Epidemiological profile and outcome in typhoid fever

A hospital based prospective study

A Dissertation submitted to THE TAMILNADU

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DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation / thesis entitled **"Epidemiological profile and outcome in typhoid fever"**– A hospital based prospective study is a bonafide and genuine research work carried by me **DR. S. SANKAR**, under the guidance of **Prof . M.JAYAKUMAR.MD,DCH** Professor in Department of paediatrics.

The dissertation is submitted to **The Tamil Nadu DR.M.G.R. Medical University** towards the partial fulfilment of the rules and Regulations for the **M.D Degree Examination VII in Paediatrics**.

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ABBREVATIONS AND ACRONYMS

PPIs	Proton Pump Inhibitors
LAT	Latex Agglutination Test
LPS	Lipo Poly Saccharide
PCR	Polymerase Chain Reaction
nPCR	nested Polymerase Chain Reaction
MDR	Multi Drug Resistance
MDRTF	Multi Drug Resistant Typhoid Fever
DCGI	Drug Controller General of India
DIC	Dessiminated Intravascular Coagulation
TNF	Tumor Necrosis Factor
CFTRR	Cystic Fibrosis Trans membrane conductance Regulator Receptor
HUS	Haemolytic Uremic Syndrome
SMP	SulfaMethaxazole with Pyrimethamine

PLAGIARISM CERTIFICATE

This is to certify that this dissertation work titled **THE EPIDEMIOLOGICAL PROFILE AND OUTCOME IN TYPHOID FEVER** of the candidate DR.S.SANKAR with registration number 201517051 for the award of MD DEGREE in the branch of PAEDIATRICS. I personally verified the Urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows TWO percentage of plagiarism in the dissertation .

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INTRODUCTION

1. HISTORY

In 1880, a German bacteriologist Karl Joseph Eberth first described Salmonella bacteria. Eberth identified the bacterial habitates in the spleen and mesenteric lymph nodes. The same study was also observed and recorded by Robert Koch. Georg Theodor August Gaffky in 1884 confirmed the Salmonella typhi bacteria (1) as the causative organism of typhoid fever. Earlier, this bacteria was coined as Salmonella by Eberth Bacillu.

Sir Almroth Wright a British pathologist and his team developed the first vaccine of heat-denatured whole-cell typhoid bacilli in 1896.British soldiers were immunized against the disease during first world war.

2. EPIDEMIOLOGY

Typhoid fever is a commonest communicable disease of public health importance which invariably affects people living in all geographical areas.Typhoid is caused by S.typhi, but the similar illness may also be caused by S. Paratyphi A,

Global Prevalence of Typhoid Fever

About 22 million new typhoid cases are emerging worldwide every year. The young children are most commonly affected particularly those who live in poor socio economic zone. Around 215,000 deaths occurring per annum. South-

east Asian countries are most commonly affected and also is common in Africa and South America. Many outbreaks was reported from Zimbabwe, Philippines. Zambia, and Fiji .B

B. Prevalence of Typhoid Fever in India

Since India is an endemic country for typhoid fever, the annual incidence of typhoid fever is about 1%. Peak incidence is found in children 5–15 years of age group, but in highly endemic areas children less than 5 years of age had the highest infection rates(3) and poor socio economic conditions of the patients. The study done by Ochiaiet al revealed that only 2% of Indian patients with enteric fever required hospitalization.

In India, typhoid fever prevalence is not decreasing even though the commercially available antimicrobial drugs and vaccines. Because of the emergence of antimicrobial resistance, the strain pattern of the pathogenic organisms and the management of typhoid fever is becoming a most challenging task in India and also there is no standard specific guidelines to treat typhoid fever in India.

Incidence of typhoid fever is decreased in affluent countries because of drastic improvements in water supply and sanitation but it still continues to be endemic in the under developed countries (4).In developed countries incidence is much lower (5)

C. Epidemiology of typhoid fever in India

Typhoid fever is caused by S.Entericae family, the subspecies called S. typhi, a gram negative bacteria .Three sero types of Salmonella subspecies namely S.paratyhphi A, S.paratyphi B (S.Schottmuelleri), and S.paratyphi C (S.hirschfeldii).The most common pathogen found worldwide is type A, type B is most common in Europe, and the rarest form is Type C seen only in the east part of the world..

Acidic PH of the stomach fluid facilitates the destruction of bacteria. So long term use of PPIs will facilitate the bacteria to pass out from stomach. Cold foods such as ice-cream is recognized as a significant risk factor for the transmission of typhoid fever. The mortality rate of typhoid is as high as 30% in developing countries.

D. Epidemiological types of Typhoid fever:

1. Endemic Residual typhoid fever: occurs throughout the year even though seasonal variation may sometimes be present.

2. Epidemic typhoid fever : which may occur in endemic or non-endemic areas irrespective of seasonal variation (`6).

E. Epidemiological Factors

The incidence of typhoid fever is low in the first few years of life, and the peak incidence is the school-going age group children and young adults and it falls in the middle age. Older people are relatively resistant to typhoid fever.

Dry weather favours the transmission of the disease in endemic areas due to ambient weather facilitates the growth of the organism. During summer season people are more indulged to drink outside water .During rainy season people may drink contaminated water.

Incidence of water borne diseases has come down due to improvement in water sanitation , although still it is common in countries with primitive sanitation and water supply (7), leading to high treatment costs and deaths (8). Typhoid fever is spread by the oral-faecal route through contaminated water, food and poor sanitation (9).

F. Food habits

Food which is prepared outside , for example ice creams, ice mixed drinks from road side vendors, consuming contaminated water, and eating raw vegetables and salads using faecal contaminated water are the culprits.Food hygiene is important to prevent most of the communicable diseases around the world (9).

G. Other contributing factors:

- Close contacts with typhoid cases,
- Low socioeconomic status
- Increased population density
- Lack of personal hygiene
- Poor sanitation
- Unsafe drinking water
- Open air defecation close to water bodies.

Typhoid fever is also transmitted by flies, laboratory mishaps, unsterile surgical instruments, recent use of antimicrobials and anal intercourse.

The commonest source for typhoid epidemics are water, milk or food. Nowadays food borne epidemics are more prevalent due to eating of raw milk and milk based products. Roadside food eating practices (10).Salmonella transmission is carried out through faecal contaminated water or food (11).

Sewage system, through flush toilets, pit latrines, contaminating surface and ground water are the notorious places for developing these organisms (12).In developing countries, poor sanitary practice is the foremost reason for communicable diseases. Hand wash before eating and after toilet use is an important tool to prevent typhoid fever (13).

Typhoid fever can also be transmitted from animals and animal products to humans (14).Untreated typhoid fever may last for 3 to 4 weeks and

death rate between12% and 30 %.Typhoid fever kill about five million babies annually and make one sixth of the world population to become sick.

Socio-economic effects has more impact on typhoid fever to get infected as well as the affected patients takes several weeks to recover especially if early treatment is not given(15).

3. CASE DEFINITION

Confirmed typhoid fever cases:

Fever more than 38 degree centigrade for at least three days with a laboratory confirmed positive culture (blood,bone marrow. bowel fluid) of S.typhi.

Probable typhoid fever case:

Fever more than 38 degree centigrade for at least 3 days with a positive sero diagnosis or antigen detection test but without S.typhi isolation.

Chronic carrier state:

Chronic carrier is defined when persistent passage of S.typhi either in urine, stools ,positive bile, duodenal string cultures for more than a year after typhoid infection .

4. CAUSATIVE AGENT

Salmonella typhi is a gram-negative bacteria belongs to Salmonella genus of Entero bacteriaece family which produce intestinal infections and diarrhoeal diseases in humans comes under the group D Salmonella as per Kauffman and

White classification (16). S.typhi is a rod-shaped organism . It is motile with peritrichate flagella (H-d antigen)(16).

S.typhi has three antigenic structures somatic or O antigen responsible for bacterial endotoxin production ,H- d antigen is a flagellar antigen and Vi-antigen is a polysaccharide antigen present on the exterior of the cell wall.Flagellar antigens are destroyed by boiling of S.typhi since these are made up of proteins (17).

Boiling can destroy the capsular Vi-antigens by removing from the cell surface. But O-antigens are not affected by boiling because these are a part of lipopolysaccharide which is heat-stable. Since flagellar antigen is composed of lipid and carbohydrate they are not species-specific to S.typhi and d-antigens are present in many Salmonella species other than S.typhi (18). It also determines phage susceptibility (19).

Salmonella Pathogenicity Islands (SPI) that may responsible for the regulation of invasion of the intestinal wall by S.typhi (20). S.typhi grows both in aerobic and anaerobic conditions. The required temperature for the growth is between 4 to 40˚C, the optimum being 37˚C (21). S.typhi is viable for a week in contaminated water and remains viable in faecal materials for 1-2 weeks (21).

5. TRANSMISSION:

Ingestion by mouth, the bacteria invade the intestine by haematogenous spread, it will reach the intestinal lymph nodes,spleen and liver and multiply in

the target organs .Gall bladder is the most susceptible organ to infect by Salmonella typhi organism. Human carriers may also be the source of infection, and no animal reservoir was found .It can be transmitted from animals and animal products to humans causing enteric fever (14) and(22).

6. PATHOGENESIS

S.typhi enters the human body by ingestion of faecal contaminated water or food. After ingestion S.typhi passes onto the small intestine where it incorporates into the tips of the villi (23) through cystic fibrosis CFTR receptor located here (24) It directly enters into the intestinal mucosa or takes several days to multiply before enter according to the theory of genes located in the Salmonella Pathogenicity Islands (25) . Lower end of the ileum is most common site involving in typhoid fever (26).

After invasion, typhoid organism reaches the lamina propria (16) and via the “M cells” of the intestinal Payer’s patches then migrate into mesenteric lymph nodes to multiply there (36)and(25). Through thoracic duct bacteria disseminate into the circulation (23)(16) (25)) called transient primary bacteremia and engulfed by macrophages lining the sinusoidal walls of the bone marrow, liver and spleen. The organisms can replicate here and re enter into the blood stream called secondary bacteremia reveals the onset of the clinical disease (23) and(16). Eliminated from circulation by the liver and excreted via biliary pathway to produce re-infection of the intestinal tract named second exposure S.typhi.

During the period of re exposure, hyperplasia, ulceration of the intestinal mucosa and necrosis of the mucosa occur (23) which predict the dangerous life threatening complications like intestinal perforation and haemorrhage.Macrophages and T lymphocytes are stimulated by S.typhi (23) (25).

Hyperplasia of payer's patches takes place during first week and necrosis occur during the second week followed by ulceration during the third weak without scaring during the fourth week of the course illness.

Typhoid ulcer is oval in shape in the long axis of the lower ileum. Exudates may be seen on the peritoneal surface. If sloughs are separated, may start to bleed and perforation. There is no association between the ulcers and severity of infection. There is hepatomegaly and typhoid nodules, which are tiny lesions consisting of confluence of kuffer cells and lymphocytes with or without central necrosis (27).

For symptomatic infection approximately 106-109 organisms must be entered into intestine .In immune compromised individuals small amount of virulent organisms are enough to cause illness.(28). In the stomach, the organisms are exposed to hydrochloric acid which decreases the number of the viable bacilli. Salmonellae species are destroyed at pH 2, Viable bacilli moves into small intestine, here the number of bacilli is further decreased or eliminated entirely,

Endotoxin produced by S.typhi triggers macrophages to produce inflammatory markers like cytokines TNF ,interferon, and many arachidonic acid metabolites (23).Cytokines acting locally where it produced,mediate the development of fever intestinal necrosis , hepatic dysfunction,pneumonitis, thrombosis, increased permeability of vessels and shock (29), bone marrow depression (23), and altered mentation (30).

7. IMMUNOLOGICAL RESPONSE

Salmonella typhi has three types of antigens are called H, O and Vi. The H antibody against the flagellar antigens may be found for many years after recovery, Agglutination is a rapid process and the agglutinated bacilli forma large fluffy clumps. H antibody do not protect further relapses (31) and (32)**.** O antibody formation is stimulated by O somatic antigens found in the first week of illness. It rarely rises above 1:640 titre.

Anti O polysaccharide chain antibody titres are lower in the first week and titre rises up to the third week of the infection . After recovery the titre falls and may persists for a year. After the onset of illness. IgG and IgM , anti O and H agglutinins persist for 2 years, 16 weeks, 16 weeks and 36 weeks respectively (33).A somatic Vi antigen may produce severe disease (32). Vi antibody probably has a value in combating infections of Vi strains.

Salmonella typhi induces immunological response by infected hosts including various components (16), secretory IgA (intestinal specific circulating antibodies) and cell-mediated immune responses. S.typhi invasion is restricted

by intestinal IgA antibodies (23).Typhoid patients will develop the circulating immune globulins IgG and IgM to O, H, Vi antigens (29).

Presence of high titre circulating antibodies reflects typhoid relapse (34).Typhoid organism is killed by macrophages which have been activated by sensitized T lymphocytes derived from lymphokines, which are active elements at the early stage of typhoid fever (19.). Stimulated T lymphocytes are more predominant in benign course of illness whereas suppressor lymphocytes are more predominantly seen in severe typhoid fever cases (35).

Live oral typhoid vaccine Ty21a produces a protective immunity mediated through antibody-dependent cellular cytotoxicity involving IgA antibodies and CD4 T lymphocytes. Re infections are always milder than the first infection. Antibodies to O and Vi antigens in the circulation are associated to develop resistance against infection and disease.

After 2- 3 weeks of infection relapses may occur in spite of circulating antibodies. Salmonella infection is prevented by secretory IgA (S IgA) antibodies Brooks, *et al.,* 1998). Antibodies may be present in the intestine for about 48 weeks. Immunity will present beyond one year after the onset of illness (33).Since Samonella is a facultative intracellular parasite ,it can survive within macrophages and requiring cell-mediated immunity for control (36).Once the illness developes, cell-mediated immunity persists for 16 weeks . Salmonella species contains glycoprotein complexes .All salmonella species produces endotoxin which is responsible for endotoxic shock (37). Endotoxin

is a thermo stable and it can survives at a temperature of 120 C for 30 minutes, and is specialized by a highly specific precipitin reaction and pronounced toxic and antigenic properties and reaches the highest titre during the end of the first week.

8. CLINICAL MANIFESTATION

A. The Diagnostic methods in typhoid Fever

Typhoid fever has the incubation period ranges from 7 days or beyond 21days but the average incubation period is 14 days (38). Clinical presentation depends upon the host immunological response,

B. Clinical Features

Typhoid fever can also be diagnosed , based on clinical symptoms and signs such as fever , abdominal pain (46) , nausea, vomiting, coated tongue, relative bradycardia (temperature elevation not accompanied by physiological tachycardia), headache, toxic look, and rose spots(rare manifestation) cough.Initially there is hepatomegaly followed by spleen enlargement during second week of illness.(39).

Rose spots are maculopapular, salmon-coloured rashes, which blanches on pressure seen over the chest, abdomen , and back .It is difficult to find out in dark-skinned individuals .Size measured about 1-4 cm in width, less than 5 in numbers.It resolves spontaneously within 2-5 days. It is due to bacterial emboli to the dermis (22)**.**

C. Atypical manifestations

Arthralgia,Symptoms of urinary tract infection, Deep jaundice,Delirium, Guillain-Barré syndrome ,Orchitis ,Abscess,Pancreatitis Meningitis Osteomyelitis.a rare complication reported (40).The clinical features vary from undifferentiated fever to a complicated typhoid. All clinical features may not be necessarily manifested in all typhoid cases(38) .Distribution of typhoid fever features may vary in different zones and hosts (26). In children typhoid fever will present as a benign illness (43)).While compare to adults, hepatomegaly (44) and diarrhoea (45) are most common presentation and relative bradycardia is the least common feature in paediatric age group .

