

Expansion of *Salmonella* Typhi clonal lineages with ampicillin resistance and reduced ciprofloxacin susceptibility in Eastern China

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Purpose: This study was aimed to investigate the dynamics of antimicrobial resistance expansion among different lineages and isolates of *S. Typhi*.

Materials and methods: The *S. Typhi* isolates were collected from the patients clinically suspected of typhoid fever in Eastern China during 2005–2017. All isolates were tested retrospectively for susceptibility to eight antimicrobials and the genes related to quinolone and ampicillin resistance, including *gyrA*, *ParC*, *qnrA*, *qnrB*, *qnrS*, *aac(6')-Ib-cr*, *qepA* and *bla*_{TEM}. The isolates were subtyped by PFGE.

Results: Of 140 isolates, all were susceptible to ciprofloxacin, cefotaxime, chloramphenicol, and trimethoprim-sulfamethoxazole, 95 (68%) were nalidixic acid resistant, and 74 (53%) were ampicillin resistant. The resistance to ampicillin and nalidixic acid was first observed in 2006. Among the 95 nalidixic acid-resistant *S. Typhi* isolates, 62 possessed S83F mutation in *gyrA* and 25 possessed D87Y mutation. All ampicillin-resistant isolates harbored gene *bla*_{TEM-1}. PFGE generated 47 distinguishable clonal lineages. Overall, 64% (89/140) belonged to seven prevalent lineages of clustering isolates. PFGE results illustrated the prevalence of nalidixic acid-resistant lineages increased steadily from 19% during 2005–2012 to 50% during 2013–2014, and thereafter to 74% during 2015–2017 and similar development of ampicillin-resistant lineages increased from 6% to 38%, and also to 39%.

Conclusion: The present study indicated the clonal expansion of *S. Typhi* with ampicillin resistance and reduced ciprofloxacin susceptibility. The findings also suggested that the differential development of antimicrobial resistance to various antimicrobial agents in *S. Typhi*, showing the rapid increase in ampicillin resistance and reduced ciprofloxacin susceptibility, and the high susceptibility to other traditional antimicrobial agents.

Keywords: ampicillin resistance, reduced ciprofloxacin susceptibility, *Salmonella* Typhi, clonal expansion

Introduction

Typhoid fever is a systemic infection caused by *Salmonella enterica* serotype Typhi (*S. Typhi*). In 2015, there were 12.5 million new cases and about 149,000 deaths worldwide.¹ Treatment of this disease greatly depends on appropriate antimicrobial regimens. Clinically, the commonly used antimicrobial drugs include β -lactams and quinolones. Among a large number of β -lactams, ampicillin and third-generation cephalosporins are often used. As to quinolones, nalidixic acid is the first used quinolone, which is viewed to be the predecessor of all members of the quinolone family. Currently, more powerful fluoroquinolones, such as ciprofloxacin, are clinically used as the first-line drugs of choice for treating typhoid fever.²

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In recent years, drug-resistant *S. Typhi* strains, especially resistant to β -lactams and quinolones, have raised concerns.³ In China, multidrug-resistant (MDR) *S. Typhi* isolates that are resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole have also been found.⁴ Globally, the most encountered β -lactams resistance in *S. Typhi* is ampicillin resistance and, for quinolone resistance, the most found is nalidixic acid resistance that renders *S. Typhi* with reduced ciprofloxacin susceptibility and has a significant impact on clinical outcome and future treatment options.⁵

Bacterial antimicrobial resistance can be spread by the horizontal genetic transfer among different clonal lineages or by dissemination of drug-resistant clonal lineages.^{6,7} Of note, the expansion of drug-resistant *S. Typhi* isolates has been facilitated by international travel.⁸ To describe the prevalence of drug resistance among bacteria, the counting of drug-resistant isolates is often used. However, under circumstances when isolates are mostly from outbreaks, the proportion of drug-resistant isolates cannot accurately reflect the actual resistance situation because the occurrence of outbreaks often varies substantially. In contrast, the counting of drug-resistant clonal lineages can reduce the impact of the inadvertent outbreaks and better reflect the real resistance level. Because of much more work being required to analyze the clonal relatedness among antimicrobial-resistant isolates, scarce studies were conducted to assess the clonal expansion of antimicrobial-resistant lineages.⁹

In the previous work, we identified the emergence and recently rapid expansion of *S. Typhi* with ampicillin resistance and reduced ciprofloxacin susceptibility.¹⁰ The investigation illustrated that the large part of isolates were from several outbreaks, which could yield fluctuations in resistance rates. Therefore, the expansion of antimicrobial-resistant clonal lineages during a more prolonged period needs to be ascertained. This study was aimed to investigate the dynamics of antimicrobial resistance expansion among different lineages and isolates of *S. Typhi*. PFGE was used to differentiate the clonal lineages.

