

FREQUENCY OF SALMONELLA TYPHI IN PATIENTS OF PYREXIA OF UNKNOWN ORIGIN ADMITTED IN PAEDIATRIC WARD

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**Abstract**

**Background**

Salmonella Typhi is a significant cause of pyrexia of unknown origin (PUO) in endemic regions, heavily influenced by socioeconomic and environmental factors. Accurate and reliable diagnostic methods are crucial for effective disease management. While various diagnostic tools exist, culture-based confirmation remains the gold standard for identifying Salmonella Typhi.

**Objective**

To determine the frequency of Salmonella typhi in patients of pyrexia of unknown origin admitted in paediatric ward of Mardan Medical Complex Mardan.

**Study Design**

Cross-sectional study.

**Duration and Place of Study**

The study was conducted from September 2024 to December 2024 at the Department of Paediatrics, Mardan Medical Complex, Mardan.

**Methodology**

A total of 127 children aged 1–12 years with PUO, defined as fever  $\geq 38.3^{\circ}\text{C}$  lasting more than 3 weeks without an identifiable source, were included. Blood samples were cultured using Wilson and Blair bismuth sulphite agar for Salmonella Typhi identification. Demographic and clinical data, including age, gender, socioeconomic status, parental education, and residential status, were recorded.

**Results**

Salmonella Typhi was identified in 38.6% of patients. Significant associations were found with low socioeconomic status, uneducated parents, and rural residency. No significant association was observed with age, gender, or fever duration.

**Conclusion**

This study demonstrates the significant prevalence of Salmonella Typhi in children with PUO and underscores the critical influence of socioeconomic and environmental factors.

**INTRODUCTION**

Salmonella typhi remains one of the most important causes of prolonged fever and systemic

illness in children worldwide, especially in areas devoid of modern sanitation and a safe and

reliable supply of drinking water.<sup>1</sup> Typhoid fever is a serious kind of infection caused by *Salmonella typhi* that can be lethal if prompt diagnosis with timely management is not undertaken.<sup>2</sup> Pyrexia of unknown origin-children (PUO) presenting with a fever lasting more than three weeks without a demonstrable source, *S. S. typhi* infection is one of the common and serious considerations, especially within endemic countries.<sup>3</sup> Knowledge of *S. typhi* prevalence in pediatric PUO cases gives a positive thrust toward clinically directed investigations to timely intervene and avoid complications.<sup>4</sup>

Children are prone to *S. typhi* infection because of an immature immune system and higher chances of exposure to food and water contamination.<sup>5</sup> In the endemic areas, *S. typhi* is considered one of the causes for PUO, accounting for 30–40% cases in pediatric populations.<sup>6</sup> Diagnosis is difficult due to the subtle and variable presentation of the disease in children. Diagnoses can be made through various techniques, including blood culture; however, the sensitivity is lowered in cases of prior antibiotic intake and in those children who are young, with a low bacterial load.<sup>7</sup> Molecular diagnostic techniques such as PCR have enhanced specificity and speed towards diagnosis, especially identifying *S. typhi* infection in children presenting atypically or with co-infections.<sup>8</sup>

Clinical manifestations by *S. typhi* in cases of PUO among children have varied presentations. Symptoms include the following: fever that does not resolve, abdominal pain, absence of appetite leading to lethargy.<sup>9</sup> Since early diagnosis and timely interventions are imperative against the complications produced by the infection which may become as serious as bowel perforation peritonitis leading to sepsis.<sup>10</sup> Though blood culture remains the gold standard in diagnosis in children, this is often not possible as it is associated with numerous logistical challenges in resource-limited settings.<sup>11</sup> Treatment generally consists of antibiotics; however, the rising tide of MDR and XDR *S. typhi* infection in children has placed in sharp focus the role of newer antibiotics such as azithromycin and carbapenems.<sup>12</sup> Appropriate antimicrobial stewardship and

timely diagnoses are key factors to reducing morbidity and mortality associated with the disease in pediatric patients.<sup>12</sup> A study conducted by Vallab Ganesh Bharadwaj B and colleagues reported a *Salmonella typhi* prevalence of 30.4% among patients presenting with pyrexia of unknown origin.<sup>13</sup>

Pyrexia of unknown origin remains a diagnostic challenge, especially in resource-limited settings where infectious diseases are prevalent. Among these, *Salmonella typhi*, the causative agent of typhoid fever, is a significant public health concern due to its association with substantial morbidity and mortality in children. Despite advancements in diagnostic methods, the frequency of *S. typhi* in patients presenting with prolonged, unexplained fever often goes underreported. Identifying its prevalence in PUO cases is crucial for timely diagnosis and appropriate treatment, thereby reducing complications and improving patient outcomes.

