Sign and Symptoms of the Typhoid Fever and ANC among the children in ICH and SSF

A Thesis paper submitted to the Department of Pharmacy, East West University in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy

Pharmacy Department

East West University

SUBMITTED BY

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ID#2007-1-70-045

Submission Date: 11-12-2011

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Dedicated

To

My parents

And

Uncle Mr. Chandan Kumar Paul

CERTIFICATE

This is to certify that the thesis submitted to the Department of Pharmacy, East West University, Mohakhali, Dhaka in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy was carried out by Biplab Chandra Paul ID-2007-1-70-045.

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CERTIFICATE

This is to certify that the thesis submitted to the Department of Pharmacy, East West University, Mohakhali, Dhaka in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy was carried out by Biplab Chandra Paul ID-2007-1-70-045 under our guidance and supervision and that no part of the thesis has been submitted for any other degree. We further certify that all the sources of information, laboratory facilities availed of this connection is dully acknowledged.

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Abbreviations

S. typhi= Salmonella typhi

ANC= Absolute Neutrophil Count

NTS= Non-Typhoidal Salmonella serovars

IL-1= Inter Leukin-1

Vi= Virulence

NPV= Negative Predictive Value

RDT= Rapid Diagnostic Test

CRP= C-Reactive Protein

NAATs= Nucleic acid amplification tests

MDR= Multi Drug Resistance

Abstract

Typhoid fever is a serious and potentially fatal bacterial infection. It can cause symptoms of fever, abdominal pain and constipation. If they are not treated, symptoms can rapidly get worse and lead to serious complications. It is a serious health problem in the African and eastern parts of Asia especially in areas with poor sanitation and no access to clean water, such as India and most of Africa. The signs and symptoms play a major role in the determination of the disease, although it is only confirmed by a proper and acute diagnosis. But in true sense, an appropriate detail of sign and symptoms gives a clear indication to the diagnosis and ultimately treatment of Typhoid fever. Thus a specific, distinctive, clear and meaningful study on the sign and symptoms is vital in the treatment of the disease. The study was a case-control one conducted at the general wards of ICH (Institute of Child Health) and SSF (Shishu Shastho Foundation) to figure out the common sign and symptoms among the Typhoid patients. To conduct the study, a structures questionnaire was used as data source and a total of 112 Typhoid and Non-Typhoid patients were taken into consideration. It was interesting to find out that among the Typhoid patients, 59% were male and 41% were female, meaning that the disease is much more prone to male. It was also found that the age group <3 years (40%) was the dominant group followed by 3-<6 years (30%), 6-<9 years (22%), and 9-12 years (8%).Vomiting, abdominal pain, loose motion and constipation etc were among the leading signs and symptoms in Typhoid ferver according to the study. It signifies that the gastro-intestinal sign and symptoms are prevalent in the disease. But a significant finding obtained during the ANC calculation and Neutropenia measurement.ANC of the group ($0\text{-}5x10^{3)}$ was dominant in Non-Typhoid patients which is not usual. Again, Neutropenia was also more prone to the Non-Typhoid patients rather than the Typhoid patients, which may be due to the exclusion of the count of the band forms of neutrophils in the complete blood count (CBC) differential or genetic or regional differences. The study result also showed that maximum (61%) no. of Typhoid patients came up with two sign and symptoms. However, it is clear from the study that an accurate and specific study of the sign and symptoms and ANC is necessary and facilitates the diagnosis and treatment of Typhoid fever.

CHAPTER- 1

INTRODUCTION

1.1 Overview

Typhoid and paratyphoid (enteric) fever are diseases caused by *Salmonella enterica* serovar Typhi and Paratyphi A respectively. Typhoid is an important infectious disease in developing countries and it is much more common than paratyphoid. It is associated with poor sanitation, reduced access to treated drinking water and poor food hygiene. There are over 22 million new cases of typhoid fever worldwide which leads to an estimated 200,000 deaths (WHO, 2002). South and South-East Asia are the most affected areas of the world with an estimated annual prevalence of > 100/100,000 (Crump, 2004). Typhoid and paratyphoid fevers are prevalent in low- or middle-income countries with inadequate sanitation and hygiene, particularly regarding food, water, and disposal of human excrement. Despite advances in technology and public health strategies, enteric fever remains a major cause of mortality in the developing world (Bhutta, 2006). Urbanization, global warming, and traditional methods of water-side living have created even greater demands for clean water in developing countries (Unicef, 2006). Both typhoid and paratyphoid are most common where standards of personal and environmental hygiene are low, and only to this extent are these diseases tropical (Gill, 2009)

The causative organism for typhoid fever is The Gram-negative bacilli which are transmitted by the faecal-oral route when food or water contaminated with infected faeces is ingested. The most important reservoirs of infection are short-term convalescent or chronic human carriers. Food handlers are a specifically vital source of transmission (Gill,2009).

The disease is mainly associated with low socio-economic status and poor hygiene, with human beings the only known natural hosts and reservoir of infection. Estimates for the year 2000 suggest that there are approximately 21.5 million infections and 200,000 deaths from typhoid fever globally each year (Crump *et al.* 2004; Bhan *et al.* 2005; Bhutta 2006). It is thus considered one of the most serious infectious disease threats to public health on a global scale, with particular concern over the rapid and widespread emergence of resistance to multiple antibiotics (Akinyemi *et al* .2005).

The clinical presentation of typhoid and paratyphoid fever varies from a mild illness with a low-grade fever, malaise and slight dry cough to a severe clinical picture with multiple complications including intestinal perforation (Ismail, 2006). Toxic apathy, blanching 'rose spots' on the trunk, abdominal organomegaly, and diarrhoea are also associated with enteric fever, but the clinical picture is highly variable between geographical location and age-groups. Typhoid and paratyphoid

can present in many different and non-specific ways, thus posing a diagnostic challenge for the health professional. Most enteric fever is diagnosed on clinical grounds and treated presumptively. As a result the diagnosis may be delayed or missed, while other febrile illnesses are being considered (Parry,2002).

1.2 Background

Typhoid is derived from the English word typhu plus the suffix -oid, meaning "like," i.e., typhoid means "like typhus." Typhus in the Greek means "smoke" or "mist." The word typhus is said to have been used first by Hippocrates (460 B.C.) to describe "stupor caused by fever" and is thought to have been used to describe many febrile illnesses causing mental aberrations, including typhus and typhoid. Typhoid was also described by various other names. The term typhoid fever (fievre typhoide) is attributed to Pierre Charles Alexander Louis (1787-1872) (Woodward *et al*, 1982).

1.3 Causative organisms

Salmonella infections in humans are divided into typhoid fever caused by *S. typhi* and *S. paratyphi* and a range of diarrhoeal diseases caused by a large number of non-typhoidal Salmonella serovars (NTS). These NTS, which usually have a broad vertebrate host range, show dramatically more severe and invasive presentation in immunocompromized individuals especially HIV carriers, including severe and progressive diseases such as chronic granulomatosis disease, blockade of IL-12/ IL-23 /IL-17 and TNF, suppurative foci and bacteremia which may be recurrent. Invasive recurrent NTS bacteremia associated with HIV disease is becoming a huge problem worldwide (Parry *et al*, 2004).

Typhoid fever is a more classical systemic infection caused by the typhoid bacillus, *Salmonella enterica* serovar Typhi (commonly referred to as S typhi), the most common cause of enteric fever, which also includes paratyphoid fever caused by S paratyphi A, B and C. These pathogens only infect humans. The disease is transmitted by ingestion of food, including dairy products, or water contaminated by excreta from patients or chronic carriers or handled by infected persons . Highest incidence usually occurs where water supplies serving large populations are contaminated by faecal matter, as existed at the end of the 19th century in many large cities in the USA and Western Europe (Levine *et al*, 2008).

1.3.1 Description and significance

There are over 2,000 various groupings (serovars) that comprise *Salmonella enterica*, each very closely related to each other making Salmonella typhi a prime example of a serovar. Salmonella typhi is a gram negative bacterium that causes systemic infections and typhoid fever in humans. This rod-shaped, flagellated organism's sole reservoir is humans. It has caused many deaths in developing countries where sanitation is poor and is spread through contamination of water and undercooked food. Eradication seems highly unlikely due to recent emergence of multi drug resistance strains. Salmonella Typhi strain Ct18 was originally isolated from a patient in a hospital in Vietnam. The chromosome sequence is 4,809,037 bp in length with a G+C content of 52.09%. The chromosome was sequenced though the method of shotgun sequencing with 97,000 shotgun reads. Since then, Salmonella typhi has undergone evolutionary change and has become resistant to antibiotics (Weng *et al*, 2003).

1.3.2 Cell structure and metabolism

Salmonella typhi is a rod-shaped, gram negative bacteria that contain features that separates itself from other types of bacteria which include: having 2 membranes (and outer and an inner), periplasm, and a Lipopollysaccharide chain that consists of α-d-galactosyl-(1 → 2)-α-d-mannosyl-(1 → 4)-l-rhamnosyl-(1 → 3)-repeating units, and has short branches of single 3,6-dideoxyhexose residues (Kita et al,1973).

Salmonella typhi has a complex regulatory system, which mediates its response to the changes in its external environment. Sigma factors, which are global regulators that alter the specificity of RNA polymerase, are examples of such regulation. Some sigma factors direct transcription to produce stress proteins, which increases the chances of the bacteria surviving environmental

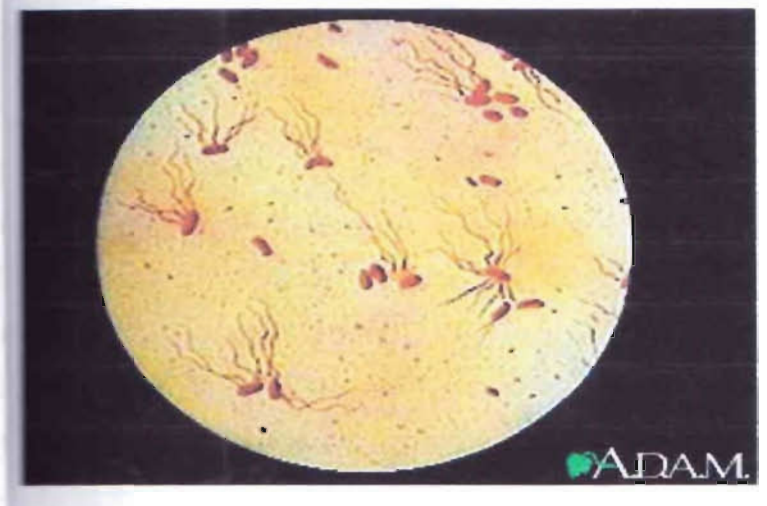


FIG. 1.1: *Salmonella typhi.* (US Center for Disease Control and Prevention, 2010)

changes. RNA polymerase S is produced in response to starvation and changes in pH and temperature. It also regulates the expression of up to 50 other proteins and is also involved in the regulation of virulence plasmids (Kita et al,1973).

In order to survive in the intestinal organs of its hosts where there are low levels of oxygen, Salmonella typhi has to be able to learn to use other sources other than oxygen as an electron acceptor. Therefore, Salmonella has adapted to grow under both an aerobic and anaerobic conditions. Salmonella's most common source of electron acceptors is nitrogen. Examples of other electron acceptors are: nitrate, nitrite, fumarate, and dimethylsulphoxide. Global and specific regulatory systems of anaerobic gene expression, like the ones mentioned above, are implemented to make sure that the most energetically favorable metabolic process is used. Evidence shows that the availability of oxygen is an environmental signal that controls Salmonella's virulence (Contreras *et al*, 1997).

1.3.3 Genome structure

The genome for Salmonella typhi has been completely sequenced. There are about 204 pseudogenes encoded in Salmonella typhi. A majority of these genes have been inactivated by a stop codon, which shows that the genes were recently modified due to evolutionary changes. Of the 204 genes, twenty seven are remnants of insert sequences and genes of bacteriophage origin.

Seventy five are involved in house keeping functions and 46 of the gene mutations have to do with host interaction.

There are two commonly used strains of Salmonella typhi, CT18 and Ty2. Salmonella typhi CT18 has a large circular chromosome consisting of 4.8 Mb and two plasmids, pHCM1 and pHCM2, one of which has multiple drug resistance (pHCM1). Salmonella typhi Ty2 has one large chromosome that is 4.7 Mb and unlike CT18, it does not have plasmids and can be affected by antibiotics. In fact, the current vaccine was developed using S. typhi Ty2. Out of the 204 pseudogenes in Salmonella, 195 genes are the same in both strains CT18 and Ty2, making them 98% identical (Parkhill *et al*, 2001).

