

## Original Article

## Frequency of Enteric Fever In Children Presenting With Acute Febrile Illness In Islamabad

Hafsah Nazar<sup>1</sup>, Sidra Gul<sup>2</sup>, Sana Zahra<sup>3</sup>, Fazal Hussain Shah<sup>4</sup>

## Abstract

**Objective:** To determine the frequency of enteric fever in children presenting with acute febrile illness in Islamabad, Pakistan.

**Methodology:** This was a cross-sectional study, conducted in the department of Paediatrics, Islamabad Medical Complex, Islamabad, from 1<sup>st</sup> of October 2024 to 30<sup>th</sup> of April 2025. After obtaining ethical approval, this study included 179 children with acute febrile illness. After a thorough clinical evaluation, venous samples from all patients were sent for diagnosis of enteric fever via blood culture. Data were analysed using SPSS version 22. The data were stratified according to the effect modifiers. Statistical significance was set at  $p \leq 0.05$ .

**Results:** The ages ranged from 1-12 years (median = 7, IQR = 4–10), and weights ranged from 8–48 kg (median = 27, IQR = 16–39). The duration of fever varied between 5 and 14 days (median = 10, IQR = 8–12), and the recorded temperature ranged from 38.6°C to 40.0°C (median = 39.2°C, IQR = 38.8–39.5°C). Of the 179 patients, 21 (11.7%; 95% CI: 7.4–17.4%) had enteric fever confirmed by blood culture. The data were stratified according to the effect modifiers (Table I). There was no difference between subgroups of age, sex, area of residence, maternal educational status, weight, and fever duration ( $p = 0.903, 0.967, 0.418, 0.383, 0.359$ , and  $0.321$ , respectively). Enteric fever was significantly higher in the low socioeconomic status group ( $p = 0.015$ ).

**Conclusion:** Our study suggests that enteric fever is a high-burden disease in the paediatric population in Islamabad, responsible for 11.7% (95% CI: 7.4–17.4%) of acute febrile illnesses, with a significantly high impact on those from low socioeconomic status. Studies incorporating multiple centres and areas would provide more comprehensive data.

**Keywords:** Typhoid Fever; Paratyphoid Fever; Fever; Cross-Sectional Studies; Socioeconomic Factors.

## Introduction

Infectious diseases are among the leading causes of morbidity and death in developing countries, such as Pakistan. According to the World Health Organization, Pakistan faces significant public health challenges, including inadequate access to clean water, poor sanitation infrastructure, low vaccination coverage, and limited healthcare resources, all of which affect the health system. Fever is one of the most common presenting complaints in emergency departments (EDs). It can be attributed to a wide range of clinical diseases, from self-limiting viral illnesses to life-threatening conditions such as sepsis, which result in mortality and morbidity, leading to admission to intensive care units or prolonged hospital stays.<sup>1</sup> Acute febrile illness can be reliably predicted using proper history, good physical examination, and laboratory tests.<sup>2</sup>

Typhoid fever is an acute systemic febrile illness caused by *Salmonella enterica* serovar Typhi. *Salmonella enterica* serovars Paratyphi A, B, and C cause paratyphoid fever, a clinically similar condition. Typhoid and paratyphoid fevers are collectively referred to as enteric fevers. While both diseases share clinical features, paratyphoid fever tends to have a more benign course. Enteric fever is an endemic disease in the tropics and sub-tropics, primarily affecting children and young adults, whereas in high-income countries, it is mainly a disease of returning travellers.<sup>3</sup> Enteric fever causes 12 to 25 million cases annually, with 1% mortality, with South-central Asia and Southeast Asia having the

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**Data Availability Statement:** The datasets generated and analysed during this study are not publicly available but are available from the corresponding author upon reasonable request, subject to institutional data governance requirements.