## Methodology:

This cross-sectional study was conducted from September 2024 to December 2024 in the Department of Paediatrics, Mardan Medical Complex, Mardan. The study included 127 children diagnosed with pyrexia of unknown origin, defined as a persistent fever above 38.3°C (100°F) by thermometer lasting for more than 3 weeks, with no obvious source of infection after initial evaluation. The sample size was calculated using the WHO sample size calculator, considering a 95% confidence level, an 8% margin of error, and an anticipated frequency of *Salmonella typhi* of 30.4% in patients with pyrexia of unknown origin.<sup>13</sup>

The inclusion criteria comprised children aged 1 to 12 years of both genders with pyrexia of unknown origin. Exclusion criteria included children with a history of pneumonia or malaria, antibiotic use prior to hospital admission, malnourishment, or immunosuppressive therapy. After obtaining approval from the ethical committee, informed consent was secured from parents or caregivers. Demographic details such as age, gender, weight, family socioeconomic

status, parental education level, and residential status were recorded.

Blood samples were collected from all children in a standardized manner. A topical anesthetic was applied to the venipuncture site, and a tourniquet was used to facilitate vein identification. After the site was cleaned and dried, 2-3 pediatric blood tubes were filled, with the tourniquet removed once blood flow was established. Samples were labeled accurately and sent to the hospital laboratory to ensure uniformity in testing.

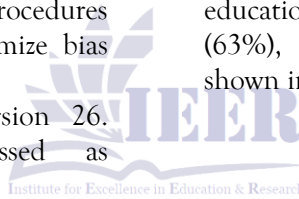
Blood samples were cultured using Wilson and Blair bismuth sulphite agar to identify Salmonella typhi. The agar plates were incubated at 37°C for 24-48 hours, and positive cultures were confirmed by identifying jet-black colonies with a metallic sheen. For quality control, known positive and negative control strains were processed simultaneously to ensure test accuracy and reliability. All equipment was calibrated prior to testing, and standard operating procedures (SOPs) were strictly followed to minimize bias and variability.

Data were analyzed using SPSS version 26. Categorical variables were expressed as

frequencies and percentages. Quantitative variables were represented as mean ± standard deviation or median (IQR) depending on the normality assessed through the Shapiro-Wilk test. Stratification was done and post-stratification, chi-square test or Fisher's exact test was applied, with a p-value ≤0.05 considered statistically significant.

**Results:**

The mean age of patients was 6.95 ± 3.43 years, and the average duration of fever was 7.89 ± 2.83 weeks. The age group distribution showed 44.9% were 1-6 years old, and 55.1% were 7-12 years old. Gender distribution included 45.7% males and 54.3% females. Regarding socioeconomic status, 43.3% of families were categorized as low, 45.7% as middle, and 11% as high. Parental education was predominantly low, with 43.3% uneducated, 37.8% educated to primary level, 15.7% to secondary, and 3.1% to higher education. Most patients resided in rural areas (63%), compared to 37% in urban areas as shown in Table-I.



**Table- I: Patient Demographics**

Demographics		Mean ± SD / n (%)
Age (years)		6.953±3.43
Duration of fever (weeks)		7.898±2.83
Age group (years)	1-6	57 (44.9%)
	7-12	70 (55.1%)
Gender	Male	58 (45.7%)
	Female	69 (54.3%)
Family Socioeconomic Status	Low	55 (43.3%)
	Middle	58 (45.7%)
	High	14 (11%)
Parents Education	Uneducated	55 (43.3%)
	Primary	48 (37.8%)
	Secondary	20 (15.7%)
	Higher	4 (3.1%)
Residential Status	Rural	80 (63%)
	Urban	47 (37%)

Salmonella typhi was identified in 38.6% of patients, while 61.4% tested negative (as shown in Table-II).

Table- II: Salmonella Typhi

Salmonella Typhi	Frequency	%age
Yes	49	38.6%
No	78	61.4%
Total	127	100%

Significant associations with Salmonella typhi presence were observed for family socioeconomic status and parental education. Low socioeconomic status (63.6% positive,  $p=0.000$ ) and uneducated parents (63.6% positive,  $p=0.000$ ) were more commonly associated with

positive cases. Rural residency also had a higher prevalence of Salmonella typhi (47.5% positive,  $p=0.007$ ). No significant association was noted with age ( $p=0.712$ ), gender ( $p=0.384$ ), or duration of fever ( $p=0.353$ ) as shown in Table-III.