1.3.4 Bacteriology

Taxonomy within the genus *Salmonella* has been the source of great confusion. The most recent classification, based on DNA sequences, has left only two species, *S. enteritica* and *S. bongori*, further subdivided into subspecies and serovars. To avoid confusion, *S. enteritica* serovar Typhi continues to be referred to as *S. typhi*. The bacteria is characterized by its flagellar antigen, H, its lipopolysaccharidic (LPS) O antigen, and, in addition, its polysaccharide (PS) capsular virulence (Vi) antigen, found at the surface of freshly isolated strains. The complete sequence of the 4 809 037-bp genome has been determined. In addition to the plasmid encoding antibiotic resistance, a virulence plasmid was found that shows homology with the virulence plasmid of *Yersinia pestis*.

Upon ingestion, typhoid bacilli rapidly penetrate the small intestinal mucosa by transcytosis through M cells and enterocytes, and are taken up by macrophages or diffuse into mesenteric lymph nodes. A primary bacteraemia follows and the pathogen rapidly attains intracellular haven throughout the reticuloendothelial system. This is followed by a sustained secondary bacteraemia associated with clinical illness. S. typhi also shows remarkable predilection for the gall-bladder where infection tends to become chronic, especially in individuals with a pathologic gall-bladder condition(Steinberg *et al*, 2004).

1.3.5 Pathogenesis

Much of the genetic and cellular studies on the pathophysiology of invasive Salmonella infection

have been carried out in the murine model using S. typhimurium, which causes invasive disease in mice but not in humans. As opposed to the Salmonella spp. associated with human diarrheal illness, S. typhi and those strains that cause typhoid fever are able to achieve cellular invasion. The pathophysiology of typhoid fever is a complex process which proceeds through several stages. The disease begins with an asymptomatic incubation period of 7-14 days, (inversely related to the size of the infecting dose), during which bacteria invade macrophages and spread throughout the reticuloendothelial system. The first week of symptomatic disease is characterized by progressive elevation of the temperature followed by bacteremia. The second week begins with the development of rose spots, abdominal pain and splenomegaly. The third week is marked by a more intense intestinal inflammatory response particularly in the Peyer's patches with associated necrosis which can result in perforation and hemorrhage. These clinical stages are associated with complex cellular events just now being understood (Wain J *et al,* 2002*).* First ingested bacteria must survive the acidic environment of the stomach. The known increased risk of typhoid fever with concomitant Helicobacter pylori infection may express itself via the hypochlorhydria associated with chronic *H. pylori* infection. Invading organisms pass through the intestinal epithelial cells and come into contact with phagocytic cells in the Peyer's patches of the intestinal wall. However the macrophages do not kill the bacteria. Thence, bacterial replication is primarily intracellular. Salmonella avoids encapsulation in lysosomes by diverting normal cellular mechanisms. Bacteria inject effector proteins into the cells of the innate immune system (macrophages and natural killer cells) though a type III protein secretion system (TTSS) which stimulate both pro and anti-inflammatory responses (Saha *et al,* 2001).

Over the asymptomatic incubation period of 7-14 days the bacteria proliferate and spread through the blood stream to other cells in the reticuloendothelial system in the liver, spleen, bone marrow and gall bladder. As replication inside phagocytic cells continues, bacteria are shed into the blood stream in sustained but low concentrations and the clinical syndrome of fever, headache and abdominal pain begins. The gallbladder is felt to be a significant sitefor ongoing exposure of intestinal epithelial cells to the pathogen. The inflammatory response to this process of repeated exposure is felt to give rise to the necrosis which is a prominent feature of the disease (Saha *et al,* 2001).

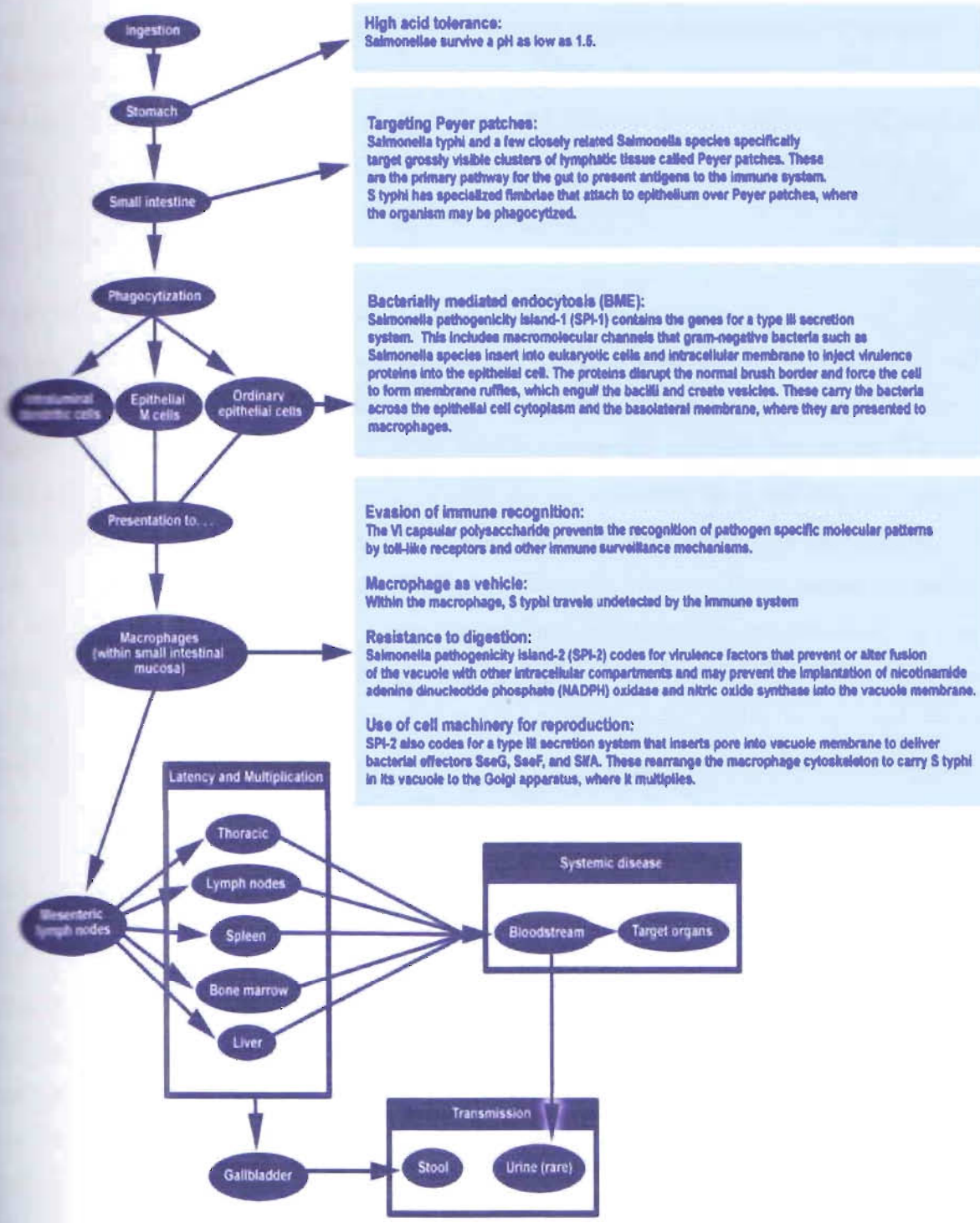


FIG. 1.2: Life cycle of *Salmonella typhi*.

(Parry *et al*, 2002)

This occurs in areas of greatest macrophage concentration such as the Peyer's patches and explains why intestinal bleeding and perforation are the most frequent complications. Elsewhere typhoid nodules, foci of macrophages and lymphocytes proliferate. As the infection progresses the typical changes of sepsis accumulate in the heart, brain and kidneys. If not interrupted this process may lead to circulatory failure and death from overwhelming sepsis (Everest *et al*, 2001).

1.4 Transmission

Typhoid and paratyphoid fevers are caused by the bacteria *Salmonella typhi* and *Salmonella paratyphi* respectively. Typhoid and paratyphoid germs are passed in the faeces and urine of infected people. People become infected after eating food or drinking beverages that have been handled by a person who is infected or by drinking water that has been contaminated by sewage containing the bacteria. Once the bacteria enter the person's body they multiply and spread from the intestines, into the bloodstream. Even after recovery from typhoid or paratyphoid, a small number of individuals (called carriers) continue to carry the bacteria. These people can be a source of infection for others. The transmission of typhoid and paratyphoid in less-industrialized countries may be due to contaminated food or water. In some countries, shellfish taken from sewage-contaminated beds is an important route of infection. Where water quality is high, and chlorinated water piped into the house is widely available, transmission is more likely to occur via food contaminated by carriers handling food.(WHO, 2002)

1.5 Disease Burden

Typhoid Fever is spread by the faecal-oral route and closely associated with poor hygiene, lack of clean drinking water and inadequate sanitation. The disease is almost exclusively transmitted by food and water contaminated by the faeces and urine of patients and carriers. Polluted water is the most common source of typhoid transmission. In addition, shellfish taken from sewage-contaminated beds, vegetables fertilized with night-soil and eaten raw, contaminated milk and milk products have been shown to be a source of infection (Graham *et al.* 2000).

A global burden of disease estimates for typhoid were based on a total of 22 community-based incidence studies with 19 from continents other than Africa and only three from Africa. On the basis of these data and a prediction rule based on climatic and socio-economic features, continental

estimates of disease burden were derived (Crump *et al.* 2004). These estimates suggested a moderate incidence of typhoid of 10–100 cases/100,000 person years in most African countries, with the incidence highest in childhood. In East Africa, incidence was estimated at 39/100,000 person years. Recently, increasing amounts of data on the prevalence of different pathogens found in sick children presenting to health facilities in Africa have been reported. These data have considerably raised the profile of non-typhoidal salmonella infections To date, however, these data have not been used to examine the burden of disease attributable to typhoid. It can be hypothesised that insights into the relative burden of disease attributable to typhoid, although not the exact burden, could be gained by examining recent facility-based information on the aetiology of invasive bacterial infections. If typhoid is a major, widespread pathogen, it should be frequently observed in situations where other major childhood pathogens, for example, *Streptococcus pneumonia* and *Haemophilusinfluenzae* are frequently observed. From the perspective of the health system and healthcare provider, we were also interested to review pertinent data on the usefulness of clinical case definitions and the Widal test in the diagnosis of typhoid in children in an African setting (Graham *et al.* 2000).

Although Typhid Fever has practically disappeared from industrialized countries, it remains a serious public health problem in several Asian regions of the former USSR and in parts of South and South-East Asia, Africa and South America. In an outbreak in the Democratic Republic of Congo, during 2004-05, around 42,564 cases of typhoid fever were reported, including 214 deaths and 696 cases of peritonitis and intestinal perforations. Also, multiresistant strains of *S. typhi* are becoming increasingly common worldwide, further compounding the risk to people living in regions with high endemic disease and to travellers. Strains resistant to chloramphenicol and other recommended antibiotics (ampicillin, cotrimoxazole and even ciprofloxacin) have become prevalent in several areas of the world.

People can transmit Typhoid Fever as long as the bacteria remain in their body; most people are infectious prior to and during the first week of convalescence, but 10% of untreated patients will discharge bacteria for up to 3 months. In addition, 2–5% of untreated patients will become permanent, lifelong carriers of the bacteria in their gall-bladder (Wain *et al*, 2004).

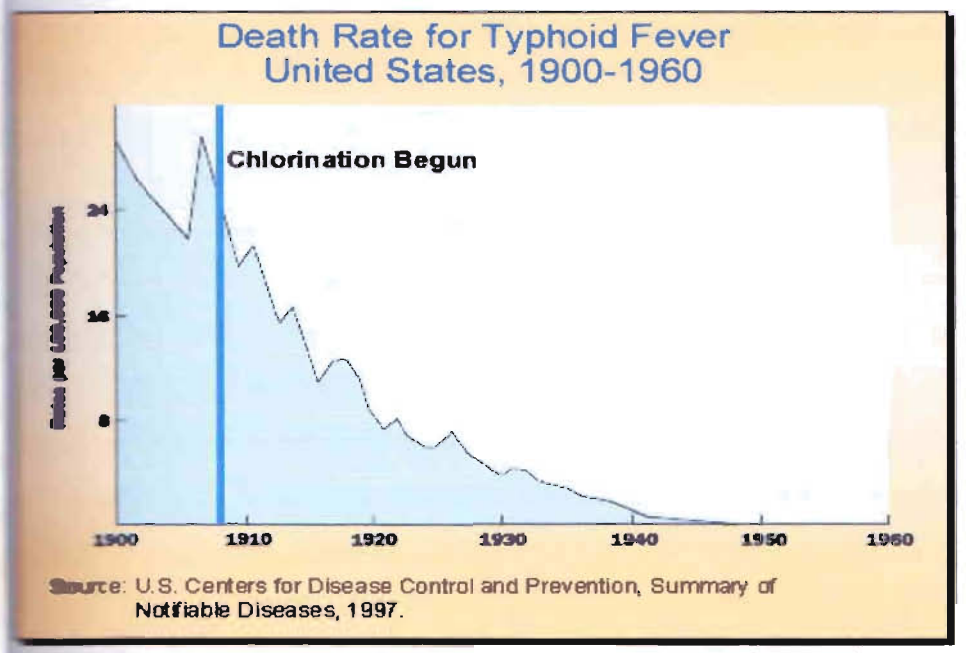


FIG.1.3: Death rate for typhoid fever in USA during 1900-1960.

