

## INTRODUCTION

Typhoid fever remains an important and persistent public health problem in India. Most of the developed countries have virtually eliminated typhoid fever by providing safe drinking water and good sanitation (Figure 1). Globally nearly 26 million cases are reported annually killing around 2 lakh people. Asia contributes 62% of the global burden. A recently conducted epidemiological survey in five Asian countries shows the highest prevalence of typhoid fever cases in India<sup>1</sup> (Table 1).

## WHY HIGH PREVALENCE IN INDIA?

- **Poor sanitation:** More than 50% of the Indians do not have access to toilets, that means nearly 65 crore people defecate and urinate in the open field every day. (Figure 2)
- **Unsafe drinking water:** Only 18% of the rural mass has access to treated water, one third have piped water supply and 50% of the piped water supply is also untreated.
- **Lack of health education:** The print media & electronic media are not giving much importance in India to health education, so also the educational curriculum in India. In addition, poverty, illiteracy, ignorance, malnutrition has compounded the issue. It is very astonishing to know that annually 38 million people in India suffer from water borne diseases leading to 7.8 lakh death. The mortality

due to water borne diseases is nearly 50% of that due to acute myocardial infarction!

- The prevalence of typhoid fever in India can be viewed as an index of sanitation in this country.

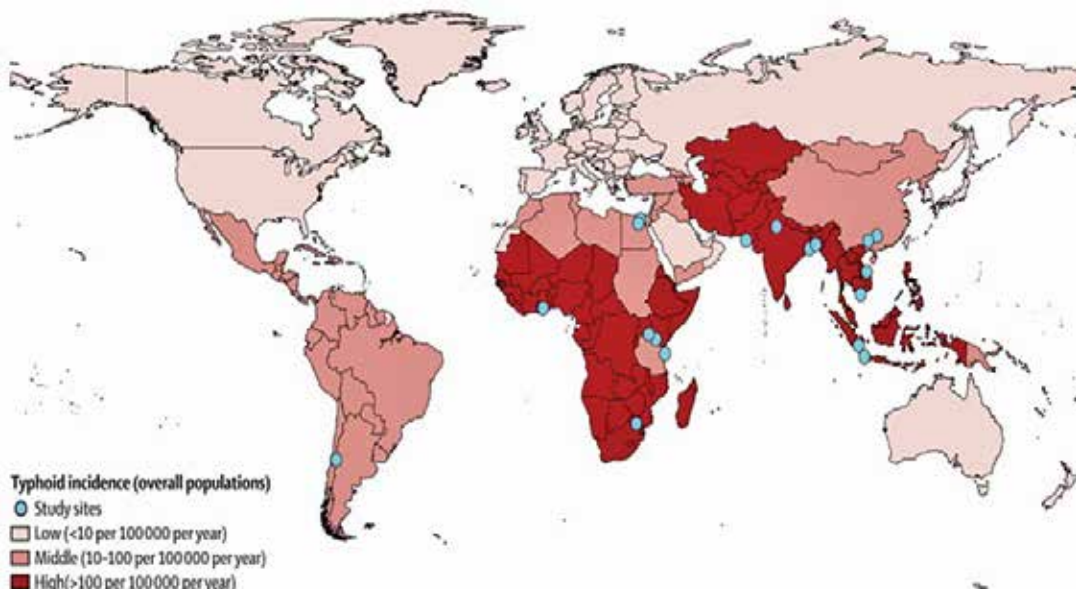
## TERMINOLOGIES

Typhoid fever- is the bacterial infection caused by *Salmonella enterica* serovar typhi.

Enteric fever- comprises both Typhoid and Paratyphoid (A, B, C) fevers.

**Table 1: Epidemiological survey in five Asian countries<sup>1</sup>**

	Site	Incidence of Typhoid fever
China	Urban and Rural	15.3 cases per 100 000 per year in people aged 5-60 years old
Vietnam	Urban	24.2 cases per 100 000 per year in people aged 6-18 years old
Indonesia	Urban Slum	81.7 cases per 100 000 per year (all ages)
Pakistan	Urban Slum	451.7 cases per 100 000 per year in children aged 2-15 years
India	Urban Slum	493.5 cases per 100 000 per year (all ages)



**Fig. 1: Global scenario in 21st century**



**Fig.2: Open air defecation in India**  
**India is supposed to be the world's largest open air toilet!**

Suspected case: Fever  $> 38^{\circ}\text{C}$  for 3 days plus at least 3 of the following

1. Toxic look
2. Bronchitic chest
3. Abdominal discomfort
4. Relative bradycardia
5. Palpable recessive spleen

Probable case: A suspected case + a positive serological test

Confirmed case: A suspected case + a positive culture

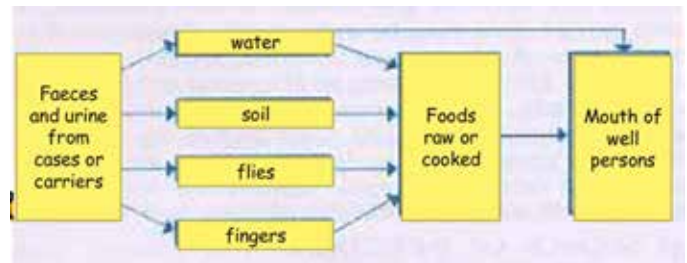
Chronic carrier: Excretion of *S.typhi* in stools or urine for longer than 1 year after the onset of acute Typhoid fever.

### SOURCE AND SPREAD OF INFECTION

Typhoid fever has no other reservoir apart from the human beings. It is essentially a "faeco-oral route" of transmission. Faeces or urine from case or carrier need to be transmitted to the mouth of the healthy person through contaminated food, water, soil, flies, fingers etc. (Figure 3) *S.typhi* can survive in the ice and ice creams for days and in dirty water for months.

### TODAY'S CHALLENGES IN TYPHOID FEVER

- Widespread resistance to Chloramphenicol, Ampicillin, Co-trimoxazole (MDR) since the last two decades.
- Decreased susceptibility to fluoroquinolones.
- Lack of availability of equipped bacteriological laboratories in the rural and suburban areas where majority of the enteric fever cases are being treated.
- Need to use newer and more expensive antibiotics, which may be unaffordable by the rural mass.
- The popular WIDAL test is becoming unreliable.
- Vaccination is less immunogenic in children who constitute the maximum burnt of the disease.
- The cost of hospitalization in severe and complicated cases, in addition, the work loss, the income loss, may all only leads to maintain the "poverty cycle".



**Fig. 3: Source and route of transmission of Enteric Fever**

### CLINICAL FEATURES

Enteric fever being one of the common acute febrile illness we come across in our day to day practice, the clinical features of which may be indistinguishable from other acute febrile illnesses in tropical countries like that of malaria, dengue, leptospirosis, typhus etc.

### UNIQUE FEATURES OF TYPHOID FEVER

- Step ladder pattern of fever (Figure 4)
- Relative bradycardia
- Diffuse abdominal pain
- Constipation/diarrhoea
- Muttering delirium
- Rose spots (Figure 5)
- Coated tongue

Atypically Typhoid fever can manifest as only fever, severe headache mimicking meningitis, arthralgias, jaundice, GB syndrome, pancreatitis, osteomyelitis, acalculus cholecystitis etc.

### FINDINGS NOT SUGGESTIVE OF TYPHOID

- Sudden onset of high fever
- High fever ushered by rigors
- Presence of herpes simplex (fever blisters)
- Presence of coryza

### RED FLAG SYMPTOMS (TABLE 2)

The appearance of any of the red flag symptoms/signs should alert the treating physician about the impending complications<sup>2</sup>.

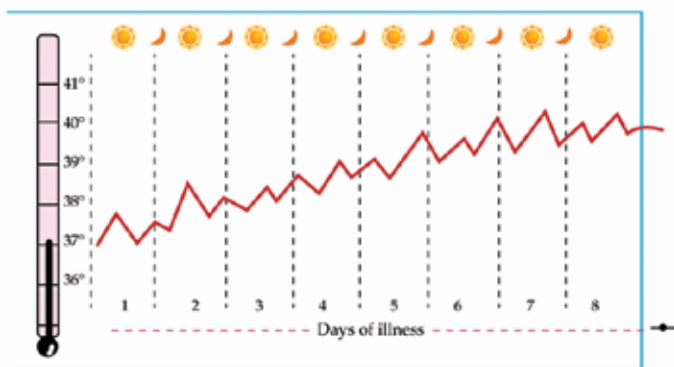
### LAB DIAGNOSIS

Routine tests: A complete blood count may reveal low to normal total leucocyte count and platelets. Liver function test may reveal slightly elevated SGOT and SGPT.

- A febrile toxic looking patient with a low count should raise the suspicion of typhoid fever.

### BLOOD CULTURE

Still the gold standard to confirm the diagnosis but it is positive only in two third of the cases, it is time consuming, not available in the peripheral centers, however antibiotic sensitivity can only be known by culture and sensitivity. Bone marrow, stool, urine, duodenal aspirate, rose spots can also be cultured.



**Fig. 4: Step-ladder Pattern of Fever**  
Fever increases a little each day, rarely seen now because of extensive use of antipyretics and early initiation of antibiotics.



**Fig. 5: Rose spots**  
2-3 mm pink papules, on the trunk & chest, fade on pressure, disappears in 3-4 days and seen in only 30% of the cases

### SEROLOGICAL TESTS

**Widal Test:** Though considered as a benchmark diagnostic test for typhoid fever for more than a century, is of little help in the treatment of typhoid fever because of delay in elevation of 'O' and 'H' titres. There is a wide inter lab difference, may be false positive in various non typhoidal fevers and due to anamnestic reactions, negative in 30% of the culture positive cases, a fourfold rise in titre over a span of one week is needed to be confirmatory.

- A single WIDAL test in endemic areas should be viewed against the background titres of the population in question.

### TYPHIDOT TEST

Done by a rapid dot enzyme immunoassay (EIA), detects the antibody against the 50kD antigen (OMP) of *S.typhi*, as early as day two of fever. It is simple, rapid, more sensitive (95%), more specific (75%), superior and reliable than WIDAL test<sup>3,9</sup>.

Typhidot-M: is a modified improved version of Typhidot, detects only IgM, highly specific and sensitive with high

**Table 2: Red flag symptoms<sup>2</sup> in Enteric fever**

Involvement	Symptoms
Central nervous	Headache, vomiting, seizures, altered states of consciousness, papilledema, and focal neurological deficits
Cardiovascular system	Chest pain, palpitations, new murmur or change in characteristics of a previous murmur, cardiac arrhythmias
Respiratory system	Chills, cough (with or without sputum), pleuritic pain, coarse crackles, and bronchial breathing
Musculoskeletal system	Local tenderness, rigidity, and pain giving rise to a loss of functionality in the affected limb; acute swelling and pain in joints with or without an effusion
Gastrointestinal system	Jaundice, nausea, vomiting and abdominal pain
Genitourinary system	Dysuria, frequency and suprapubic or pelvic discomfort

negative predictive value<sup>3</sup>. Typhidot rapid cards are also commercially available which are based on lateral immunochromatography, which serves as an effective diagnostic tool in resource limited setups and in handling the epidemics.

- Typhidot tests are slowly replacing and should replace the unreliable Widal test.

Though PCR is more sensitive and specific, its routine use in clinical practice in India is far from reality, however IDL Tubex test, IgM Dipstick test are quite useful in practice. Newer tests in pipeline include salivary IgM test, molecular immunology based tests and nano technology based tests<sup>4</sup>.

### MANAGEMENT

90% of the enteric fever patients can be managed on outpatient basis, hospitalization maybe needed in severe and complicated cases<sup>5</sup>. Supportive cares like tepid sponging, antipyretics like paracetamol, good oral hydration and soft diet should constitute important supportive treatment in all cases.

### ANTIBIOTICS

Early administration of appropriate antibiotics is the key point in the treatment of typhoid fever. Before 1990 chloramphenicol was the drug of choice followed by ampicillin and co-trimoxazole. With the development of plasmid mediated wide spread resistance to these drugs (MDR) and the marrow toxicity of chloramphenicol has forced to keep them back into the shelf<sup>6,8</sup>. Currently Fluoroquinolones, azithromycin and third generation cephalosporins are widely used (Table 3).

### CEFTRIAZONE

Is the drug of choice in all severe and complicated enteric

**Table 3: Recommended antibiotic treatment for typhoid fever (adapted from WHO<sup>5</sup> and Bhutta<sup>7</sup>)**

Susceptibility	Optimal treatment			Alternative effective treatment		
	Drug	Daily dose (mg/kg)	Course (days)	Drug	Daily dose (mg/kg)	Course (days)
<b>Uncomplicated typhoid fever</b>						
Fully sensitive	Fluoroquinolone (such as ofloxacin or ciprofloxacin)	15	5-7*	Chloramphenicol	50-75	14-21
				Amoxicillin	75-100	14
				TMP-SMX	8-40	14
Multidrug resistance	Fluoroquinolone or	15	5-7	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistance†	Azithromycin or	8-10	7	Cefixime	20	7-14
	Ceftiaxone	75	10-14			
<b>Severe typhoid fever requiring parenteral treatment</b>						
Fully sensitive	Fluoroquinolone (such as ofloxacin)	15	10-14	Chloramphenicol	100	14-21
				Ampicillin	100	14
				TMP-SMX	8/40	14
Multidrug resistant	Fluoroquinolone	15	10-14	Ceftriaxone or	60	10-14
				Cefotaxime	80	
Quinolone resistant	Ceftriaxone or	60	10-14	Fluoroquinolone	20	14
	Cefotaxime	80				

\*Three day courses also effective, particularly so in epidemic containment.

†Optimum treatment for quinolone resistant typhoid fever has not been determined. Azithromycin, third generation cephalosporins, or a 10-14 day course of high dose fluoroquinolone is effective. Combinations of these are now being evaluated.

**Table 4: Comparison of Vi-PS and Ty21a vaccines**

Vaccine Name	How given	Number of doses necessary	Time between doses	Minimum age for vaccination	Booster needed every....
Ty21a (Live attenuated Vaccine)	1 capsule by month	4	2 days	6 years	5 years
ViCPS (Killed Vaccine)	Injection	1	N/A	2 years	2 years

fever, where there is fluoroquinolone resistance, it should be used with a dosage of 60-75mg/kg/day, IV for 7 to 14 days. It is better to slightly overdose than underdose when trying to adjust the dose bearing in mind the strength available in the market. It is safe in pregnancy and children.

#### SINGLE VERSUS MULTIPLE DRUG REGIMENS<sup>4</sup>

There are no clear cut guidelines to use monotherapy/combination therapy, but the available data shows that there is no difference in time taken for defervescence after single/multiple drug groups. Combination therapy may be considered only when monotherapy fails. Avoid fixed drug combinations as they lack dosage flexibility.

#### IAP RECOMMENDATIONS<sup>6</sup>

- Third generation cephalosporins are recommended in all cases of typhoid fever as the first line of treatment. Oral, in uncomplicated cases and parenteral, in severe and complicated cases.
- Oral cephalosporins need to be given in the higher

dose as compared to their non-enteric indications.

- Azithromycin is the preferred alternative agent in uncomplicated cases.
- Fluoroquinolones may be used in infections resistant to all other recommended antibiotics.
- Carbanopems are potential second line drugs.
- The “Right drug-Right dose-Right duration” is crucial;
- Antibiotics should be continued for minimum of 5 days after defervescence.

#### PARATYPHOID FEVERS (A, B, C)

- It is in no way different from typhoid fever in epidemiology, pathogenesis, pathology, clinical features, diagnosis and treatment
- Milder in severity
- Fewer in complications
- Better in prognosis



- Paratyphoid C is not reported in India

### PREVENTION OF ENTERIC FEVER

Deserves a serious consideration in India. Supply of safe drinking water, improvement of basic sanitation, promotion of personal hygiene and food hygiene, health education using mass media and incorporating health education in primary and secondary education. Simple advices like boiling the water, washing the hand before handling/eating the food and after using the toilets are very cost effective in preventing not only typhoid fever but also other water borne diseases<sup>5,10</sup>.

- “Wash it-peel it-boil it” or “forget it”

### VACCINATION

Two routinely used vaccines (Table 4) are less immunogenic in young children and also they do not induce a long term immunity, hence IAP recommends a Vi-PS conjugate vaccine<sup>10</sup> at less than one year of age which also gives a long time immunity. WHO recommends targeted vaccinations to travellers to endemic areas and people living in endemic areas whose personal hygiene is unreliable.

### CONCLUSIONS

India has got the highest prevalence of typhoid fever in the world which should be viewed as an index of poor sanitation in this country. Hence emphasis should be on prevention, by improving basic sanitation and the supply of safe drinking water and health education should be geared up at all levels. The early initiation of treatment with the “Right drug-Right dose-Right duration” is crucial. WIDAL test is of little help in the treatment of the enteric fever which should be replaced by much simple, rapid and reliable typhidot test. Lastly the diagnostics in India do not meet the daily challenges of physicians in differentiating the causes of fever, there is a need to

develop a ‘fever stick’ which can rule in or rule out the common infections like malaria, typhoid, typhus, dengue, leptospirosis etc.

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