Materials and methods

The study isolates

All procedures in the study involving human participants were approved by the Institutional Ethical Committee of Ningbo First Hospital, Ningbo, Zhejiang, People's Republic of China (approval no. 201812) and followed the ethical standards of the 1964 Helsinki declaration. Patient consent was waived, as the deidentified samples were obtained as part of routine

hospital procedure during 2005–2017. This study was conducted in Ningbo China that has a population of 9 million and a land area of 9 400 square kilometers. The *S. Typhi* isolates were collected from the patients clinically suspected of typhoid fever during 2005–2017. A total of 140 isolates were identified by biochemical reactions using the API20E biochemical identification system (bioMérieux, Paris, France) and the serological test using antisera (polyvalent O, O9, Hd, and Vi, Denka Seiken, Japan). All the patients did not go abroad before one month of diagnosis.

Antimicrobial susceptibility testing (AST)

All the *S. Typhi* isolates were tested retrospectively for susceptibility to eight antimicrobials using the Kirby-Bauer disc diffusion method specified in the Clinical and Laboratory Standards Institute (CLSI) document M02-A12.¹¹ AST results were interpreted according to the guidelines in CLSI document M100-S27.¹² The eight antibiotic discs (Oxoid, Hampshire, England) included ampicillin (10 μ g), ciprofloxacin (5 μ g), nalidixic acid (30 μ g), chloramphenicol (30 μ g), tetracycline (30 μ g), gentamicin (10 μ g), cefotaxime (30 μ g), and trimethoprim-sulfamethoxazole (1.25/23.75 μ g). *Escherichia coli* ATCC 25922 was used as the quality control strain. Isolates that were intermediate to ciprofloxacin were generally resistant to nalidixic acid. Therefore, these were reported to be with reduced ciprofloxacin susceptibility.¹³

Detection of genetic elements related to quinolone and β -lactam resistance

The genes that were related to quinolone resistance in ciprofloxacin-nonsusceptible isolates were detected using previously described primers¹⁴ (Table 1), including *gyrA*, *ParC*, PMQR genes *qnrA*, *qnrB* and *qnrS*, aminoglycoside acetyltransferase-encoding enzyme variant *aac(6')-Ib-cr*, and efflux-pump-encoding *qepA*. Amplicons of *gyrA* and *ParC* were sequenced and their mutations were determined via aligning the sequenced amplicons against the counterpart sequence of *Salmonella* Typhimurium LT2. Additionally, β -lactam-resistant *S. Typhi* isolates were tested for β -lactamase gene *bla*_{TEM} that was previously found in β -lactam-resistant *Salmonella* isolates using primers listed in Table 1.

Pulsed-field gel electrophoresis (PFGE) and interpretation of clonal expansion of antibiotic-resistant lineages

All the *S. Typhi* isolates were subtyped by PFGE using the restriction enzyme *XbaI* following the PulseNet standardized

Table 1 Primers used for amplifying genes associated with quinolone and ampicillin resistance

Gene	Primers (5'→3')	Amplicon size (bp)	Reference
For sequencing quinolone resistance-determining region			
<i>gyrA</i>	gyrA-1: CGT TGG TGA CGT AAT CGG TA gyrA-2: CCG TAC CGT CAT AGT TAT CC	251	[14]
For plasmid-mediated quinolone resistance-encoding genes			
<i>aac(6)-Ib-cr</i>	aac(6)-Ib-1: TTG CGA TGC TCT ATG AGT GGC TA aac(6)-Ib-2: CTC GAA TGC CTG GCG TGT TT	482	[14]
<i>qnrA</i>	QnrA-1: TCA GCA AGA GGA TTT CTC A QnrA-2: GGC AGC ACT ATT ACT CCC A	627	[14]
<i>qnrB</i>	QnrB-1: GGM ATH GAA ATT CGC CAC TG QnrB-2: TTT GCY GYY CGC CAG TCG AA	264	[14]
<i>qnrS</i>	QnrS-1: ATG GAA ACC TAC AAT CAT AC QnrS-2: AAA AAC ACC TCG ACT TAA GT	491	[14]
For ampicillin resistance-encoding genes			
<i>bla_{TEM-1}</i>	TEM-1: TGT CGC CCT TAT TCC CTT TT TEM-2: ATA GTT GCC TGA CTC CCC GT	783	This study