(US center for disease control and prevention, 2010)

A study conducted by the US center for disease control and prevention showed that rates of net [illegible] patients from typhoid fever was high enough during the early1900s.But typhoid fever death [illegible] decreased significantly after 1910 and onwards (US CDC,2010).

The true burden of Typhoid Fever in developing countries is difficult to estimate. According to [illegible] estimates, 22 million (range 16 million - 33 million) cases occur each year causing 216,000 [illegible] predominantly in school-age children and young adults .Asia, with 274 cases per 100,000 [illegible] has the highest incidence of Typhoid Fever cases worldwide, especially in Southeast Asian [illegible]ries and on the Indian subcontinent, followed by sub-Saharan Africa and Latin America with [illegible] cases per 100,000 persons. In an urban slum in Dhaka, incidence of bacteremic TF was found to be 390/100,000 population, with a 9-fold higher risk for pre-school children than for older persons (Brooks *et al*, 2005).

Recent prospective population-based disease-surveillance studies supported by the Bill and Melinda Gates Foundation and conducted by the Diseases of the Most Impoverished (DOMI) Program at five sites in China, India, Indonesia, Pakistan and Vietnam revealed high rates of TF

among children in urban slums, including children below 5 years of age. In three urban slums in Karachi, Kolkata and North Jakarta, incidence of blood-confirmed TF cases among children 5 to 15 years of age ranged from 180 cases to 494 cases per 100,000 (WHO, 2004).

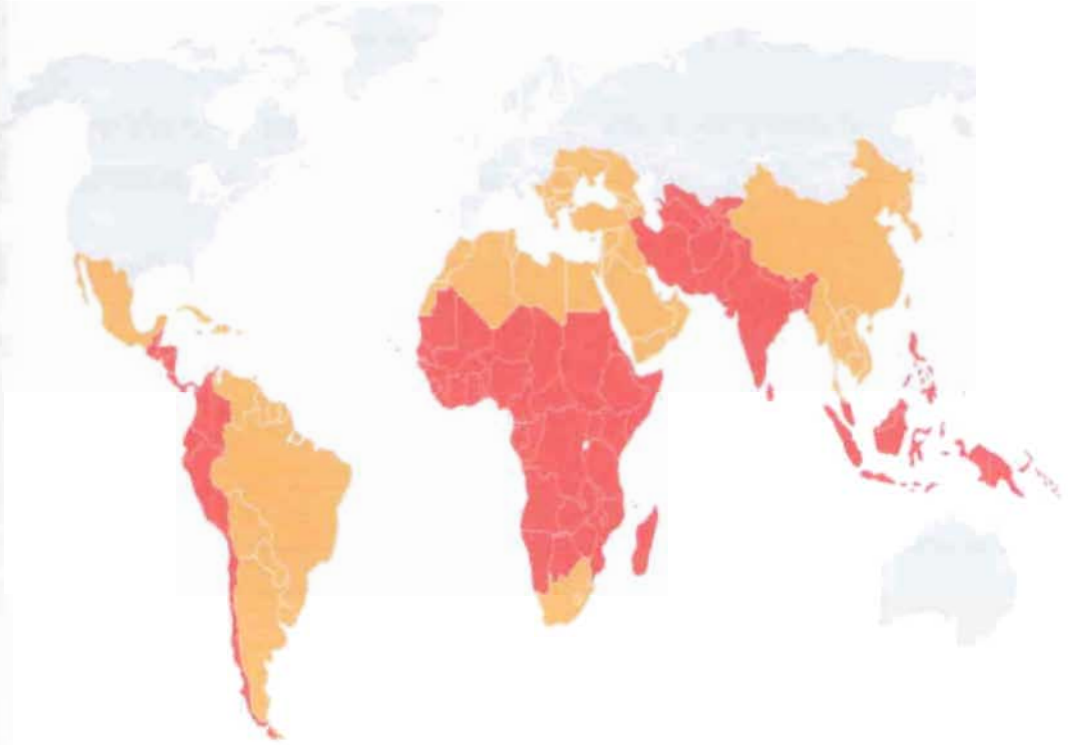
The introduction of Typhoid Fever vaccines in routine vaccination programs in Asia would be highly beneficial in view of the burden of disease and cost of illness to governments and individuals . But, so far, only two countries, China and Vietnam, have incorporated typhoid vaccination into their routine immunization programs, and only in a limited fashion. The Dehli State, India, also introduced vaccination in 2004 in 2-5 years old children through community-based campaigns. The reason why these efforts have not be more generalized lies in part in the fact that most developing countries are uncertain of their true Typhoid Fever disease burden, due to lack of rapid diagnostic tools, infrequency of laboratory testing and poor reporting system (Chaignat *et al*, 2007).

1.6 Epidemiology

Transmission occurs via ingestion of faecally contaminated food or water, as *S. typhi* is shed in the faeces during acute illness and by asymptomatic chronic carriers. there is an associated apparent risk of sexual transmission through oral or anal intercourse.4 enteric fever is endemic in less developed countries where poor sanitation and food hygiene and reduced access to treated water facilitate spread. Approximately 1.2 billion people do not have access to clean drinking water, while a further 2.6 billion lack adequate sanitation services. An estimated 16–22 million cases of typhoid and 200 000–600 000 deaths occur annually, while paratyphoid caused approximately 5.4 million illnesses in 2000. Surveillance information is sparse due to poor reporting and diagnostic inaccuracy. The highest incidence (more than 100 cases per 100 000 population/year) occurs in the Indian subcontinent, including India, Pakistan, Bangladesh and Sri lanka. Incidence is also high in Southeast Asia (except Japan and Singapore), including Indonesia and Papua new Guinea, with moderate prevalence in Malaysia, south Korea and Mongolia. Incidence is also high in the African continent (moderate in Mediterranean north Africa including morocco, Algeria, Tunisia, Libya and Egypt and excluding south Africa) and the middle east (except Kuwait and Bahrain). Incidence is moderate in Latin America.(Whittaker *et al*,2004)

1.7 Prevalence of typhoid

Typhoid fever is highly prevalent in Asia and sub-continent countries. According to Evanson *et al,* Asian countries, especially developing countries this region is reported to have a high prevalence of typhoid fever. Only 2/6 studies conducted in different Asian countries reported prevalence >1%, with 5.51% prevalence in Dhaka, Bangladesh and 6.1% in Malaysia (Choo*et al.* 1993; Sinha*et al.* 1999; Feng 2000; Brooks *et al.* 2005; Siddiqui*et al.* 2006).



♦ Strongly

♦ Endemic

♦ Sporadic cases

FIG. 1.4: Incidence of typhoid fever

(www.ireferance.ca, 2010)

But the rate of prevalence is usually higher in studies performed on selected populations. This time the reported prevalence is between 8.6% and 71.5% (Wain *et al.* 1998; Vollaard *et al.* 2004).

According to Evanson *et al* Vietnam has the highest % of *S. typhi* in screened patients which is around 71.65%(Wain *et al*, 1998).it is also noticeable that the % of *S .typhi* of +ve culture is also highest in Vietnam which counts for 98.40%.

While other countries like India china having a variety in the total % of *S.typhi* +ve culture and screened patients. As for example, Sinha *et al* found the *S.typhi* % of +ve culture in india to be 5.18 while another study found it to be as high as 80.64 (Walia *et al*,2005).

Countries like Malaysia and china have a relatively lower *S.typhi* % of +ve culture with 6.1 and 6.59 respectively (Choo *et al*,1993) (Wong *et al*,1994)

1.7.1 Prevalence in developing countries

The country which has a relatively moderate rate is Pakistan. Although the rate for *S.typhi* % of +ve culture in Pakistan varies from as low as 0.36 (Siddui *et al.*, 2006) to as high as 18.69 (Brooks *et al.*, 2005)

Another developing nation, Egypt has a rate of prevalence of enteric fever of around 13/100,000 people according to a recent survey conducted in 2003(Crump *et al.*, 2004)

Fewer studies have been conducted in Bangladesh on the prevalence of typhoid fever. It has been found tht Bangladesh have a higher rate of prevalence. According to a study conducted in 2005 *S.typhi* % of +ve culture in the country was around 75.38% and *S.typhi* % in screened peatients was found to be 5.51 out of 889 patients (Brooks *et al.*, 2005)

1.8 Risk to travelers

Cases of typhoid fever in deve loped countries (where the incidence of typhoid fever has steeply declined) are usually travel related, as are most of the 50–80 cases of typhoid fever reported annually in Australia, (Connor *et al*,2005) where it is a notifiable disease.Rarely, nontravelling family members of travelers develop the disease. Risk to the traveler is associated with exposure, especially when prolonged, to potentially contaminated food and drink. overall risk is about 1:30 000 for those staying for 4 weeks or more in typhoid endemic countries, but rises to 1:3000 in the Indian subcontinent, north and west Africa, and south America.The risk is highest

in the Indian subcontinent, and is increased in postdisaster areas where typhoid is already endemic(Sutiono *et al*, 2010).

The risk of typhoid fever and paratyphoid fever to travelers is extremely low in the Nordic countries and European countries where the incidence of typhoid and paratyphoid fever per 100,000 travelers ranges from 0.00-0.21.while in the eastern Mediterranean and in USSR countries,the rate is a bit higher with 1.02-1.54 per 100000 people. However this rate of risk toi travelers is moderate in the American and Australian continent where the usual range is 0.00-5.55 (Sutiono *et al*, 2010).

But the African countries are prone to higher degree of risk to travelers.as for example, in the east region of Africa, the risk for typhoid and paratyphoid fever per 100000 ppeople is as high as 11.32 indicating relatively poor hygiene and environment.

While the sub-continental countries have the highest risk of typhoid and paratyphoid fever to travelers. in the Indian sub-continent the risk to travelers is as high as 59.25 per 100000 due to its unhygiene atmosphere(Connor *et al*, 2005).

The incidence of paratyphoid fever, which is not covered by available vaccines, is increasing in parts of Asia. Severe complications and death due to enteric fever are rare in travelers, probably because they tend to present early and have access to high quality medical care. Among travelers, those visiting friends and relatives, particularly in the Indian subcontinent, are at greatest risk; as this group is less likely to present for pretravel advice or may present late. Specific destinations found to be associated with typhoid fever in returning travellers include India, Pakistan, Mexico, Bangladesh, the Philippines and haiti. Persons with decreased gastric acid barrier due to gastric atrophy, acid suppressive medications or gastrectomy, and immuno compromised individuals (eg. due to human immunodeficiency virus [HIV] infection or chemotherapy) are at greater risk of severe illness children are at high risk of typhoid fever, and account for a considerable proportion of cases associated with travel(Giovanetti *et al*,2010).

1.8.1 Pregnancy

Typhoid may be a more serious disease during pregnancy with a higher incidence of diarrhea, complications such as gastrointestinal bleeding, hepatic dysfunction and intestinal perforation as well as maternal death. there is also an increased risk of abortion and fetal death, and potential Trans placental infection of the fetus, although a recent study showed that typhoid fever does not appear to affect pregnancy outcome. While the risk of disease must outweigh the potential risk of the vaccine, generally the use of Vi vaccine in pregnancy is advised for women travelling to endemic areas (Carroll *et al*, 2008).

1.9 Seasonal Patterns

A study on the seasonal patterns of typhoid and paratyphoid fever found that both typhoid and paratyphoid fevers have a seasonal pattern with a distinct risk peak in July (Figure 1.5). For typhoid fever a second smaller peak has been noted in January to March, coinciding with the incidence peaks in Indian travelers. A second risk peak for paratyphoid fever has been seen in February to March, coinciding with incidence peaks in travelers from both India and Thailand.