## Institutional Review Board

## Approval

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highest incidence.<sup>4</sup> Globally, 14.3 million cases of enteric fever occurred in 2017, including 136,000 deaths. South Asia reported the largest number of enteric cases, 10.3 million, in 2017, which accounts for 72% of the global burden, with the highest incidence rate of 549 cases per 100 000 population. Enteric fever is endemic in Pakistan, with an incidence rate of 451.7 enteric fever cases per 100,000 persons/year. Enteric fever is also the most common bacterial infection found in children in Pakistan, with incidence rates as high as 1000 cases per 100,000 children per year reported from Karachi.<sup>5</sup>

Enteric fever spreads through contaminated water resources and poor sanitation or hygiene and occurs most commonly in low-resource environments, with children being most at risk.<sup>6,7</sup> In one study, enteric fever was present in 8.1% of patients with acute febrile illness.<sup>8</sup>

The rationale of this study was to determine the frequency of enteric fever in children presenting with acute febrile illness at our institution. This study will help determine the disease burden. Previous studies<sup>1,8</sup> on this topic have selection bias as they were conducted in the monsoon season, when dengue fever and malaria are common, and enteric fever is underreported. Moreover, no such study has been conducted in our population. This study would help determine the burden of enteric fever in our population so that further preventive strategies can be implemented accordingly. Islamabad was specifically chosen as the study site because it represents a semi-urban capital city with a diverse socioeconomic and geographic mix, yet no prior culture-confirmed prevalence data existed for the paediatric population of this region. While substantial literature exists on enteric fever globally and from other Pakistani cities, the evidence gap from Islamabad—particularly outside the monsoon season when co-circulating dengue and malaria tend to overshadow enteric fever diagnoses—makes this study uniquely valuable for informing local public health policy.

## Methodology

This prospective observational cross-sectional study was conducted from 1<sup>st</sup> of October 2024 to 30<sup>th</sup> of April 2025 in the Department of Paediatrics, Islamabad Medical Complex, Islamabad. Ethical approval was obtained from the Institutional Review Board of Islamabad Medical Complex-NESCOM (IRB Reference No: NESCOM-44(33)/2023-IMC) before the recruitment process. Written informed consent was obtained from the parents or guardians of all participants, and patient assent was obtained from children aged seven years and above. No funding was received for this study. A total of 179 children aged 1–12 years of either sex suffering from acute febrile illness were selected. All patients who had taken antibiotics in the last 10 days for fever were excluded from the study. The sample size was calculated using the WHO sample size calculator by taking the frequency of enteric fever in acute febrile illness as 8.1%.<sup>8</sup> The confidence level was 95% with an absolute precision of 4%. Acute febrile illness was defined as an axillary temperature  $>38.5^{\circ}\text{C}$  for  $>4$  days and  $<14$  days without any obvious source of infection. Demographic data, such as age, sex, residence, maternal education level, socioeconomic status, weight of children, and duration of fever, were noted. Eight millilitres (8 mL) of venous blood was drawn aseptically before initiation of antibiotics, inoculated into aerobic blood culture bottles (BD BACTEC™ system), and sent to the institutional microbiology laboratory for blood culture. Enteric fever was labelled when there was evidence of a positive culture for *Salmonella typhi*. All patients were managed according to the standard hospital protocols. The patients were managed with intravenous third-generation cephalosporins, and the regimen was changed after the culture report was available.

All data collected were entered into an Excel sheet and analysed using SPSS version 22.0. The mean and standard deviation were calculated for quantitative variables such as age, body temperature, weight of the child, and duration of fever. The Shapiro-Wilk test was used to check for normal distribution, and in the case of non-normal distribution, the median and IQ range were calculated. Frequencies and percentages were calculated for categorical variables such as gender, area of residence, maternal educational status, socioeconomic status, and enteric fever. Effect modifiers such as age, gender, duration of fever, area of residence, maternal educational status, and socioeconomic status were addressed through data stratification. Post stratification, the chi-square test was applied for categorical variables with expected cell frequencies of five or more; Fisher's exact test was used when expected cell frequencies were fewer than five. Statistical significance was set at  $p \leq 0.05$ . The 95% confidence interval for the primary outcome (frequency of enteric fever) was calculated using Wilson's score method. No missing data were encountered, as all enrolled patients completed the study protocol. Potential confounders, including socioeconomic status, area of residence, and maternal education, were addressed through stratified analysis. Blood culture results were reported within five to seven days of sample collection. Antibiotic therapy was initiated empirically as per hospital protocol and adjusted upon receipt of culture results and clinical response.

