

Estimated Percentage of Typhoid Fever in Adult Pakistani Population (TAP) Study

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Abstract

Typhoid fever is a serious infection with high morbidity and mortality in untreated cases. It is one of the very common infections in developing countries due to various factors involving hygiene and sanitation.

Objective: To determine the estimated percentage of typhoid fever in Pakistani population and to find the commonly prescribed antibiotics for the disease.

Material and Methods: This cross sectional study was conducted on 1036 patients, selected from forty five general practitioner clinics, between June to October 2010. Patients of > 18 years of age with > 3 days

history of fever (> 100°F) and high index of suspicion for typhoid fever were tested for typhoid fever using Typhidot kits and positive cases were recruited for monitoring response to treatment. The febrile patients with clear cut history of urinary or respiratory infection, hypovolemic shock or hepatobiliary disease were excluded and not tested by typhidot kit. The antibiotics prescribed to study population by various general practitioners were noted. Data was analysed on SPSS. Results were expressed in percentages and proportions.

Results: Total 1036 patients were recruited. Typhidot test was negative in 63.9% and positive in 36.1% patients with highest percentages of positive cases in Karachi, Rawalpindi and Hyderabad. The maximum number of cases were reported in summer season especially from June to August. Most of the patients were between ages of 19 – 39 years. The commonest antibiotics prescribed were Ofloxacin, Ciprofloxacin and Levofloxacin.

Conclusion: Typhoid fever is very common infection in Pakistan caused by *Salmonella typhi* which is transmitted among humans through faeco-oral route. Disease can be controlled not only by antibiotics like fluoroquinolones but by patient education, improvement in hygiene and sanitation, safe supply of clean drinking water and prophylactic vaccination as well. However, timely diagnosis and appropriate management with proper antibiotics is the key to avoid the acute complications and chronicity of the disease.

Key Words: Typhoid fever, Ofloxacin, Ciprofloxacin, Levofloxacin Typhidot test.

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Introduction

The global incidence of typhoid fever is approximately 16 million cases annually with seven million in South East Asia alone. Typhoid accounts for > 600,000 deaths annually.¹ In Pakistan, the incidence of clinical typhoid fever in children is 11.69/1000.² It is one of the very common infectious diseases in Pakistan needing prompt diagnosis and treatment. It is more commonly seen among low socioeconomic groups due to lack of access to clean drinking water, improper hygiene and sanitation measures.³ The gold standard diagnostic test is blood culture in the first week of infection⁴. However, for rapid diagnosis of suspected cases typhidot test can be done. It is ELISA based on detection of IgM and IgG antibodies directed against outer membrane protein of the causative agent, the *Salmonella typhi*.⁵

Objectives

TAP is the first multi-centered study conducted at large scale on national level that was designed to:

1. Provide an estimate of the burden of typhoid fever in adult population presenting with fever at general practitioners' clinics in Pakistan.
2. Document the therapeutic management of patients presenting with typhoid fever.

Methodology

This cross – sectional, multi – centered study was conducted during peak summer season with monsoon rains between June and October, 2010. Fifty – four general practice clinics of qualified physicians were selected from the data base available with the sponsor (Sanofi Aventis) (Figure 1). Each practitioner recruited 20 patients. Inclusion criteria were age > 18 years and ≥ 3 days history of high grade fever ($> 100^{\circ}\text{F}$) and positive typhidot test. Patients with high clinical suspicion of urinary tract infections, respiratory tract infect-

ions, acute hepatitis, haemodynamic instability and history of pre-existing biliary disease were not eligible. Although blood culture is gold standard diagnostic investigation, but due to lack of proper facility at general practitioner clinics it was not done and we used typhidot test kit for diagnosis of suspected cases. It was performed instantly at the clinic using MBDr Typhidot[®] diagnostic kits after obtaining patients consent. Typhidot[®] helps rapid detection of specific IgM antibodies against a specific antigen for *Salmonella*. The sensitivity and specificity of test kit is 100% and 80% respectively in bacteriaemic patients.⁶ In Pakistan the reported sensitivity and specificity of typhidot test kit are 84 – 93% and 77 – 89% respectively.⁷ A case of typhoid was defined as a patient meeting the inclusion/exclusion criteria with a positive Typhidot[®] test. Physicians also recorded profile of all febrile patients and the antibiotics prescribed for the patient positive on Typhidot[®].