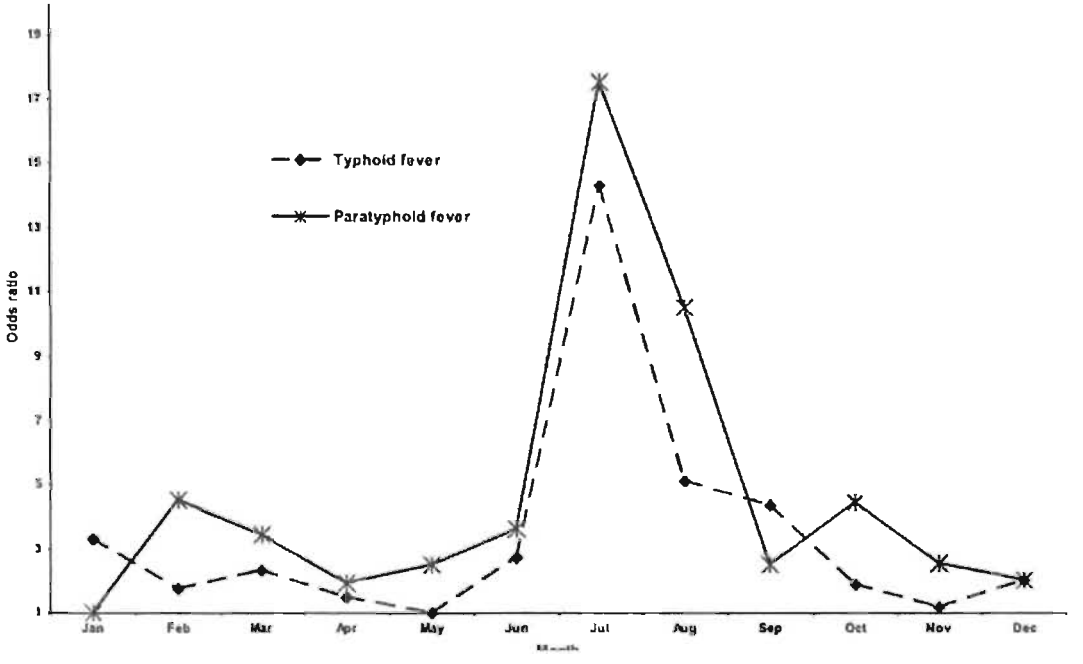


FIG.1.5 Seasonal pattern of cases of paratyphoid fever and typhoid fever during 1997 to 2003.

The month refers to the month of travel in the controls and the month prior to notification in the cases. The monthly odds ratios are adjusted for age, sex, and number of travelers in a multivariate logistic regression model. The odds ratios should be interpreted as the relative risk compared with the month with the lowest risk, estimated for each region separately. (A theoretic region with the same risk each month would then have an odds ratio of 1.0 each month, regardless of the number of cases (Ekdahl *et al*, 2005).

1.10 Signs and symptoms.

Typhoid Fever is characterized by the sudden onset of sustained fever, severe headache, nausea, abdominal pains, loss of appetite, constipation or sometimes diarrhoea. The illness can last for several weeks and even months. The most frequent complications, which arise with a frequency of 1% to 4%, include gastro-intestinal bleeding and intestinal perforation. Severe neurological forms also have been described with mental dullness, stupor, delirium and shock. Hospitalization of Typhoid Fever cases varies from 10% to 40% of cases and usually lasts for 10-15 days or more. Case-fatality rates, which varied from 10% to 30% before the advent of antibiotics, has now been reduced to about 1%-4% with appropriate antibiotic therapy. Paratyphoid fever, which is caused by any of three serotypes of S. paratyphi A, B and C, is similar in its symptoms to typhoid fever, but tends to be milder, with a lower fatality rate(Crump *et al*, 2004).

Owing to the historical significance of typhoid fever, excellent literary and cinematic descriptions of this disease exist. The usual incubation period is 7–14 days with a range of 3–60 days(Mann *et al*, 1901).

Typical symptoms include:

- fever, which increases with disease progression
- dull frontal headache
- malaise
- myalgia
- anorexia

- dry cough
- constipation (or less commonly diarrhoea, which occurs more often in young children),
- abdominal pain and tenderness,
- relative bradycardia
- splenomegaly and
- rash ('rose spots') may also occur.

Complications include gastrointestinal bleeding, intestinal (usually ileal) perforation and typhoid encephalopathy which tend to occur after 14 or more days of illness in 10–15% of patients. Milder or nonspecific, as well as atypical presentations can occur, so a high index of suspicion is important in febrile travellers (including children) who have visited endemic areas (Luxemberger *et al*, 2005).

The overall fatality rate is 10%; less than 1% with appropriate antibiotic treatment. Relapse may occur 2–3 weeks after initial defervescence in 5–10% of patients. up to 5%, regardless of treatment, may become chronic, asymptomatic carriers with continued shedding of the organism in the stool or urine for more than 1 year. this is a public health risk, especially if the carrier works in the food industry,1,2 as illustrated by the well known case of 'typhoid Mary' mallon early last century. Chronic carriage is more frequent in older people and those with gallstones.(Yung *et al*, 2004)

S. typhi is an immunomodulatory pathogen which seeks to avoid detection by the host immune defences. tissue invasion is thought to occur via m cells on Peyer's patches in the terminal ileum, and the infection eventually localises to the bone marrow and finally the gall bladder, which explains biliary shedding of organisms. infection leads to a reduction in host inflammatory response, which explains the lack of classic gastroenteritis symptoms associated with other gastrointestinal pathogens. the Vi capsular polysaccharide of *S. typhi* (not found in *S. paratyphi A*) further limits immune response and can be targeted by vaccines(Baker *et al,* 2010).

According to a study conducted in Diyarbakir, Turkey on common symptoms, clinical signs and laboratory findings reveal that abdominal pain, vomiting, high fever, abdominal distension etc are the most common symptoms for typhoid fever. However other major sign and symptoms include

Diarrhoea, Constipation, Abdominal rigidity, Confusion etc. the laboratory findings include the following:

- Anemia
- Thrombocytopenia
- Leucopenia
- Gas under diaphragm
- Increased Air-fluid levels
- Elevated transaminase level etc (Hosoglu *et al*, 2004).

The common signs and symptoms present in patients (both adults and children) with culture-proven typhoid fever from nine published studies are summarised in **Table 1.1**. The signs that are most commonly reported are fever followed by diarrhoea, vomiting, abdominal pain, headache, splenomegaly, anorexia and hepatomegaly. There is no obvious difference in clinical presentation of typhoid between Asia and Africa. There are two studies that have explored the performance of a clinical case definition for typhoid fever, one study in Turkey (Hosoglu*et al.* 2006) and one in Indonesia (Vollaard *et al.* 2005). In Turkey, seven variables has been considered to be highly indicative of typhoid infection: Age <30 years, abdominal distension, confusion, relative bradycardia, typhoid tongue, a positive Widal test and leucopoenia. In *post-hoc* analyses, the authors created a scale based on these features and reported an optimum diagnostic performance of sensitivity 86.2%, specificity 76.9%, positive predictive value (PPV) 78.7%, and negative predictive value (NPV) 84.0% in their study population aged ≥15 years who presented at hospital with a febrile illness. The Indonesian study, however, concluded that no symptom and sign combination performed adequately to be useful in clinical practice for identifying typhoid (Vollaard *et al.* 2005).

Table 1.1. Prominent signs and symptoms in culture confirmed cases of typhoid fever

	Amma h *et al* (1999)	Sinha *et al.* (1999)	Ispaha ni *et al.* (2000)	Kumar *et al.* (2002)	Nsuteb u *et al.* (2003)	Papaev angelou *et al.* (2004)	Mathu ra *et al.* (2005)	Walia *et al.* (2005)	Siddiqui *et al.* (2006)
Fever	+	+	+	+	+	+	+	+	+
Anorexia	+	+	–	–	–	–	–	–	+
Vomiting	+	+	+	+	–	+	+	+	+
Hepatome galy	–	–	+	–	+	–	+	–	–
Diarrhoea	+	+	+	+	+	+	+	+	+
Abdomina l pain	+	+	+	+	–	–	+	–	+
Constipati on	–	+	–	+	+	–	–	–	+
Headache	+	+	–	+	–	–	+	–	+

(Evanson *et al*, 2008)

1.11 Diagnosis

The clinical diagnosis of enteric fever can be difficult because of the nonspecific nature of symptoms and signs. In patients with enteric fever, the peripheral WBC count is usually normal to low, and mild hepatic involvement may be reflected in slightly abnormal liver function test results. The definitive diagnosis of enteric fever requires the isolation of S. Typhi or S. Paratyphi from specimens of blood, bone marrow, or another extra intestinal site. Blood cultures are the standard diagnostic method, and the results can be positive in 60%–80% of patients, provided that a large volume of blood (typically 15 mL for adults) is cultured. Bone marrow cultures increase the diagnostic yield of blood cultures by ~30%, reflecting a higher concentration of bacteria in this sample type. The results of stool cultures are positive for ~60% of children and 25% of adults with enteric fever; for the detection of carriers, several samples should be examined because of the irregular nature of shedding (Wang et al, 2005).

S. Typhi is occasionally excreted in the urine, especially in the presence of structural abnormalities of the urinary tract, including Schistosoma haematobium infection. Several serologic tests have been developed to detect S. Typhi antibodies. The role of the classic Widal test is controversial, with divergent views on the test's utility in various areas of endemicity. Newer rapid S. Typhi antibody tests may be useful in areas where enteric fever is endemic and resources are limited. However, no current serologic test is sufficiently sensitive or specific to replace culture-based tests for the diagnosis of enteric fever in developed countries (Bhutta et al, 1999).

The diagnosis of typhoid and paratyphoid fever is based on different diagnostic tests including the Rapid Diagnostic Tests (RDTs) and different types of other alternative tests that include the following:

•Blood culture

• Bone marrow culture

• Widal test

• Nucleic acid amplification tests (NAATs)

• C-Reactive Protein(CRP)

1.11.1 Blood Culture and Bone Marrow Culture

The gold standard for diagnosing enteric fever has been culture of the *Salmonella enterica* serovar Typhi or Paratyphi A organism from either bone marrow or peripheral blood. The mainstay of diagnosis in clinical practice is a positive blood culture, although the test is only positive in 40 to 60% of cases, usually early in the course of the disease (WHO, 2002). This lack of sensitivity may be due to the low number of bacteria circulating in the blood, or may be affected by prior antimicrobial therapy (Wain, 1998). Bone marrow culture gives a higher culture-positive rate, probably because the concentration of organisms is higher than in the blood, and may even yield a positive culture after antibiotic therapy has been started (Wain, 2001). Bone marrow culture is positive in 80 to 95% of patients with typhoid and paratyphoid, even in patients who have been taking antibiotics for several days regardless of the duration of the illness (Parry, 2002). Although bone marrow cultures are more sensitive, they are difficult to obtain, relatively invasive, and of little use in public health settings. Even with sophisticated laboratories, confirming the diagnosis of enteric fever can still be difficult as samples of blood or bone marrow may still not show evidence of the disease despite a patient actually having typhoid or paratyphoid (Wain, 2001).

False negative blood cultures depend on numerous factors including: volume of blood sample taken; the type of culture medium used; and the length of the incubation period .The sensitivity of blood culture is higher in the first week of illness (Parry, 2002). Widespread antimicrobial availability and prescribing contributes to the low sensitivity of blood culture (WHO, 2002). The ratio of blood to broth in preparing the blood culture could affect culture positivity rates and highlights the issues of the quality assurance of laboratories in endemic countries (Parry, 2002).

1.11.2 Widal test

The Widal test (WT) is an example of a serological test. It detects agglutinating antibodies to lipopolysaccharide (LPS) (O antigen) and flagella (H antigen). It is still widely used for the serological diagnosis of typhoid. In its original format the WT required both acute and convalescent-phase serum samples taken approximately 10 days apart. More recently, the test has

been evaluated for use as a single, acute-phase serum sample (Saha,1996). In enteric fever, titres often rise before the clinical onset, making it very difficult to demonstrate the diagnostic four-fold rise between initial and subsequent samples (Gill,2009).

The role of the WT is controversial because the sensitivity, specificity, and predictive values vary considerably among geographic areas (Parry,2002). Test results need to be interpreted carefully in the light of previous history of typhoid / paratyphoid and vaccination. Interpretation of the result is also greatly helped by knowledge of the background levels of antibodies in the local healthy population. The widespread use of typhoid vaccines, and the large number of cases of repeated exposure to *Salmonella* species, are found to lower the specificity of the WT (House 2001). Several other diseases caused by non-*Salmonella* organisms (eg malaria, dengue, brucellosis) have been shown to exhibit cross-reactivity in typhoid-endemic regions. There is considerable variation in agglutinin levels among non-infected populations. These levels are susceptible to change over time, and depend on the degree of endemicity (Parry, 2002). Despite these shortcomings of both sensitivity and specificity the WT, both simple and inexpensive, is still widely used as a diagnostic test (Fadeel,2004).

