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1 # *Salmonella* Typhi acquires diverse plasmids from other Enterobacteriaceae to develop
2 # cephalosporin resistance

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23 **Abstract:**

24 **Background**: Recent reports have established the emergence and dissemination of extensively
25 drug resistant (XDR) H58 *Salmonella* Typhi clone in Pakistan. In India where typhoid fever is
26 endemic, only sporadic cases of ceftriaxone resistant *S.* Typhi are reported. This study aimed at
27 elucidating the phylogenetic evolutionary framework of ceftriaxone resistant *S.* Typhi isolates
28 from India to predict their potential dissemination in endemic regions.

29 **Methods:** Five ceftriaxone resistant *S.* Typhi isolates from three tertiary care hospitals in India
30 were sequenced on an Ion Torrent Personal Genome Machine (PGM). A core genome single-
31 nucleotide-polymorphism (SNP) based phylogeny of the isolates in comparison to the global
32 collection of MDR and XDR *S.* Typhi isolates was built. Two of five isolates were additionally
33 sequenced using Oxford Nanopore MinION to completely characterize the plasmid and
34 understand its transmission dynamics within Enterobacteriaceae.

35 **Results:** Comparative genomic analysis and detailed plasmid characterization indicate that while
36 in Pakistan (4.3.1 lineage I) the XDR trait is associated with $bla_{\text{CTX-M-15}}$ gene on IncY plasmid, in
37 India (4.3.1 lineage II), the ceftriaxone resistance is due to short term adaptation of resistance
38 plasmids such as IncX3 or IncN.

39 **Conclusion:** Since the bacterial acquisition of smaller resistance plasmids such as IncX3 or IncN
40 from other Enterobacteriaceae can be much faster than the larger IncY plasmids, the rapid
41 expansion of these genotypically novel XDR *S*. Typhi could potentially cause large outbreaks.
42 Therefore, continuous monitoring of *S*. Typhi lineages carrying cephalosporin resistance on
43 IncX3 or IncN plasmids is vital not just for India but globally.

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44 **Keywords:** *Salmonella* Typhi; Typhoid fever; cephalosporin resistance; XDR; India, H58
45 lineages

46 **Importance**

47 Genomic analysis of cephalosporin resistant *S*. Typhi isolated from India indicates the potential
48 of *S*. Typhi to develop cephalosporin resistance by acquiring diverse plasmids from other
49 Enterobacteriaceae. We identified the occurrence of independent acquisition of drug-resistant
50 plasmids such as IncX3 and IncN with genes encoding beta-lactamases in H58/4.3.1.2 lineage. A
51 short term adaptation of drug-resistant plasmids in H58/4.3.1.2 lineage can be the reason for the
52 sporadic cases cephalosporin resistant *S*. Typhi in India. However, the IncY plasmid acquired by
53 isolates that belong to H58/4.3.1.1 lineage appeared to be well adapted as observed in XDR S.
54 Typhi outbreak in Pakistan. Plasmid acquisition and maintenance of cephalosporin resistant *S*.
55 Typhi appears to be specific to the phylogenetic lineage as lineages differ in compensating the
56 initial cost imposed by the plasmid. The stable maintenance of these resistance plasmids without
57 a fitness cost, are determinant in understanding the future spread of cephalosporin resistance in *S*.
58 Typhi. Therefore, critical strategies in monitoring and control of cephalosporin resistant *S*. Typhi
59 is needed to tackle further public health crisis.

60

61 **Introduction**

62 Enteric fever is a severe systemic infection caused primarily by *Salmonella enterica*
63 serovar Typhi and, serovar Paratyphi A [1]. These typhoidal serovars are restricted to human
64 hosts and typically occur in low and middle – income countries (LMIC) [2]. Although direct
65 faecal-oral route is the predominant mode of transmission, recent reports suggest that indirect

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66 transmission may also occur as the bacteria can survive for extended periods in the environment
67 [3]. The global burden of typhoid fever is estimated to be between 11 and 21 million with 128,
68 000 to 161, 000 deaths annually (WHO, 2019). Global data suggests that the majority of the
69 reported enteric fever morbidity and mortality takes place in endemic regions of South Asian,
70 Southeast Asian and African countries [4].