Typhoid fever starts with insidious onset (41) with anorexia, lethargy, and malaise (35). But more than one third of the patients will develop the clinical features in abrupt onset including chills (41).

Fever, vague abdominal pain and tenderness, distension may be the clinical features during first week of illness.(46).Majority of cases will suffer from abdominal discomfort or pain (41).Loose stool may occur more frequently than constipation in children (46).Diarrhoea is more common in young children and in AIDS patients. Incidence of constipation is more common than loose stool during start of illness and abdominal discomfort (35).Patient will have coated tongue in second and third week(45). May or may not present with altered mentation and toxic appearance (23).Only 33 % typhoid cases will have

headache (23) (26) (47). Cough with wheeze and crackles in severe cases seen (35). Non-productive cough may present in 1/3 to 2/3 cases (35) (46).Epistaxis may occur in very few cases (41)

Distended tender abdomen with soft splenomegaly will be seen (47) (35).Splenomegaly may manifest in 11-71% of cases and hepatomegaly will seen in 14-65% of typhoid fever cases(48)(23)(49) (50) (51) (52).Liver enlargement seen in 14-65% of cases. Urinary tract infection may also coexist with the features of typhoid(53) particularly in the places more endemic to Shistosomiasis(23)

Sustained fever may run in the second week of illness,altered mental alertness (46,) Patients without fever may showed positive blood culture (46),During second or third week rose spots may be seen over the chest wall, abdomen(22)**.** Rose spots (pale pink macules seen over lower chest and abdomen, may appear during second and third week of illness (53).Most of the studies did not reveal the rose spots (47) (54)

Bowel perforation and haemorrhage may occur in third week, beyond third week resolution or death may happened.(41)..Because of mucosal congestion and haemorrhage, occult blood will present (44,). At the end of the third week of illness fever will begin to drop(35).Less than 50% of typhoid cases manifests relative bradycardia. Leukocyte counts fall in normal limits in most of the typhoid cases(47.)(26)(46). In severe cases delirium may present (35).

9. DIAGNOSIS

Patients with typhoid suspects and leucopenia may be more related to typhoid fever or a viral disease .Leucocytosis has a great significance in sepsis or perforation,Eosinopenia and thrombocytopenia may arise the great suspicious of typhoid fever (39) ..

Typhoid fever can be diagnosed by blood culture and bone marrow culture (55).).There are different types of cultures namely blood culture,stools culture and urine culture available and are less definitive for the diagnosis of typhoid fever may be positive in chronic carriers also (55) (56) (57). Instead of low efficacy of these tests, it is still required.

In endemic areas culture positive typhoid fever may be rarely diagnosed. Culture positive non-typhoidal pyelonephritis are reported in some cases (51)(58). Only 40–80% of typhoid cases will show positive culture The Sensitivity and specificity of blood culture varies based on the stage of illness, the volume of blood inoculated and prior antibiotic treatment. Duration of illness and administration of antibiotics prior to culture study will determine the sensitivity of blood, stool, and urine cultures (25).

In developing countries where poor resource settings for culture studies and in typhoid endemic areas widal test with rise in titre (or) four fold rise in titre is the very useful test modality to diagnose typhoid fever .Faecal carriers with S.typhi are confirmed by cultures from duodenal juice.

Base line investigations:

Complete blood count:

- Haemoglobin-Mild anaemia
- Total leucocytic count - low -normal - elevated
- Eosinopenia. (60),
- Platelet-Low or normal

Liver function test

- Serum transaminase level rises 2 to 3 times the upper limit of normal

Blood culture:

The specificity of a blood culture is 100%. At least 5-10 ml of blood is required for a good yield. If the volume of blood is larger, the yield will be better. The ideal time to collect blood for culture is when the patient is having chills.Blood for culture should be taken before starting the first dose of antimicrobial drugs. By doing antibiotic sensitivity test along with the culture,it will help to select the most appropriate antibiotic .Culture should be repeated after an hour and then after 24 hours .A single culture should not be encouraged. The blood culture yield decreases due to the administration of antibiotic Most of the times contaminants like coagulase negative staphylococci in the blood culture may cause a false-negative report. A clot culture is also being done.

To inoculate the specimen (blood, bone marrow or stool) into an enrichment broth ,and when a growth appears, making subcultures on solid agar. Biochemical testing is done to identify the colonies obtained .This is

further confirmed by slide agglutination with appropriate antisera.The sensitivity ranges between40% and 80%. The sensitivity maybe low in endemic areas with high rates of antibiotic use.

Due to the higher levels of bacteraemia in children as compared to that in adults, at least 10-15 ml of blood from school children and adults, and 2-4ml from toddlers and preschool children should be taken to achieve optimal isolation rates. Because of less sensitive for diagnosis of infection among children ascompared to adults .positive culture yields only in 40-60% of cases,usually early in the course of the disease.

Under aseptic precaution, 1-3ml of un heparinised blood is inoculated into a tube .A second sample is collected 5 days later. Serum is separated and tested soon or stored for a week ,which does not affect the antibody titre(61). Sensitivity 55 to 75% was reported by (41)(55)(62).The positivity of the blood culture is in first week – 90%, 2nd week – 75%, 3rd week – 60%,4th week – 25%.

Stool culture:

A sterile, wide-mouthed plastic containers are used to collect stool samples to detect typhoid carriers. Results depends on the volume of samples collected for test. Rectal swabs also be collected but it is difficult to isolate the organism.(61). Stool culture is the easiest one to carry out effectively in children than in adults ,it will becomes positive after the first week of infection.

Has low sensitivity as compared to blood cultures (60).40-55%, sensitivity was reported by (41)(55)

Urine culture:

Urine culture yields more positive results in carriers with urinary tract abnormalities.(61)The sensitivity of urine culture for typhoid fever ranges from 0-58%.(60).5-23% sensitivity was reported by (41) (55).

Bone marrow culture:

Bone marrow culture is the gold standard forthe diagnosis of enteric fever(61)since it's yield is irrespective of antibiotics.(63). it can be done in patients who have been treated in the past(23), have a chronic history of illness and had a negative blood culture with the recommended appropriate blood volume(61)

We can get nearly 100% positive results by using FAN culture medium and automated culture medium is used for monitoring .(63.The sensitivity of the test is 55-67% and a specificity is 30%.(60),85-95%Sensitvity reported by (41) (55).

Rose spot culture:

Sample is taken by punch-biopsy from the rose spots and cultured to get the results.The sensitivity of the test is 63%.It can be done in patients irrespective of taking antibiotics.(64)

Duodenal culture

Duodenal culture is a simple,economical and can be done with minimal facilities.(65).Due to poor tolerance of the string device by children it is not widely used (66). Duodenal string cultures also offer little benefit in young children.Other test materials which can be cultured include Pus, bile, CSF or sputum and bile.During autopsy, culture from gall bladder, spleen, liver and mesenteric lymph nodes can also show positive reports.(39)

Polymerase chain reaction(PCR)

PCR is a good sensitivity test as compared to blood culture, but it is less specific18.It has sensitivity of >90% . PCR test can amplify DNA from dead or unculturable bacteria. This test could not cover all the antigens of typhoid fever, it has less sensitivity and specificity

Nested polymerase chain reaction (NPCR)

This test has more sensitivity than PCR by using H1-d primers to amplify the specific genes of S.typhi in the blood.(60).It undergoes two rounds of PCR using two primers with different sequences and within the H1-d flagelline gene of Salmonella typhi.(64)..

Because of it's high sensitivity and specificity, nested PCR can be branded as a gold standard test tool to diagnose clinically suspected but culture negative cases of typhoid.(67) .It has 100% sensitivity and 76.9% specificity. Irrespective of stages it can be used to diagnose typhoid fever and it is not affected by antimicrobials.

SEROLOGICAL TEST

In developing countries like India, serological tests are still the most important tool to diagnose typhoid fever.(68).

Widal test:

As per WHO reports , Widal test is the most commonest test used widely in India, and also in other developing countries .This test can be done after first week of infection .False-positive results may found in the first week of illness. Widal test is validated by the demonstration of a rising titre of antibodies in paired samples (69). O and H antigens of all subspecies are utilised in this test.(72) Minimal 1 ml of blood sample is required for a good yield .About 6-8 days are needed for appearance of O antibodies and 10-12 days required for H antibodies.(61)

Widal test is based on agglutinating antibody titres against O and H antigens of S.typhi (21). In case of classical clinical features suggesting that typhoid fever where single widal titres for O antibody (IgM, IgG) $\geq$ 1:320 may be enough for the diagnosis of typhoid fever(46). Less than 74% sensitivity was reported for widal test and it will become positive in second week of illness.

Widal titre need not be rised in all cases (21)Antibody response in widal test depends upon the duration of illness and prior antibiotic use (110).

Since all Salmonella species are sharing both O and H-antigens,widal is

considered as a non specific test,(21).False positive results can occur in previous typhoid infections, chronic carriers, schistosomiosis, typhoid vaccination, recent other salmonella species infections, chronic liver disease, rheumatoid arthritis, rheumatic fever, multiple myeloma, nephritic syndrome and ulcerative colitis (Johnson, *et al.*, 1996). (61).

The utility of widal test is limited to culture negative cases of typhoid fever with the clinical features are suggestive of typhoid fever (21)... A titre of 1:160 or more for O somatic antigen is considered as positive for typhoid fever (27).

The anti-H antibody titer may persist for a longer period than the anti-O antibody (71).Diagnosis of typhoid fever is considered only after a fourfold increase in antibody titer in a paired serum(68) .Widal has a sensitivity of 47-77%and specificity of 50-92% (60).Negative Widal test has a good predictive value for the absence of the disease, a positive test has a low predictive value for its presence (72) .

Advantages of Widal test

Less expensive, ideal test for screening in endemic areas(60). Slide agglutination test gives faster results than tube agglutination tests (73)

Drawback:

Reagents should be standardized and quality assured (74).The sensitivity, specificity, and predictive values vary in different geographic regions.The

antibody response is affected by prior antimicrobial use (61) . Widal test is not recommended in culture positive typhoid cases(61).

Latex agglutination test:

LAT has a sensitivity of 100%, and specificity of 97.6%, and positive and negative predictive values of90.9% and 100%, respectively, This test is used for the presumptive diagnosis of typhoid fever in rural health facilities (75).LAT can detect the antigen in100% of the samples with negative blood culture and positive widal, showing a good sensitivity than blood culture(76).

IDL Tubex test:

Tubex is an antibody-detection test .The sensitivity and specificity of the test is75-85% and 75-90%, respectively (73).The O9 antigen used and is extremely specific, to detect IgM O9 antibodies in very few minutes. Since it detects only IgM antibodies, it is highly useful in the diagnosis of current infections, and performs better than widal, both has the same sensitivity and specificity(61)

Disadvantages: Affected by other sub species.

Ig M dipstick test:

To detect IgM antibodies in serum or blood. rapid, cheap, easy to perform.

Upcoming investigations:

1.Molecularnanotechnology-based tests

2.Salivary IgM test

3.Nanotechnology-based tests(39)

Latest diagnostic tests

Newly emerging tests to detect S.typhi antigens, antibodies or DNA (77). Because of low sensitivity and specificity of widal test, we need a simple, reliable, cheapest, fastest and easy to perform serological diagnostic test with a higher sensitivity and specificity than widal .

Typhidot–M is a rapid serodiagnostic test for typhoid fever.There is no adequate studies available in our country to substantiate the specificity and sensitivity as compared to blood culture. Few studies conducted in south India and other parts of Asia have reported encouraging results. Based on this background this study was conducted to know its utility and effectiveness as compared to widal test. IgM antibodies can be measured and lipopolysaccharide antigen was explained to detect the anti-salmonella antibodies as early as 4 days of fever onset (83)(73),

It is widely used because of simple to use and inexpensive (78). Rise of antibody titre is not affected by antibiotic treatment in typhoid fever .The early rising antibody titre to (LPS) O is mostly Ig M in nature, also considered as an early marker for detection of acute infection.

Another modality called Rapid antigen detection test is used to diagnose typhoid fever by using vi-specific DNA probes (79) the sensitivity of this test depends on the concentration of S.typhi in the circulation (80) (81) Monoclonal antibodies are used to detect S.typhi flagellin (H1-d antigen) inserum samples

obtained from patients who contracted typhoid fever of an endemic area. Blood culture-proven cases of typhoid fever is the gold standard controls, the sensitivity and specificity of this test was 95.5% and 91.5%, respectively.

Antigen detection is not interfered by Flagellein antibodies (80,) nested polymerase chain reaction (nPCR) based on the H1d-flagellin may identify typhiinblood. d-antigens can also found in many salmonella species other than S.typhiH1-d.

Both the flagellin test and nested PCR,used to detect bacteraemia due to non typhoidal salmonella in stool samples, PCR test may detect other Salmonella serotypes with H1d-flagellin gene or antigen. Fluorescent antibody test which demonstrate Vi antigen .On socio-economical background, typhoid fever get infected in several patients and takes several weeks to recover especially if early treatment is not given.(15).

Screening for Carriers

Typhoid fever still remains the cause for transmission of the disease through carriers.(84), the ideal test for carriers is stool culture.Vi antibody titre is higher level in chronic cases than acute illness .Vi antibody assays is the another method to identify the carriers (85)

10. COMPLICATIONS

Incidence of complication is 15%.Untreated cases are more prone to develop complications in the third and fourth weeks of typhoid illness. Gastrointestinal bleeding, intestinal perforation, bronchitis, encephalopathy

toxic myocarditis(86) dehydration, toxemia, altered sensorium, and abdominal rigidity and guarding in these patients early, Children are more prone to get bronchitis and males are prone to develop intestinal perforations (39)

Intestinal Complications

The incidence of glossitis, esophageal ulcer, intestinal perforation or bleeding.is 10%. Among them 2% of cases, there may be a need for blood transfusions. Has high morbidity and mortality (86).

Acalculous cholecystitis, perforation of the gall bladder, or gangrene (87).Salmonella cholecystitis (Charcot's triad).tender hepatomegaly and distended gallbladder are the common clinical findings(88).

Perforation:

India has a higher rate of intestinal perforation due to typhoid fever,this is due to poor socio economic status and proliferation of MDR bacterial strains.ileal perforation is more common in rural areas. Risk factors for perforation include male patients, leukopenia, short duration, presence of MDR strains ,partial antibiotic therapy (89) (93).Mortality rate 0 to 2% in developed country and 9 to 22% in the developing countries.

Bleeding:

Necrosis in the small intestine leads to ulceration, which in turn cause intestinal bleeding. 20% of patients had occult blood in their stool. Massive bleeding is rare, gross bleeding may be seen in 10% of the typhoid patients.The

commonest sites are terminal ileum,ileocecal site,ulcers are multiple in number with punched out and elevated margins(90).(93)

Extra intestinal complications:

Haemolytic anemia,HUS,DIC,Eosinopenia ,Prolonged ,PT (86).

Central Nervous System:

3-35% cases may develop e ncephalopathy, cerebral oedema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia seizures, Guillain–Barré syndrome, psychosis.. Meningismus and acute confusion are the most frequent manifestations. Confusion may have an intermittent character and appears as apathy in many patients.(86).(92)

Cardiovascular: 1-5% Endocarditis, myocarditis(98), pericarditis, arteritis, congestive heart failure.

Pulmonary: 1-6% Pneumonia(97), empyema, bronchopleural fistula.

Bone and joint: Less than 1%developed Osteomyelitis, septic arthritis.

Hepatobiliary:1-26% Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus.