Results

Of the 1036 patients recruited, 391 patients were detected to be Typhidot[®] positive.

Most patients presented in summer season especially during monsoon (from June to August), followed by rapid decline in the cases during months of September and October (Figure 1).

There was a significant difference in the incidence rate of typhoid cases across cities ($p < 0.01$). The highest number of typhidot positive cases were seen in Karachi, Rawalpindi, Hyderabad followed Lahore, Gujranwala, Multan, Faisalabad, Peshawar, Bahawalpur, Sukkhar and Sargodha (Table 1).

Epidemiology of typhoid fever within the country was heterogeneous both in time and location. Patients presented with typhoid fever even in places with little rainfall (e.g. Multan). However, the incidence sharply increased in places with wetter conditions (Rawalpindi and Faisalabad) compared to those with moderate rainfall (e.g. Lahore). The average temperature during the

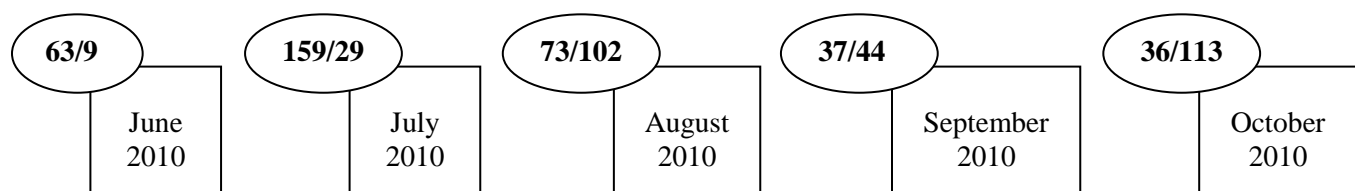


Figure 1: Recruitment calendar (numerator = typhoid patients; denominator = febrile patients).



Figure 2: Location of centers (Numeric represent the number of sites per city).

Table 1:
Typhidot test result of suspected cases across various cities of Pakistan.

Cities	Typhidot® Positive n (%)	Typhidot® Negative n (%)	Total
Lahore	37 (37.0)	63 (63.0)	100
Karachi	75 (48.1)	81 (51.9)	156
Rawalpindi	69 (59.0)	48 (41.0)	117
Faisalabad	27 (27.0)	73 (73.0)	100
Gujranwala	28 (37.3)	47 (62.7)	75
Bahawalpur	18 (18.4)	80 (81.6)	98
Hyderabad	53 (42.7)	71 (57.3)	124
Multan	27 (27.0)	73 (73.0)	100
Sukkur	09 (19.1)	38 (80.9)	47
Sargodha	05 (12.5)	35 (87.5)	40
Peshawar	26 (32.9)	53 (67.1)	79
Overall (Total)	374 (36.1)	662 (63.9)	1036

Table 2: Profile of patients showing age, gender, vital signs and symptoms.

Typhidot Test				
Parameters	Positive (n = 374)	Negative (n = 662)	Odds ratios	p-value
Gender				
Male	180 (48.1)	347 (52.4)	1.19	0.19
Female	194 (51.9)	315 (47.6)		
Age (years)	28.9 ± 12.9	64.3 ± 13.6	-	< 0.01
Weight (kg)	61.9 ± 12.9	64.3 ± 13.6	-	< 0.01
Height (cm)	158.2 ± 12.4	156.8 ± 19.7	-	0.28
Pulse rate / min	93.6 ± 14.1	92.5 ± 15.2	-	0.27
Body Temperature (F)	101.9 ± 1.1	101.9 ± 1.2	-	0.81
Symptoms and Signs				
Chills	254 (67.9)	458 (69.4)	0.94	0.7
Abdominal Discomfort	274 (73.9)	444 (67.5)	1.4	0.04
Delusions	64 (17.4)	141 (21.7)	0.76	0.10
Constipation	121 (32.6)	153 (23.3)	1.59	< 0.01
Burning Micturation	59 (15.9)	176 (26.9)	0.52	< 0.01
Cough	101 (27.3)	215 (32.5)	0.77	0.07
Flu like symptoms	77 (20.8)	234 (35.6)	0.47	< 0.01
Bloody Stool	16 (4.3)	33 (5.0)	0.85	0.62
Diarrhea	75 (20.1)	167 (25.3)	0.74	0.06
Splenomegaly	46 (12.5)	50 (7.7)	1.72	0.01
Hepatomegaly	30 (8.2)	39 (5.9)	1.39	0.19
Episode of typhoid fever in the past	102 (28.1)	168 (25.8)	1.10	0.50
Frequency of diarrhea (stools / day)	4.8 ± 1.7	6.1 ± 3.1	-	< 0.01

study period ranged from 29°C to 42°C in cities where temperature by the meteorological department was recorded.

The mean age of patients with typhoid fever was 28.9 ± 12.9 years (Table 2). The mean temperature of our cases was 101.9°F (± 1.1) and a mean pulse rate of 93.6 ± 14.1 per minute (Table 2).

Bivariate analysis demonstrated that patients positive on Typhidot® test compared to those with negative results were more likely to present with chills (OR 1.5, CI 1.1 – 2.0; p 0.02), abdominal discomfort (OR 1.8, CI 1.4 – 2.4; p 0.01) and past history of typhoid fever (OR 1.6, CI 1.2 – 2.1; p 0.003). Altered bowel habits (constipation and diarrhea) were not a predictor of ty-

phoid (Table 2). Some positive cases had neurological complaints, cough, burning micturition and flu like symptoms. Splenomegaly was commonly seen among positive cases than negative typhidot cases (p value < 0.01).

Relative bradycardia is a well known feature of typhoid fever and is very commonly seen. In our study it was observed both in patients with and without typhoid fever (Table 3). The difference between the two groups may not be clinically significant though it was statistically significant (p < 0.05).

Patients who presented with fever were mostly prescribed fluoroquinolones. The most prescribed antibiotic was ciprofloxacin, followed by levofloxacin,