## Results

We had data from 179 patients at the end of our study period. Normality tests showed that the data for age, weight, duration of fever, and temperature of the patients were not normally distributed (W values 0.937, 0.940, 0.940, and 0.952, respectively,  $p < 0.0001$ ) after application of the Shapiro-Wilk test. The ages ranged from 1-12 years (median = 7, IQR = 4–10), and weights ranged from 8 to 48 kg (median = 27, IQR = 16–39). The duration of fever varied between 5 and 14 days (median = 10, IQR = 8–12), and the recorded temperature ranged from 38.6°C to 40.0°C (median = 39.2°C, IQR = 38.8–39.5°C). The gender distribution showed almost equal distribution; that is, 86 (48%) were males (Figure 1). Urban and rural participants were 83 (46.4%) and 96 (53.6%), respectively. Regarding maternal educational level, 40 (22.3%) were illiterate, 39 (21.8%) had primary education, 42 (23.5%) had secondary education, and 58 (32.4%) had matriculation or above. The mixed picture of socioeconomic status was evident as 31.3%, 32.4%, and 36.3% belonged to the low, middle, and high classes, respectively. Of the 179 patients, 21 (11.7%; 95% CI: 7.4–17.4%) had enteric fever confirmed by blood culture, defined as isolation of *Salmonella Typhi* confirmed by blood culture (Figure 2). The data were stratified according to the effect modifiers (Table 1). There was no difference between subgroups of age, sex, area of residence, maternal educational status, weight, and fever duration ( $p = 0.903, 0.967, 0.418, 0.383, 0.359$ , and  $0.321$ , respectively). Enteric fever was significantly higher in the low socioeconomic status group ( $p = 0.015$ ).