Genitourinary Less than 1% Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis.Nephritis(99,100,103)

Soft tissue: Psoas abscess, gluteal abscess, cutaneous vasculitis.

H**aematological:** Hemophagocytosis syndrome (91). Immune compromised people are more risk for developing typhoid fever (94,96)

First trimester abortion is also one of the complication of typhoid fever (26) (101).Transmission of S.typhi in intra uterine period is also evidenced by few studies(102).

11.TREATMENT:

Antibiotics should be selected on the basis of susceptibility,affordability ,tolerance,availability feasibility,and defervescence.In developing countries the commonest antimicrobials used are chloramphenicol, ampicillin, amoxicillin, and SMP(55). Other antimicrobials are ceftriaxone, cefixime, ciprofloxacin, and norfloxacin.

Typhoid fever should be treated in appropriate time ,It will reduces morbidity and mortality. Supportive care antipyretics,hydration, nutrition, timely recognition and treatment of complications. Nearly 90% or more of typhoid fever patients can be treated at home level.Fluoroquinolones are the optimal choice for the treatment of typhoid fever in all age groups..

A. Uncomplicated typhoid fever:

a. Quinolone sensitive areas:

Responders

Cefixime 15-20 mg/kg body weight/day × 10 days

Non Responders

1. Chloramphenicol 50-75 mg/kg body weight × 14-21 days

2. Amoxicillin75-100 mg/kg body weight × 14 days

b. Quinolone resistance areas:

1. Azithromycin 10-20 mg/kg body weight/day × 7 days

2. Cefixime 15-20 mg/kg body weight/day × 14 days

B. Complicated typhoid fever:

a. Quinolone sensitivity areas

Responders

Ceftriaxone or Cefotaxime 50-75 mg/kg body weight/day IV × 14 days

Non responders:

1. Chloramphenicol 100 mg/kg body weight/day IV × 14-21 days

2. Amoxicillin 100 mg/kg body weight/day IV × 14 days

b. Quinolone resistance areas

Ceftriaxone or Cefotaxime 50-75 mg/kg body weight/day IV × 14 days.

Inadvertent use of antimicrobials particularly broad spectrum drugs will lead to emergence of antibiotic resistance (49). Chloramphenicol susceptibility of 95% was witnessed in few areas of India, Chloramphenicol can be combined with third-generation cephalosporin, ciprofloxacin resistant typhoid fever.(43)

Because of fluroquinolone resistance the usage of Azithromycin and cephalosporins is in increasing trend.

12. COMPLICATION OF ANTIBIOTICS

Idiosynchrotic reaction to chloramphenicol characterized by severe aplastic anaemia occurs in about 1of 25,000persons treated with this antibiotic. Ampicillin and amoxicillin cause rashes and hypersensitivity reactions and

SMP.may cause bone marrow suppression and abnormalities in hepatic function.

13. RELAPSE:

Relapse occur in about 8-12% of patients who have not received antimicrobial therapy. Antimicrobial therapy may increase the rate of relapse. relapse can occur during convalescence ,relapse rate is higher in patients treated with chloramphenicol (15-20%)(40)**.**Approximately 1,650 children were developed relapse in culture-proven typhoid fever with MDR strains over 15 years in south Asia. More or less 10% of the typhoid cases with immune competent individuals develop relapse in typhoid fever. Relapse due to ineffective treatment in drug resistant typhoid fever is double that of those infected with sensitive strains. Relapse rate was 2-3% that may occur days or weeks after apparent cure of illness (49).More or less 10% of the typhoid cases with immune competent individuals develop relapse in typhoid fever.

14. CARRIER STATE

Since the organism is a bile resistant one ,they may stay for a long time in the bile and can produce an active infection otherwise called cholecystitis carrier state. About 3 to 5% of typhoid patients may be turned out to carriers, especially those with gallbladder diseases, they can survive asymptomatically for many years.They will excrete the organisms continuously for long time,

and they become potential source of infection(104). Hepatobiliary carcinoma is a potential threat due to chronic carriers and in gall stone cases.(104)

Typhoid mary:

A sanitary engineer George Soper explained the truth on his study regarding typhoid outbreak at Charles Henry Warrens home who was a wealthy New York City banker. 6 of the 11 people in the house had suffered typhoid fever, found out that the family's cook Mary Mallon, an Irish immigrant was a healthy carrier of the typhoid bacteria(56)..Typhoid Mary was the first healthy carrier of typhoid in the United States of America.

CHRONIC CARRIER STATE

There is some association between age and incidence of endemicity of the disease and the level of sanitation (105).Faeces of asymptomatics are more important source of infection than those of classical cases(91).

Convalescent carrier: patient those who continuously shedding typhoid bacilli in faeces from three weeks to three months after clinical cure .

Temporary carriers: are those who shed the bacilli for more than three months but less than a year.

Chronic carriers: those who shed the bacilli for over a year (59).

Females and old age people are more vulnerable to develop carrier following a past infection. The shedding of the bacilli is usually intermittent in this case (106). Chronic carriers are the most risk factors to the community (23)

(26).Incidence of chronic carrier was roughly 2 to 3 % (18) few carriers may have bacilli in the urine over a period of many years and not having any symptoms and signs of typhoid fever.

Diagnosis of carriers:

The Widal test has no role to diagnose carriers in endemic regions. The detection of faecal carriers is by isolation of the bacillus from faeces or from bile (56). Bile culture is usually positive for the detection of the carrier.

Incidence of development of chronic typhoid carrier state after typhoid fever increases with age (56). In most cases carrier state is due to persistence of gallbladder infections. Typhoid cholecystitis is probably initiated during the bacterimic phase, represents the reservoir from which all cases are directly or indirectly acquired (22).

In most carriers, the organism persists in the gallbladder, particularly if gallstones are present, and in the biliary tract (91).Patients with Schistosomiosis in the urinary tract, will become chronic urinary carriers after infection. Urinary carriers may continue to excrete large number of bacilli in urine for months or a year (56).

Treatment of chronic carriers:

A combined therapy including pharmacological therapy along with a vaccine. Some chronic carriers was cured by ampicillin alone (91). Elimination

of the carrier state may require combined cholecystectomy, pyelolithotomy or nephrectomy (6).

15. RESISTANCE

Nalidixic acid resistance being an indirect marker of fluoroquinolone resistance. About 57% of isolates were found resistant to nalidixic acid, 1.6% to ciprofloxacin .Increasing rates of antibiotic resistance may necessitate the replacement of inexpensive antibiotics with newer expensive agents, which may be unavailable.

MDR typhoid Fever

Chloramphenicol resistance was first reported in 1972.following that chloramphenicol or MDRTF was reported in all outbreaks from various areas of the world. School-going children are more prone to develop MDRTF and it can affect young children also. MDRTF is commonly associated with liver and spleen enlargement. Resistance to third generation cephalosporins was reported many studies, indicating that S.typhi is developing resistance to all other quinolones .Resistance to individual drugs depends on serotype, phage type, and country of origin of Salmonella,(5).

16.PREVENTION

1.Primary prevention will help to avoid getting infection or prevent establishment of the disease.(18)

2.Secondary prevention will reduce the morbidity and mortality of typhoid fever.

Primary Prevention

1. Environmental factors like potable drinking water, good sanitation, carrier identification, treatment and vaccination (18)

2.Education regarding good sanitation and using un contaminated utensils.

3.Chlorination of drinking water at home can be advised.

4. Treated water should be stored in a narrow-mouthed articles

5. People should be educated and encouraged to promote the use of latrines at home.

6.Waste materials should be disposed in closed sewerage systems.

7.Raw fruits and vegetables should be washed thoroughly.and raw vegetables should be avoided.

8.Good hygienic practices should be followed in places where milk storage and milk products prepared (108)

Secondary Prevention

The aim of secondary prevention is to decrease the clinical severity of enteric fever and its complications,.The judicious use of efficacious antimicrobials early in the disease is the most important component of secondary prevention (108).

17.VACCITINATION:

Vaccination is adviced to those who travelling to typhoid endemic areas or close contact with typhoid carriers, animal handlers.

1.Monivalent vaccine (only S.typhi),

2.Bivalent vaccine (S.typhi and S.paratyphi A)

3.Typhoid ,Paratyphoid A and B (TAB) vaccine (containing S.typhi,S.paratyphi Aand B)

Currently only two types of typhoid vaccines are available.

1. Vi polysaccharide (Vi-PS) vaccine

2. Ty21a oral vaccine.

In india ,Vi-PS vaccine was approved for clinical use since 2013. The sero conversion rate was 98.05%, but 18 months later a significant dip in the antibody titres .which recommends booster dose. Appropriate time for administration of the booster dose should be determined only on long term follow-up.(109)

A fourth generation Vi-TT conjugate typhoid vaccine was indigenously developed by an Indian biotechnological company In 2013, this vaccine was launched in Hyderabad. Efficacy of this vaccine is demonstrated by four fold increase in the serum IgA T responses. Seroconversion rate was of 98% found in infants between 6 and 24 months of age,99% in children aged 2 to 15 years,and 92% in individuals belonging to the 15-45 year age group. When

compare to Vi-PS typhoid vaccine,it is considered as superior than the previous one.It offers a safe and better tolerance for all age groups.

REVIEW OF LITERATURE

1.Ramasamy Ganesh et al-2010:

A 3 year retrospective Study included a total number of 316 children About 178 male children and 138 were female with ratio of 1.29:1 .Around 32% cases between 2 to 5 years age and 49.3% were above 5 years, About 38% cases were enrolled around January to april month. About 59% children were in unimmunised group. Distribution of symptoms and sign include fever 100% ,vomiting 49% ,diarrhoea 29%, hepatomegaly 71%, splenomegaly 34 % , toxaemia 16%, leucopenia 8% leucocytosis 12% ,eosinopenia 72% , elevation of serum transaminases were seen in 57 % cases.USG showed 6 children had gall bladder hydrops, gall bladder thickening was seen in 8 cases , abdominal free fluid noted in 13(4%)children ,gall bladder sludge was found in 1 child.

2. Devaranavadagi.R.A. et al 2017 :

Total number of cases enrolled was 113 among them 63.8% were males and 36.2% were females, the most common age group was 5 to 10 years. Fever was found in 100% cases followed by 61% cases were anorexia, vomiting was found in 44% and abdominal pain was found in 18%. Incidence of toxic look was found in 68% cases followed by coated tongue was seen in 49% cases, hepatomegaly in 44%, leucopenia was found in 34% , eosinopenia 39% anemia 16%, thrombocytopenia was found in 15%. Corporation water usage for drinking was found in 65% and outside eating was found in 40% cases, unhygienic practice was found in 64%, duration of hospital stay varied from 3 to 10 days .Cases elevated SGOT was in 9% cases and SGPT was in 12% cases. Azithromycin sensitivity was found 60% cases. No mortality was encountered in this study.

3. K.C. Mathura et al 2005:

This study was conducted over a period of one year. Total number of cases studied were 46 ,out of 46 cases 71.7% were males and 28.3% were females.Fever was present in 100 % and headache was present 82.6% cases, constipation was present 13% and diarrhoea 28.3% , coated tongue was present 58.7% , relative bradycardia 43.5% and splenomegaly 28.3% , leucopenia was present 2.2% ,abdominal pain was present 26.1% and vomiting was present in 21.7%.of patients.

4. Malangori A .Parandeet al 2011

Total 172 enteric fever cases the possible causes for enteric fever being common in school going age group include their mobility, consumption of unhygienic food and water in schools and roadside vendors .Male to female ratio of 1.6:1.This might be due to contract infection outside the house.Out of 172 cases, 49.70% were illiterate and 50.30% were literate. A significant association was found between literacy status and occurrence of enteric fever ($p< 0.001$). About 65.70% cases had poor personal hygiene. More than 79.65 % patients had Kacha house. About 72.09 % cases had unhygienic storage of drinking water associated with lack of clean and safe water. More than half of cases 54.65 % was found to have unhygienic storage of cooked food. Insanitary waste disposal was seen in more than 68.02% of cases. The average duration of hospital stay varies from 2 to 35 days with mean 7.91 days and S.D. 5.45 days. Mortality rate in this study was 1.74%.

5. Asish kakaria et al 2014

This study reported that the incidence of fever 100%, chills 26%, vomiting 44%, diarrhoea 28%, abdominal pain 64%, headache 26% splenomegaly 36%, hepatomegaly 42%, rose spots 6%, relative bradycardia 34% were reported. Anemia 42 .9%, leucocytosis 10%, leukopenia 21% and elevated liver enzymes 45% were found . Incidence of S.typhi was 80% .No mortality was reported in this study.

6. Modi et al 2015

This study reported as commonest age group for enteric fever were 6–10 years.This study revealed that those who exposed to unhygienic foods from outside roadside vendors are more prone to contract typhoid. Male:female ratio was 0.81:1.Anemia was found in 39.79% patients in this study .Fever was present in all patients (100%). Abdominal pain was present in 57.14% patients and vomiting in 50% patients. Constipation was observed in

only 2.04% patients in this study.Toxic look was found in 92% and coated tongue 66.32% were observed. Liver enlargement was found in 36.73% patients in this study.. Splenomegaly was found in only 20.40% patients in this study.Complications were seen in only 8.1% patients. two cases were hepatitis.

7. Dr.Kumar.S et al 2016

This study reported majority of the patients presented with pain abdomen and males are more affected than females..Fever is the most common feature in cases of typhoid fever. Abdominal pain in 100% of the patients were noted .In this study 91.54% were widal positive. There were no life threatening complications in this study.

8.Tsonyo Dimitrov et al 2007

This study reported among 135 cases ,100% all are suffered from fever and 52.6% patients were found diarrhoea. Chills were present in 25.2% cases and vomiting was present in 48% patients. Around 28.9% patients were found to

had abdominal pain and 18.5 % cases suffered from cough followed by 17.8% patients had anorexia. Only 3.7 % cases were found to had constipation, headache was 29.6% and sore throat was 12%. Clinical signs including 9.6% had hepatomegaly,20.7% were having splenomegaly and rose spot was present in 2.2% cases. Laboratory investigation revealed that leucopenia was seen in 25.2% cases, anemia was found in 54.8% cases , thrombocytopenia was seen in 9.6% cases and mean duration of symptoms was 6.6 days along with history of recent travel was 88%.

9. K.C. Mathura et al 2003

In this study, among 30 casesthe major clinical presentation was fever (100%),headache (90%), and abdominal pain (37%). 33% cases were presented with constipation and 27% cases with diarrhoea. Splenomegaly (36%), relative bradycardia (27%) and hepatomegaly (17%) were found in this study.This study reported relative bradycardia was present in 27% in this study.

10. ShahriarKabir et al 2002

This study showed male to female ratio was 1.7:1.45. Majority of thepatients were falling under (69.23%).low socio economic group. Clinical features revealed that abdominal discomfort was seen in 29.23% ,malaise 50.76%, cough 35.38%, myalgia 73.84% ,sweating 46.15%, arthralgia 36.92%, arthritis 53%,diarrhoea 27.69%, malena 2% ,constipation 23.07%, anemia ,36.92%, coated tongue 32.30%, toxic look 20% ,splenomegaly 23.07%,

hepatomegaly16.92% ,dehydration 26.15%,rashes 3.07% ,abdominal tenderness 12.3% ,jaundice 1.53% and meningism 4.61%, were found. Both blood culture and widal was positive in 13.84% cases , positive blood culture and negative widal was seen in 16.92% cases and both blood culture and widal were negative in 69.23% cases.

11. Sharma N et al 2003

This study revealed that 100 % cases presented with fever and 43.80% cases presented with headache,chills were present in 41.1% patients,vomiting in 6.3% cough 15.2%, abdominal pain 10.7%, diarrhoea in 8%,constipation 5.4% Laboratory investigations revealed that leucopenia was found in 32.1% cases, normal count was seen in 62.5% cases and leucocytosis was found in 5.3% cases, Splenomegaly was found in 2.7%patients, positive blood culture was reported in 49.2% cases and widal was positive in 52.7% patients.