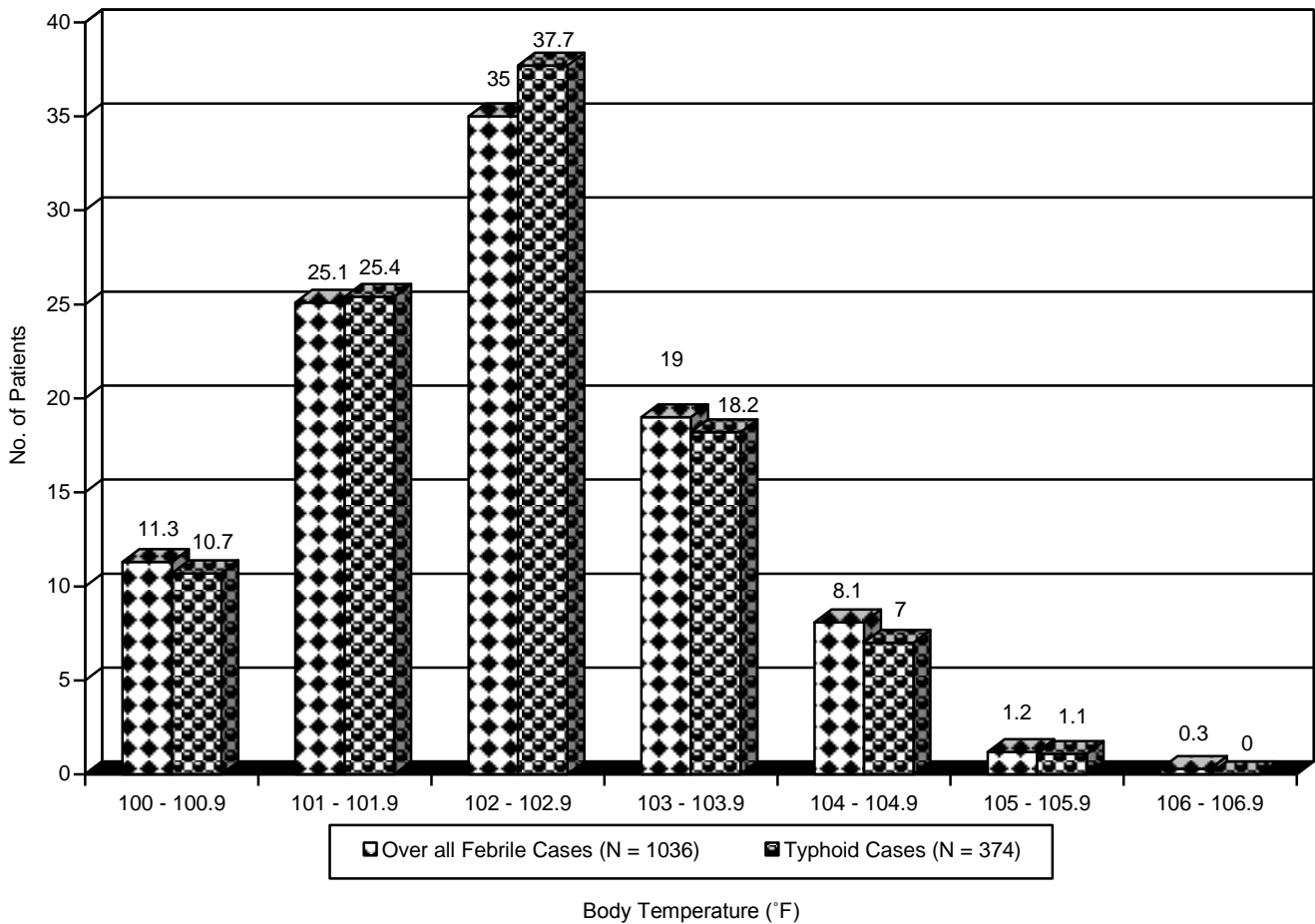


Figure 3: Temperature of febrile patients.

Table 3: Pulse at various body temperatures.

Typhidot® Test					
Temp. (°F)	Ideal Pulse Rate ⁵	Positive Mean Pulse ± S.D	Negative Mean Pulse ± S.D	Positive Deviation from Ideal Pulse	Negative Deviation from Ideal Pulse
100	NA	98.4 ± 12.6	92.9 ± 8.9	—	—
101	110	93.3 ± 13.2	95.0 ± 11.7	-16.7	-15
102	120	89.9 ± 16.9	97.4 ± 15.8	-13.1	-22.6
103	120	97.2 ± 14.02	101.6 ± 15.0	-22.8	-18.4
104	130	94.6 ± 16.81	98.0 ± 19.3	-35.4	-28.7
105	140	96.0 ± 5.8	98.0 ± 2.8	-44	-42
107	NA	—	68.0 ± 0.0	—	—

ofloxacin, macrolides ,ceftriaxone, and trimethoprim-sulfamethoxazole. Following diagnosis of typhoid

fever with typhidot test kit, physicians preferred to prescribe ofloxacin (58.1%), ciprofloxacin (23.3%),

levofloxacin (7.5%) and others (11.1%) including ceftriaxone, levofloxacin, azithromycin and chloramphenicol.

