India. *Value Health* 2012; *15* : S116-9.

86. McGettigan P, Roderick P, Kadam A, Pollock A. Threats to global antimicrobial resistance control: Centrally approved and unapproved antibiotic formulations sold in India. *Br J Clin Pharmacol* 2019; *85* : 59-70.

87. Gandra S. *Scoping Report on Antimicrobial Resistance in India*. Available from: *https://cddep.org/publications/scoping-report-antimicrobial-resistance-india/*, accessed April 3, 2018.

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