protocol.¹⁵ *S. Braenderup* (H9812) was used as the reference strain. PFGE images were analyzed using the BioNumerics software (Applied Maths, Sint-Martens-Latum, Belgium). The unweighted pair-group method (UPGMA) with a position tolerance of 1.2% was used to construct the PFGE dendrogram. PFGE patterns were defined by groups of bands obtained at over 90% Dice similarity cutoffs on the dendrogram. The *S. Typhi* lineage was defined for the isolates that had the same PFGE pattern.

Statistical method

S. Typhi isolates and lineages per isolation year with ampicillin resistance and reduced ciprofloxacin susceptibility were counted. We used Fisher exact χ^2 tests to assess the difference between the prevalence of resistant clonal lineages and the prevalence of resistant isolates. Statistical significance was accepted at P -value <0.05.

Results

Of 140 isolates collected during 2005–2017, 135 were isolated from the blood and five from the stool of patients. Demographic information for patients included age median (35.3 years), age interquartile ranges (IQR, 22–50 years) and sex ratio (82 men and 58 women). The isolates were all susceptible to ciprofloxacin, cefotaxime, chloramphenicol, and trimethoprim-sulfamethoxazole. The rare resistance to tetracycline ($n=2$) and gentamicin ($n=2$) was solely found

during 2014–2015. The most encountered pattern of ampicillin and nalidixic acid resistance (with reduced ciprofloxacin susceptibility) was first observed in 2006 and rapidly increased in 2013 (Figures 1 and 2 and Table 2). Overall, 74 that were ampicillin resistant were also nalidixic acid resistant and 21 were solely nalidixic acid resistant. The total prevalence of nalidixic acid resistance was 68% (95/140). Among 95 *S. Typhi* isolates with reduced ciprofloxacin susceptibility (nalidixic acid-resistant), 62 had S83F mutation, 25 had D87Y mutation, and eight had no mutation. No PMQR genes were detected. All ampicillin-resistant isolates harbored *bla_{TEM}*.

PFGE classified 140 isolates into 47 clonal lineages that were designated as Lineage 1 through 47 (Figures 1 and 2). Overall, 64% (89/140) belonged to seven prevalent lineages of clustering isolates (Table 3). Except for Lineage 6, 9, and 30, the remaining four lineages were ampicillin- and nalidixic acid-resistant, accounting for 64 isolates. To obtain the comparable number of isolates in each period, we grouped the isolates into three groups according to isolation year, ie, 2005–2012, 2013–2014 and 2015–2017 (Table 2). The ampicillin- and nalidixic acid-resistant isolates began to appear during 2005–2012. The prevalence of ampicillin and nalidixic acid resistance substantially increased during 2013–2014 and lasted toward the end of this study. When comparing the rate of drug-resistant isolates with the rate of drug-resistant

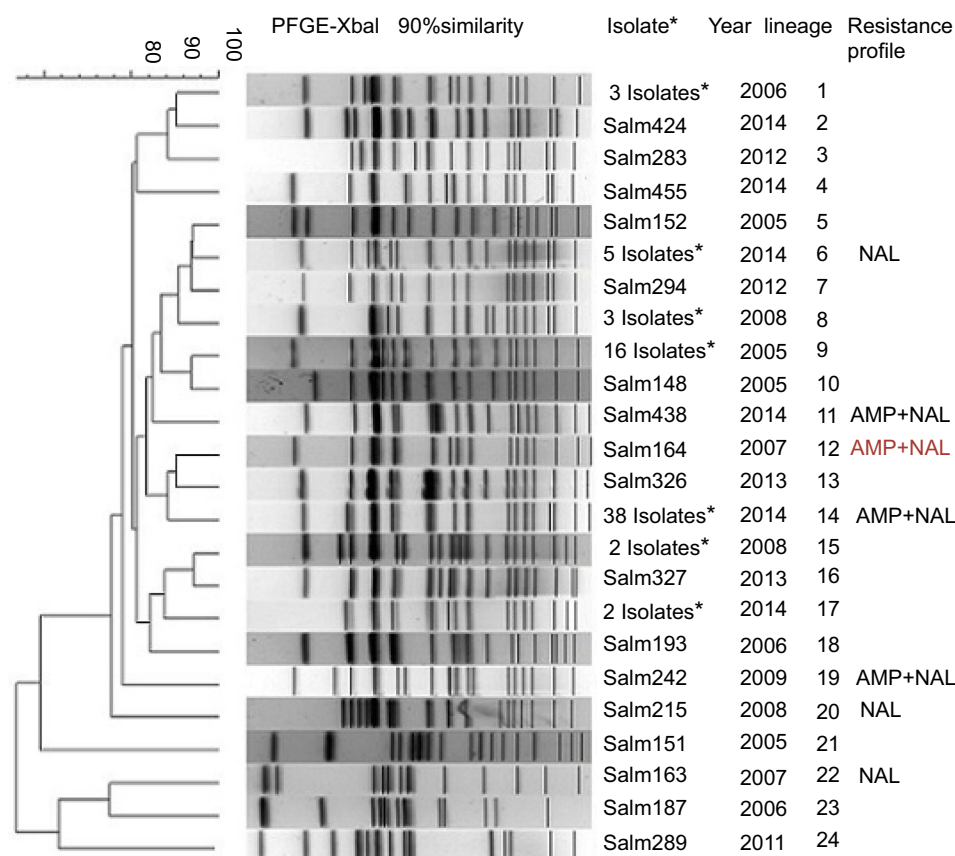


Figure 1 Clonal lineages by PFGE and antimicrobial resistance profiles for *S. Typhi* isolates collected in eastern China, 2005–2014.
Abbreviations: AMP, ampicillin; NAL, nalidixic acid.

lineages among three periods of 2005–2012, 2013–2014, and 2015–2017, we found inconsistency between two rates due to varied numbers of isolates in prevalent lineages (Table 2).

The trend in the prevalence of nalidixic acid-resistant lineages increased steadily from 19%, to 50%, and thereafter to 74%, whereas the trend in the prevalence of nalidixic acid-resistant isolates increased from 9%, rapidly to 88% due to a serious outbreak (Lineage 14 in Figure 1) during 2013–2014, and to 89% (Table 2). Very similar trends were present in the development of ampicillin resistance, ie, a steady increase from 6%, to 38%, and to 39% in the prevalence of ampicillin-resistant lineages, as well as a rapid increase from 3% to 78% due to a serious outbreak during 2013–2014, and a slight decrease to 63% during 2015–2017. When comparing the development of nalidixic acid- and ampicillin-resistant clonal lineages between 2013–2014 and 2015–2017, we observed a clonal expansion of *S. Typhi* with ampicillin resistance and reduced ciprofloxacin susceptibility during 2013–2017. However, the trends were less clear in terms

of nalidixic acid- and ampicillin-resistant isolates during these two periods (Table 2).

Discussion

Although timely, effective antimicrobial treatment is crucial for the cure of typhoid fever, AST results are not always available for all patients who may be diagnosed with typhoid fever by a serological test. The selection of antimicrobial agents depends on the accurate assessment of the prevalence and expansion of antimicrobial-resistant *S. Typhi*. The present study found three characteristic features concerning the prevalence and expansion of antimicrobial-resistant *S. Typhi*, including the differential development of drug resistance among different antimicrobials, the influence of outbreaks on the interpretation of spread of drug resistance, and the rapid clonal expansion of *S. Typhi* with ampicillin resistance and reduced ciprofloxacin susceptibility.

In the present study, the *S. Typhi* isolates remained highly susceptible to cefotaxime, chloramphenicol, and trimethoprim-sulfamethoxazole, even the rare resistance