71 The management of enteric fever is challenging due to the emergence of antibiotic
72 resistant *S.* Typhi strains and their changing resistance profiles [5]. The indiscriminate use of first
73 line antimicrobial agents (ampicillin, chloramphenicol and co-trimoxazole) during the 1960s led
74 to the emergence of multi drug resistance (MDR) in sporadic cases initially, followed by larger
75 outbreaks during 1970-1990 [6]. Fluoroquinolones (FQs), such as ciprofloxacin, then became the
76 drug of choice for treatment of MDR *S.* Typhi. However, the decreased ciprofloxacin
77 susceptibility (DCS) phenotype became dominant globally within a few years, resulting in
78 clinical failures [7]. Currently, ceftriaxone and azithromycin are the drugs of choice. However,
79 there are increasing reports of ceftriaxone resistant and azithromycin resistant *S*. Typhi [8].

80 *S.* Typhi isolates with extensive drug resistance (XDR) have emerged in Sindh, Pakistan,
81 with resistance to ampicillin, chloramphenicol, co-trimoxazole, fluoroquinolones and third-
82 generation cephalosporins [9]. This large scale outbreak reported a total of 5274 XDR *S*. Typhi
83 cases between 2016 and 2018 (WHO, 2018). The XDR *S*. Typhi isolates carried an IncY plasmid
84 harboring a $bla_{CTX\text{-}M\text{-}15}$ and *qnrS1* gene while the antimicrobial resistance (AMR) cassette
85 conferring resistance to first-line drugs was integrated into the chromosome as a composite
86 transposon [9, 10]. In India where typhoid fever is endemic, only sporadic cases of ceftriaxone
87 resistant *S.* Typhi have been reported [11-13].

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88 Until recently, phylogenetic inferences of the evolution of cephalosporin resistant *S.*
89 Typhi were limited to the reported XDR *S.* Typhioutbreak in Pakistan [9], possibly because only
90 sporadic cases are reported across other locations in South Asia. Since *S.* Typhi H58 lineage can
91 acquire MDR plasmids (p60006) from other Enterobacteriaceae, this event could also occur in
92 other regions of Asia where typhoid is endemic [9]. Our study investigated the
93 evolutionary trajectories of cephalosporin resistancein *S*. Typhi with special reference to the
94 endemic regions in South Asia. We also investigated the role of plasmid in this clonal expansion
95 to predict the possibility of the rise and spread of cephalosporin resistant *S*. Typhi in India.

96 **Materials and Methods**

97 **Bacterial Isolates, Identification and AST**

98 Five clinical isolates of ceftriaxone resistant *Salmonella* Typhi from three different
99 tertiary care hospitals in India between 2015 and 2018 were confirmed by serotyping according
100 to the *Kauffmann-White* scheme [14] and standard microbiological techniques. Antimicrobial
101 susceptibility testing (AST) was performed by using agar disk diffusion (DD) method for six
102 antimicrobial agents including ampicillin (10 µg), chloramphenicol (30 µg), co-trimoxazole
103 (1.25/23.75 µg), ciprofloxacin (5 µg), ceftriaxone (30 µg) and azithromycin (5 µg). Minimum
104 inhibitory concentration (MIC) for ceftriaxone was determined using the broth micro dilution
105 (BMD) method in accordance with the Clinical and Laboratory Standards Institute (CLSI) 2018
106 guidelines and interpretative criteria [15].

107 **DNA Extraction and Whole genome sequencing**

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108 Genomic DNA of the study isolates was extracted from an overnight culture (14 - 16 hrs)
109 grown at 37°C on blood agar, using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany)
110 according to the manufacturer's protocol. The extracted DNA was subjected to whole genome
111 sequencing (WGS) using the Ion Torrent PGM sequencer (Life Technologies, Carlsbad, CA)
112 with 400 bp read chemistry. Two of five isolates were sequenced using the Oxford Nanopore
113 MinION sequencer (ONT, Oxford, UK) per standard protocol to fully resolve the plasmid
114 structure.