1.11.3 Nucleic Acid Amplification Tests

Nucleic acid amplification tests (NAATs) for typhoid and paratyphoid diagnosis, such as polymerase chain reaction (PCR), are being explored. Theoretically, NAATs could amplify DNA from dead or unculturable bacteria, thus addressing the concern of poor culture positivity because of pre-treatment with antimicrobials (Wain, 2001). However, a novel three-colour real-time PCR technique has been found to have the same limitations as culture in terms of sensitivity, and deemed an unsuitable methodology for the routine diagnosis of typhoid and paratyphoid. Methods combining culture and PCR methods have been also been explored (Zhou 2010). However, the use of NAATs in developing countries will most likely be limited in the medium-term for reasons of cost (Olsen, 2004).

1.11.4 Rapid Diagnostic Tests (RDTs)

Simple, reliable, point-of-care rapid diagnostic tests (RDTs) for typhoid and paratyphoid (enteric) fever have been a long-felt need of clinicians working in endemic areas. The tests need to be

suitable for use in remote areas with limited diagnostic facilities and relatively untrained staff. They should be designed to yield a simple 'positive/negative' result at thresholds pre-set by the manufacturers, similar to a pregnancy test. These results should normally be made available within 15 minutes, so that they can be used while the healthcare provider is dealing with suspected patients .Finally, such tests must be made available at low cost for use in resource-limited settings (Jesudason, 2006).

The lack of RDTs in areas without microbiology facilities means that the burden of enteric fever is underestimated worldwide (Parry 2002). RDTs could help rationalise antimicrobial treatment and thus contribute to tackling the problem of resistance in endemic areas (Bhutta, 2006). RDTs could be incorporated into clinical algorithms for patients with fever from endemic areas to help guide management(Jesudason, 2006).

Typhoid and paratyphoid RDTs comprise a heterogenous group of different methods and formats. RDTs have been applied to either blood or urine samples. Blood RDTs (using either venous and/or capillary samples) are more common than urine tests. These RDT products include test formats based on lateral flow, flow-through, agglutination or solid phase methods (Pastoor, 2008).

RDTs may detect antigens (components of the causative *Salmonella* organism) or antibodies (markers of the human's immune response to the antigen). The type of antibody class or immunoglobulin detected could be either Immunoglobulin-M (IgM), which may be indicative of recent exposure, or Immunoglobulin-G (IgG), which can indicate recent or previous exposure. Examples of commercial RDTs for typhoid and paratyphoid which have been undergoing evaluation in recent years include *Typhidot*®, *Typhidot-M*®, and *TUBEX*™ (Baker, 2010).

New RDT developments are likely to take a serological approach, although the identification of novel antigens free of cross-reacting materials and antigen pools is a major challenge (Baker, 2010).

1.12 Treatment

With the emergence of resistant strains, fluoroquinolones and third generationcephalosporins, particularly ciprofloxacin and ceftriaxone, are used as first line antibiotics. however, significant

resistance to these drugs is emerging, especially in Asia, although fluoroquinolones remain superior for preventing clinical relapse and are still recommended for empirical therapy in adults. children may be treated with third generation cephalosporins. Azithromycin has been shown to be an effective alternative for treatment of uncomplicated typhoid fever and may perform better than ceftriaxone in this setting.

Table1.2: Treatment of uncomplicated Typhoid Fever.

	Optimal Therapy			**Alternative effective drugs**		
Susceptibility	Antibiotic	Daily Dose mg/kg	Days	Antibiotic	Daily Dose mg/kg	Days
Full sensitive	Fluoroquinolone e.g. Oflooxacin	15	5-7	Chloramphenicol Amoxicillin TMP-SMX	50-75 75-100 8-40	14-21 14 14
Multidrug resistance	Fluoroquinolone Or Cefixime	15-20	5-7 7-14	Azithromycin Cefixime	8-10 15-20	7 7-14
Quinolone resistance	Azithromycin or Ceftriaxone	8-10 75	7 10-14	Cefixime	20	7-14

(WHO, 2007)

1.13 Interventions

Public health interventions to prevent typhoid and paratyphoid include:

- health education about personal hygiene, especially regarding hand-washing after toilet use and before food preparation; provision of a safe water supply;
- proper sanitation systems;
- excluding disease carriers from food handling.

Control measures to combat typhoid include health education and antibiotic treatment. A vaccine is available, although it is not routinely recommended except for those who will have prolonged exposure to potentially contaminated food and water in high-risk areas. The vaccine does not provide full protection from infection (WHO, 2002).

1.14 Prevention

Contaminated water and food are important vehicles for transmission of typhoid fever. Historical surveillance data suggest that enteric fever was endemic in Western Europe and North America and that rates decreased in parallel with the introduction of treatment of municipal water, pasteurization of dairy products, and the exclusion of human feces from food production. At present, enteric fever prevention focuses on improving sanitation, ensuring the safety of food and water supplies, identification and treatment of chronic carriers of *S. Typhi*, and use of typhoid vaccines to reduce the susceptibility of hosts to infection (Ochiai *et al*, 2005).

1.14.1 Vaccination

The heat-killed, phenol-preserved, injectable whole-cell *S. typhi* vaccine that was utilized as far back as 1896 in England and Germany, is still licensed today in several countries in spite of its high reactogenicity. Two new vaccines are currently licensed and widely used worldwide, a subunit (Vi PS) vaccine administered by the intramuscular route and a live attenuated S typhi strain (Ty21a) for oral immunization. Several typhoid vaccination programs that involve annual children vaccination campaigns using the injectable Vi vaccine have been carried out in Asia, resulting in a marked reduction or near disappearance of the disease, including in age groups not targeted for vaccination, thus suggesting a possible herd protective effect of vaccination (Guzman *et al*, 2006).

1.14.2 Vaccines in development

The clinical and laboratory diagnosis of typhoid fever remains challenging. the present gold standard is direct blood culture followed by microbial identification, but this is expensive and impractical in many settings; *S. typhi* and *S. paratyphi* may also be difficult to culture. Bone marrow culture is most sensitive, but invasive and impractical. the organism may be shed in stools or urine for culturing, but only sporadically. typhoid serology is not ideal as antibody response may be weak, and in addition, exposure to *S. typhi* in endemic areas may lead to serological evidence of

past exposure despite a lack of clinical illness. the first typhoid diagnostic, the Widal test, was developed in 1896; it is a visual test that monitors agglutinating antibodies that react with *S. typhi.* it has a high false positive rate due to cross reactivity of antibodies, and remains a controversial diagnostic too Polymerase chain reaction (PCR) is also of limited value as none are as yet validated for use and interpretation. Current research is directed at all of the above modalities including culture, DNA methodologies and serological approaches. Antigen based rapid diagnostic test kits in particular could potentially save lives, time and money. Rapid detection methods, including multiplex PcR and stool dipstick testsas well as a fast blood culture PCR method, are currently being developed to aid early diagnosis.. Previously, children aged 5–19 years were considered at greatest risk.2 Vaccines that are immunogenic in infants less than 2 years of age after a single dose are being developed6 to improve on current vaccination programs.3 A Vi conjugate vaccine has been trialled3 and a Vi conjugate/diphtheria toxoid combination vaccine may soon be available,(Jain et al,2010) while others are being developed. A more effective vaccine is also needed for travellers with the rise of multidrug resistant organism strains, as well as a vaccine for *S. paratyphi*.15 single dose oral typhoid vaccines m01Zh09, cVD 908, cVD 908-htrA, cVD 909 and ty800 have undergone preliminary testing in adults (Ivon *et al*, 2009).

1.15 Resistance

There are a number of reasons why there is significant resistance of *Salmonella enterica* serovar Typhi / Paratyphi A to antimicrobials worldwide. For example, Health professionals in the tropics over prescribe antimicrobials for many reasons, including cultural factors and patient expectation (Okeke,2005). The purchase of drugs such as antimicrobials from untrained vendors and unlicensed pharmacists are commonplace in the developing world (Larsson,2008). A major challenge is the inability to confirm diagnoses in resource-limited settings where traditional laboratory methods of diagnosing typhoid and paratyphoid are not available. Health care workers are therefore reliant on their clinical skills to make an educated guess of the cause of illness, and/or prescribe an antimicrobial that targets several bacteria (Shetty,2008). This over-treatment has contributed to increasing resistance to fluoroquinolones (eg ciprofloxacin) and multi-drug resistance of *Salmonella enterica*serovarTyphi / Paratyphi A within endemic Asian countries (Chuang, 2009).

Resistance to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole and streptomycin is now common, and these agents have not been used as first line treatment now for almost 20 years. Typhoid that is resistant to these agents is known as multidrug-resistant typhoid (MDR typhoid).

Ciprofloxacin resistance is an increasing problem, especially in the Indian subcontinent and Southeast Asia. Many centres are therefore moving away from using ciprofloxacin as first line for treating suspected typhoid originating in South America, India, Pakistan, Bangladesh, Thailand or Vietnam. For these patients, the recommended first line treatment is Ceftriaxone. It has also been suggested Azithromycin is better at treating typhoid in resistant populations than both fluoroquinolone drugs and ceftriaxone.Azithromycin significantly reduces relapse rates compared with ceftriaxone.

There is a separate problem with laboratory testing for reduced susceptibility to ciprofloxacin: current recommendations are that isolates should be tested simultaneously against ciprofloxacin (CIP) and against nalidixic acid (NAL), and that isolates that are sensitive to both CIP and NAL should be reported as "sensitive to ciprofloxacin", but that isolates testing sensitive to CIP but not to NAL should be reported as "reduced sensitivity to ciprofloxacin". However, an analysis of 271 isolates showed that around 18% of isolates with a reduced susceptibility to ciprofloxacin (MIC 0.125–1.0 mg/l) would not be picked up by this method. It is not certain how this problem can be solved, because most laboratories around the world (including the West) are dependent on disc testing and cannot test for MICs (Cooke *et al*, 2006).

1.16 Current Research

Much research is going on since the global emergence of multi drug resistant strains. A study has been conducted in India, samples of 21 Salmonella typhi strains has been tested for their vulnerability to antimicrobial agents. Three different antibiotics has been considered: chloramphenicol (256 mg/liter), trimethoprim (64 mg/liter), and amoxicillin (>128 mg/liter). Eleven of the S. typhi strains were resistance to chloramphenicol, trimethoprim , and amoxicillin. Four of the isolates were resistant to all of them except for amoxicillin. Other antimicrobial agents were also tested. All the S. typhi isolates were susceptible to cephalosporin agents, gentamicin,

amoxicillin plus clavulanic acid, and imipenem. One of four plasmids encoded each S. typhi isolate. The genes responsible for the resistance of the antibiotics listed above (chloaramphenical and etc.) are: chloramphenicol acetyltransferase type I, dihydrofolatereductase type VII, and TEM-1 β-lactamase. Pulsed-field gel electrophoresis analysis of XbaI-generated genomic restriction fragments identified a single distinct profile (18 DNA fragments) for all of the resistant isolates. After comparing this, six different profiles were recognized among the sensitive isolates. It was found that a single strain containing a plasmid having multi drug-resistance has emerged in the S. typhi population and has been able to adapt and survive the antibiotics as they are introduced into clinical medicine (Philippa *et al*,1998).

With the current spread of Salmonella, researchers are looking for easier ways to detect typhoid fever in order to better treat patients. Another project has to do with dipstick assay which detects antibodies and analyzes the effect of typhoid fever in patients. It found specific IgM antibodies on patients in 43.5%, 92.9%, and 100% for samples collected 4-6 days, 6-9 days, and greater than 9 days after the onset of fever, respectively, the number of antibodies increasing during the length of the duration. Testing of serum samples from culture negative patients with a clinical diagnosis of typhoid fever resulted in staining of the dipstick in 4.3% of the samples collected on the day of admission and in 76.6% one week later(Hatta *et al*, 2002).

More people have taken a greater interest in Salmonella typhi since the decreasing effects of antibiotics. In 2006, more research was done in order to find the global gene expression by Salmonella typhi during infection. Global expression profiles of typhi grown in vitro and within macrophages at different time points were obtained and studied. Virulence factors, such as the SPI-1- and SPI-2-encoded type III secretion systems, were found as expected during infection by Salmonella. The results concluded that Salmonella typhi had an increased expression of genes encoding resistance to antimicrobial peptides, which used the glyoxylate bypass for fatty acid utilization, and did not induce the SOS response or the oxidative stress response. It was also found that genes coding for the flagellar apparatus, chemotaxis, and iron transport systems were down-regulated in vivo. This experiment allowed a better understanding of Salmonella and found a safer and more effective way to determine the bacterial transcriptome in vivo. This could possibly lead to the investigation of transcriptional profiles of other bacterial pathogens without the need to recover much bacterial mRNA from the host (Faucher *et al*, 2006).