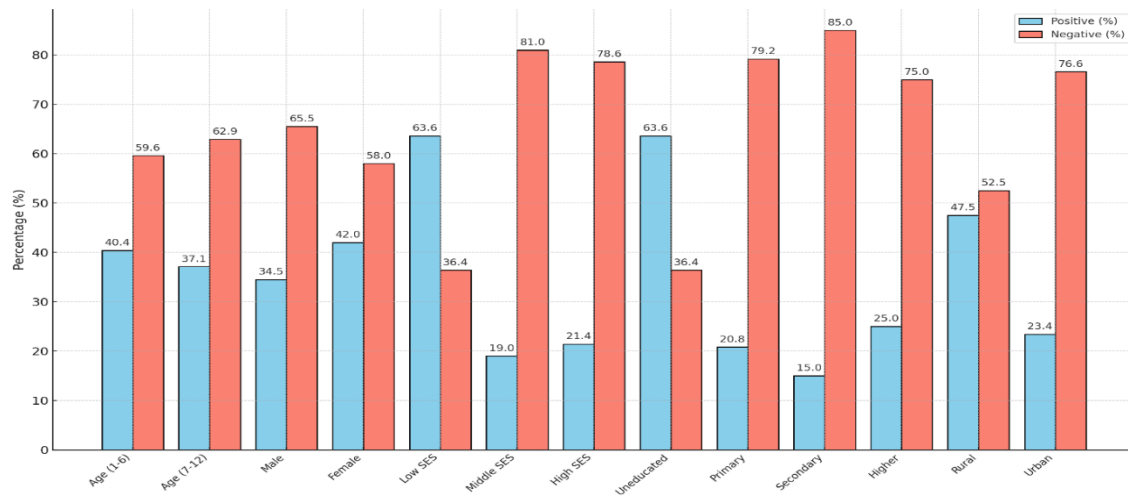
Table-III: Association of Salmonella Typhi with clinical and demographic factors

Clinical and Demographic Factors		Salmonella Typhi		p-value
		Yes n(%)	No n(%)	
Age (years)	1-6	23 (40.4%)	34 (59.6%)	0.712
	7-12	26 (37.1%)	44 (62.9%)	
Gender	Male	20 (34.5%)	38 (65.5%)	0.384
	Female	29 (42%)	40 (58%)	
Family Socioeconomic Status	Low	35 (63.6%)	20 (36.4%)	0.000*
	Middle	11 (19%)	47 (81%)	
	High	3 (21.4%)	11 (78.6%)	
Parents Education	Uneducated	35 (63.6%)	20 (36.4%)	0.000*
	Primary	10 (20.8%)	38 (79.2%)	
	Secondary	3 (15%)	17 (85%)	
	Higher	1 (25%)	3 (75%)	
Residential Status	Rural	38 (47.5%)	42 (52.5%)	0.007
	Urban	11 (23.4%)	36 (76.6%)	
Duration of fever (weeks)	3-6	19 (44.2%)	24 (55.8%)	0.353
	>6	30 (35.7%)	54 (64.3%)	

\*Fischer Exact Test

There were significant associations between Salmonella Typhi positivity and clinical-demographic factors. Positivity was highest in children from low socioeconomic families (63.6%) and with uneducated parents (63.6%). Rural residents had a higher positivity rate

(47.5%) compared to urban residents (23.4%). Gender and age showed less variation, with females (42%) and the 1-6 years' age group (40.4%) slightly more affected as shown in Graph-I.



Graph-I: Key Associations of Salmonella Typhi Positivity

**Discussion:**

The study revealed a Salmonella Typhi positivity rate of 38.6% among patients with pyrexia of unknown origin, reflecting its significant burden in endemic regions. The higher prevalence in children from low socioeconomic backgrounds (63.6%) underscores the critical impact of inadequate sanitation and poor hygiene, which are key contributors to the transmission of enteric fever. Uneducated parents correlated much more strongly with higher infection rates and showed an acute level of lack in general knowledge regarding preventive practices; thus, their education played another important role in the research study. Moreover, living in rural areas makes a person far more at risk compared to an individual living in the cities and towns of Kenya, as represented from most variables resulting due to various variables affecting accessibility: clean water and hygiene facilities to accommodate more persons living, and availability or infrastructure regarding access to proper medical facilities. It is essential that these findings accent the role of factors related to the physical and socioeconomic environments instead of some inherent biological factors, age or sex in dictating the infection burden. Results obtained by Vallab Ganesh Bharadwaj et al.<sup>13</sup> showed that the prevalence of enteric fever by Widal test was 27.3%, which is comparable to our findings of positivity for Salmonella Typhi in 38.6% patients