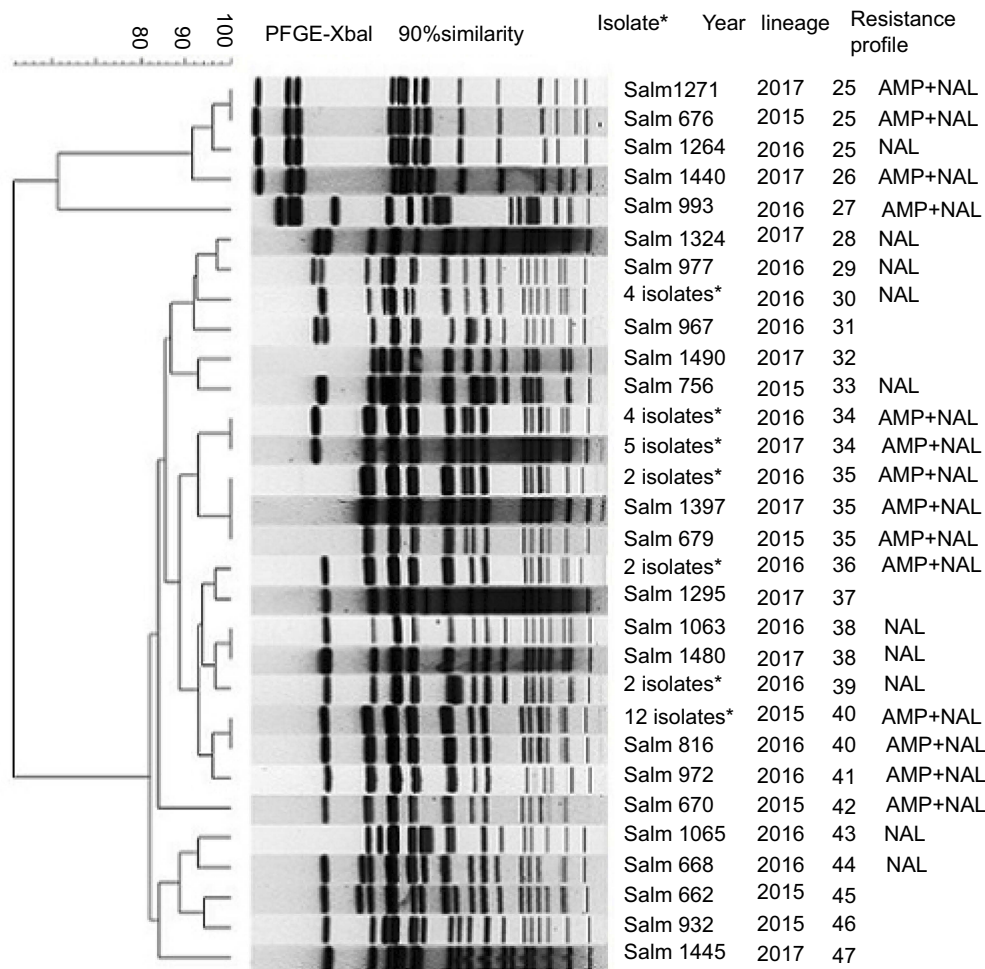


Figure 2 Clonal lineages by PFGE and antimicrobial resistance profiles for *S. Typhi* isolates collected in eastern China, 2015–2017.

Abbreviations: AMP, ampicillin; NAL, nalidixic acid.

Table 2 Spread of ampicillin and nalidixic acid resistance among the lineages and isolates of *S. Typhi* during different periods

	Period	2005–2012	2013–2014	2015–2017	P1*	P2*	Trend 1**	Trend 2**
No. of lineages	Total	16	8	23	–	–		
	NAL-resistant (%)	3 (19)	4 (50)	17 (74)	0.1	0.20	Slightly up	Slightly up
	AMP-resistant (%)	1 (6)	3 (38)	9 (39)	0.08	>0.9	Slightly up	No trend
No. of isolates	Total	36	50	54	–	–		
	NAL-resistant (%)	3 (9)	44 (88)	48 (89)	<0.01	>0.9	Significantly up	No trend
	AMP-resistant (%)	1 (3)	39 (78)	34 (63)	<0.01	0.09	Significantly up	Slightly down
No. of isolates per lineage		2	6	2	–	–		
No. of isolates in prevalent lineages (%)		16 (46)	43 (84)	30 (56)	–	–		

Notes: * P1 and P2 are for the differences in the resistance rates between 2005–2012 and 2013–2014, as well as between 2013–2014 and 2015–2017, respectively. ** Trend 1 and Trend 2 are referred to the trends from 2005–2012 to 2013–2014 and from 2013–2014 to 2015–2017, respectively.