12. Allen Malisa et al 2010

This study reported about 60% patients were females and 40% patients were males. 15% patients were from limited formal education group, 72.5% patients from primary education group and 12.5% coming from secondary education level.Patients who aware about typhoid was 87.5% and those who unaware was 12.5%. Aware about the symptoms and signs were

60% and unaware people were 40%. Patients who aware aboutthe transmission of typhoid were 42.5% and unaware patients were 57.5%.Those who aware about the control measures of typhoid were 47.5% and not aware about that was 52.5%. Only 30% of patients were using boiled water for drinking ,12.5% were using chemically treated water and 57.5% patients were not using potable water for drinking.

13. M.N.Chowta et al 2005

This study reported that all 44 (100%) patients were presented with fever vomiting was present in 20.4% patients ,diarrhoea was present in 20.4% patients, headache was present in 18.! % cases , abdominal pain was in 11.3% patients. 9.1% patients were came with constipation , body pain was present in 2.3% cases dry cough was found in 6.8% patients breathlessness was present in 2.3% weight loss was seen in 2.3% burning micturition was present in 2.3% patients. Relative bradycardiawas found in 22.7% cases rectal bleeding was present in 2.3% cases and myocarditis was present in 4.5 % patients.

14.Ganesh Shah et al 2014

This study reported among 119 patients, male patients (54%) were commonly affected as compared to female cases (46%). Common age group were between (2-10) years of age (63%).In this study, fever was present in 100% cases, vomiting in 31.09% cases, abdominal pain in 26.05%, diarrhoea 22.68%,cough

20.16%, and headache was seen only in 10.08% Patients. Hepatomegaly(34.45%),splenomegaly(21%),toxiclook7.56%,lungcrepitations8.4% convulsions 5.88%,were present in this study.Relative bradycardia was not observed . 26% of complications were observed in this study.

15.Shakil Ahmad et al 2016

In this study, the mean age of presentation was 7.6 years and the male to female ratio was1.4:1. Fever was the most common presenting symptom in all 100% cases, Anorexia was found in 70.3% of cases,headache was seen in 54.1%patients.Vomiting was found overall in 41.9% cases .Abdominal pain was found in 37.8% children. Diarrhea was found in 24.3% patients.Constipation was found in 18 (24.3%) patients. Coated tongue was found in 9.5% children. Abdominal distention was found in 64.9% patients.Splenomegaly was present in 54.1% patients and hepatomegaly was found in 52.7% children.Relative bradycardia was found in 5.4% children. Leucopenia was not observed in any cases,leucocytosis was found in 21.6% patients .Eosinopenia was found in 31.4% of children.Anemia was found in 53% patients S.typhi culture was positive in only 2 patients.

16. V. Jesudason et al 2006

This study reported that the sensitivity and specificity of the test for typhoid fever diagnosis were 78.9 and 98.9 per cent, respectively.

17.D.Narayanappa et al 2009

In this study among 41 culture positive patients ,38 patients were typhidot –M positive.The sensitivity of Typhidot-M was 92.6%. Typhidot-M can be used for early diagnosis of typhoid fever.

18. Atif Sitwat Hayat et al 2011

In this study, male patients were (75%) and female patients were (25%) with male to female ratio was f 3:1.. Out of 100 clinically diagnosed typhoid patients, 19 patients were found to be blood culture poaitive for S.typhi and 71 patients were typhidot-M positive. Out of 19 culture positive cases, 94.73% were true typhidot-IgM positive and false positive were 0.83%. The sensitivity, specificity, positive and negative predictive values of typhidot-M test using blood culture as gold standard were 94.73%, 90%, 97.72% and 78.26% respectively for patients having typhoid fever.

19.Sherwal et al 2004

36 patients were clinically suspected typhoid fever ,24 patients were non typhoid cases.Positive blood culture for typhoid was 68% 57% patients widal positive and 79% patients were Typhidot positive.In non typhoid cases,17% were widal positive and 12.5% were Typhoid positive. Out of 38 culture positive cases, 35 cases were positive for Typhidot while widal was positive in 25 cases.This study reported that sensitivity and specificity for Typhidot was

92% and 87.5% as compared to widal which had sensitivity and specificity of 74% and 83%.

AIM & OBJECTIVE

To evaluate the epidemiological features and outcome of typhoid fever

STUDY JUSTIFICATION

In developing countries where typhoid fever is endemic and laboratory resources are poor, diagnosed mostly based on clinical signs and symptoms in rural areas.This is often leads to over or under diagnosis of typhoid fever. Even though culture has remained the gold standard test in diagnosis of typhoid fever and its utility in early diagnosis has been limited in early phase of illness thereby making the isolation of the organism difficult.

MATERIAL & METHODS

SAMPLE SIZE **:** Six months duration

STUDY DESIGN : Hospital based prospective study

STUDY PLACE : Institute of social paediatrics, Government Stanley Medical College Hospital, Chennai.

STUDY PERIOD : 6 months from ethical clearance

STUDY POPULATION: Children attending both out patient clinic and hospitalised children

INCLUSION CRITERIA

1.Clinical suspects of typhoid cases with serological evidence of either blood culture ,widal ,Typhidot-M.

2. Children aged 2 to 12 years

EXCLUSION CRITERIA

1. Children with other febrile illness

2. Children less than 2 years

3. Chronic malnutrition

METHODOLOGY

After institution ethical committee approval , informed and written consent was obtained from parents/ guardians of the subjects. Detailed epidemiological history and clinical examination was done according to pre designed proforma. .Socio economic status was graded according to modified kuppusamy's scale.All subjects included in this study were undergone complete hemogram, Liver function test, USG abdomen, blood culture and sensitivity, Widal,and Typhidot–M test. All variables including socio economic details, clinical signs and symptoms and the results of laboratory tests was recorded. and analysed using IBM SSPS 22 version.The findings will be tabulated in percentage and mean standard deviation will be calculated wherever applicable..

All epidemiological and clinical variables are compared according to protocol and proforma..

Under aseptic precaution 7 ml of venous blood was collected sample sent for complete blood count,Liver function test, widal ,blood culture and sensitivity and Typhidot-IgM as per protocol. Complete blood count was done in our central lab with auto analyser as a routine procedure.Liver function test was done in Bio chemistry central lab as a routine procedure.Enteric culture was done in Microbiology lab. Ultrasonogram was done in Radiology department .

Blood culture:

Five ml of venous blood was sent for culture ,using Brain Mouse Broth Agar.After incubation of blood, the bottle was kept in the upright position. For the subculture, the bottle was merely tilted so that the broth runs on to the surface of agar. It was re incubated in the upright position. If Salmonella was present, colonies would appear in the slant side. A second subculture was performed on brilliant green bismuth sulphite agar, MacConkey agar and Salmonella–shigella agar media. It was incubated at 37 C for another 24-48 hours. After that the plates were followed up for growth. If there was growth ,non-lactose fermenters (SSA),sometimes with clear edge and black colonies with metallic sheen in BBSA, then Salmonella to be strongly suspected and further identification tests are performed.

WIDAL TEST

Widal tube agglutination test was done with 1 ml of venous blood in order to the manufacturer's instruction using reagents containing O and H antigens of S. Typhi. Positive and negative serum controls are included, a titre of 1:160 or rising titer was considered significant of typhoid fever. The results were correlated with blood culture results and interpreted in correlation with the patient's clinical and epidemiological profile,

TYPHIDOT-M

The Typhidot-M test becomes positive within 2-3 days of infection and separately identifies M antibodies. The test was based on the presence of specific IgMantibodies to a specific 50KD OMP. antigen, which is impregnated on nitrocellulose strips.

PRINCIPLE OF THE TEST

This an indirect solid-phase immune chromatographic assay. The specific S.typhi OMP antigen is immobilized onto cellulose nitrate membrane as test lines. When the test sample is added to the sample pad, it migrates upwards. If anti-S.typhi IgM antibodies are present in the test sample (serum or plasma), they will react with colloidal gold-anti-human IgM to form a complex. The complex will continue to move on the cellulose nitrate membrane and then captured at the test window zone by the immobilized specific S. typhi OMP antigen, giving a pink-purplish coloured band. The control line contains rabbit anti-mouse IgM antibody binds with the gold conjugated mouse anti-human IgM antibodies. The control band serves as an indication of proper migration plus reagent control.

PROCEDURE

Add 35 µl serum or plasma to each sample well. No air bubble should be present in the well. Serum or plasma will start wicking up the membrane. The

cassette may be tapped gently on the table to facilitate the sample to flow up the membrane. Wait until the wet sample front of the serum or plasma reaches the area where C is marked .Then add 1 drop of buffer to each sample well. Read result within 15-20minutes.

INFERENCE

1. Positive **:** Coloured bands appear at the control line (C) and Test lines (T).

2. Negative : Only Control line (C) is visible.

3. Invalid **:** Control line (C) is absent. If this occurs, the assay should be repeated using a new test case.

RESULTS

A study of 300 children with clinically suspected typhoid fever undergoing treatment in tertiary care hospital has revealed the following findings. The mean age of the sample is 5.77 with a standard deviation of 1.948 (N=300). Of which 72 of them were Typhidot-M positive and out of 72 Typhidot-M positive cases,70 cases were Widal positive. Since two cases were outlier, the following analysis pertains to the Widal positive cases. A study of 70 children with fever in tertiary center revealed the following findings.

The mean age of the sample is 5.74 with a standard deviation of 2.111 (N=70). Majority of them (67.1%. n=47) were above the age of five years while 23 (32.9%) of them were below the age of five years. A greater part of the sample is occupied by males (55.7%, n=39) while females occupied 44.3% (n=31). Majority of them (52.9%, n=37) came from upper lower socioeconomic status. Majority of them (60%, n=42) came from urban areas. Majority of them (61.4%, n=43) stayed between 5 and 7 days. Only 14.3% (n=10) of them had a past history of typhoid.85.7% (n=60) of the children were not vaccinated among 70 of them. Blood culture growth was found in only 1.4% (n=1) of the samples. Seventy children (100%) of them were positive for blood Widal. Seventy children (100%) of them were positive for Typhidot M. None of them had any complications. All of them recovered from illness. 64.3% (n=45) of them had access to corporation water while 28.6% (n=20) of them had access to can

water. Majority of them (45.7%,n=32) had average personal hygiene. Majority of them (71.4%, n=50) had access to toilet.

Age distribution of the participants

The following figure illustrates the age distribution of the participants. The mean age of the sample is 5.74 with a standard deviation of 2.111 (N=70). Majority of them (67.1%. n=47) were above the age of five years while 23 (32.9%) of them were below the age of five years.

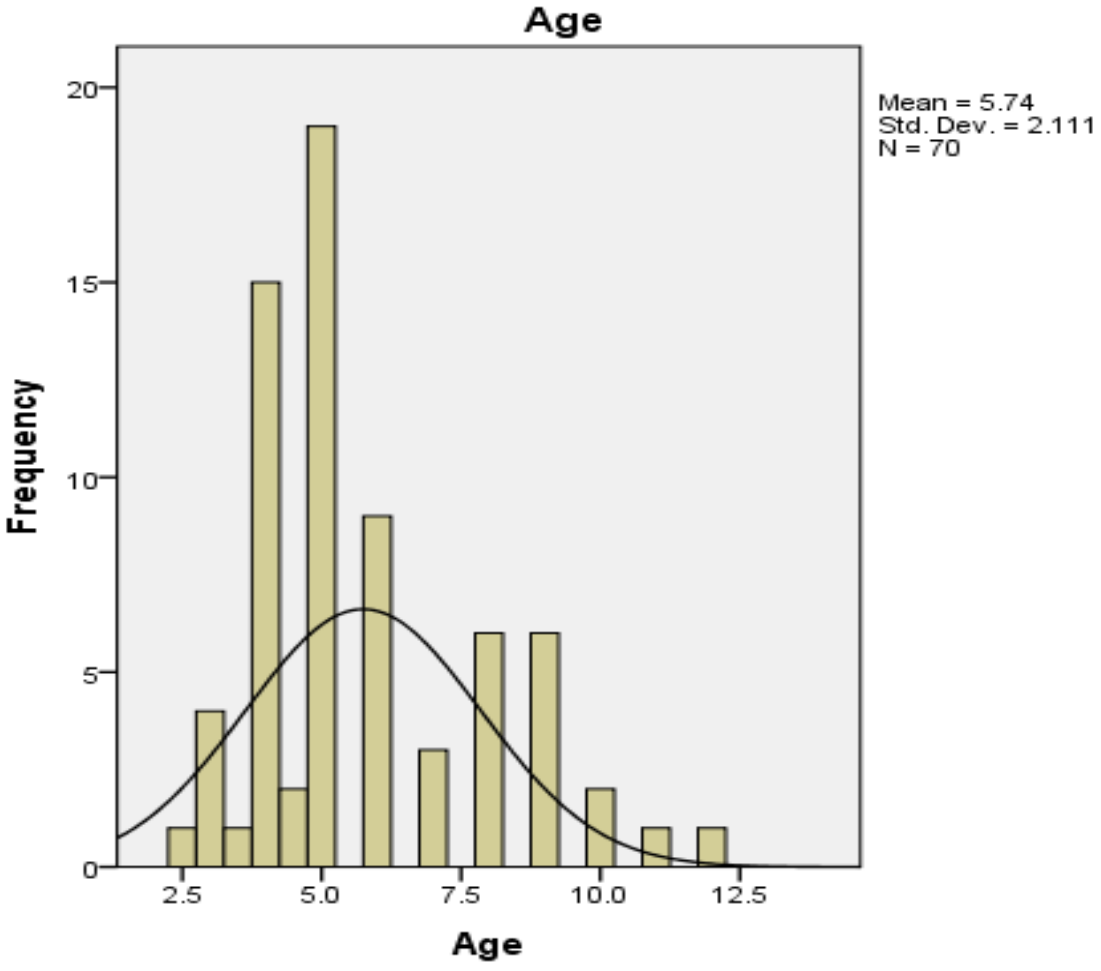

Figure 1: Age of the participants

Gender of the participants

A greater part of the sample is occupied by males (55.7%, n=39) while females occupied 44.3% (n=31). The following figure depicts the gender distribution of the subjects under study.

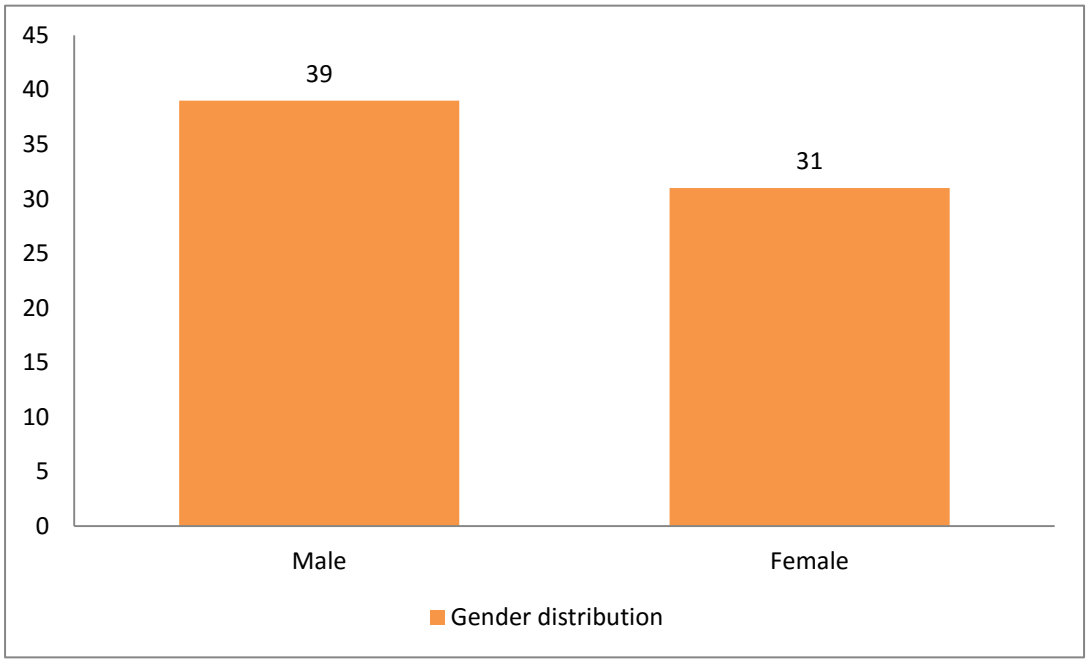

Figure 2: Gender distribution of the subjects under study

Socioeconomic status of the participants

The following table depicts the overall socioeconomic status of the participants. Majority of them (52.9%, n=37) came from upper lower socioeconomic status.