presenting with pyrexia of unknown origin (PUO). The slight difference in prevalence could be attributed to the diagnostic approach, as our study utilized culture confirmation while Bharadwaj et al. relied on the Widal test, which has known limitations in sensitivity and specificity. Both studies highlight the endemic nature of enteric fever in resource-limited settings and the age-related distribution, with the highest prevalence observed among younger individuals. Our findings align with those of Durfishan Dilshad et al.<sup>14</sup> who reported extensive drug resistance (XDR) in 82.6% of pediatric typhoid cases in Pakistan. Similarly, our study observed significant antimicrobial resistance trends, particularly for commonly used antibiotics like ciprofloxacin, underscoring the critical need for judicious use of antibiotics in both regions. Both studies recommend azithromycin and carbapenems as effective therapeutic options, emphasizing the importance of antimicrobial stewardship to combat resistance. The study by Lin Jiang et al.<sup>15</sup> on fever of unknown origin (FUO) in China identified infectious diseases as the leading cause (69.3%), with brucellosis and urinary infections being prominent. In comparison, our study identified Salmonella Typhi as a significant infectious agent in PUO, accounting for 38.6% of cases. The higher diagnostic rate in Jiang et al. could be attributed to the structured diagnostic scheme

utilized, which included advanced imaging and serological tests, suggesting the potential benefit of integrating such protocols in endemic regions to improve diagnostic accuracy.

Similar to Muche et al.<sup>16</sup> who reported a 30% prevalence of typhoid fever in Ethiopia, our study confirms the high burden of enteric fever in low-resource settings. Both studies found strong associations between disease prevalence and socioeconomic factors such as unemployment and rural residence, highlighting the role of environmental and social determinants in disease transmission. The comparable prevalence rates across these regions suggest that enteric fever remains a public health challenge in developing countries with limited access to clean water and sanitation.

Melese Yeshambaw Teferi et al.<sup>17</sup> reported a wide variation in prevalence based on diagnostic methods, with 3% for culture-based diagnoses and 33% for Widal tests. Our study, using a culture-based approach, found a prevalence of 38.6%, consistent with their observations that culture tests yield lower prevalence rates but provide greater diagnostic reliability. The similarities in antimicrobial resistance trends, such as high susceptibility to ceftriaxone and resistance to older antibiotics like chloramphenicol, reflect shared challenges in antimicrobial management.

The study by Tadele Amsalu et al.<sup>18</sup> reported a prevalence of enteric fever of 5.3%, out of which 75% were due to *S. Typhi* and 66.7% showed MDR. In contrast, our study had a higher prevalence of 38.6%, probably due to differences in the study populations and diagnostic criteria. Both studies show similar resistance patterns, especially to tetracycline and chloramphenicol, and recommend judicious use of cephalosporins to avoid the development of further resistance.

The study at hand underlines the scenario of the presence and risk factors of *Salmonella Typhi* infection among pyrexia of unknown origin patients in a rather valuable and informative manner. Such findings follow regional and international data and spell common, serious challenges faced with regard to poor diagnosis and overall management of enteric fever in the

impoverished settings. These observations suggest the identification of an integrative approach in the diagnostic strategy and treatment modules, according to local scenarios vis-à-vis this important public health concern of enteric infection. This of course, would imply some limitations: being a single-center study somewhat excludes the representation across wider populations; the fairly small sample could raise the issue of results that are less generalizable with reduced power for detection in minor associations; and diagnostics dependent on cultures have missed the cases treated with antibiotics prior to testing. Future studies need to be directed at multicenter studies with larger cohorts, using advanced diagnostic tools, for a wider understanding of enteric fever dynamics.

#### Conclusion:

Our study has established that *Salmonella Typhi* is still one of the major causes of pyrexia of unclear origin in endemic regions; and that socioeconomic and environmental factors are a landmark for the prevalence of the disease burden. These results again guarantee that improvement in sanitation and hygiene should be accompanied by public health education and availability of diagnostic tools to help bring down enteric fever.

**Conflict of interest:** None

**Disclaimer:** None

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#### Author

#### Contributions:

The authors have played significant roles in the development of this manuscript.

**Dr. Hazrat Anus** designed the study, drafted the manuscript, and collected data from the hospital.

**Dr. Kiramat Ullah** contributed to the refinement of the manuscript, shaping the study

design, and conducting data analysis and interpretation.

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