Objectives of the study

- To have an overall idea of the common sign and symptoms of Typhoid fever
- To figure out the amount of Typhoid patients having Neutropenia.
- To outline the difference between the Typhoid and Non-Typhoid patients in terms of Absolute Neutrophil Count (ANC).

Significance of the study

Typhoid fever is a systemic infection caused by *Salmonella enterica* serotype Typhi (*S. typhi*). The disease remains an important public health problem in developing countries. In 2000, it was estimated that over 2.16 million episodes of typhoid occurred worldwide, resulting in 216 000 deaths, and that more than 90% of this morbidity and mortality occurred in Asia. Improved water quality and sanitation constitute ultimate solutions to this problem recommended by WHO for the long term (WHO, 2002).

Although children with typhoid fever sometimes become sick suddenly, signs and symptoms are more likely to develop gradually — often appearing one to three weeks after exposure to the disease and may be mild or severe. They include high fever, malaise, headache, constipation or diarrhea, rose-colored spots on the chest etc.

Bangladesh, being a south-east Asian country is in a high risk of Typhoid fever exposure. The poor sanitation, hygiene lack of proper safe drinking water, environmental factors and unhygienic food habits contribute to this high risk to the disease.

Although Bangladesh is in an endemic region for the disease, there is a lack of appropriate and accurate trends in the sign and symptoms of Typhoid fever, which generally complicates the diagnosis process and ultimately leads to the improper treatment of the patients. Again, majority of the affected population are children and their sign and symptoms are a bit different from that of the adults. So, a study on the sign and symptoms of Typhoid fever among the children is of paramount importance in the treatment of the disease.

To develop a rational treatment and control strategy, the identification of the common sign and symptoms is vital.

This study can also serve the policy makers as indication for the diagnosis of the disease which will finally lead to the proper treatment.

As the study includes the trend of ANC and Neutropenia, health professionals related to the sector will be well aware of the real situation of the above two parameters in the children Typhoid patients in the country as the hospital represents the country although to a smaller extent.

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Ultimately the study will serve as a guideline for both the general and experts to know and understand the common sign and symptoms in the disease, thus facilitating the treatment procedure.

CHAPTER- 2

MATERIALS AND METHODS

2.1 Type of the study

It was a prospective study.

2.2 Place of the study

The study was done at the general ward in ICH and "Shishu Shasthya Foundation" (SSF) Hospital, Mirpur, Dhaka, Bangladesh. The hospital has five wards in total. Every ward was equipped treatment facilities.

2.3 Study population

In this study 112 cases of typhoid fever were taken from the total number of children who were suspected to be infected by *S. typhi* and 112 cases of others diseases (such as diarrhoea, AGE, acute gastroenteritis etc.) as a control.

2.4 Inclusion criteria

The following was included-

- Male and female children diagnosed with typhoid fever and others diseases
- Patient within the age of 0-12 years
- Children who were admitted in the hospital for the treatment i.e. indoor patient

2.5 Exclusion criteria

The following was not included in the study-

- Outdoor patient
- Children above 12 years of age

2.6 Research approach

After getting approval of the research proposal from the honourable faculty members, formal permission was obtained from the concerned authorities of "Shishu Shasthya Foundation" (SSF).

2.7 Sampling technique

In this study, purposive sampling was followed.

2.8 Study period

Study period was more than one year beginning from June, 2010 to August, 2011.

2.9 Data collection paper

A data collection paper was made in order to compile all the information and data of the patient in an organized manner.

2.10 Data analysis

All the data were checked after collection then the data were entered into Microsoft Excel 2010 sheet. The result was shown in bar, pie and column chart and calculated the percentage of the
parameter of typhoid fever and others diseases of children.

CHAPTER- 3

RESULTS

3.1 Gender distribution of Typhoid patients (n=112).

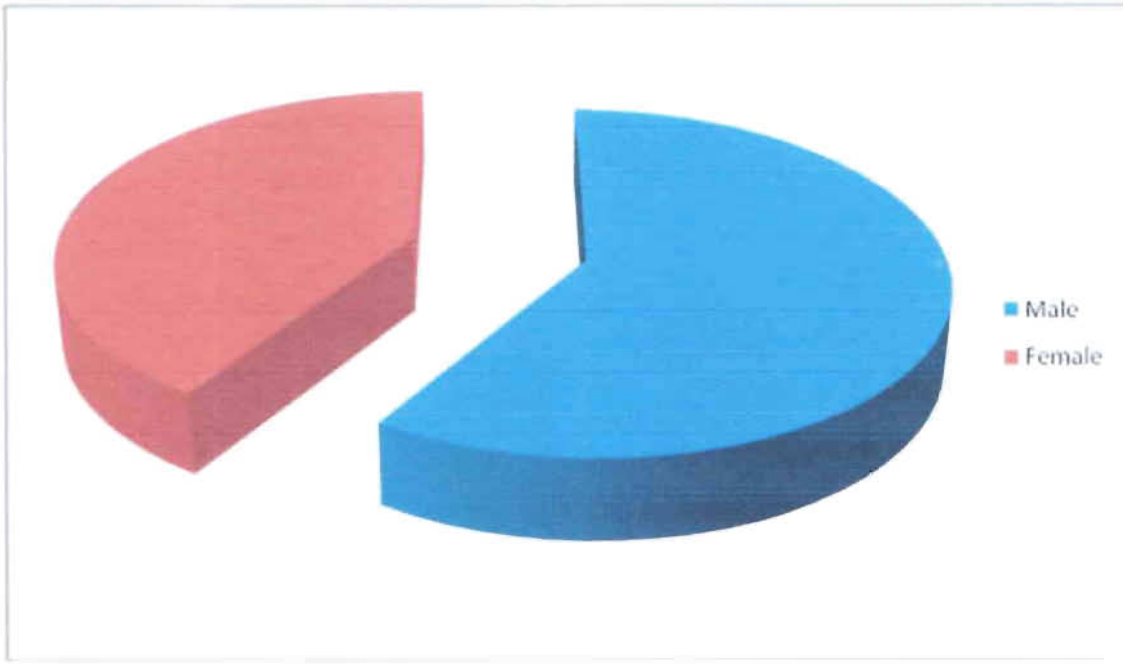

Figure 3.1: Gender distribution of Typhoid patients (n=112).

Among the Typhoid patients, 59% were male and 41% were female. So, males are more prone to Typhoid fever than females.

3.2 Distribution of Typhoid patients according to their age (n=112).

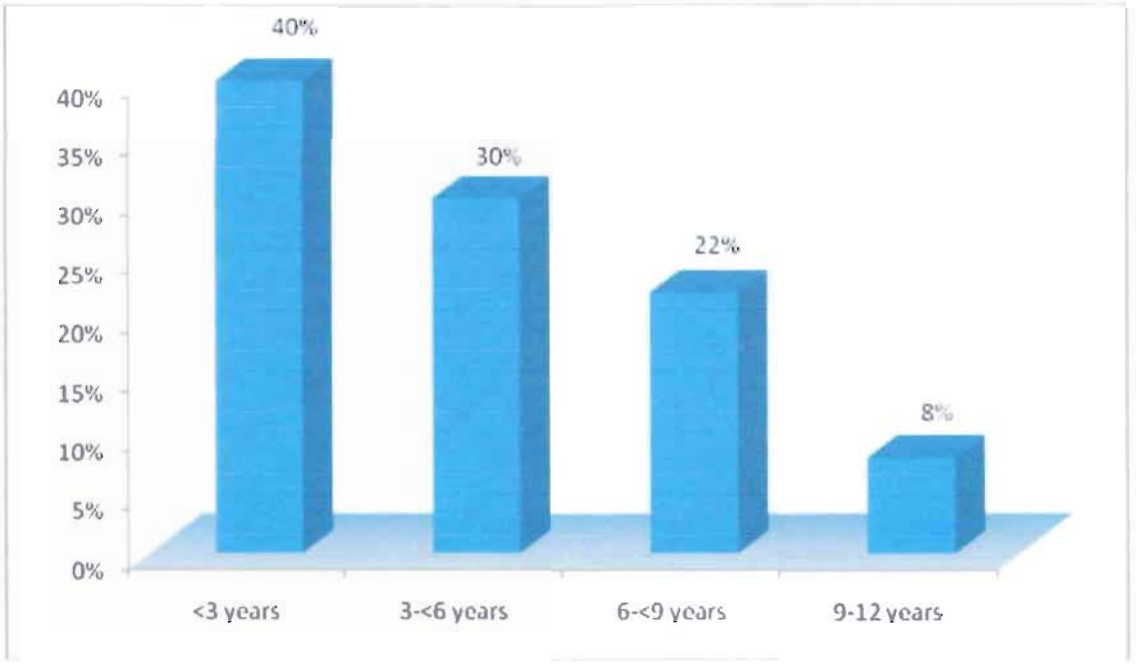

Figure 3.2: Age distribution of Typhoid patients.

The above figure resembles that Typhoid fever is most prevalent in patients with the age range <3 years (40%).The age range 3-<6 years was found to be the second most prevalent group with 30%.

3.3: Percentage Distribution of Typhoid patients according to Sign and Symptoms (n=100).

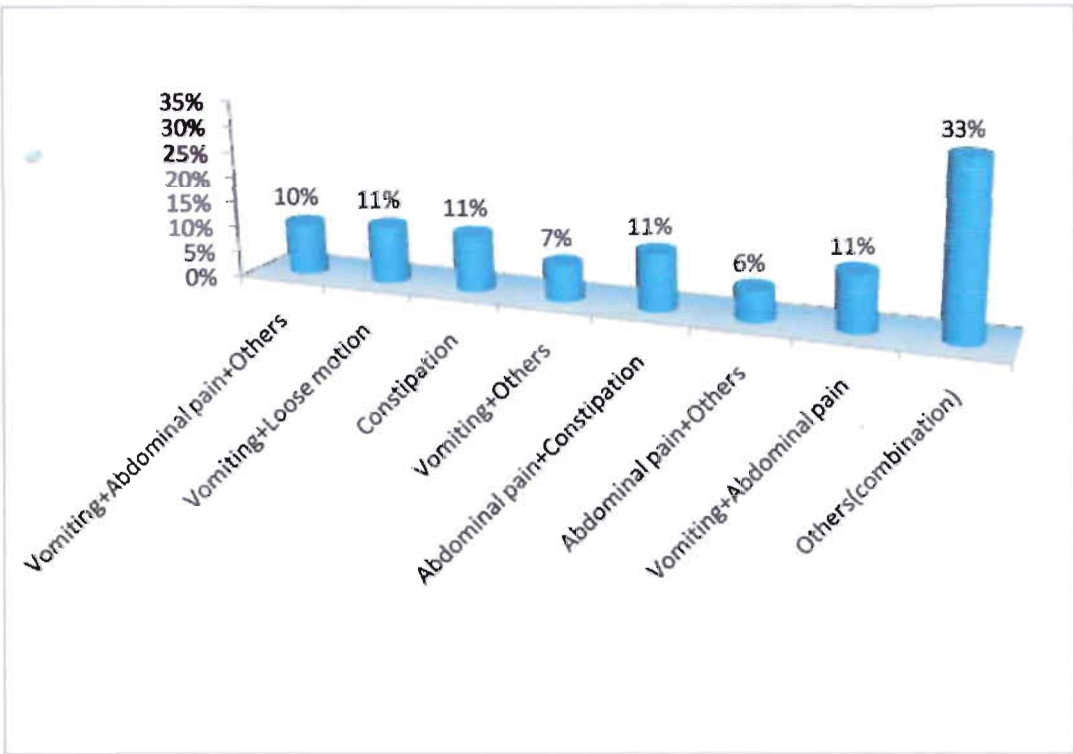

Figure 3.3: Percentage Distribution of Typhoid patients according to Sign and Symptoms.

Others (combination) include the following:

Loose motion + Vomiting

Constipation + Abdominal pain

Vomiting + Constipation etc.

The above figure shows that Vomiting associated with loose motion is the most common sign and symptom. Other major sign and symptoms include abdominal pain, constipation etc.

3.4: Percentage Distribution of Non- Typhoid patients according to Sign and Symptoms(n=100).

