

# Emergence of *Salmonella* Paratyphi A and Submergence of *Salmonella* Typhi and Their Trend Over Four Years

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## ABSTRACT

**Background:** Enteric fever is classically caused by *Salmonella enterica* serotype Typhi. There has been increase in enteric fever cases from different parts of India caused by *Salmonella enterica* serotype Paratyphi A. Thereby a retrospective study was conducted to determine the rate of isolation and antimicrobial susceptibility pattern of *Salmonella* Paratyphi A in comparison to *Salmonella* Typhi. **Methods:** A retrospective analysis of laboratory records was carried out from January 2011-December 2014. Conventional blood culture method was used. *Salmonella* were confirmed by serotyping using group and type specific anti-sera. Antibiotic susceptibility was performed for ampicillin, cotrimoxazole, ciprofloxacin, chloramphenicol and ceftriaxone, using Kirby Bauers disk diffusion method. **Results:** Out of 258 *Salmonella* isolates, 127 (49.2 %) were *Salmonella* Typhi and 131 (50.8 %) were *Salmonella* Paratyphi A. *Salmonella* Paratyphi A cases increased from 23.4% in 2011-2013 to 91.3% in 2014. *Salmonella* Typhi were 98.4 % sensitive to ampicillin and ceftriaxone and 99.2% sensitive to chloramphenicol and cotrimoxazole. Only 29.9% were sensitive to ciprofloxacin. Similarly, *Salmonella* Paratyphi A isolates were 99.2 % sensitive to ampicillin and 100 % sensitive to cotrimoxazole and ceftriaxone and 96.9 % sensitive to chloramphenicol and only 14.5 % sensitive to ciprofloxacin. **Conclusion:** The present study confers *Salmonella* Paratyphi A as the rapidly emerging pathogen of enteric fever. The antibiogram of *Salmonella* Typhi and *Salmonella* Paratyphi A showed decreased susceptibility to fluoroquinolones and a notable decrease in the multi drug resistant strains of *Salmonella* isolates with re-emergence of susceptibility to first line antibiotics.

**Keywords:** First line antibiotics, Fluoroquinolones, Incidence, *Salmonella* Paratyphi A.

## INTRODUCTION

Enteric fever is of major aetiological consideration in both acute and prolonged fever of unknown origin in the tropical regions. According to World Health Organisation, globally, the annual incidence of typhoid and paratyphoid fever accounts to 21.7 million and 5.4 million cases respectively.<sup>[1]</sup> *Salmonella enterica* serotype Paratyphi A is the second most common cause of enteric fever after *Salmonella enterica* serotype Typhi and the incidence of it is increasing in South- East Asia including the Indian subcontinent.<sup>[2]</sup> There has been an upsurge in the occurrence of enteric fever due to *Salmonella* Paratyphi A and variation in the antimicrobial susceptibility pattern from various parts of India.<sup>[3-5]</sup>

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The present study was carried out to study the rate of isolation and the antimicrobial susceptibility pattern

of *Salmonella* Paratyphi A in comparison to *Salmonella* Typhi from cases of enteric fever.

## MATERIALS AND METHODS

Two hundred and fifty eight *Salmonella* isolates obtained from blood cultures of clinically suspected cases of enteric fever, received by the microbiology department of Indira Gandhi Medical College and Research Institute, Puducherry, from January 2011 to December 2014 were included in the study. Only one isolate per patient was included. Conventional blood culture method was used. *Salmonella* isolates were confirmed by serotyping using group and type specific antisera (Denka Seiken Co. Ltd, Niigata, Japan). Antibiotic susceptibility was performed using the Kirby-Bauer disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI) guidelines for the corresponding years using commercially available disks (Hi-media, Mumbai): ampicillin (10 µg), co-trimoxazole (1.25/23.75 µg), ciprofloxacin (5 µg), chloramphenicol (30 µg) and ceftriaxone (30 µg).<sup>[6,7]</sup> *Escherichia coli* ATCC 25922 was used as the quality control strain. Isolates with intermediate levels of resistance in disk diffusion were included in

the percentage of resistant organisms for final analysis.