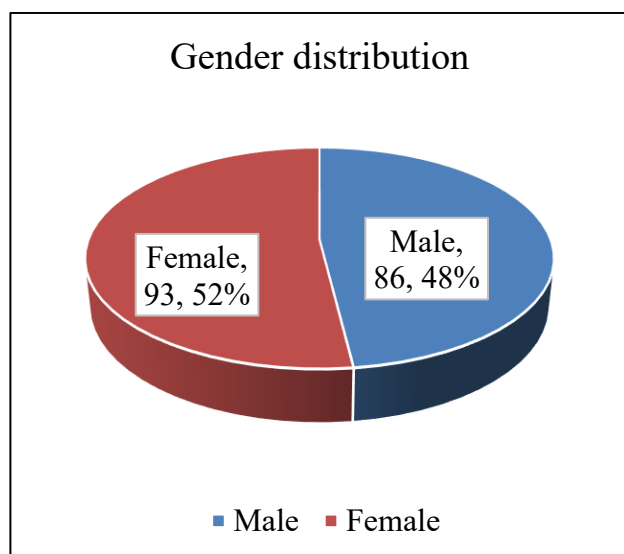


Figure 1: Gender distribution

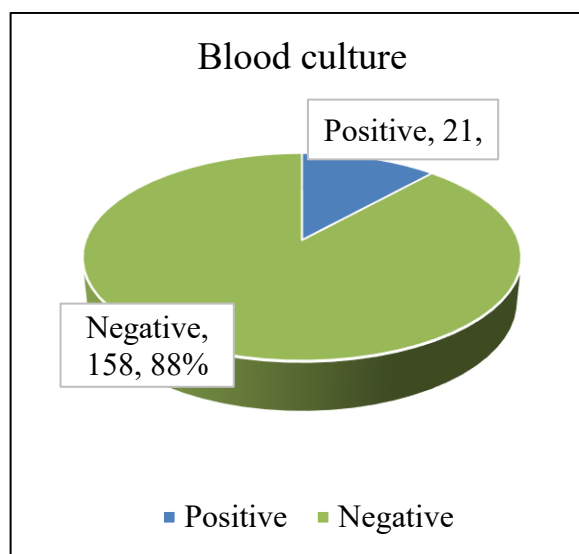


Figure 2: Culture positive enteric fever

Table 1: Enteric fever in stratification subgroups

| Stratification groups                   | Culture +ve        | Culture -ve | P value |
|-----------------------------------------|--------------------|-------------|---------|
| <b>Age</b>                              | <6 years           | 10 (47.6%)  | 0.903   |
|                                         | >6 years           | 11 (52.4%)  |         |
| <b>Gender</b>                           | Male               | 10 (47.6%)  | 0.967   |
|                                         | Female             | 11 (52.4%)  |         |
| <b>Area of residence</b>                | Rural              | 8 (38.1%)   | 0.418   |
|                                         | Urban              | 13 (61.9%)  |         |
| <b>Maternal educational status</b>      | Illiterate         | 6 (28.6%)   | 0.383   |
|                                         | Primary            | 2 (9.5%)    |         |
|                                         | Secondary          | 4 (19.0%)   |         |
|                                         | Matric or above    | 9 (42.9%)   |         |
| <b>Socioeconomic status (PKR/month)</b> | Low (<20K)         | 12 (57.1%)  | 0.015   |
|                                         | Middle (20 to 50K) | 6 (28.6%)   |         |
|                                         | High (>50K)        | 3 (14.3%)   |         |
| <b>Weight</b>                           | <28 kg             | 13 (61.9%)  | 0.359   |
|                                         | >28 kg             | 8 (38.1%)   |         |
| <b>Duration of fever</b>                | <7 days            | 7 (33.3%)   | 0.321   |
|                                         | >7 days            | 14 (66.7%)  |         |

## Discussion

This prospective study examined the current burden and epidemiological profile of culture-confirmed enteric fever in children presenting with acute febrile illness in Islamabad, Pakistan. The high prevalence of culture-positive enteric fever, that is, 11.7% (21 out of 179) in acutely febrile children, shows that enteric fever is one of the leading bacterial causes of childhood morbidity in this urban setting. This prevalence of enteric fever shows community-level transmission with significant implications for public health policies and clinical practice. Moreover, the stratified analysis showed that the most common cohort infected with enteric fever belonged to the lower socioeconomic class. This underscores the socioeconomic dimensions of this preventable disease.

The burden of enteric fever in our study was substantially higher than that in other local studies. The study by Ali et al. in a tertiary care hospital in Karachi showed the prevalence of enteric fever to be 6.5%.<sup>1</sup> The difference may arise due to geographical variations, seasonal fluctuations, and different levels of community transmission. When the prevalence of enteric fever is viewed from a global perspective, the data show a relatively low culture-positive enteric fever. A sub-Saharan African study by Deksisia and Gebremedhin reported that culture-positive enteric fever was only present in 2.7% of the cases.<sup>3</sup> Another study from Vientiane showed an exceptionally low annual incidence.<sup>6</sup> These data disparities highlight that enteric fever should be considered a focal threat driven by the complex interplay of population density, climate, and infrastructure.

One of the most compelling contexts for our data on enteric prevalence comes from a multicounty study. The Surveillance for Enteric Fever in Asia Project (SEAP) included various centres of Pakistan and declared enteric fever as a more than high-burden disease as its prevalence crossed the threshold for the high-burden disease definition (100 per 100,000 person-years). Garrett et al. calculated rates ranging from 176 to 1033 per 100,000 person-years in Pakistan.<sup>9</sup> From India, a comprehensive study by John et al. found incidences between 576-1173 per 100,000 child-years in the urban population.<sup>10</sup> Although annual incidence and point prevalence (11.7%) cannot be feasibly compared, the message is clear that urban areas of South Asia, including Islamabad, have a huge burden of enteric fever, which is alarming. Our study suggests that out of 10 febrile children, one has bacteraemia by *Salmonella* Typhi. This shows that there is a heavy load on healthcare facilities with this single entity.

Our study showed a significant association between enteric fever and low socioeconomic status. The 57.1% (12 out of 21) belonged to households with a monthly income below 20,000 PKR/month. This should not be considered a novel association, but our data reinforce the fundamental truth that enteric fever is a disease of inequity and poverty. This cohort is more vulnerable to diseases spread by the faecal-oral route of transmission, such as enteric fever. Living conditions such as overcrowding, improper sanitation, poor waste management, and limited access to clean water favour disease spread. In SEAP analysis, Andrews et al. strongly supported the argument that the economic condition of the household is a key determinant of the ultimate risk of enteric fever spread as well as early treatment.<sup>11</sup> Unsafe water resources are one of the key risk factors for enteric fever spread.<sup>12</sup> The stratification analysis in our study underscores the importance of addressing socioeconomic issues to halt the cycle of enteric transmission.