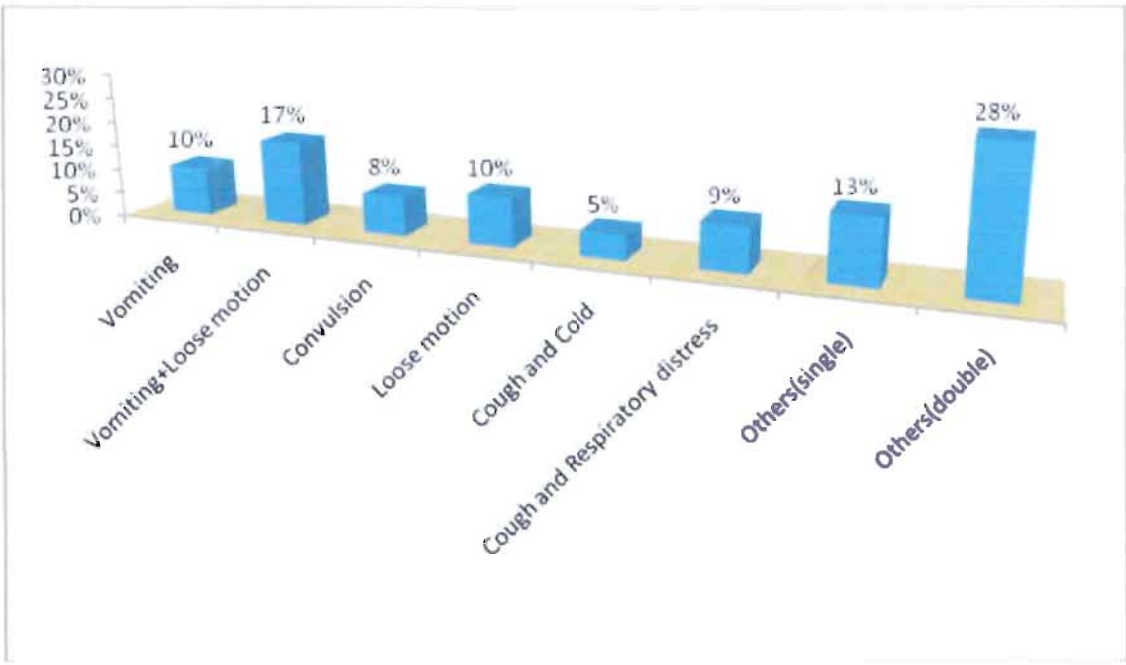

Figure 3.4: Percentage Distribution of Non- Typhoid patients according to Sign and Symptoms.

Here, the other combinations used are of Vomiting, Loose motion, Cough and Cold etc.

From the above figure, it can be seen that Vomiting and Loose motion are the two most common sign and symptoms in the non-typhoid patients. However, Cough and Cold and Respiratory distress are also common.

3.5 Percentage Distribution of Typhoid patients according to Absolute Neutrophil Count(ANC)(n=112).

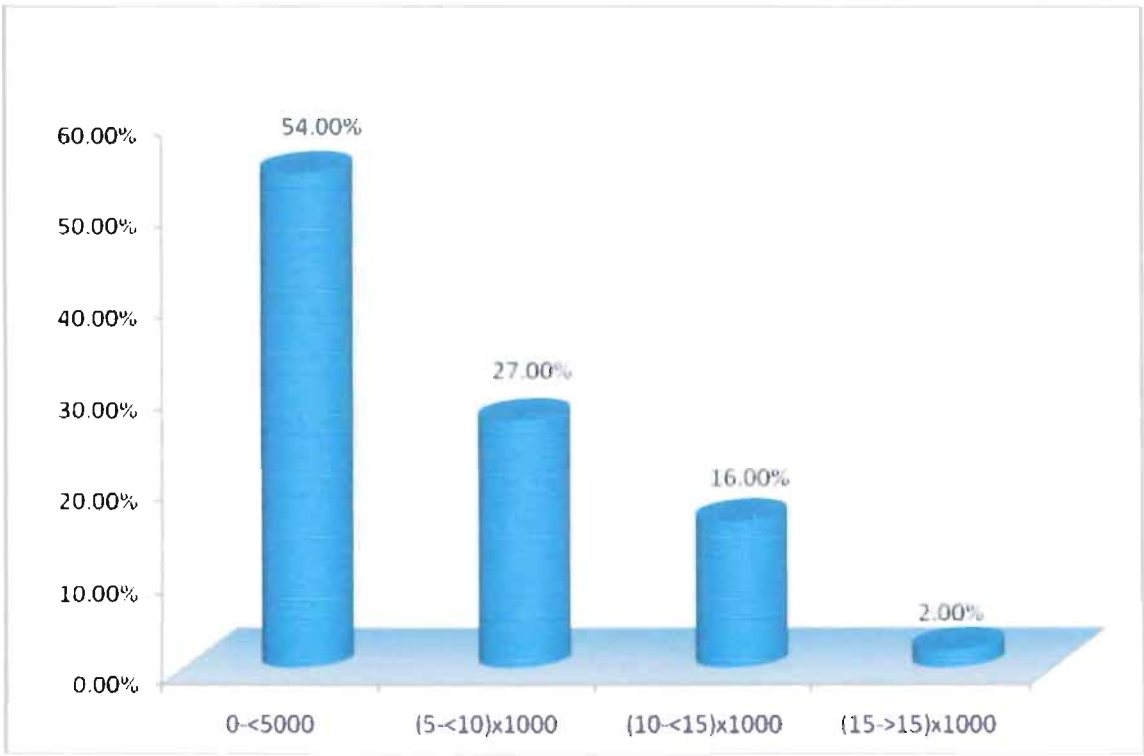

Figure 3.5: Percentage Distribution of Typhoid patients according to Absolute Neutrophil Count (ANC).

The study shows that the group (0-<5000) per μL is the most prevalent group of ANC in the Typhoid patients followed by the group (5000-<10000) per μL.

3.6 Percentage distribution of Non-Typhoid patients according to Absolute Neutrophil Count (ANC). (n=112)

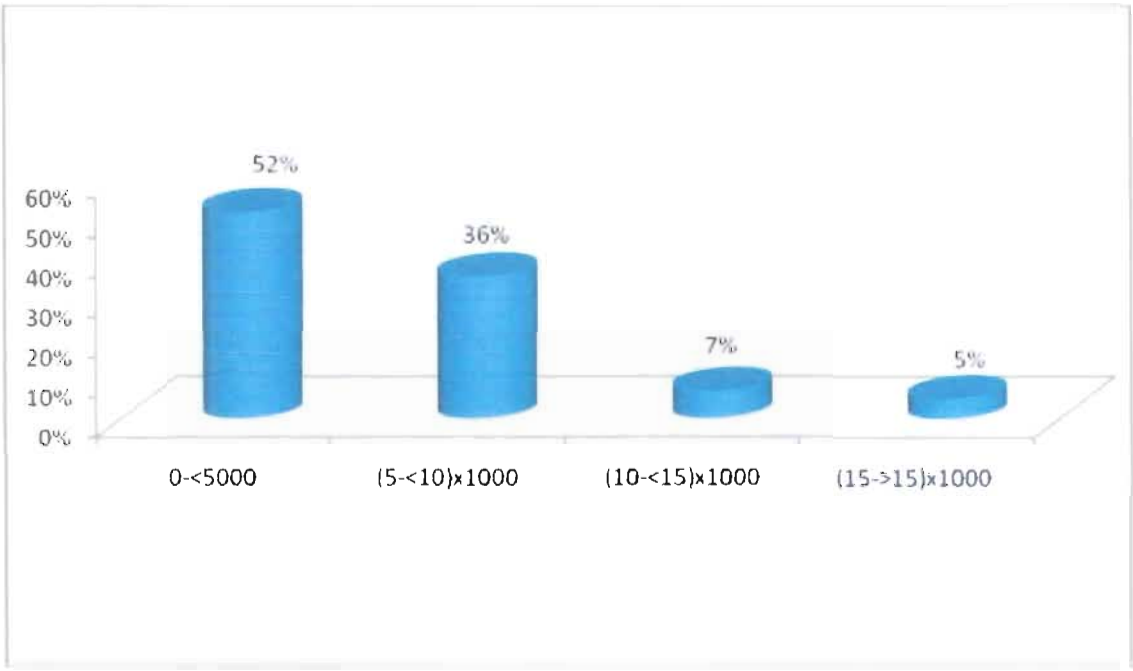

Figure 3.6: Percentage distribution of Non-Typhoid patients according to Absolute Neutrophil Count (ANC)

The study shows that the group (0-<5000) per µL is the single most prevalent group of ANC in the Non-Typhoid patients followed by the group (5-<10000).It is notable here that the dominant group has a much larger percentage than the other groups compared to the Typhoid patients ANC.

3.7 Percentage distribution of Typhoid patients according to the Neutropenic condition.(n=112)

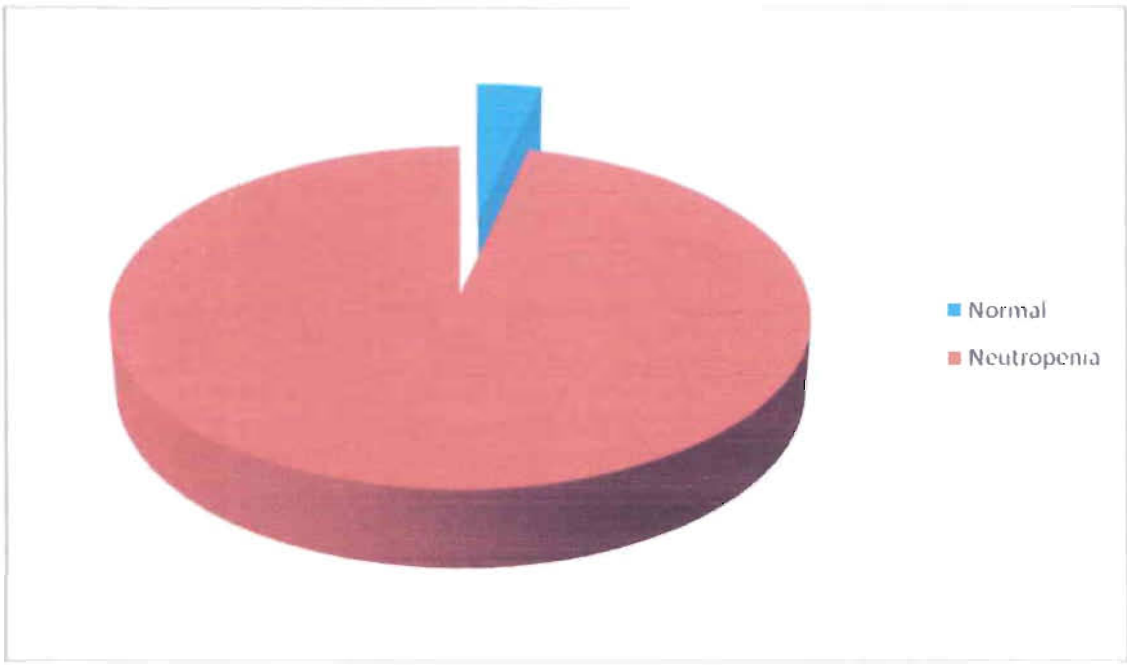

Figure 3.7: Percentage distribution of Typhoid patients according to the Neutropenic condition.

The comparative figure of Neutropenic and Non-Neutropenic conditions among the patients of Typhoid fever shows that the amount of patients having Neutropenia is very very low.the term Neutropenia is used to define patients who have a significantly lower Neutrophil count(usually less than 2000 micro liter).

3.8 Percentage distribution of Non-Typhoid patients according to the Neutropenic condition. (n=112)

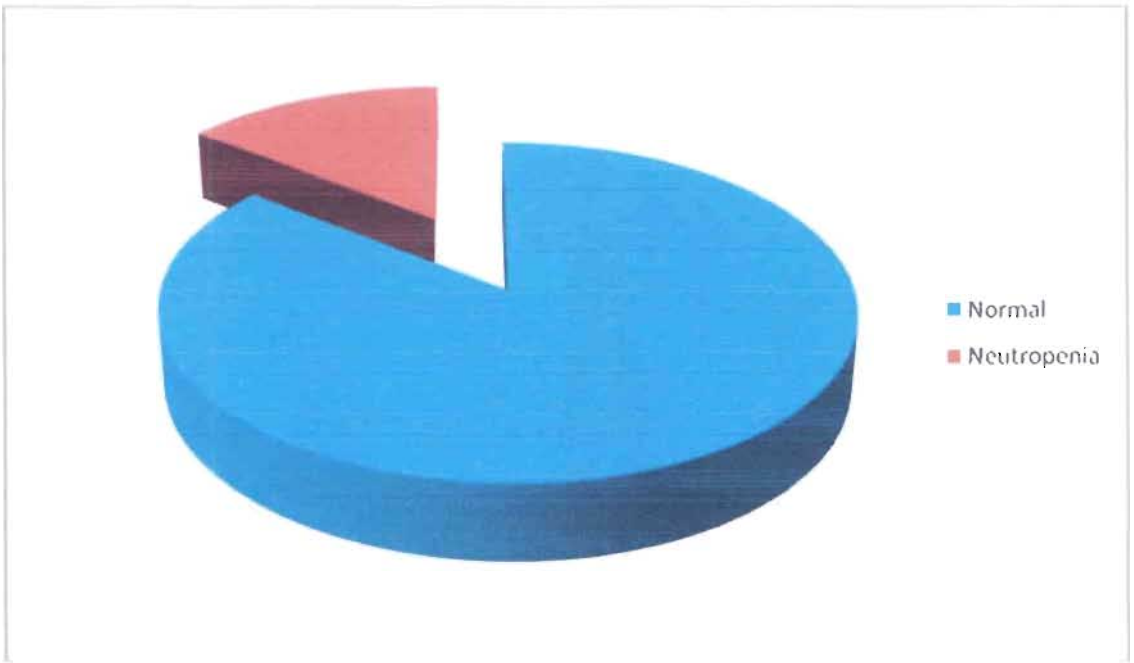

Figure 3.8: Percentage distribution of Non-Typhoid patients according to the Neutropenic condition.