Socioeconomic Status	Frequency	Percent
Lower middle	10	14.3
Upper lower	37	52.9
Lower	23	32.9

Table 1: Socioeconomic status of the participants

Residence

Majority of them (60%, n=42) came from urban areas. The following figure depict the distribution among age groups.

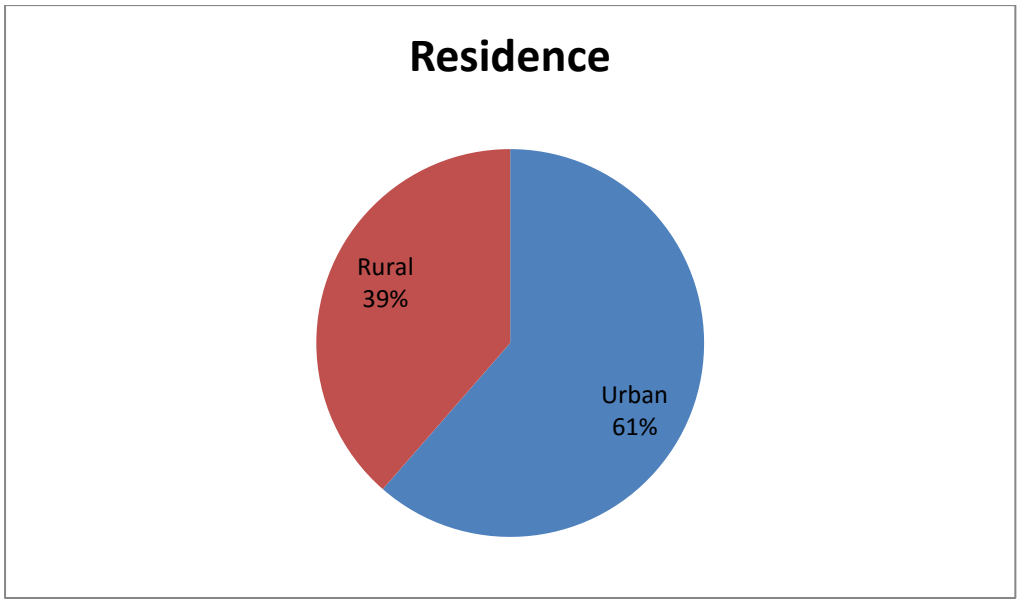

Figure 3: Residence of the participants

Duration of stay

The following table depicts the number of days they stayed in hospital. Majority of them (61.4%, n=43) stayed between 5 and 7 days.

Duration of stay (in days)	Frequency	Percent
5-7	43	61.4
8-10	17	24.3
>11	10	14.3

Table 2: Duration of stay

Vaccination Status

85.7 percent (n=60) of the children were not vaccinated among 70 of them. Figure 4 depicts the vaccination status of children.

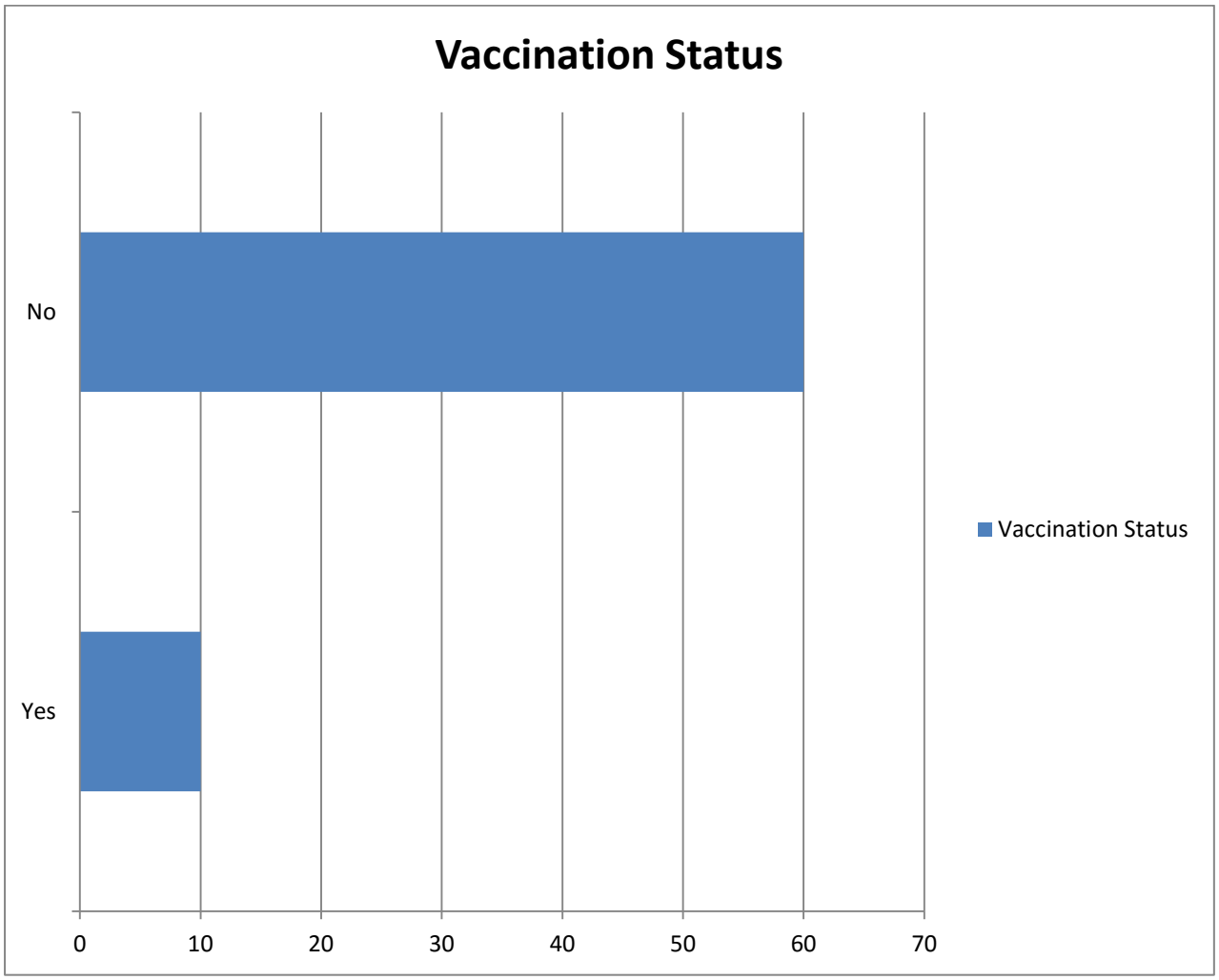

Figure 4: Vaccination status in children

Past History of Typhoid

Only 14.3% (n=10) of them had a past history of typhoid. Figure 5 depicts the past history of typhoid of children.

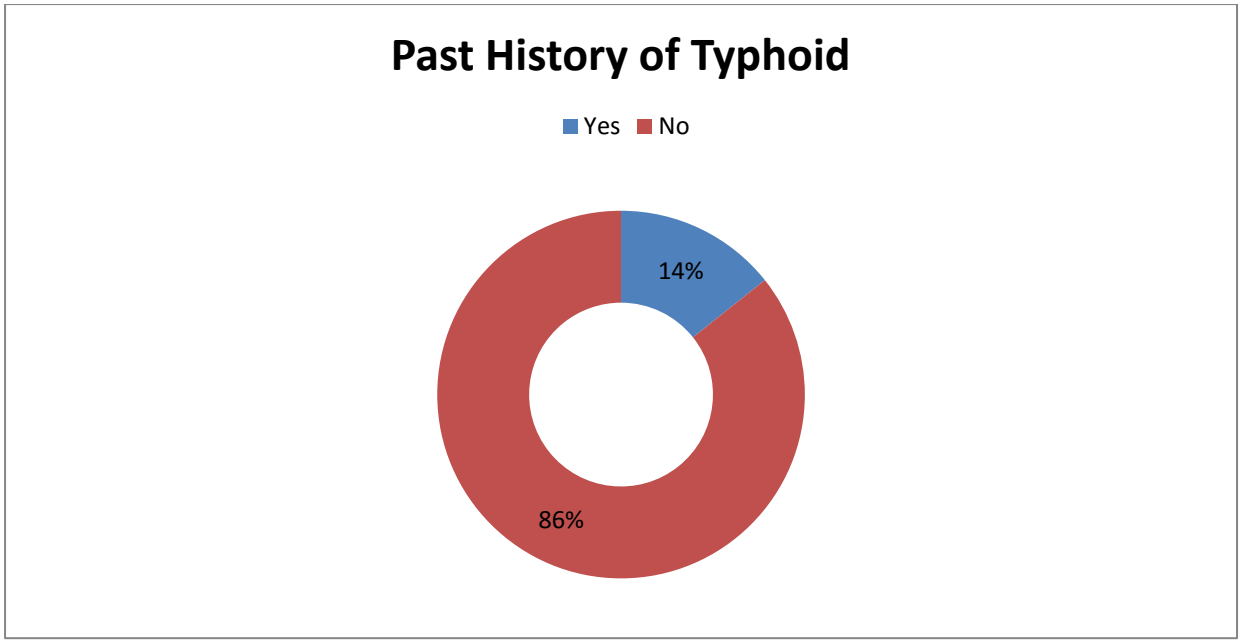

Figure 5: Past history of typhoid among children

Blood count

The blood count of 70 patients revealed that a majority of them 41.4% (n=29) had count in the range of 4000-11000. Table 3 depicts the blood count among children.

Blood count	Frequency	Percent
<4000	27	38.6
4000-11000	29	41.4
>11000	14	20

Table 3: Blood count of the children (N=70)

Blood culture

Blood culture growth was found in only 1.4% (n=1) of the samples.

Blood Widal and Typhidot-M

Seventy children of them were positive for blood Widal.Seventy two children of them were positive for Typhidot-M. The following figure represents blood Widal and Typhidot- M.

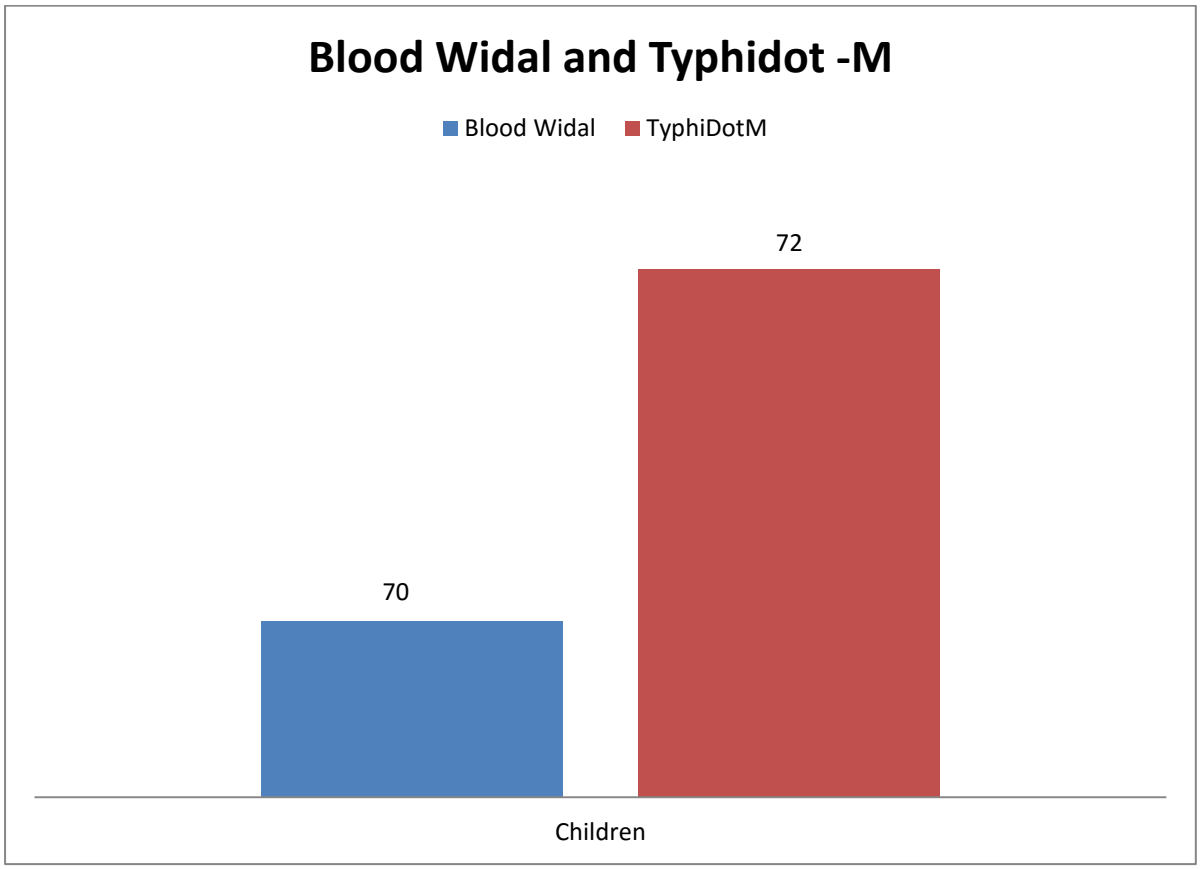

Figure 6: Blood Widal and Typhidot M

Complications

None of them had any complications

Outcome of the disease

All of them recovered from illness.

Personal Hygiene

Majority of them (45.7%, n=32) had average personal hygiene. Figure 7 depicts the personal hygiene of the children.

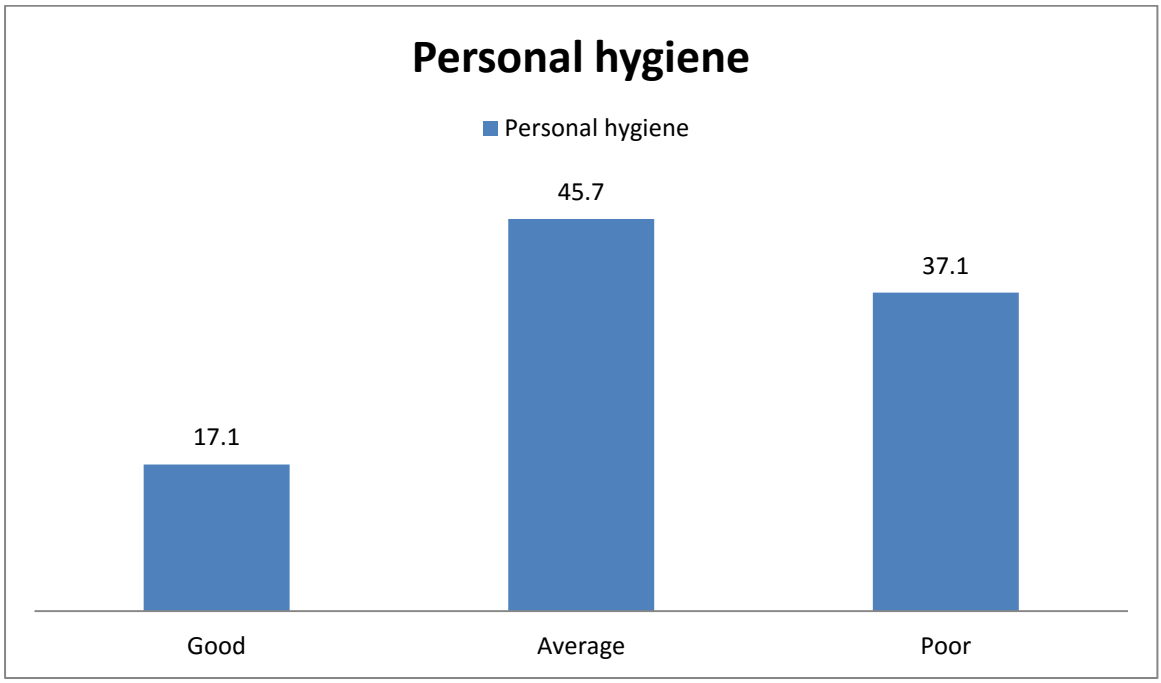

Figure 7: Personal Hygiene of the children

Housing type

Majority of them (72.9%, n=51) lived in pucca houses. Figure 8 depicts the housing type among the respondents.

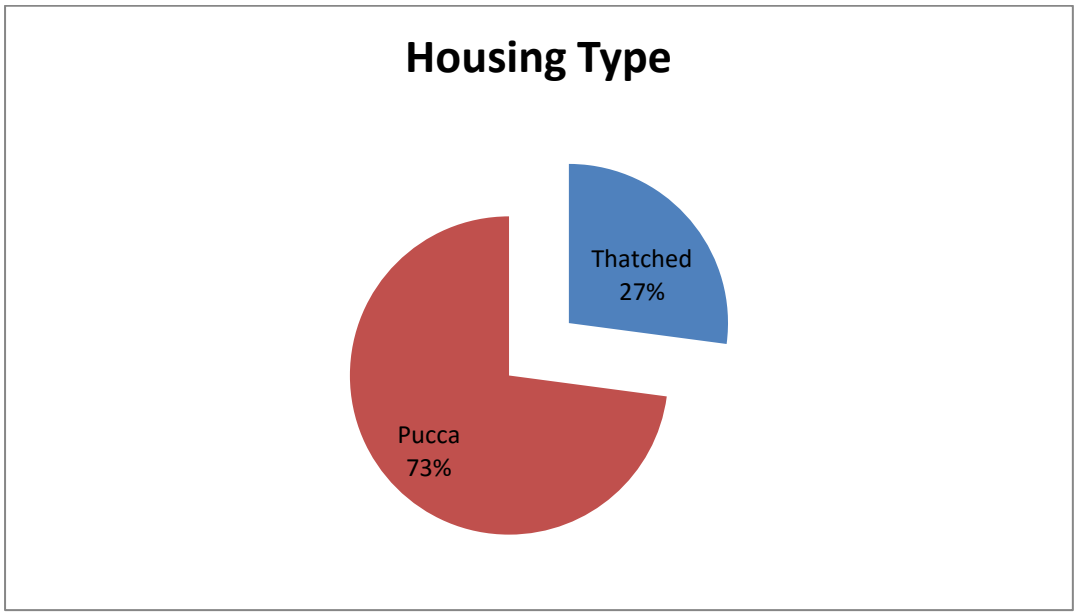

Figure 8: Housing of the respondents

Overcrowding

Around 52.9% (n=37) of the respondents indicated overcrowding. Figure 9 depicts the overcrowding among the respondents.

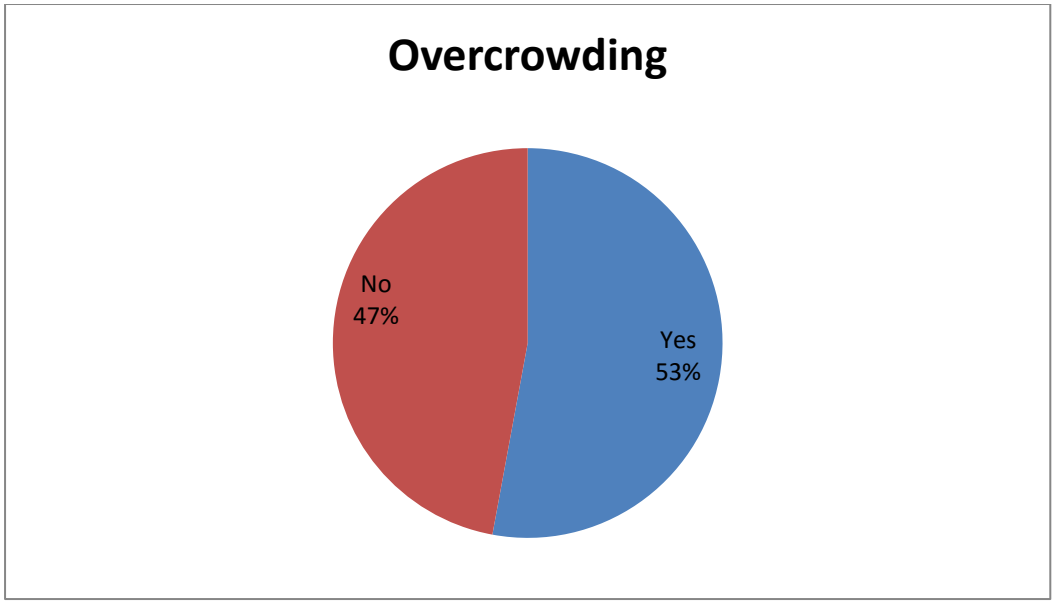

Figure 9: Overcrowding of the respondents

Water Source

64.3% (n=45) of them had access to corporation water while 28.6% (n=20) of them had access to can water. Figure 10 shows the water source of the sample.

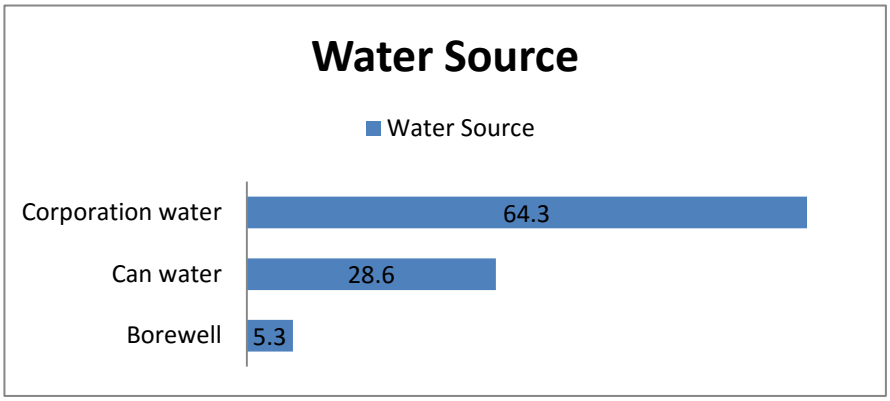

Figure 10: Water source among the samples

Water Treatment Method

Only 28.6% (n=20) of them used boiled water. Water treatment method among the samples is given below (figure 11).

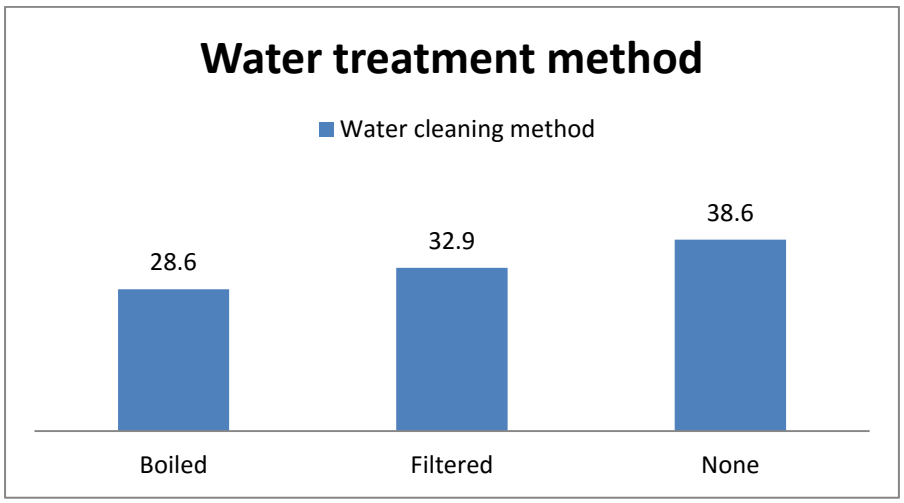

Figure 11: Water Treatment method among the samples

Storage of cooked food

Majority of them (77.1%, n=54) had protected storage of cooked food. Storage of cooked food among the samples (Figure 12).

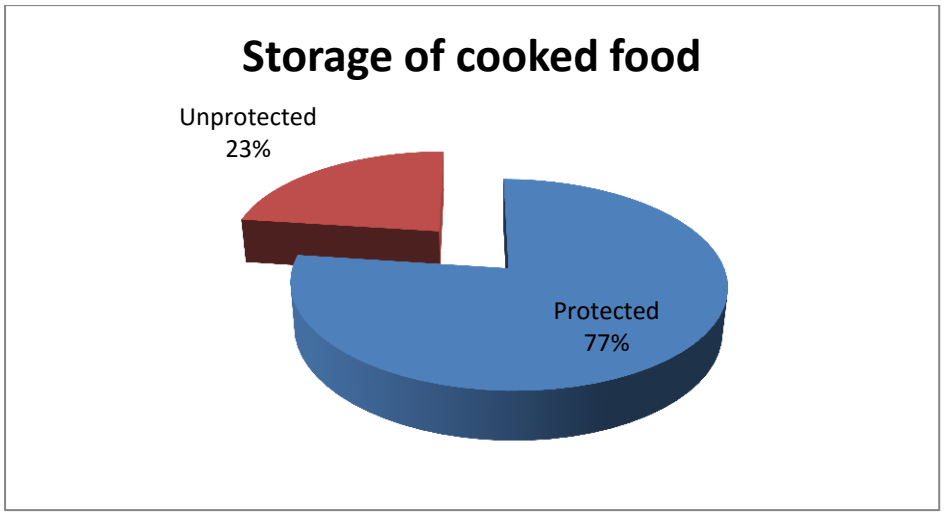

Figure 12: Storage of cooked food among the samples

Storage of drinking water

Majority of them (81.4%, n=57) had protected storage of drinking water. Storage of drinking water among the samples (Figure 13).

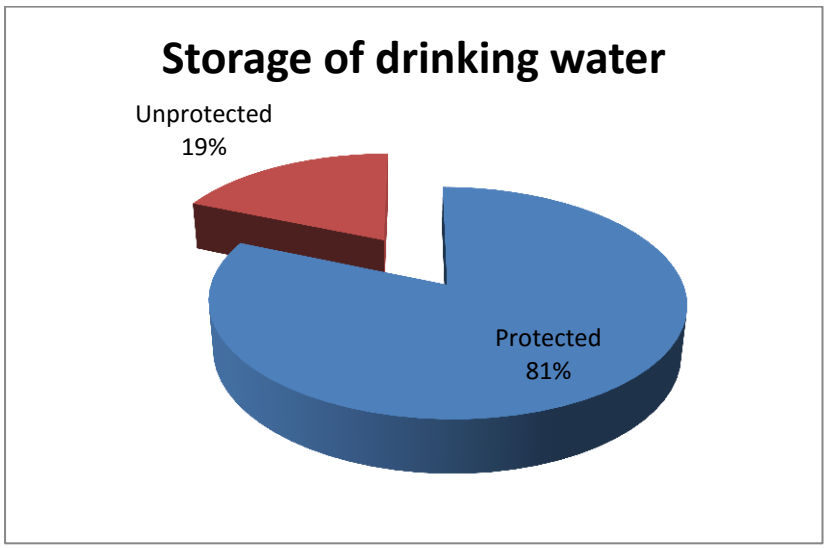

Figure 13: Storage of drinking water among the samples

Toilet facility

Majority of them (71.4%, n=50) had access to toilet. Toilet use among the samples (Table 4).

Sanitation -toilet use	Percent
Yes	71.4
No	28.6

Table 4: Toilet use among children

Waste disposal

Majority of them (51.4%, n=36) had open bin for waste disposal. Waste disposal among the samples (Figure 14).

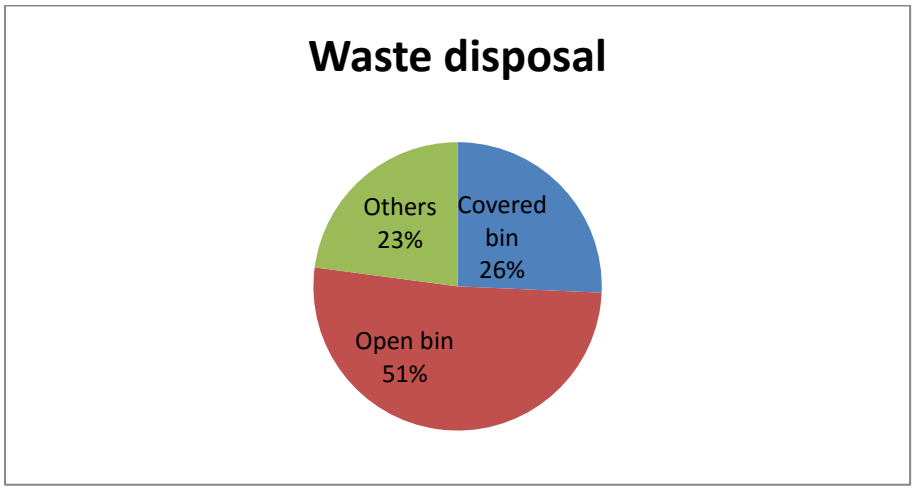

Figure 14: Waste disposal among children

Road side food intake

Most of them (72.9%, n=51) had road side food intake. Table 5 summarizes the road side food intake among the children.

	Yes in percent (n)	No in percent (n)
Outside food intake	72.9 (51)	27.1 (19)

Table 5: roadside food intake among the children

Liver enzymes

Liver enzymes were elevated in 24.3% (n=17) of the children. Figure 15 depicts the liver enzymes in children.