Abbreviations: AMP, Ampicillin; NAL, Nalidixic acid.

to tetracycline and gentamicin disappeared. In contrast, ampicillin resistance and reduced ciprofloxacin susceptibility rapidly increased in 2013 (Table 2). Based on the criteria that *S. Typhi* resistant to ampicillin,

chloramphenicol, and trimethoprim-sulfamethoxazole was referred to as multidrug-resistant *S. Typhi* (MDR *S. Typhi*), no MDR *S. Typhi* was identified in the present study. A review of global antimicrobial susceptibility

Table 3 Prevalent lineages of *S. Typhi* identified during 2005–2017 by PFGE

Lineage	No. of isolates	Year	AMP and NAL resistance
6	5	2014	NAL
9	16	2005	
14	38	2013–2014	AMP and NAL
30	4	2015–2017	NAL
34	9	2016–2017	AMP and NAL
35	4	2015–2017	AMP and NAL
40	13	2016–2017	AMP and NAL
Total	89		

Abbreviations: AMP, Ampicillin; NAL, Nalidixic acid.

results shows a substantial regional difference among *S. Typhi* isolates. In Peru, *S. Typhi* isolates were reported to be highly resistant only to ampicillin and nalidixic acid, which is very similar to our findings.¹⁵ The high susceptibility to the above mentioned antimicrobial agents was also found in a study in west India that reported the re-emergence of susceptibility to conventionally used drugs such as chloramphenicol, ampicillin, and trimethoprim among *S. Typhi*.¹⁵ However, a lot of other findings of disagreement were also reported. About 15–30% of *S. Typhi* isolates recovered during 2002–2007 from the Middle East and Central Asia were MDR *S. Typhi* [5]. Another report argued that a single dominant H58 MDR lineage has emerged and expanded throughout Asia and Africa over the last 30 years and is displacing the antibiotic-sensitive isolates.¹⁶ Nevertheless, the findings in the present study that were based on the current sources of isolates indicated the high prevalence of resistance to ampicillin and reduced ciprofloxacin susceptibility, as well as high susceptibility to other traditional antibiotics.

As to the mechanisms for ampicillin and reduced ciprofloxacin susceptibility in this study, most *S. Typhi* isolates with reduced ciprofloxacin susceptibility had S83F or D87Y mutation. As showed in our previous study, this D87Y mutation was detected only in the *S. Typhi* with reduced ciprofloxacin susceptibility.¹⁷ The present findings concerning the reduced ciprofloxacin susceptibility are the same as that in Peru.¹⁵ Additionally, ampicillin-resistant isolates all had *bla*_{TEM-1}, which is consistent with several reports.^{16,18}

The present study also indicated that clustering isolates in several possible outbreaks influenced the interpretation of the development of antimicrobial resistance. Usually,

the prevalence of resistance events among bacteria is evaluated by counting the resistant isolates. This method is accurate only if the isolates are from evenly distributed sporadic cases. For typhoid fever, as illustrated in previous studies as well as in this study (Table 3), isolates might be obtained from large outbreaks with the same drug resistance profile and made the prevalence fluctuate by time. This situation might be misleading when it was used to interpret the real trend in the prevalence and expansion of antimicrobial-resistant *S. Typhi*. Therefore, this study used the lineages by PFGE instead of isolates as the basic units to count the resistance events. The trend in the prevalence of ampicillin and nalidixic acid resistance increased more steadily when being counted by lineages than by isolates from 2005 to 2017 (Table 2). Due to the considerable proportion of 38 ampicillin- and nalidixic acid-resistant isolates during 2013–2014 (Lineage 14 in Figure 1), it seemed that the prevalence of nalidixic acid resistance remained almost the same and the prevalence of ampicillin resistance decreased slightly by counting isolates between 2013–2014 and 2015–2017. Drawing such a conclusion of decreasing resistance may be misleading because of the occasional outbreaks of drug-resistant *S. Typhi*.

As the present study showed, the prevalence of ampicillin and nalidixic acid resistance (reduced fluoroquinolone susceptibility) began to increase rapidly in 2013, and this distinctive profile of antimicrobial resistance spread among *S. Typhi* clonal lineages continued. Notably, most prevalent lineages were ampicillin and nalidixic acid resistant (Table 3). PulseNet China began to collect national PFGE data only since 2017. Due to the difficulty in acquiring comparable results by molecular typing method for *S. Typhi*, the failure to compare the PFGE patterns of prevalent lineages in this study with the patterns in publications caused a limitation of the present study.

Conclusion

In summary, the present study illustrated that the development of antimicrobial resistance to different antimicrobial agents in *S. Typhi* is dramatically contrasting, showing the rapid increase in ampicillin resistance and reduced ciprofloxacin susceptibility in recent years and the high susceptibility to other ever used antimicrobial agents. To accurately assess the development of antimicrobial resistance, counting the drug-resistant lineages is a more suitable method than counting the drug-resistant isolates, which can make the impact of outbreaks to a minimum level.

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Disclosure

The authors report no conflicts of interest in this work.

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