The above figure shows that the percentage of cases having Neutropenia is significant in the Non-Typhoid patients. It is also notable that the condition is much more prevalent in the Non-Typhoid patients than in the Typhoid patients.

3.9 Percentage Distribution of Typhoid patients in terms of no. of Sign and Symptoms.(n=112)

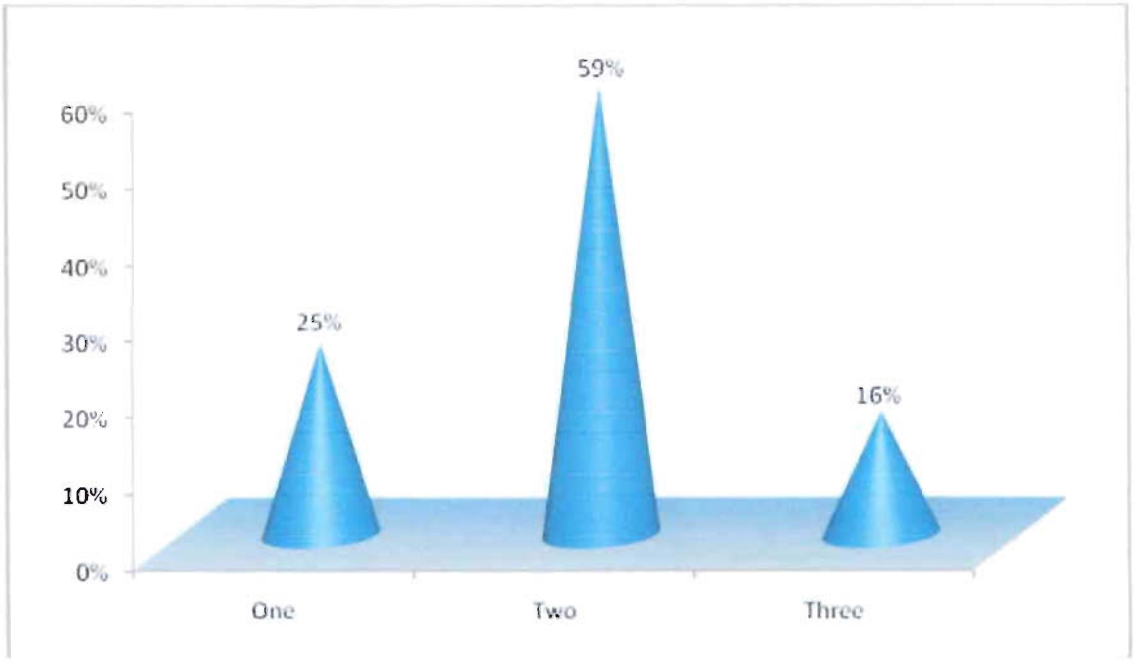

Figure 3.9: Percentage Distribution of Typhoid patients in terms of no. of Sign and Symptoms.

The above figure shows that maximum no. of Typhoid patients admitted in the hospital have two symptoms, while both 1 and 3 sign and symptoms are relatively lower in number.

3.10 Percentage Distribution of Non-Typhoid patients in terms of no. of Sign and Symptoms.(n=112)

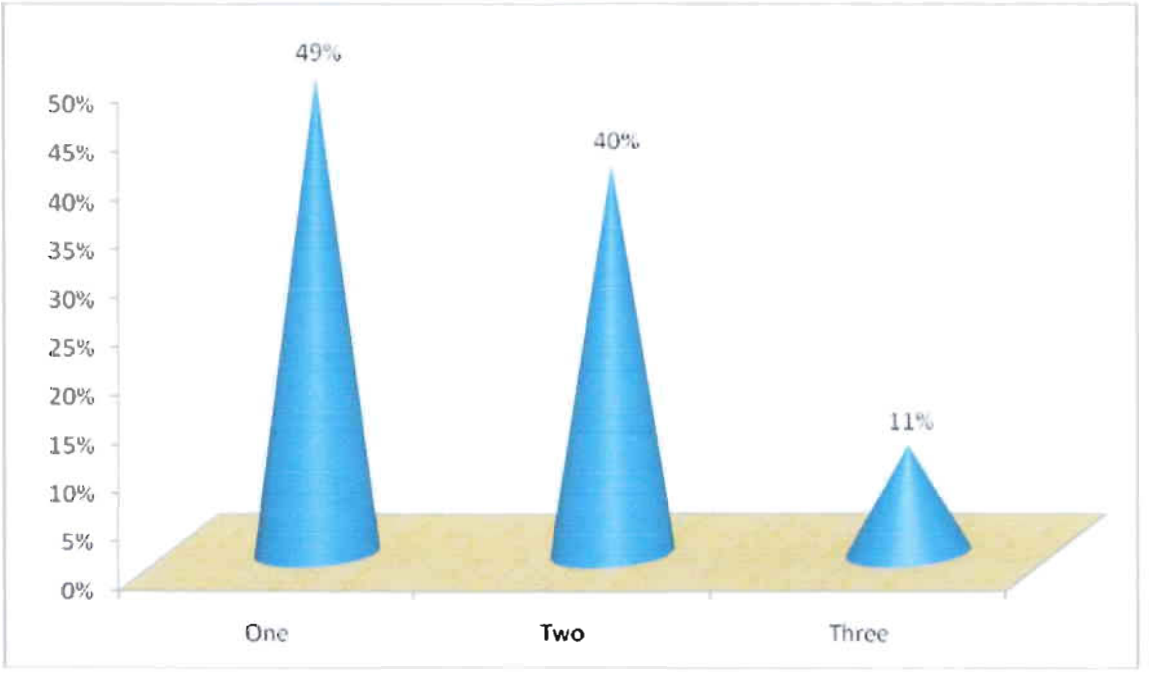

Figure 3.10: Percentage Distribution of Non-Typhoid patients in terms of no. of Sign and Symptoms

The study revealed that the Non-Typhoid patients experience mostly 1 and 2 sign and symptoms. the occurrence of 3 sign and symptoms is very little.

3.11 Comparison between Typhoid and Non-Typhoid patients in terms of TC-WBC. (n=112)

Table 3.1: Comparison between Typhoid and Non-Typhoid patients in terms of TC-WBC.

	Mean	Standard Deviation	Standard Error Mean	P Value
Typhoid	9.1651	5.04673	0.47687	0.027
Non-Typhoid	10.6110	4.66138	0.44046	0.027

3.12 Comparison between Typhoid and Non-Typhoid patients in terms of ANC. (n=112)

Table 3.2: Comparison between Typhoid and Non-Typhoid patients in terms of ANC.

	Mean	Standard Deviation	Standard Error Mean	P Value
Typhoid	5.7532	4.14587	0.39175	0.941
Non-Typhoid	5.7935	3.95497	0.37371	0.941

Here, P value = 0.001 to 1

CHAPTER- 4

DISCUSSION AND CONCLUSION

Discussion

As a third world developing country, Bangladesh has a poor sanitation system, unhygienic environment, inappropriate access to safe drinking water. All of these result in the high prevalence of the Typhoid fever in this region. To come up with a specific accurate trend in the sign and symptoms of the disease that will facilitate the treatment process of the disease, we conducted a case-control study in a tertiary level hospital in Dhaka, the capital of Bangladesh. The patients having an age limit less than 12 were considered as we focused on the sign and symptoms of Typhoid in Childs. This is because they are the most Typhoid prone population in the country.

This case-control prospective study was carried out with 112 patients as case and another 112 patients as control. It has been revealed from the study that majority (59%) of the patients belong to the gender Male. It implicates that the males are more prone to the disease than the females. Trivedi *et al* (2010) found the same result in India even to a higher extent. In their study they found that 71.7% patients were male while only 29.3% were females.

In the age group segmentation it has been found that children below the age limit 3 years were the most prevalent group (40%).The frequency of the typhoid patients decrease gradually with an increase in the age group meaning that the older child patients are less susceptible to Typhoid fever than the younger ones. the age group 9-12 years thus have the least percentage of patients with only 8% of the total patients. A study conducted by Trivedi (2010) also resembles the same thing in case of age distribution.

While studying the sign and symptoms of the disease it was found that vomiting, abdominal pain, loose motion etc are the common sign and symptoms in the children suffering from Typhoid fever. In addition, the relatively older child patients experience constipation frequently as well. It is notable from the results that patients generally experience two sign and symptoms at a time when they are admitted in the hospital. Patients complaining about only 1 and 3 sign and symptoms are less in number counting only 27% and 17% respectively. According to a study conducted in Diyarbakir, Turkey on common symptoms, clinical signs and laboratory findings reveal that abdominal pain, vomiting, high fever, abdominal distension etc are the most common

symptoms for typhoid fever. However other major sign and symptoms include Diarrhoea, Constipation, Abdominal rigidity, Confusion etc (Hosoglu *et al*, 2004).

A significant result obtained in the ANC calculation. The ANC group of 0-<$5x10^3$ was found to be dominant in non-Typhoid patients than in the Typhoid patients. It may be due to the exclusion of the count of the band forms of neutrophils in the complete blood count (CBC) while other factors may also contribute to this abnormality. Here in both Typhoid and Non-Typhoid patients the second prevalent ANC group was 5-$10x10^3$.

The study results showed that only 3.57% patients experience Neutropenia in Typhoid fever. While, 14.29% Non-Typhoid patients experience Neutropenia. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 2000/microL. The ANC is equal to the product of the white blood cell count (WBC) and the percentage of polymorphonuclear cells (PMNs) and band forms noted on the differential analysis:

$$ANC = WBC\ (cells/microL) \times percent\ (PMNs + bands) \div 100$$

Mallouh *et al* (1987) conducted a study where he found only 3% Typhoid patients experienced Neutropenic condition. Another study conducted in Durban revealed that Neutropenia in typhoid patients was 25% (Gaffar *et al*, 2006). Although neutropenia is said to be common in diseases like Typhoid fever, there may be differences in various studies.this difference may be sue to several factors. It has to be mentioned here that we did not include the count of band forms in CBC count. However, considering the facts, the results obtained are significant enough.

A significant difference obtained between the Typhoid and Non-Typhoid patients in case of TC-WBC (0.027) while there was insignificant difference between these two in terms of ANC (0.941).the mean value of ANC found was (5.7532±4.14587) while that of Non-Typhoid patients was found (5.7935±3.95497).

Conclusion

The findings that we have reported in this paper can assist in making decisions on which signs and symptoms to target and ANC to consider while diagnosis in Bangladesh against typhoid fever. Although improvements in sanitation and water systems are the ultimate solutions to the control of the disease, vaccination can be considered in the near-to-intermediate term. Recognizing the limitations in generalizing our site-specific data, we propose that our findings are consistent with the notion that countries in south Asia and possibly south-east Asia have a high burden of typhoid fever. Recent data from Bangladesh also suggest a very high burden of the disease (Trivedi *et al*,2010).

However, a subsequent awareness among the people about the sign and symptoms, accurate diagnosis, proper and specific use of Antibiotics may reduce the prevalence of Typhoid fever in Bangladesh.

CHAPTER- 5

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Typhoid Fever

Hospital ID Patient ID AdmissionDate

Name of the patient.....Age.....yrs Sex....M/F
C/F:

Fever for.....

Vomiting.....

Abdominal Pain.....

Loose motion/constipation.....

Cough/respiratory distress.....

Others.....

Antibiotic treatment before admission.....

Antibiotic treatment After admission.....

Maximum Temp.....

Day of discharge.....

Hematological parameters:

Hb%	TC of RBC	TC of WBC	N%	L%	M%	E%	Platelet	ESR	CRP	[illegible]

Comments of PBF:

*Blood culture: Positive/Negative

*If positive:

S:

R:

M:

Name with signature: