



## Original Research Article

## Enteric fever among febrile children aged 1 to 18 years: Prevalence, diagnostic performance of the Typhoid dot IgM and antibiotic multi-drug resistance

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## ABSTRACT

**Introduction:** Typhoid is a bacterial infection that can lead to a high fever, diarrhoea, and vomiting. It can be fatal. It is caused by the bacteria *Salmonella typhi*. Globally, around 21.5 million people a year contract typhoid. If typhoid is caught early, it can be successfully treated with antibiotics; if it is not treated, typhoid can be fatal.

**Materials and Methods:** This is a retrospective and observational study conducted in Department of Pediatrics from the 1 January 2016 to 30 December 2019. Epidemiological data, clinical features, blood culture, Typhidot IgM test and other laboratory parameters from all the patients were collected and it was analyzed by using the Statistical package for social sciences (SPSS) version 21 Fisher's exact test.

**Results:** During the study period total 290 febrile patients with symptoms suggestive of Enteric fever were included. Incidence of enteric fever among these 290 patients was 32.41% (n=94), of which laboratory confirmed culture positive incidence was 17.09% (n=55) and probable cases of enteric fever based on positive serodiagnosis where culture showed no growth was 17.09% (n=39). Out of 290 patients, 170 (58.62%) were male and rest 120 (41.37%) were female. The serological positivity by Widal test in this study was 32.06% (n=93/290). Serodiagnosis by Typhidot IgM was 27.24% (n=79/290).

**Conclusions:** High rate of MDR *S. Typhi* is alarming and suggests need for better living standards, health education, correct diagnosis and proper treatment as control strategies.

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### 1. Introduction

Typhoid fever is endemic disease and is a major health problem in developing countries and its diagnosis on clinical ground is difficult. Children are disproportionately affected by typhoid fever, with peak incidence long known to occur in individuals aged 5 to <15 years of age.<sup>1</sup> It is a systemic infection caused by *Salmonella typhi*, usually through ingestion of contaminated food or water (faecal-oral route). A similar but often less severe disease, paratyphoid fever, is caused by *Salmonella paratyphi* A, B or C.<sup>2</sup> The often-nonspecific presentation of typhoid fever makes clinical diagnosis difficult as it may be confused with a wide

range of other common febrile illnesses in regions where typhoid fever is endemic.<sup>3</sup>

There are no 100% sensitive or ideal tests available for enteric fever. The sensitivity of a single blood culture is approximately 60% and is affected by the volume of blood obtained for culture.<sup>4</sup> Sensitivity of blood culture is further reduced by the common practice of starting treatment with antibiotics prior to confirmation of the diagnosis. Blood culture is not always available and, when it is, it takes at least 2 to 3 days.<sup>5</sup> As a result, diagnosis may be delayed or overlooked and patients without typhoid fever may receive unnecessary and inappropriate antimicrobial treatment. For this reason, typhoid rapid antibody tests can facilitate diagnosis and disease management.<sup>6</sup>

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Typhidot IgM is widely used serological test. In latest, a Cochrane database systematic review study has been published in May 2017. It has conducted a meta-analysis of 37 studies with total 5080 participants (mostly from Asia) with the aim to assess the diagnostic accuracy of commercially available rapid diagnostic tests (RDTs) and prototypes for detecting *Salmonella typhi* or paratyphi. A infection in symptomatic persons living in endemic areas. It concluded that these tests had moderate diagnostic accuracy. Across all forms of the Typhidot test, the average sensitivity was 84% (95% CI 73% to 91%) and specificity was 79% (95% CI 70% to 87%).<sup>7</sup>

## 2. Aim and Objectives

The objectives of this study were to study the prevalence of enteric fever in children admitted to pediatric ward with acute febrile illness aged 2 to 15 years and compare the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Typhidot IgM compared to Bactec blood culture which is the gold standard for diagnosis of enteric fever and to analyze the effect of antibiotic taken prior to testing, on sensitivity and specificity of Typhidot IgM and Bactec blood culture and also study to the emergence of antibiotic multidrug resistance.

## 3. Materials and Methods

This is a retrospective and observational study conducted in Department of Pediatrics from the 1 January 2016 to 30 December 2019.

### 3.1. Inclusion criteria

The children aged 1 year to 18 years with clinically compatible enteric fever (The acute illness with high-grade fever (95%), coated tongue (76%), anorexia (70%), vomiting (39%), hepatomegaly (37%), diarrhea (36%), toxicity (29%), abdominal pain (21%) with blood leukocyte counts are frequently low in relation to the fever and toxicity) with either Typhidot IgM or blood culture positive for *Salmonella* species were sampled and analyzed.

### 3.2. Exclusion criteria

Children with alternative proven diagnosis or incomplete details were excluded.

Epidemiological data, clinical features, blood culture, Typhidot IgM test and other laboratory parameters from all the patients were collected and it was analyzed by using the

### 3.3. Statistical analysis

Statistical package for social sciences (SPSS) version 21 Fisher's exact test. P-value of less than 0.05 was considered as statistically significant. The study was conducted after getting ethical approval from the Apollo Institute of Medical

Sciences and Research, Jubilee Hills, Hyderabad.

## 4. Results

During the study period total 290 febrile patients with symptoms suggestive of Enteric fever were included. Incidence of enteric fever among these 290 patients was 32.41% (n=94), of which laboratory confirmed culture positive incidence was 17.09% (n=55) and probable cases of enteric fever based on positive serodiagnosis where culture showed no growth was 17.09% (n=39).

In Table 1, out of 290 patients, 170 (58.62%) were male and rest 120 (41.37%) were female.

In Table 2, age of the participants ranged from 2 years to 15 years and 60% study population were less than 2-9 years old (n=162/290) with mean age of 8.51 years. The results of enteric fever cases and its association with sociodemographic factors were shown in Table 2.

### 4.1. Widal tube agglutination test

The serological positivity by Widal test in this study was 32.06% (n=93/290). Whereas blood culture showed only 55 (17.09%) febrile patients as culture confirmed cases, with one Widal false negative test result (Table 3). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Widal test were 95.75%, 76.27%, 49% and 97.02% respectively as compared with the gold standard test of blood culture (Table 4).

### 4.2. Typhidot test

Serodiagnosis by Typhidot IgM was 27.24% (n=79/290) (table-3). The sensitivity, specificity, PPV and NPV for Typhidot IgM test were 100%, 88.88%, 70.24% and 100% respectively (Table 4).

In Table 6, the patterns of susceptibility for *S. typhi* and *S. paratyphi* were comparable and the overall rate of antibiotic resistance to three or more agents was 52.1%.

## 5. Discussion

Typhoid is a bacterial infection that can lead to a high fever, diarrhoea, and vomiting. It can be fatal. It is caused by the bacteria *Salmonella typhi*. The infection is often passed on through contaminated food and drinking water, and it is more prevalent in places where handwashing is less frequent.<sup>8</sup> Globally, around 21.5 million people a year contract typhoid. If typhoid is caught early, it can be successfully treated with antibiotics; if it is not treated, typhoid can be fatal.<sup>9</sup>

The current study identified higher seropositivity (32.41%) while lower prevalence from blood culture (17.09%). The varied positivity rate among serodiagnosis and blood culture may be because of difference in time of sample collection, false positivity in Widal test and

**Table 1:** Distribution of gender of Suspected Febrile Patients (n=290) and in Laboratory Diagnosed Enteric Fever Cases (n=94) and their Association

Gender	Total Numbers Tested (n=290)	Enteric Fever Positive (n=94)	% Prevalence	p - value
Male	170	54	31.7	<b>0.0932</b>
Female	120	40	33.3	

**Table 2:** Distribution of age of Suspected Febrile Patients (n=290) and in Laboratory Diagnosed Enteric Fever Cases (n=94) and their Association

Age	Total Numbers Tested (n=290)	Enteric Fever Positive (n=94)	% Prevalence	p - value
2-5 yrs.	79	31	39.2	<b>0.0032</b>
6-9 yrs.	83	16	19.2	
10-12 yrs.	67	18	26.8	
13-15 yrs.	61	29	47.5	

**Table 3:** Comparison of Incidence of Enteric Fever by Laboratory Diagnosis by Blood Culture, Widal Test, and Typhidot Test

Laboratory Investigations (n=290)	Organisms Identified	No. of Positive Results	% Incidence
Blood culture	S. Typhi	49	16.89
	S. Paratyphi A	6	2.06
Widal tube agglutination test	S. Typhi	95 TO ( $\geq 1:80$ ) + TH ( $\geq 1:160$ ) =93, TO ( $\geq 1:80$ ) =6	32.75
	S. Paratyphi A	12 TO ( $\geq 1:80$ ) +AH ( $\geq 1:160$ )	4.1
Typhidot IgM test	S. Typhi	79	27.24

**Table 4:** Comparative evaluation of widal test and typhidot test as compared with blood culture

Parameters	Widal Test	Typhidot
Sensitivity	95.75%	100%
Specificity	76.27%	88.88%
Positive Predictive Value	49%	70.24%
Negeitive Predictive Value	97.2%	100%

**Table 5:** Clinical features of patients evaluated for typhoid fever

Parameter	Typhoid suspects N= 290 n (%)
Fever	290 (100.0)
Headache	229(79.1)
Anorexia	198 (68.3)
Diarrhea	168 (58.0)
Discomfort /pain	155(53.3)
Tachycardia	145(49.9)
Vomiting	137(47.4)
Constipation Abdominal	46(16.0)
Hepatomegaly	45 (15.4)
Pallor	33 (11.5)
Splenomegaly	16 (5.6)
Relative bradycardia	9 (2.8)
Jaundice	7 (2.3)

**Table 6:** Patterns of antibiotic multi-drug resistance (MDR) in isolates from febrile patients with typhoid fever, as confirmed by culture

MDR pattern	S. Typhi (N=31) n (%)	S. Paratyphi (N=63) n (%)	Total (N=94) n (%)
R3	6 (19.0)	16 (25.0)	22 (23.4)
R4	4 (12.9)	5(7.9)	9 (9.5)
R5	3 (9.5)	9 (14.2)	12 (12.7)
R6	1(3.2)	3 (4.7)	4 (4.2)
R7	1(3.2)	1(1.5)	2 (2.1)
Total	15(48.3)	34 (53.9)	49(52.1)

local endemicity of enteric fever with patients having raised antibody titre from old diseases. Blood tests when gathered past 7-10 days history of fever, had lesser opportunity to give blood culture positive report, while Widal seropositivity expanded. Likewise, Widal false negative report with blood culture and Typhidot IgM test positive report was because of fever was 5-7 days.

Widal false positive is additionally normal and could exist due to infection with other Enterobacteriaceae with cross responding immune response or Malaria. In addition, in our study, Widal test however commonly utilized as normal screening test, it had low specificity (76.27%) and PPV (49%) in our investigation showing high false positive revealing. Comparable examinations by Felgner J et al. likewise indicated lower affectability, explicitness, PPV, NPV of Widal tests.<sup>10</sup> Therefore, rapid tests with better sensitivity and specificity are required for the correct determination of enteric fever.

The Typhidot IgM test is a rapid dot-enzyme immune assay that gets positive in enteric fever as early as in the first week of fever. It had high sensitivity (100%) and sensitivity (88.88%) with preferred execution over Widal test in our investigation. Comparative investigation by Dittrich S et al. likewise demonstrated that Typhidot-M was better than Widal test in their analytic affectability and particularity.<sup>11</sup>

More febrile patients were under 6-9 years age group; however, the burden of enteric fever was most extreme under 2-5 years age group and it is the solitary significant risk factor related with prevalence of enteric fever (by Chi-square test,  $p=0.0032$ , 95% CI-Confidence Interval) (Table 2). Superior expectations for everyday comforts with great water source, improved disinfection and better cleanliness gauges alongside right determination and legitimate treatment may add to control endemicity of enteric fever by conceivably disposing of fecal transporters and shedders from the populace. Additionally, expanding pace of MDR S. Typhi is disturbing and proposes need for wellbeing schooling and successful control methodologies.

The most common clinical features in our patients with positive typhoid cultures were fever, abdominal pain/ discomfort, anorexia, headache, diarrhoea, vomiting and tachycardia. However, only anorexia, constipation, abdominal pain/discomfort, splenomegaly and relative bradycardia showed statistically significant differences when compared with the clinical features of febrile patients with negative typhoid cultures. In accordance with our observations, fever (90–100%), headache (50–98%) and anorexia (65–90%) were the most consistent findings among typhoid fever patients in other settings.<sup>12–15</sup> Although diarrhoea (19–56%), abdominal pain (11–48%) and vomiting (20–46%) were commonly reported by other studies, the proportions of individuals with these symptoms were lower than that seen in our current study.<sup>16–19</sup>

## 6. Conclusion

The high rate of MDR S. Typhi isolation recommends the requirement for proper AST reporting and safely utilization of antibiotics agents for treating enteric fever. These measures are fundamental to prevent rise and spread of XDR S. Typhi, again changing enteric fever into a lethal and untreatable condition. Despite the fact that blood culture is the highest quality level test for its conclusion, the quantity of culture affirmed enteric fever cases is low. Along these lines, we regularly rely upon serodiagnosis. For right determination of enteric fever, quick serological tests with better sensitivity and specificity are required. Likewise, better expectations for everyday comforts, wellbeing schooling, and right treatment are needed to control endemicity of enteric fever.

## 7. Conflicts of Interest

All contributing authors declare no conflicts of interest.

## 8. Source of Funding

None.

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