115 **Genome assembly, Genotyping and Plasmid typing**

116 Hybrid genome assembly was carried out according to the standardized protocol
117 developed in-house [16] using Unicycler hybrid assembly pipeline (v0.4.6). Ion torrent reads
118 assembly was achieved *de novo* in the SPAdes assembler (v 5.0.0.0) embedded in the Torrent
119 suite server (v.5.0.3). The quality metrics of the assembled genome was analysed using
120 Quast(v.4.5) and genomes were annotated using Prokaryotic genome annotation pipeline (PGAP
121 v.4.9) before being submitted to NCBI.

122 In-*silico* Multi-Locus Sequence Typing (MLST) was determined using Enterobase
123 database (https://enterobase.warwick.ac.uk) available in pubMLST. The resistance profile of the
124 assembled genomes was identified using ResFinderv.3.1 available from
125 (https://cge.cbs.dtu.dk/services/ResFinder/). Isolates were genotyped using the genotyping
126 scheme as described on the GitHub repository (https://github.com/katholt/genotyphi). Plasmid
127 typing was carried out using Plasmid finder available from the CGE server
128 (https://cge.cbs.dtu.dk/services/).

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129 **SNP calling and Phylogenetic tree construction**

130 Core genome single-nucleotide polymorphisms (SNPs) were identified using Snippy
131 v.0.2.6 (https://github.com/tseemann/snippy) with CT18 (NC_003198) as the reference [17]. The
132 recombination within the alignment file was filtered and removed using the Gubbins algorithm v.
133 2.0.0 [18] and the non-recombinant SNPs, were used to construct the phylogenetic tree using
134 Fast tree. The maximum - likelihood tree with 100 bootstrap values was rooted to the reference
135 genome CT18 and labelled using the interactive tree of life software iTOL v.3 [19].

136 **Plasmid characterization and comparative genomics**

137 Plasmidsfrom two representative isolates (One isolate each from Mumbai and Vellore)
138 were circularized by combining the reads of Ion torrent and MinIon sequencing platforms as
139 described earlier. The remaining three IncX3 plasmids (carried by Mumbai isolates) were
140 extracted from short reads using plasmidSPAdes [20] with representative plasmids as the
141 reference. The plasmid comparison was visualized and analyzed using CGview server v.1.0 [21].

142

143 **Results**

144 **Identification of ceftriaxone resistant *S*. Typhi**

145 All the study isolates werephenotypically and biochemically identified as *S*. Typhi and
146 serologically confirmed by traditional serotyping.The antimicrobial susceptibility profiling of our
147 study isolates showed resistance to ampicillin, ceftriaxone and ciprofloxacin whilst being
148 sensitive to chloramphenicol, co-trimoxazole and azithromycin. Among the five isolates, none

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149 were MDR and all showed similar AST patterns. The demographic details and the resistance
150 profiles of the study isolates are given in Table 1.

151 Genome based MLST analysis classified the isolates to ST1 and identified them as 4.3.1.2 (H58)
152 genotype. Resistome analysis from the whole genome revealed the presence of $bla_{\text{SHV-12}}$, and
153 *qnrB7* genes in four Mumbai isolates, while the Vellore isolate carried $bla_{\text{TEM-1B}}$, $bla_{\text{DHA-1}}$,
154 *qnrB4*, aac(6)Iaa, and *sul-1* resistance genes. Ciprofloxacin resistance could be attributed to
155 QRDR triple mutations (gyrA: S83F, D87N, parC: S80I) for the Mumbai isolates and double
156 mutations (gyrA: S83F, parC: E84K) for the Vellore isolate.