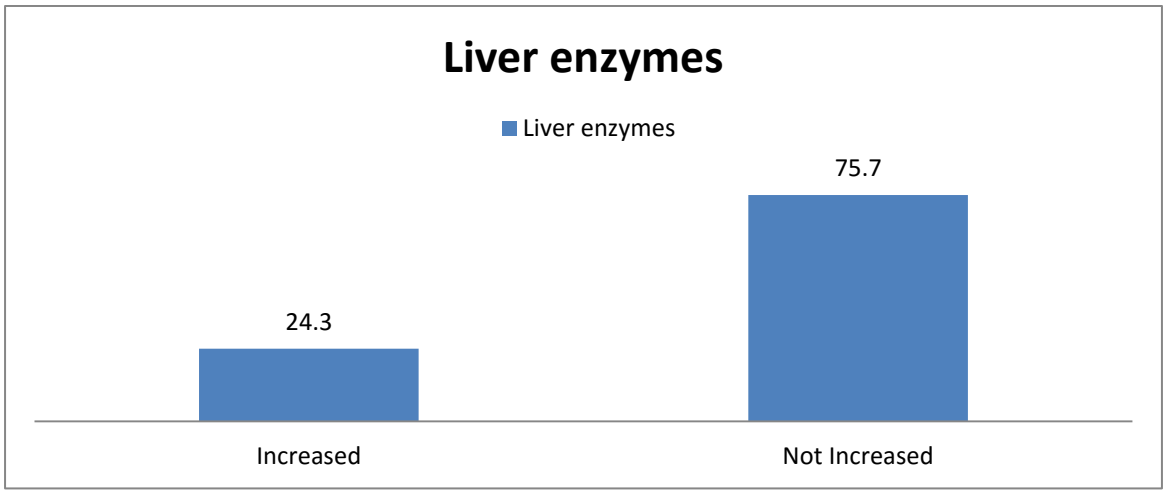

Figure 15: Liver enzymes among children

Thrombocytopenia and Eosinopenia

Thrombocytopenia was noted in 15.7% (n=11) of the children. Eosinopenia was noted in 34.3% (n=24) of the sample. Table 6 summarizes the results.

	Thrombocytopenia in percent (n)	Eosinopeniain percent (n)
Yes	15.7% (11)	34.3% (24)

Table 6: Thrombocytopenia and Eosinopenia among the children

USG abdomen

USG abdomen revealed that 42.9% (n=30) had hepatomegaly, 27.1% (n=19) had splenomegaly and 22.9% (n=16) had hepatosplenomegaly. Table 7 summarizes the results.

USG Abdomen	Percent
Hepatomegaly	42.9
Splenomegaly	27.1
Hepatosplenomegaly	22.9
None	7.1

Table 7: USG results among children

Hemoglobin Levels

The following table summarises the haemoglobin levels in the children. Majority of them (60%, n=42) had between 7 and 11 g%.

Hemoglobin level (g%)	Frequency	Percentage
<7	15	21.4
7-11	42	60
>11	13	18.6

Table 9: Hemoglobin levels

Clinical features

The following table summarizes the clinical signs present in 72 children.

Sl.No	Clinical sign	Percentage (N=72)
1	Fever	100 (72)
2	Abdominal pain	51.4 (36)
3	Vomiting	48.6 (34)
4	Constipation	18.6 (13)
5	Loose stool	38.6 (27)
6	Headache	35.7 (25)
7	Body pain	27.1 (19)
8	Sore throat	34.3 (24)
9	Anorexia	60 (42)
10	Step ladder fever	7.1 (5)
11	Arthralgia	10 (7)
12	Toxic look	44.3 (31)
13	Pallor	57.1 (40)
14	Coated tongue	44.3 (31)
15	Hepatomegaly	42.9 (30)
16	Splenomegaly	24.3 (17)
17	Hepatosplenomegaly	22.9 (16)
18	Tender abdomen	44.3 (31)
19	Rose spot	-
20	Relative bradycardia	4.3 (3)
21	Dehydration	40 (28)

Table 8: Clinical Signs

DISCUSSION

A Study of 300 children with clinically suspected typhoid fever undergoing treatment in tertiary care hospital has revealed the following findings. The mean age of the sample is 5.77 with a standard deviation of 1.948 (N=300). Of which 72 of them were Typhidot-M positive and and out of 72 Typhidot-M positive cases,70 cases were Widal positive. Since two cases were outlier, a study of 70 children with fever in tertiary center revealed the following findings.

The mean age of the sample is 5.74 with a standard deviation of 2.111 (N=70). Majority of them (67.1%. n=47) were above the age of five years while 23 (32.9%) of them were below the age of five years. A greater part of the sample is occupied by males (55.7%, n=39) while females occupied 44.3% (n=31).The male to female ratio is 1.25:1. This is similar to the ratio observed in studies by ShahriarKabir et al in 2002 and Ramasamy Ganesh et al in 2010, Shakil Ahmad et al in 2016 and Ganesh Shah et al in 2014.

Majority of them (52.9%, n=37) came from upper lower socioeconomic status. Majority of them (60%, n=42) came from urban areas. The sampling from tertiary care hospital setting in the urban area can be attributed to the larger

participation from urban areas and upper lower socioeconomic status. ShahriarKabir et al 2002 reported that 69.2% came from lower socioeconomic status which correlates with this study. 85.7 percent (n=60) of the children were not vaccinated among 70 of them. Ramasamy Ganesh et al in 2010 had 41% of children immunized in the study of 316 children.

Only 14.3% (n=10) of them had a past history of typhoid. Majority of them (61.4%, n=43) stayed between 5 and 7 days. The blood count of 70 patients revealed that a majority of them 41.4% (n=29) had count in the range of 4000-11000.Blood culture growth was found in only 1.4% (n=1) of the samples.

Only one child less than five years and positive showed blood culture growth. This can be attributed to the prior intake of antibiotics before taking the culture. Seventy children (100%) of them were positive for blood Widal.For instance, in the following studies by Dr.Kumar.S et al in 2016 , only 91.54% were widal positive, ShahriarKabir et al in 2002 (13.84% cases), Sharma N et al in 2003 (52.7%) and Sherwal et al in 2004 (57%).

Seventy children (100%) of them were positive for Typhidot-IgM.This is related to the previous studies; 38 patients were positive (D. Narayanappa et al, 2009), 71 patients (AtifSitwat Hayat et al, 2011) and 79% patients (Sherwal et al, 2004).None of them had any complications in this study as reported by K.C. Mathura et al (2003) and Dr.Kumar.S et al (2016).

Majority of them (45.7%, n=32) had average personal hygiene. About 65.70% cases had poor personal hygiene in a study of 172 cases of enteric fever by Malangori A .Parande et al in 2011. Majority of them (72.9%, n=51) lived in pucca houses. This is different from the 79.65% of kachcha house found in the study by Malangori A .Parande et al 2011. Around 52.9% (n=37) of the respondents indicated overcrowding. 64.3% (n=45) of them had access to corporation water while 28.6% (n=20) of them had access to can water.This can be compared to the Corporation water usage for drinking was found in 65% in a study by Devaranavadagi R.A. et al in 2017, and 72.09% cases had unhygienic storage of drinking water (Malangori A .Parande et al, 2011). Only 28.6% (n=20) of them used boiled water which is very low compared to the 57.5% patients reported by Allen Malisa et al 2010. Majority of them (77.1%, n=54) had protected storage of cooked food in contrast to the 54.65% found by Malangori A .Parande et al 2011. Majority of them (81.4%, n=57) had protected storage of drinking water. Majority of them (71.4%, n=50) had access to toilet. Insanitary waste disposal was seen in more than 68.02% of cases in the study by Malangori A .Parande et al in 2011 while a majority of them (51.4%, n=36) had open bin for waste disposal in this present study. Outside eating was found in 72.9% (n=36) of the children with fever which is comparable to the 40% cases of Devaranavadagi R.A. et al in 2017.

Liver enzymes were elevated in 24.3% (n=17) of the children while 45% were found by Asishkakaria et al in 2014 and 57% by Ramasamy Ganesh et al in 2010.

In this study, Thrombocytopenia was noted in 15.7% (n=11) of the children and Eosinopenia was noted in 34.3% (n=24) of the sample which can be compared to the thrombocytopenia- 9.6% (TsonyoDimitrov et al, 2007), eosinopenia- 31.4% (Shakil Ahmad et al, 2016), eosinopenia -39%, thrombocytopenia-15% (Devaranavadagi R.A. et al, 2017), eosinopenia- 72% (Ramasamy Ganesh et al, 2010).Majority of them (60%, n=42) had haemoglobin between 7 and 11 g%.

USG abdomen revealed that 42.9% (n=30) had hepatomegaly, 27.1% (n=19) had splenomegaly and 22.9% (n=16) had hepatosplenomegaly. The previous studies vary widely as seen from the following information: hepatomegaly-71%, splenomegaly-34 % (Ramasamy Ganesh et al, 2010) ; hepatomegaly-44% (Devaranavadagi R.A. et al, 2017); splenomegaly-36%, hepatomegaly-42% (Asishkakaria et al, 2014); hepatomegaly-9.6%, splenomegaly – 20.7% (TsonyoDimitrov et al,2007), hepatomegaly-17% (K.C. Mathura et al, 2003); splenomegaly- 23.07%, hepatomegaly-16.92% (ShahriarKabir et al, 2002); Hepatomegaly- 34.45%, splenomegaly- 21% (Ganesh Shah et al, 2014); Splenomegaly was present in 54.1% patients and hepatomegaly was found in 52.7% of children (Shakil Ahmad et al, 2016).

The clinical signs and symptoms correlate with all the previous studies with all of the children reporting fever, majority of them having abdominal pain, vomiting, loose stools, headache, body pain, toxic look, tender abdomen, etc. The variation in signs and symptoms between various studies can be attributed to the difference in epidemiological factors that contribute to the symptomatology.

Further studies are required to find out the relationship between various factors and symptoms through controlled studies.

CONCLUSION

A study of 300 children with clinically suspected typhoid fever undergoing treatment in tertiary care hospital has revealed the following findings. The mean age of the sample is 5.77 with a standard deviation of 1.948 (N=300). Of which 72 of them were Typhidot-M positive and out of 72 Typhidot-M positive cases,70 cases were Widal positive. Since two cases were outlier, a study of 70 children with fever in tertiary center revealed the following findings.

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85.7 percent (n=60) of the children were not vaccinated among 70 of them.Blood culture growth was found in only 1.4% (n=1) of the samples. Seventy children them were positive for blood Widal. Seventy two of them were positive for Typhidot-IgM.None of them had any complications. All of them recovered from illness. 64.3% (n=45) of them had access to corporation

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Further studies are required to find out the relationship between various factors and symptoms through controlled studies.

LIMITATIONS

1) The ingestion of antibiotics before testing of blood samples has yield no results in blood culture.
2) Since low yield of blood culture, widal and Typhidot-M could not be compared to the gold standard test.
3) Small number of samples were analysed in this study.

FUTURE RECOMMENDATIONS

1) This study is limited in various aspects, so a wide spread study with broader sampling is required to understand the true nature of the study.
2) Typhidot-M test is also as good as widal
3) Typhidot–M can be used for early diagnosis than widal .
4) The evaluation of epidemiological factors revealed that people who consume outside food, have low hygiene, poor personal hygiene and low levels of sanitation were more prone to getting typhoid. This calls for a wide spread preventive measures.
5) Awareness programs should be created targeting the young children using the latest technology like social media and audio visuals.
6) Separate programs to support research and evaluation of typhoid fever are recommended to ascertain the true nature of the disease and take appropriate measures.
7) There should be public health programs that focus on addressing the preventive measures of this disease.

BIBILIOGRAPHY

1. Statistical Notes, South Africa 2000.Vol.2. No.12.

2.Chandel, D.S. Chaudhry, R. Shawn, B. Pandey, A. Dey, A.B. (2000). *Drug-Resistant Salmonella enterica*serotype *paratyphi*A in India. *Emer.Infec. Dis.* 6 (4):p. 56-59.

3.Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al. Typhoid Study Group. A study of typhoid fever in five Asian countries: disease burden and implications for controls. *Bull World Health Organ* 2008;86:260-8.

4. Thong, K.L. Nair, S. Chaudhry, R. Kapil A. Chandel D.S. (1998).Molecular analysis of *Salmonella paratyphi*A from an outbreak in New Delhi,India, by ribotyping and pulsed-field gel electrophoresis. *J. Emer. Infec. Dis*. 4: p.507-8.

5. Threlfall, E.J. Ward, L.R. (2001).Decreased Susceptibility to Ciprofloxacin in *Salmonella enterica serotype typhi*, UK. *J. Emer. Infec. Dis*. 7 (3):21-26.
Van pelt, W. van der Zee, H. Wannet, W.J. van de Giessen, A.W. Mevius,

6. Johnson, A.G**.** Ziegler, R.G. Lukasewycz, O.A. Hawley, L.B. (1996). *Microbiology and Immunology* 3rded.Mass Publishing Co. Cairo.p59-61.

7.Twort, A. Law, F. and Crawley, W. (1990). Water Supply Third edition.Holder and Stonington Limited, London.

8. Winfred, W. and Julia M. (2005). ***Comprehensive Geography***. Longhorn Publishers Limited, Nairobi, Kenya.

9.Wood, H. Vaughan, P. and Glanville, H. (1992) ***Community Health***. Amref, Nairobi, Kenya.

10.Rowe, B.Ward, L.R. Threlfall, E.J.(1997). *Multi resistant Salmonella typhi*: a worldwide epidemic . *J.Clin. Infec. Dis*. 24 (11) :p. 2106-9

11.Ray, C. (2002). ***Epidemic deadly disease through History Typhoid Fever***. The Rosen Publishing Group Inc, New York.

12.Pruss, U. and Corralan, C. (2006). ***Preventing Diseases through Healthy Environment towards anEestimate of the Environmental Burden of Diseases.***World Health Organization, France. 74
.
13. WHO (1994). ***Fact sheets on Environmental Sanitation***. World Health Organization, Geneva, Switzerland.

14.Brooks, G.F. Bult, J.S. Morse, S.A. (1998). *Jawetz, Melnick, and delberge's Medical microbiology*. 21thed.;Appleton and Longman, Lebanon . p.226-8.

15. WHO (1998). ***Vaccination against Typhoid Fever***, ***Present Status.***World Health Organization, Geneva Switzerland.

16.Ivanoff B, Levine MM, Lambert PH. Vaccination against typhoid fever. Bull WorldHealth Organ 1994; 72: 957-71.

17.LeMonor L. The genus *Salmonella*. In: Starr MP, Stoup H, Trupper HG, (eds). TheProkaryotes. A Handbook on Habitat, Isolation, and Identification of Bacteria. Vol.2.Berlin, Springer-Verlag, 1981, pp. 1148-59.

18.Levine MM. Typhoid fever. In: Evans AS, Brachman PS, (eds). Bacterial Infectionsof Humans. Epidemiology and Control.Third edn. New York, Plenum Medical BookCompany, 1998,pp.839-58.

19.Kuesch GT. Typhoid fever. In: Braude A, Davies GE, Frierer J,(eds).InfectiousDiseases and Medical Microbiology. Second edn. Philadelphia, WB Saunders, 1981,pp. 1189-94.

20.Wain J, House D, Parkhill J, et al. Unlocking the genome of the human typhoidbacillus. Lancet Infect Dis 2002; 2: 163-70.

21.AC. Smith Enteric bacilli. In: Principles of Microbiology. 8th edn.St.Louis, C.V.Mosby, 1977, pp. 367-8.

22.MacSween, R.N.M. Whaley, K. (1992). *Muir's Textbook of Pathology*.13th ed.;Copublished in the USA by Oxford university press. P.706-7.
23. Hoffman SL. Typhoid fever. In: Strickland GT, (ed). Hunter's Tropical Medicine.Seventh edn. Philadelphia, WB Saunders, 1991, pp. 344 –58.

24.Pier GB, Grout M, Zaidi T, et al. *Salmonella typhi*uses CFTR to enter intestinalepithelial cells. Nature 1998; 303: 79-82.

25.Everest P, Wain J, Robersts M, et al. The molecular mechanisms of severe typhoidfever. Trends Microbiol 2001; 9: 316-20.

26.Adams EB. Typhoid and Paratyphoid fevers. In: Weatherall DJ, Ledingham JGG,Warrell, DA. (eds). Oxford Textbook of Medicine.Second edn. New York, OxfordUniversity Press, 1987, pp. 5.218 – 24.

27.Elfaki, M.E.**(**1987).*Pattern of typhoid fever in Sudanese Children*. M.Sc thesis,University of Khartoum.

28.Khan M, Coovadia Y, Connolly C, Sturm AW. Typhoid fever complicated by acuterenal failure and hepatitis: case reports and review. Am J Gastroenterol 1998;93:1001-3.

29. Tracey KJ, Beautler B, Lowry SF, et al. The role of cytokine mediators in septicshock.AdvSurg 1990; 23: 21-56.

30. Newton CR Krishna S. Severe falciparum malaria in children: current understandingof pathophysiology and supportive treatment. PharmacolTher 1998; 79: 1-53.

31.Stokes, E.J. Ridgway, G.L.(1983).*Clinical Bacteriology* 5th ed. ; Edward Arnold, Britain. P.263.

32.Stokes,E.J. Ridgway, G.L.Wren, M.W.D. (1993). *Clinical Microbiology*, 4thed.;EdwardArnold,London, Britain.p. 288.

33.Sarasombath, S. Banchuin, N. Sukosol, T. Rungpitarangsi, B. Manasatit, S.(1987). Systemic and intestinal immunities After natural typhoid infection*J. Clin. Mirobiol.*25(6) :p.1088-93.

34.Woodward TE, Smadel JE, Ley HR Jr., et al. Preliminary report on the benefit ofchloromycetin in the treatment of typhoid fever. Ann Intern Med

1948; 29:131-34.111. Rankin ALK, Grimble AS.Treatment of typhoid fever with chloramphenicol.Lancet1950; 258:615-8.

35.Hornick RB. Typhoid fever. In: Hoeprich PD, Jordan MC, Ronald AR, (eds).Infectious Diseases.A Treatise of Infectious Processes.Fifth edn. Philadelphia, J BLippincott Company, 1994, pp. 747 –53.

36.Youmans, G.P.Paterson, P.Y. Sommers, H.M. (1986). *The biologic and Clinical Basis of Infectious Diseases*.3rd ed. ;Saunders Company West; Washington squire Philadelphia. 501p.

37.Ochei, J. Kolhatkar, A. (2000).*Medical Laboratory Science Theory and Practice*.;TataMcGrow-Hill Publishing Company Ltd. p. 689-96.

38. Manson-Bahr PH. Enteric fever. Manson's Tropical Diseases. A Manual of theDiseases of Warm Climates. Twelfth edn.Baltimore, Williams and Wilkin'sCompany, 1945, pp.304-12.

39. Enteric Fever Conclave, 2015.

40. Ananthanarayan**,** R. and Paniker C.KJ.(1997).*Text book of microbiology* 5thed.:Orient Longman ltd. New Delhi, India. P. 267-280.

41. Stuart BM, Pullen RC. Typhoid fever: clinical analysis of three hundred and sixtycases. Arch Intern Med 1946; 78: 629-61.

42. Robertson RP, Wahab MFA, Raasch FO. Evaluation of chloramphenicol andampicillin in *Salmonella* enteric fever. N Engl J Med 1968; 278:171-76.

43.Aschroft MT. Typhoid and paratyphoid fever in the tropics. J Trop Med Hyg 1964;67:1985-89.

44.Typhoid fever. In: McCare T, (ed). Osler's Principle and Practice of Medicine.Eleventh edn. New York, Appleton and Company, 1933,pp.1-45.

45.Mahle WT, Levine MM. *Salmonella typhi*infection in children younger than fiveyears of age. Pediatr Infect Dis J 1993; 12: 627-31.32

46.Wicks ACB, Holmes GS, Davidson L. Endemic typhoid fever: a diagnostic pitfall.QJ Med 1971; 40: 341-44.

47.Chalmers IM. Typhoid fever in an endemic area: a great ‘imitator’. S Afr Med J1971; 45: 470-72.

48.Seebaran AA, Coovadia YM, Bhana RH, Rajput MC, Naidoo BI, Haffejee IE.Typhoid fever in the adult and paediatric Indian population of Durban.S Afr Med J1990; 77:14-17.

49..Weeranmanthri TS, Corrah PT, Mabey DCW, Greenwood BM. Clinical experiencewith enteric fever in The Gambia, West Africa, 1981-1986. J Trop Med Hyg 1989;92:272-75.

50.Dauod AS, Zaki M, Pugh RNH, Al-Mutairi Get al. Clinical presentations of entericfever: its changing pattern in Kuwait. J Trop Med Hyg 1991; 94:341-47.

51.Samantray SK, Johnson SC, Chakrabarti AK. Enteric fever: an analysis of 500 cases.Practitioner 1977; 218:400-8.

52.Yew FS, Chew SK, Goh KT, Monterioro EHA, Lim YS. Typhoid fever in Singapore:a review of 370 cases. J Trop Med Hyg 1991; 94:352-57.

53.Christie AB. Typhoid and paratyphoid fevers. In: Infectious Diseases. Epidemiologyand Clinical Practice. Fourth edn. Vol.1. Edinburgh, Churchill Livingstone,1987,pp.42-147.

54.Watson KC. Chloramphenicol in typhoid fever: a review of 110 cases. Trans R SocTrop Med Hyg 1954; 48: 526-532.

55.Punjabi NH. Typhoid fever. In: Conn, HF (ed). Current Therapy. Latest ApprovedMethods of Treatment for the Practising Physicians. Philadelphia, WB Saunders,2000,pp.161-65**.**

56. Mandal BK. Salmonella infections. In: Cook GC, (ed). Manson’s Tropical Diseases.Twentiethedn. London, WB Saunders, 1996,pp.851.

57. Parry EHO. Typhoid fever. In: Parry EHO, (ed). Principles of Medicine in Africa.2nd edn. Nairobi, Oxford University Press, 1984,pp.268-76.

58.Kamat SA, Herzog C.Typhoid.Clinical picture and response to (1972)chlorampheicol: a prospective study in Bombay Infection 1977; 5:85-91.

59. MandalBK.*Salmonellatyphi*and other salmonellas.Gut 1994; 35:726-28.33

60.Bhutta ZA, Dewraj HL. Current conceptsin the diagnosis and treatment of typhoidfever. *BMJ* 2006; 333:78–82.

61 Background document: The diagnosis,treatment and prevention of typhoid fever.Communicable Disease Surveillance andResponse Vaccines and Biologicals. WorldHealth Organization [Internet] [cited 2015April 6]. Available from: http://www.who.int/rpc/TFGuideWHO.pdf

62.Svenungsson B. Typhoid fever in a Swedish hospital for infectious diseases: a 20-year review. J infect Dis 1982; 5:139-50.

63.Singh S. Pathogenesis and laboratorydiagnosis. *JIACM* 2001; 2:17-20.

64. Brusch JL. Typhoid Fever [Internet] 2015[cited 2015 April 7]. Available from: http://emedicine.medscape.com/article/231135-clinical#showall

65. Benavente L, Gotuzzo J, Guerra O, Grados H,Bravo N. Diagnosis of typhoid fever using astring capsule device. *Trans R Soc Trop Med Hyg*1984; 78:404-6.

66.Vallenas C, Hernandez H, Kay B, Black R,Gotuzzo E. Efficacy of bone marrow, blood,stool and duodenal contents cultures forbacteriologic confirmation of typhoid feverin children. *Pediatr Infect Dis J* 1985; 4:496-8.

67.Khan S, Harish BN, Menezes GA, AcharyaNS, Parija SC. Early diagnosis of typhoidfever by nested PCR for flagellin gene of*Salmonella enterica*serotype Typhi. *IndianJ Med Res* 2012; 136:850-854.

68.Sanjeev H, Nayak S, Pai AKB, Rai R, KarnakerV, Ganesh HR. A systematic evaluation ofrapid dot-EIA, blood culture and Widal test in the diagnosis of typhoid fever. *NUJHS*2013; 3:21-4.7

69.Prouty AM, SchwesingerWH,GunnJS.Biofilm formation and interaction with thesurfacesof gallstones by Salmonella spp.*Infect Immun*2002; 70:2640-9.

70.Anderson**,** E.S. Smith**,** H.R. (1972). Chloramphenicol resistance in the typhoidbacillus.*Brit. Med. J*.; 3:p. 329-31.

71.Pokhrel BM, Karmacharya R, Mishra SK,Koirala J. Distribution of Antibody titeragainst Salmonella enterica among healthyindividuals in Nepal. *Ann ClinMicrobiolAntimicrob*2009; 8:1.

72.Andualem G, Abebe T, Kebede N, Gebre-Selassie S, Mihret A, Alemayehu H. Acomparative study of Widal test with bloodculture in the diagnosis of typhoid fever infebrile patients.*BMC Research Notes* 2014;7:653.

73.Tam FCH, Ling TKW, Wong KT, Leung DTM,Chan RCY. The TUBEX test detects notonly typhoid- specific antibodies but alsosoluble antigens and whole bacteria. *J MedMicrobiol*2008; 57: 316-323.

74.Kumar S, Rizvi M, Berry N. Rising prevalenceof enteric fever due to multidrug resistantSalmonella: an epidemiological study. *JMed Microbiol*2008; 57:1247-50.

75.S.Tantivanich, Chongsanguan M,Sangpetchsong V, Tharavanij S. A simple and rapid diagnostic test for typhoid fever.*Southeast Asian J Trop Med Public Health*1984; 15:317-22.

76.Kaur I, Talwar V, Gupta H. Latex agglutinationtest for rapid diagnosis of typhoid fever.*Indian J Med Microbiol*1990; 8:78¬83.

77.HashimotoY,IthoY,FujinagaY,et al. Development of nested PCRbased on theViaB sequence to detect *Salmonella typhi*.JClinMicrobiol 1995; 33:775-77.

78.Lim, P.L. Tam, F.C. Cheong, Y.M . Jegathesan, M. (1998). One step 2-minutes test to detect typhoid specific antibodies based on practical separation in tubes. *J. Clin. Microbial.*36 (8):p. 227-8.

79.Rubin FA, McWhirter PD, Punjabi NH, et al. Use of a DNA probe to detect *Salmonella typhi*in the blood of patients with typhoid fever. J ClinMicrobiol 1989;27:112-20.

80. Song JH, Cho H, Park MY, et al. Detection of *Salmonella typhi*in blood of patientswith typhoid fever by polymerase chain reaction. J ClinMicrobiol 1993; 31:1439-43.

81.Sadallah F, Brighouse G, Giudice CD, et al. Production of specific monoclonalantibodies to *Salmonella typhi*flagellin and possible application to immunodiagnosisof typhoid fever. J Infect Dis 1990; 161:59-64.

82.Department of Health. Health trends in South Africa. 1995,pp.93.

83.Collee, J.G. Fraser, A.G. Marmio, B.P. Simon, A. Old, D.C. (1996). *Mackie andMcCarteny practical medical microbiology*.14th ed.; Longman Singapore publishers (Pte) Ltd. Singapore.P.385-402.

84.Ismail A. New advances in the diagnosis oftyphoid and detection of typhoid carriers.*Malays J Med Sci*2000; 7:3-8.

85.Baker S, Favorov M, Dougan G. Searchingfor the elusive typhoid diagnostic. *BMCInfectious Diseases* 2010; 10:45.

86. BuzğanT, Evirgen O, Irmak H, KarsenH, Akdeniz H. A case of typhoid feverpresenting with multiple complications.*Eur J Gen Med* 2007; 4:83-6.

87.Pandove PK, Moudgil A, PandoveM, Aggarwal K, Sharda D, Sharda VK. Multiple ileal perforations and concomitantcholecystitis with gall bladder gangrene ascomplication of typhoid fever. *J Surg CaseRep* 2014; 2014:rju070.

88.Ali R,AhmedS,QadirM,AtiqH,HamidM.S.cholecystitis: atypical

presentation of a typical condition.*JCollPhysiciansSurg Pak* 2013; 23:826-7.

89.Shrivastava D, Kumar JA, Pankaj G, Bala SD,Sewak VR. Typhoid intestinal perforationin Central India – A surgical experience of155 cases in resource limited setting. *IntJof Biomed and Adv Res* 2014; 05:600-4.

90. Kumar S. Management of Enteric fever.Available at http://www.apiindia.org/pdf/monograph_2015_update_on_tropical_ fever/013_management_of_enteric_fever.pdf

91.Brooks WA, Hossain A, Goswami D, NaharK,Alam K, Ahmed N. Bacteremic typhoid feverin children in an urban slum, Bangladesh. *Emerg Infect Dis* 2005; 11:326-9.

92.Lakhotia M, Gehlot RS, Jain P, Sharma S,Bhargava A. Neurological Manifestationsof Enteric Fever. *JIACM* 2003; 4:196-9.

93.Gaffar MSA, Seedat YK, Coovadia YM, Khan Q. The white cell counts in typhoidfever. Trop Geogr Med 1992; 44: 23-27.

94.Gotuzzo E, Firsancho O, Sanchez J, et al. Association between the acquired immunodeficiency syndrome and infection with *Salmonella typhi*or *Salmonella paratyphi*in an endemic typhoid area. Arch Intern Med 1991; 151: 381 - 82.

95.Katz S, Jimenz MA, Lehmkuhler WE, Grosfeld JL. Liver bacterial clearancefollowing hepatic artery ligation and portacaval shunt.J Surg Res 1991; 51: 267-70.

96.Greenberg P. Immunopathogenesis of HIV infection. HospPract 1992; 27: 109 - 24.

97.Hovetta P, Camara P, Petrognani R, Donzel C. Pleuropulmonary manifestations ofsalmonellosis. Med Trop (Mars) 1998; 58:403-7.

98.Khosla SN. The heart in enteric (typhoid) fever.J Trop Med Hyg 1981; 84:125-31.

99.Faierman D, Ross FA, Seckler SG. Typhoid fever complicated by hepatitis, nephritis,and thrombocytopenia. JAMA 1972; 221: 60-1.

100.Khajehdehi P, Rastegar A, Kharazmi A. Immunological and clinical aspects ofkidney disease in typhoid fever in Iran. Q J Med 1984; 53: 101 - 7.

101.Awadall SG, Mercer LJ. Pregnancy complicated by intraamniotic infection by*Salmonellatyphi.* ObstetGynecol 1985; 65(Suppl): 30-31.

102.Hicks HT, French H. Typhoid fever and pregnancy with special reference to foetalinfection. Lancet 1905; 1:1491-93.35

103.Musa, A.M. Saleh, S.Y. Abu Asha, H.(1981).Transient nephritis during typhoid fever in five Sudanese patients. *Annals of trop. Med.Andparasitol.*75(5):p.181-4.

104.Pegram GC, Rollins N, Espey Q. Estimating the costs of diarrhoea and epidemicdysentery in KwaZulu Natal and South Africa. Water SA 1998; 24: 11 - 20.

105.Cheesbrough, M. (2000).*District Laboratory Practice In Tropical Counties*. Part 2; Cambridge University Press, Cambridge.P.182-6.

106.Paniker,C.K.J. Vilma,K.N. (1997).Transferable Chloramphenicol resistance inSalmonella typhi. *Nature.*239:p. 109-10.

107. Levine MM, Lepage P. Prevention ofTyphoid Fever. In: Pollard AJ, Finn A, editors.Hot Topics in Infection and Immunity inChildren. New York: Springer. 2005 :161-73.

108. Sharma PK. Ramakrishnan R, Hutin Y,Manickam P, Gupte MD. Risk factors fortyphoid in Darjeeling, West Bengal, India:evidence for practical action. *Trop Med IntHealth* 2009; 14:696-702.

109. Murugunathan A, Mathai D, Sharma SK,editors. Adult Immunization 2014.2nd Ed. New Delhi: Jaypee Brothers MedicalPublishers (P) Ltd. for the Association ofPhysicians of India. 2015. p. 220-3.