Discussion

Typhoid fever is a serious health problem presenting mostly with classical step ladder pattern of fever. However many cases are often misdiagnosed owing to non-specific symptoms because of injudicious use of improper antibiotics by primary health care providers early in the course of disease.¹

Typhoid is generally considered an illness of the pediatric age group in South Asia.² Our study in adults revealed that more than half the patients were ≥ 30 years of age. The overall incidence of Typhidot® positive cases was 36 per 100 adult patients presenting with fever of $> 100^\circ\text{F}$ for ≥ 3 days to general practice clinic. This corroborates with data from South Asia and possibly South East Asia where the burden of typhoid fever is also high in adults.³

In Asia, disease burden estimates are based on clinically diagnosed cases of typhoid fever gathered at secondary and tertiary care facilities.⁴ In our study Typhidot®, a rapid, reliable and affordable serological test was used for diagnosis of the febrile cases.⁵ This methodology provides a better estimate of the disease burden at the community level.^{6,7}

Our study reported relative bradycardia in Typhidot® positive patients, as also suggested by Osler in 1892.⁸ Additionally our study revealed that patients with negative Typhidot® test also presented with relative bradycardia. This observation correlated with a study from Denmark in 1996 which suggests that relative bradycardia as a clinical sign is not diagnostic of typhoid fever.⁹

There are many serotypes of Salmonella, but according to P. Anjum et al, the most prevalent serotype is Salmonella Enterica paratyphi A which is commonly sensitive to fluoroquinolones.¹⁰

Patients with typhoid presented in various cities. Presentation of typhoid fever cases within the country was heterogeneous both in time and location irrespective of the amount of rainfall suggesting that it had a role in defining high and low disease periods. Factors other than climatic conditions may also had contributed to a greater incidence of typhoid fever. A study conducted by A. Farooqi et al showed correlation of outbreaks of typhoid fever with consumption of unhealthy and contaminated water. Therefore, it is very

important to ensure supply of safe drinking water at community level and proper disposal of sewage waste to curb the disease and morbidity because of its associated complications.¹¹

Our study depicted that chills and abdominal discomfort in association with high grade fever of ≥ 3 days were commonly seen in typhoid fever and this finding was consistent with published literature¹². Altered bowel habits presented a non-significant picture of the disease in many cases with positive typhidot test.

A prescribing practice consistent with WHO guidelines was observed following serological diagnosis of typhoid whereby physicians preferred to prescribe fluoroquinolones.¹³ More than half of the patients with typhoid were prescribed ofloxacin (58%) followed by ciprofloxacin (23.3%) and levofloxacin (8.2%). During last two decades, emergence of multidrug resistance to conventional treatment of typhoid fever has encouraged the use of fluoroquinolones as effective antibiotics. However, frequent use of these drugs has also led to development of partial resistance against this group, especially ciprofloxacin.¹³

Study Limitations

1. A strict case definition and history of antibiotic usage may underestimate the true burden of typhoid fever.
2. Microbiological confirmation by blood cultures was not undertaken because lack of proper test facility at many general practitioner clinics. That is why typhidot test kit was used because of its documented high sensitivity and specificity in febrile patients with typhoid fever.
3. Inability to account for patients not seeking medical care.

Conclusion

Typhoid is a serious public health problem that can result in high morbidity and mortality in untreated cases. Outbreaks of typhoid are not only associated with climatic changes but factors involving hygiene and sanitation as well. The primary care providers need to be clinically vigilant for early diagnosis and appropriate management of suspected cases. Primary care physicians in our country usually follow the WHO treatment guidelines for typhoid and prefer to prescribe fluoroquinolones especially ofloxacin and ciprofloxacin.¹⁴

The impact of this disease can be reduced by strategies such as improved sanitation, proper hygienic measures and prophylactic vaccination in high risk groups. Single dose vaccination against typhoid provides three years of protection.¹⁵

Our study provides a platform to justify surveillance programs for adults which can complement pediatric studies and provide the overall burden due to typhoid fever.

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