157 **Multiple, independently evolving, ceftriaxone resistant lineages circulating in India**

158 To determine the emergence of ceftriaxone resistance in Indian *S*. Typhi isolates, the
159 phylogenetic relationship of study isolates were compared with the representative isolates (H58
160 and non-H58) from the global *S*. Typhi collection (**Fig. 1**). Ceftriaxone resistant isolates from
161 the recently reported XDR *S*. Typhi outbreak in the Sindh, Pakistan as well as sporadic
162 ceftriaxone resistant isolates from Gurgaon, India and Dhaka, Bangladesh were included in the
163 phylogenetic tree (Supplementary Table S1). The XDR *S*. Typhi isolates from Pakistan formed a
164 distinct clade (4.3.1.1P) within the H58 lineage. Isolates reported to have originated from a direct
165 travel history from Pakistan were also found to be in the same cluster. The two documented
166 ceftriaxone resistant isolates from Bangladesh clustered with the non-H58 lineage along with the
167 ceftriaxone sensitive isolates from the same location. Interestingly the five study isolates from
168 India did not cluster together, and were distributed across the 4.3.1 lineage II. The four
169 cephalosporin resistant isolates from Mumbai, India formed a subclade within the H58 lineage II
170 and differed by 2 SNPs from the closest isolates within the subclade. However the recently

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171 reported ceftriaxone resistant *S*. Typhi from Gurgaon, India clustered within the subclade of
172 4.3.1 lineage I with a difference of 3 SNPs from the ceftriaxone sensitive isolates. It is therefore
173 likely that all the ceftriaxone resistant *S*. Typhi isolates from India have evolved independently
174 from respective geographical locations.

175 **Non-IncY plasmids carrying ceftriaxone resistance**

176 The complete circular plasmids of two representative isolates were used as a reference to
177 reconstruct plasmids from the short read assembly in other isolates. Four study isolates from
178 Mumbai carried the $bla_{\text{SHV-12}}$ and *qnrB7* AMR genes on an IncX3 plasmid (**Fig. 2**). The
179 antibiotic resistance loci from the plasmid were found to be a composite transposon inserted into
180 the IncX3 backbone. However, the plasmid IncN from the Vellore isolate carried $bla_{\text{TEM-1B}}$,
181 $bla_{\text{DHA-1}}$, *qnrB4*, and *sul-1* resistance genes. The IncX3 plasmid responsible for the cephalosporin
182 resistance in *S.* Typhi in India is very closely related to the IncX3 plasmid in other
183 Enterobacteriaceae.

184

185 **Discussion**

186 Currently, ceftriaxone and azithromycin are the drugs of choice and resistance to these
187 agents challenges the treatment of typhoid fever. This has been demonstrated by the emergence
188 of ceftriaxone resistant *S*. Typhi in Pakistan, with resistance to five classes of antimicrobials,
189 including all three first-line agents, fluoroquinolones and ceftriaxone. This study provides
190 evolutionary insights into the emergence of cephalosporin resistant *S*. Typhi in India to predict
191 possible further clonal expansion.

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192 The emergence of Indian cephalosporin resistant *S*. Typhi appears to be by multiple
193 independent genetic events by acquisition of different resistance plasmids. This is in line with the
194 global emergence of cephalosporin resistance in *S*. Typhi as summarized in Table 1. So far, 18
195 studies have reported cephalosporin resistant *S*. Typhi across the globe, with the earliest report of
196 $bla_{\text{CTX-M-15}}$ gene in Western Asia during 2003-2006 [22]. While the majority of reports were
197 based on phenotypic data, a few have reported genetic AMR and plasmid profiles. Except for the
198 outbreak event reported from Pakistan [9], all other reports are of sporadic cases from different
199 locations. Hence there is a lack of a global perspective of the evolution and spread of
200 cephalosporin resistant *S*. Typhi.

201 In our study, the genetic characterization of cephalosporin resistant *S*. Typhi isolates from
202 India showed that as in Pakistan, cephalosporin resistant isolates belong to the H58 lineage.
203 However, within the H58 lineage, the cephalosporin resistant *S*. Typhi were distributed in
204 different sub-lineages. The Indian isolates belonged to the dominant 4.3.1 lineage II while the
205 isolates from Pakistan clustered with 4.3.1 lineage I. These results are in agreement with
206 previous reports as the MDR associated lineage I is dominant in Pakistan and lineage II (QRDR
207 triple mutants) is more prevalent in India [9, 23-25]. The only exception is the previously
208 reported ceftriaxone resistant *S*. Typhi from Gurgaon, India which originated from lineage
209 4.3.1.1 [13]. In contrast to the above observations, isolates from Bangladesh, Democratic
210 Republic of Congo (DRC) and Philippines clustered with the non-H58 phylogenetic lineages
211 (26-29).

212 The evolutionary pattern observed in cephalosporin resistant *S*. Typhi in India may not be
213 driven by acquisition of plasmids already carrying cephalosporin resistance, but by adaptation

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214 due to antibiotic usage selection pressure. This is supported by earlier evolutionary events such
215 as the integration of the MDR gene cassette (composite transposon) in the chromosome and the
216 replacement of lineage I by lineage II in India [30]. Further, the emergence and regional
217 dominance of QRDR triple mutant lineage II in India was associated with high fluoroquinolone
218 exposure in the region [6, 24]. Based on available data, it appears that the H58 lineage I with a
219 chromosomal AMR cassette and single QRDR mutation can acquire and maintain
220 extrachromosomal elements, such as plasmids harboring AMR determinants, as in the XDR
221 Pakistan isolates and in the Indian isolate from Gurgaon. Conversely, lineage II strains with
222 double/triple QRDR mutations develop cephalosporin resistance by short term adaptation of
223 resistance plasmids such as IncX3 or IncN. This could probably be the reason for lineage I
224 acquiring IncY to have had potential to cause larger outbreaks and as well its persistence till
225 date, which is in contrast to lineage II in India with lack of potential to spread unlike lineage I in
226 Pakistan. In general, the rise and spread of plasmid mediated AMR in clinical settings is based
227 on the ability of bacteria to compensate for the initial fitness cost imposed by the plasmid [31].
228 Since the QRDR triple mutant (lineage II) carries the highest fitness cost among fluoroquinolone
229 resistant *S*. Typhi [32], the spread of the plasmid-carrying cephalosporin resistant clone may be
230 limited. Notably, when the lineage can alleviate the cost imposed by the plasmid through
231 compensatory mutations, the spread of these clones will cause even greater therapeutic
232 difficulties.

233 The global spread of MDR *S*. Typhi was associated with independent acquisitions of
234 IncHI1 plasmids of varying plasmid types (PST) at different locations between the 1970s and
235 1980s [33]. In contrast, a single plasmid type (PST6) of IncHI1 was responsible for the clonal
236 expansion of H58 haplotype [23, 33]. Similarly in the Pakistan outbreak, a single acquisition

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237 event of IncY plasmid harboring *bla*$_{CTXM-15}$ led to the expansion of XDR *S*. Typhi (4.3.1.1P) with
238 a difference of 6 SNPs from the MDR associated *S*. Typhi [9]. Though the fitness of the host
239 strain may have compromised while acquiring the IncY plasmid, the XDR clone appears to have
240 alleviated the cost bycompensatory evolution. As a result, the IncY plasmid appears to be stable
241 and maintained in the genome, as XDR outbreaks are still reported from Pakistan [10]. Our data
242 along with a previous report from northern India [13] indicates that the development of
243 cephalosporin resistance in *S*. Typhi in India has occurred by at least three independent and
244 distinct events. This includes the transfer of IncN plasmid in a single isolate, IncX3 in 4 other
245 isolates and IncY as observed in Pakistan. Plasmid characterization of our study isolates with
246 respect to phylogenetic lineages indicates a short term adaptation of IncX3/IncN plasmids in H58
247 lineage II (QRDR triple mutant) which are identified sporadically, while successful host
248 adaptation of IncY plasmid in XDR H58 lineage I has led to persistence in Pakistan.

249 Although our study is limited in sample size and geographical representation, the preliminary
250 observation derived from this study highlights the ability of *S*. Typhi to acquire diverse plasmids
251 to develop cephalosporin resistance. A follow up study on large number of samples, collected
252 evenly across the country, would be required to establish the rate of evolution and clonal
253 expansion in these newly discovered cephalosporin resistant *S.* Typhi.

254 **Conclusion**

255 Even though ceftriaxone resistant *S.* Typhi are not widely seen in India at present,
256 emergence and spread is possible due to the current high use of azithromycin and ceftriaxone for
257 the treatment of typhoid fever. As a result, there are potential risks for the occurrence of plasmid
258 transmission events. This is based on the following evidence, (i) endemicity of *bla*$_{SHV}$and *bla*$_{CTX-}$

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259 $_{M\text{-}15}$carrying plasmids in *E.coli* and *Klebsiella* sp. in India favoring horizontal gene transfer to *S*.
260 Typhi, (ii) high use of ceftriaxone for the management of complicated typhoid fever posing
261 antibiotic pressure, and (iii) the dominant H58 lineage in India being capable of acquiring
262 plasmid harboring AMR determinants. Considering the prolonged maintenance of newly
263 acquired $bla_{CTX\text{-}M\text{-}15}$ carrying IncY plasmid in 4.3.1 lineage I in Pakistan, any trigger could
264 possibly lead to similar events in India. Therefore we propose that MDR H58 lineage II are
265 capable of acquiring MDR plasmids from other Enterobacteriaceae and could potentially cause a
266 large outbreak. Hence, monitoring of cephalosporin resistant *S*. Typhi and its lineages associated
267 with plasmid acquisition is required for early detection, in conjunction with rational use of
268 antibiotics and prevention strategies for control of enteric fever.

269 **Acknowledgments**

270 This project was supported by grants from Bill and Melinda Gates Foundation, USA
271 (Investment ID INV-009497 OPP1159351) for the Project "National Surveillance System for
272 Enteric Fever in India"

273 **Conflicts of interest**

274 The authors declare that there is no potential conflict of interest

275 **Author contribution statement**

276 BV conceived and designed the research, JJJ and AKP supervised the research and wrote the
277 manuscript. KV, GK, JJ, VN and AM have reviewed and corrected the manuscript. All authors
278 have read and approved the manuscript.

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378 **Table 1: Molecular fingerprint of cephalosporin resistant *S*. Typhi**

Country of Origin (Reference)	Location	Isolate Id & Accession No.	Year	Acquired Resistance			Chromosomal resistance (QRDR)	Lineage
				Beta lactamases	Other AMR determinants	Plasmids		
DRC (28)		ERR1862943	2015	*CTX-M-15, TEM-1D*	*dfrA7, sul1, aac6'*	IncY	S83F	Non-H58 (2.5.1)
Philippines (29)	Travel associated	ERS525820 ERS525821	2012	*TEM-1B, SHV-12*	*dfrA19, aac6', aph3', aph6', tetD, MCR-9*	IncHI2	Absent	Non-H58 (3)
Pakistan (9)	Sindh Outbreak	ERR2093236 - ERR2093334	2016-2017	*CTX-M-15, TEM-1*	*dfrA7, catA1, sul1 and sul2, qnrS, StrAB*	IncY	S83F	H58 Lineage I (4.3.1.1P)
Bangladesh (26, 27)	Dhaka	ERR2059823	2000	*CTX-M-15, TEM-1B*	*aac6'*	IncI1	S83Y	Non-H58
	Gurgaon, Haryana (n=2)	Gurgaon01 (ERR3527963)	2019	*TEM-1B, CTX-M-15*	*dfrA14, sul1/2, tetA, qnrS1, aac6', aph6', aph3'*	IncY (lost while sub culturing)	S83Y	H58 Lineage I (4.3.1.1)

India (11, 12, 13)		Gurgaon02 (ERR3527964)	2019		*aac(6'')Iaa, tetA*	IncY	S83Y	H58 Lineage I (4.3.1.1)
*This study	Mumbai* (n=4)	458426 (MQUO00000000)	2015	*SHV-12*	*qnrB7*	IncX3	S83F, D87N, S80I	H58 Lineage II (4.3.1.2)
		430040 (MQUM00000000)						
			2019					
		429038 (MQUL00000000)						
		LHST_2018 (CP052767 and CP052768)						

Vellore* (n=1)	CMCST_CEPR_1LSAR00000000	2015	TEM-1B, DHA	*qnrB4, aac6', sul1*	IncN	S83F, E84K	H58 Lineage II (4.3.1.2)

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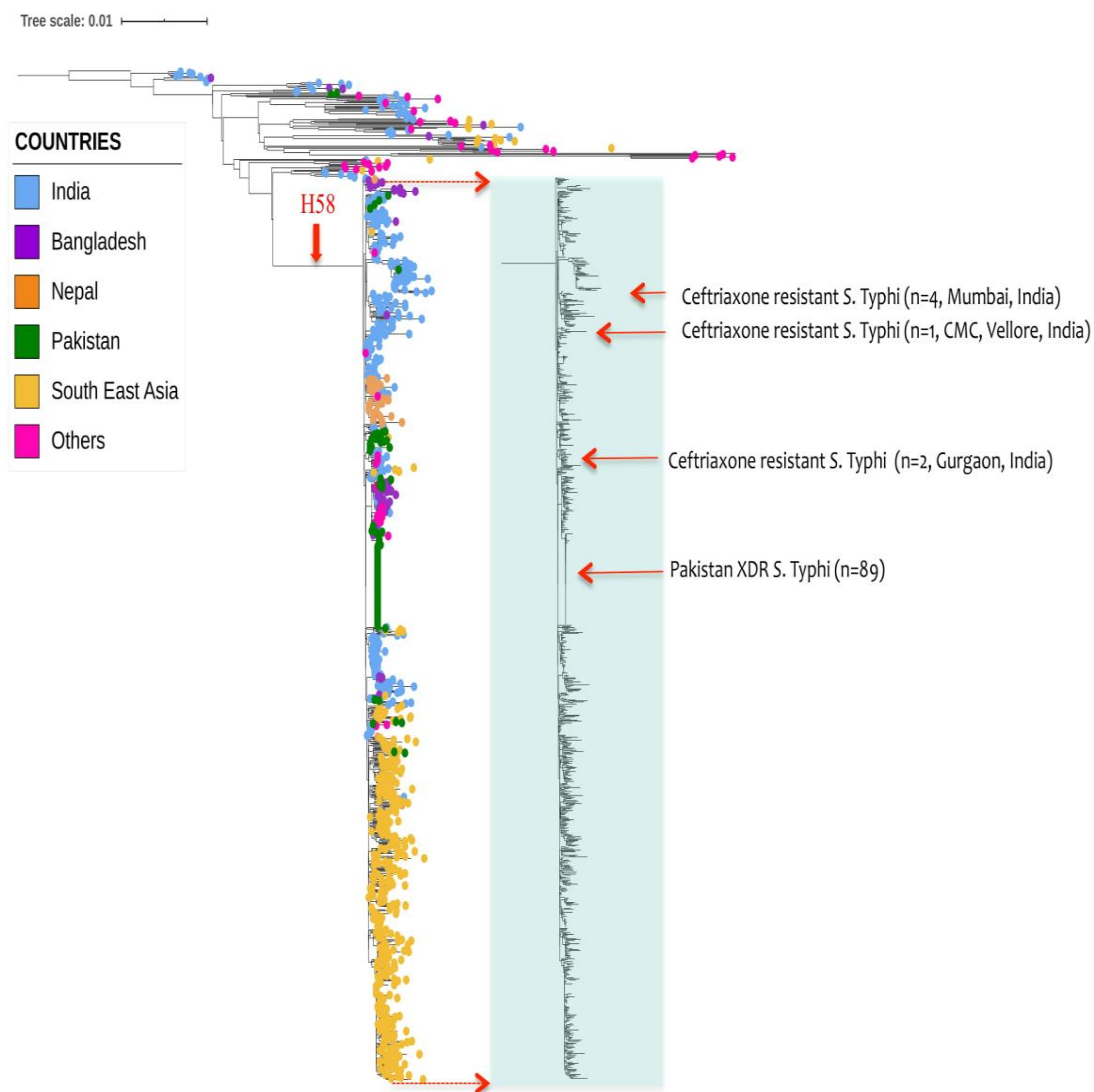

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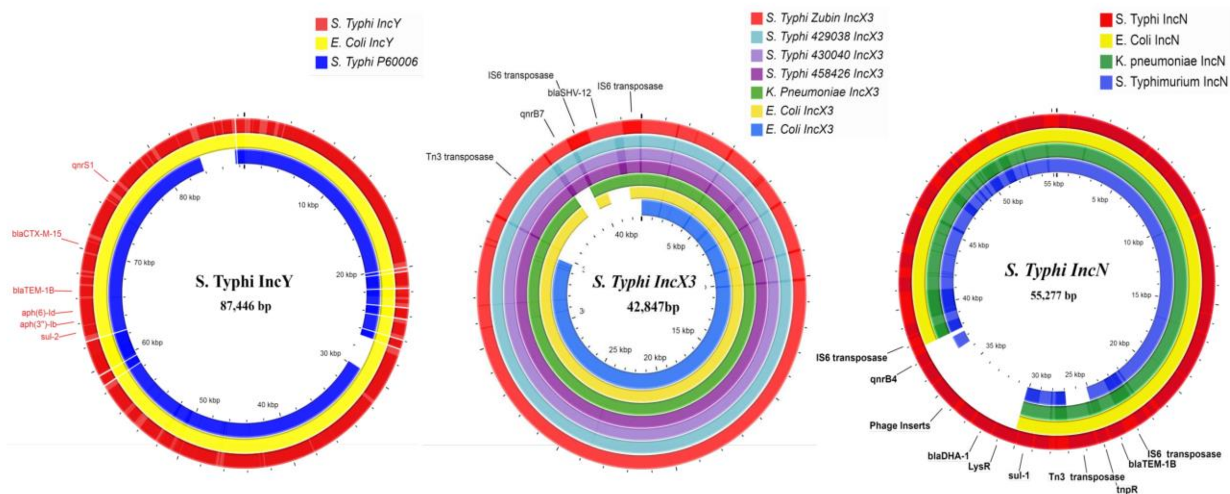

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393

394 **Figure Legends:**

395 **Fig 1:** Maximum likelihood tree of 1005 *S.* Typhi (H58 and non-H58) inferred from 2072 SNPs
396 and rooted against the reference genome CT18. Light shaded box indicates non-H58 population,
397 while the rest are H58 group. The tips of the tree are coloured according to the geographical
398 origin of the genomes. Red colored squared boxes with arrows indicates the position of
399 ceftriaxone resistant *S.* Typhi in the context of global phylogeny, indicating similarity with
400 respect to the geographical locations. Tree scale indicates the number of substitutions per
401 genome.

402 **Fig 2:** Circular representation of plasmids assembled from *S*. Typhi isolates displayed using CG
403 view server with reference genomes. (a) The IncY plasmid from cephalosporin resistant *S*. Typhi
404 isolate from Gurgaon, India is compared with similar plasmids identified from XDR Pakistan *S*.
405 Typhi (Plasmid p60006) and highly similar *E. coli* IncY plasmid. (b) Comparison of IncX3
406 plasmid from cephalosporin resistant Indian *S*. Typhi isolates (n=4) with global
407 Enterobacteriaceae associated IncX3 plasmids. (c) The IncN plasmid assembled from
408 cephalosporin resistant *S*. Typhi Vellore isolate was compared with representative isolates from
409 Genbank

410

411 **Table Legends:**

412 Table 1: Molecular fingerprint of cephalosporin resistant *S*. Typhi

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