## RESULTS

During the four-year study period, a total of 258 cases of enteric fever were culture confirmed. The ward to outpatient department ratio was 3:1. The majority of patients were males (63.6%) with a male to female ratio of 1.7:1. Enteric fever occurred in all age groups with a peak occurrence in the second decade (Median - 19 years). The cases peaked in the months of May – August. A total of 127 (49.2 %) were *Salmonella* Typhi and 131 (50.8 %) were *Salmonella* Paratyphi A. *Salmonella* Paratyphi A

cases increased from 23.4% in 2011-2013 to 91.3% in 2014 [Table 1] & [Figure 1]. The rate of isolation of *Salmonella* Typhi were 1.98% in 2011 which fell to 0.34% in 2014, whereas, *Salmonella* Paratyphi A isolates were 0.37% in 2011 and raised to 3.66% in 2014 [Table 2]. *Salmonella* Typhi were 98.4 % sensitive to ampicillin and ceftriaxone and 99.2% sensitive to chloramphenicol and cotrimoxazole. Only 29.9% were sensitive to ciprofloxacin. Similarly, *Salmonella* Paratyphi A isolates were 99.2 % sensitive to ampicillin and 100 % sensitive to cotrimoxazole and ceftriaxone and 96.9 % sensitive to chloramphenicol and only 14.5 % sensitive to ciprofloxacin [Table 3].

**Table 1: *Salmonella* isolates from 2011–2014.**

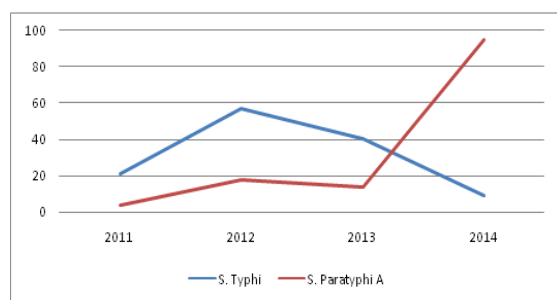
Year	<i>Salmonella</i> Typhi		<i>Salmonella</i> Paratyphi A		Total number of <i>Salmonella</i> isolates
2011	21(84%)	118 (76.6%)	4 (16%)	36 (23.4%)	25
2012	57 (76%)		18 (24%)		75
2013	40(74%)		14(26%)		54
2014	9(8.7%)		95(91.3%)		104
<b>Total</b>	127(49.2%)		131(50.8%)		258

**Table 2: Rate of isolation of *Salmonella* isolates from 2011–2014.**

Year	Total number of Blood cultures received	<i>Salmonella</i> Typhi	Rate of isolation of <i>Salmonella</i> Typhi	<i>Salmonella</i> Paratyphi A	Rate of isolation of <i>Salmonella</i> Paratyphi A
2011	1060	21	1.98%	4	0.37%
2012	2907	57	1.96%	18	0.61%
2013	3753	40	1.06%	14	0.37%
2014	2592	9	0.34%	95	3.66%
<b>Total</b>	10312	127	1.23%	131	1.27%

**Table 3: Antimicrobial sensitivity pattern of *Salmonella* isolates.**

	Ampicillin	Cotrimoxazole	Chloramphenicol	Ciprofloxacin	Ceftriaxone
<i>Salmonella</i> Typhi (n=127)	125 (98.4%)	126 (99.2%)	126 (99.2%)	38 (29.9%)	125 (98.4%)
<i>Salmonella</i> Paratyphi A (n=131)	130 (99.2%)	131 (100%)	127 (96.9%)	19 (14.5%)	131 (100%)



**Figure 1: Changing trends in the occurrence of *Salmonella* Typhi and *Salmonella* Paratyphi A from the year 2011-2014.**

## DISCUSSION

*Salmonella enterica* serotype Typhi and *Salmonella enterica* serotype Paratyphi A are the predominant cause of enteric fever globally. It is widespread throughout the tropics and is one of the leading

causes of morbidity and mortality.<sup>[8]</sup> In a systematic review and meta-analysis of the published studies in India between 1950 and 2015 by John J et al, the incidence and prevalence of typhoid and paratyphoid fever was 377 and 105 per 100,000 person years. This reflects the burden of the disease in India.<sup>[9]</sup> In our study, in the retrospective analysis done during the 4 year study period (2011-2014), a total of 258 cases of enteric fever were culture -confirmed. Out of 258 *Salmonella* isolates, 127 (49.2 %) were *Salmonella* Typhi and 131 (50.8 %) were *Salmonella* Paratyphi A. *Salmonella* Paratyphi A cases increased from 23.4% in 2011-2013 to 91.3% in 2014 among culture confirmed enteric fever, with a significant p value of < 0.05. [Table 1] & [Figure 1]. This is an alarming increase conferencing *Salmonella* Paratyphi A as the rapidly emerging pathogen of enteric fever. This is in concordance with the reports from Nagpur (46.15%), Sevagram (53.33%) during 2001-2003 and Chandigarh (34.18% and 40.63%)

during 2006 and in the early months of the year 2007 which showed a dramatic rise in the number of *Salmonella* Paratyphi A isolates.<sup>[3,4,5]</sup> High degree of clinical suspicion leading to the evaluation of even a low grade fever, vaccination to *Salmonella* Typhi and the possible presence of carrier state, especially in food handlers could be the important contributing factors for the upsurge of paratyphoid fever.<sup>[3,10]</sup>