The other data insights in our study showed that there was no significant association between enteric fever and other demographic variables, such as age, sex, residence area, or maternal educational level. The almost equal distribution between males and females suggests that environmental exposure is not discriminated by sex. Moreover, Islamabad has unique demographic features due to the lack of a clear urban-rural division. Densely populated urban slums share similar sanitation-related problems with rural areas. In our study, maternal educational level had no impact on enteric fever prevalence, which is intriguing as maternal literacy is often associated with good hygienic practices and health-seeking behaviours.<sup>3</sup> The potent role of contaminated water supply should be considered as educated households become vulnerable.

We enrolled children who presented with classical clinical scenarios of fever (median of 10 days) and pyrexia (median temperature of 39.2°C); however, both these variables were found to be insignificant for the culture-positive status of enteric fever. The child's weight was also not associated with culture-positive status, which is an approximate status of nutrition. These findings make clinical diagnosis more challenging because of the non-specific symptoms of enteric fever and the overlap of clinical pictures with other causes of acute febrile illness, such as malaria, dengue fever, viral syndromes, etc.<sup>13-15</sup>

We reinforced blood culture for the definitive diagnosis of enteric fever, which is considered the gold standard. This is the key point in the diagnosis of drug resistance, which is now at its peak. The use of broad-spectrum antibiotics for acute febrile illnesses is the main reason for drug resistance. A study by Karthikeyan et al. documented this practice in India, where a high percentage of patients with acute febrile illness were given antibiotics without a

confirmed diagnosis.<sup>16</sup> Culture-confirmed diagnosis practices should be adopted to break this cycle because powerful antibiotics should be reserved for proven bacterial infections.

Our study has public health implications, and two essential strategies should be focused on: infrastructure development and vaccination. The aggressive and sustained implementation of typhoid conjugate vaccines is an essential step. The recent introduction of this vaccine in Pakistan's immunisation program is the most significant public health step to combat enteric fever.

Although our study did not focus on antimicrobial susceptibility testing, the increasing drug-resistant *Salmonella* typhi poses significant clinical challenges. Memon et al. reported that 53% of isolates in Karachi were extensively drug-resistant. The resistance to ampicillin, chloramphenicol, co-trimoxazole, fluoroquinolones, and third-generation cephalosporins is quite alarming.<sup>5</sup> Similarly, Chapagain et al. in Nepal documented rising resistance to azithromycin and fluoroquinolones.<sup>17</sup> The accelerated drug resistance in enteric fever can lead to a plethora of complicated cases, and most cases then land in the arena of surgeons to intervene.<sup>18</sup>

While our study provides valuable findings and insights, there are several limitations that should be considered. There is always limited statistical power when the sample size of 179 has 21 positive cases, and a multivariate analysis is planned. This has the potential for type II errors. A large multicentre study incorporating a more diverse population would be more significant. Moreover, in our study, the true community prevalence was not reflected as the disease burden was shown in care-seeking families. Many asymptomatic, subclinical, or home-managed cases may have been missed. This is an important issue that was discussed by Andrews et al. in their healthcare utilisation analysis.<sup>11</sup> Another limitation may be the diagnostic reliance. We focused only on blood cultures, which can have low sensitivity because they are influenced by various factors, such as prior antibiotic use, disease stage, and volume of blood drawn. More sensitive methods, such as PCR, in future studies would uncover a greater burden of the disease. Most critically, we had no data on antimicrobial susceptibility, which prevents us from commenting on the appropriateness of current empiric treatment guidelines in Islamabad.

## Conclusions

Our study suggests that enteric fever is a high-burden disease in the paediatric population in Islamabad, responsible for 11.7% (95% CI: 7.4–17.4%) of acute febrile illnesses, with a significantly high impact on those from low socioeconomic status. Our findings strongly suggest the need for timely reinforcement of preventive strategies, including the widespread use of typhoid vaccines and investments in water and sanitation infrastructure, to reduce this significant public health burden. Studies incorporating multiple centres and areas would provide more comprehensive data.

## Author Information

<sup>1,3</sup>Postgraduate Trainee, Pediatrics Department, IMC, NESCOM

<sup>2</sup>Consultant Pediatrician, IMC, NESCOM

<sup>4</sup>Consultant Surgeon, THQ Hospital.

**Corresponding author:** Dr. Fazal Hussain Shah  drfazal3@hotmail.com

## Contributions:

HN SG - Conception, Design

HN SZ FHS - Acquisition, Analysis, Interpretation

HN - Drafting

SG SZ FHS - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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