The rate of isolation of *Salmonella* Typhi dropped from 1.98% in 2011 to 0.34% in 2014, whereas *Salmonella* Paratyphi A increased from 0.37% in 2011 to 3.66% in 2014 [Table 2]. This is in partial comparison with the study conducted by Verma S *et al* from 2000-2006, in which there was a significant increase in the occurrence of serotype Paratyphi A in comparison to serotype Typhi in the year 2003 (*P* value, 0.05), with significant resurgence of serotype Typhi thereafter.<sup>[11]</sup> Persistence of *Salmonella* Paratyphi A needs to be followed up.

In our study, the isolation rate of *Salmonella* spp was more from May to August, it fell down from October and again started rising from January. The peak of the disease usually occurs from July to September, as shown by few studies, which relates it to rainfall with water contamination.<sup>[12]</sup> However, the occurrence of enteric fever was throughout the year, as stated by the World Health Organization.<sup>[8]</sup>

Out of 258 *Salmonella* isolates, 127 (49.2 %) were *Salmonella* Typhi and 131 (50.8 %) were *Salmonella* Paratyphi A. *Salmonella* Typhi were 98.4% fully susceptible to ampicillin, chloramphenicol and cotrimoxazole. *Salmonella* Paratyphi A isolates were 96.9% fully susceptible to ampicillin, chloramphenicol and cotrimoxazole [Table 3]. This reveals a trend of increased susceptibility to first line antibiotics compared to previous studies done from Pondicherry (2005-2009); *Salmonella* Typhi isolates showed 65.9% and *Salmonella* Paratyphi A showed 76.4% susceptibility to first line antibiotics.<sup>[2, 13]</sup>

Only one (0.78%) of the *Salmonella* Typhi isolate was multi-drug resistant. However, it was sensitive to ceftriaxone. This is also in concordance with the other studies done from various parts of India showing a low percentage of MDR isolates 10% (2006-2007) in Karnataka and 4.7% (2008-2009) in Himachal Pradesh.<sup>[14,15]</sup> Our study reveals a higher susceptibility to all first line drugs, < 1% MDR rate, which is indeed welcoming.

Fluoroquinolones had become the drug of choice in the early 1990's, following the evolution of Multidrug resistant (MDR) strains of *Salmonella* spp conferring resistance to ampicillin, cotrimoxazole and chloramphenicol.<sup>[16]</sup> Consequent to the widespread use of ciprofloxacin, especially in the community, resistance to same and failure of treatment were reported.<sup>[17]</sup> Capoor RM *et al* also has documented high MICs ( $8 \geq 512$  µg/ml) to ciprofloxacin in their isolates. In the present study, *Salmonella* Typhi showed 29.9% susceptibility

while *Salmonella* Paratyphi A showed only 14.5% susceptibility to ciprofloxacin by disc diffusion method. It reveals that most of the isolates of *Salmonella* Typhi and *Salmonella* Paratyphi A are resistant to ciprofloxacin.<sup>[18]</sup> To have a clinical relevance it might be required of us to further determine the exact MICs of all our *Salmonella* isolates to ciprofloxacin and document its true susceptibility pattern.

Ceftriaxone, an injectable drug, is now considered to be the first drug of choice for the treatment of enteric fever. In a study from North India the sensitivity was 95% to ceftriaxone.<sup>[19]</sup> In this study, only two isolates of *Salmonella* Typhi showed intermediate levels of resistance to ceftriaxone with 98.4% sensitivity. However, both the patients responded clinically. *Salmonella* Paratyphi A showed 100% sensitivity to ceftriaxone. With the development of resistance to first line antibiotics, then and fluoroquinolones now, cephalosporins indeed need to be used with caution.

## CONCLUSION

*Salmonella* Paratyphi A has emerged as the predominant isolate in the year 2014. However, it did not show much variation in the susceptibility pattern in comparison to *Salmonella* Typhi isolates. There has been re-emergence of susceptibility to first line antibiotics and a notable decline in multi drug resistant strains of *Salmonella* isolates. Most of our isolates showed resistance to ciprofloxacin. Ciprofloxacin can no longer be considered as the drug of choice in treating *Salmonella* infections. Though ceftriaxone and first line antimicrobials still have a role to play in the treatment of enteric fever, cautious use of them is mandatory to prevent antimicrobial resistance.

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