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A Review on Shigella Dysenteriae and Salmonella Typhi: Implications for Food Handlers

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Abstract
This paper has reviewed researches that obtained from peer-reviewed literatures on Salmonellosis and Shigellosis. Foodborne diseases related to unhygienic food handling practices remain a major public health problem across the globe. The problem is severe in developing countries due to limitations in securing optimal hygienic food handling practices. Data shows that an estimated 70% of cases of diarrheal diseases are associated with the consumption of foods contaminated with pathogenic microorganisms. Among these microorganisms Salmonella and Shigella are the major ones. In this review, it is noted that these potentially pathogens are still public health problems. Therefore, there needs to be frequent monitory and evaluation system so as to plan intervention strategies for at risk population in the area of water sanitation and hygienic food handling practice to minimize the burden posed by the diseases associated with Salmonellosis and Shigellosis.
Keywords: Diarrheal diseases; Foodborne diseases; Salmonellosis; Shigellosis.

Introduction

Food borne diseases remain a major public health problem across the globe. The problem is severe in developing countries due to difficulties in securing optimal hygienic food handling practices. In developing countries, up to an estimated 70% of cases of diarrheal disease are associated with the consumption of contaminated food (Zeru and Kumie, 2007). Transmission of enteropathogenic bacteria is affected directly or indirectly through objects contaminated with faeces. These include food and water indicating the importance of faecal-oral human-to-human transmission (Gashaw *et al*., 2008).

Acute infective diarrhoea and gastroenteritis are major causes of ill health and premature deaths in developing world due, in large part, to the lack of safe drinking water, sanitation and hygiene, as well as poorer overall health and nutritional status. According to the latest available figures, an estimated 2.5 billion people lack improved sanitation facilities, and nearly one billion people do not have access to safe drinking water. These unsanitary environments allow diarrhea causing pathogens to spread more easily (UNICEF, 2009). Ranging from mild annoyances during vacations to devastating dehydrating illnesses that can kill within hours, acute gastrointestinal illnesses rank second only to acute upper respiratory illnesses as the most common diseases worldwide. In children <5 years old, attack rates range from 2–3 illnesses per child per year in developed countries to as high as 10–18 illnesses per child per year in developing countries (Kasper *et al.,* 2005).

Diarrhoea is one of the most common childhood illnesses, in both developing and developed countries. Estimation by World Health Organization WHO indicates that the world population

suffered from 4.6 billion incidences of diarrhea causing 2.2 million deaths in the year 2004. While the disease is rarely a cause of death in developed countries, it is estimated that approximately 1.6 million children die each year from diarrhoea in the developing world. Africa and South Asia are home to more than 80 percent of child deaths due to diarrhoea. In addition, by contributing to malnutrition and thereby reducing resistance to other infectious agents, gastrointestinal illnesses may be indirect factors in a far greater burden of disease(UNICEF, 2009 and WHO, 2004).

All over the world, severe acute bacterial gastroenteritis is caused mainly by *Shigella*, whereas *Salmonella*, *E. coli* (chiefly enteropathogenic *E. coli*, or EPEC, but also enterohemorrhagic

E. coli or EHEC, enteroinvasive *E. coli* or EIEC and other types), *Campylobacter* and *Vibrio* spp. have been shown to play a role in the epidemiology of diarrhea, especially in certain areas of the globe (Diniz-Santos *et al.,* 2005).

Bacillary dysentery was first differentiated from amoebic dysentery in 1887 and an etiologic agent, Bacillus dysenteriae, was isolated and described by Shiga in 1898. *Shigella flexneri* was originally described by Flexner in 1900. *Shigella sonnei* was first isolated in 1904, but it was not until 1915 that its pathogenic potential was recognized by Sonne (Gillespie and Hawkey, 2006). The subsequent painstaking process of epidemiological, physiological, and serological characterization of related dysentery bacilli culminated with the recommendations of the 1950. Congress of the International Association of Microbiologists *Shigella* Commission that *Shigella* be adopted as the generic name and that species subgroups be designated A (*Shigella dysenteriae*), B (*S. flexneri*), C (*S. boydii*), and D (*S. sonnei*) (Hale, 1991).

Bacteria of the genus *Salmonella* are widespread and important causes of foodborne infections in man, and are the most frequent etiologic bacterial agents of foodborne disease outbreaks. According to the latest nomenclature, which reflects recent advances in taxonomy (Grimont and Weill, 2007), the genus *Salmonella*

consists of only two major species: *S. enterica* and *S. bongori*. Serotypes Typhi (*S*. Typhi), *S*. Paratyphi are highly adapted to man. *S*. Typhi and *S*. Paratyphi have humans as their main reservoir, and enteric fever (typhoid and paratyphoid fever) as their most important clinical manifestation. Enteric fever continues to be an important cause of morbidity and mortality in developing countries. Although primarily intestinal bacteria, salmonellae are widespread in the environment and commonly found in farm effluents, human sewage and in any material subject to faecal contamination. Typhoid fever is a life threatening illness caused by the bacterium *Salmonella typhi*, and was observed by Karl J. Eberth (1880) in the mesenteric nodes and spleen of fatal cases of typhoid fever.

Operational Definition

Shigellosis and Salmonellosis

Shigellosis is an acute invasive enteric infection caused by bacteria belonging to the genus *Shigella*; it is clinically manifested by diarrhea that is frequently bloody. Shigellosis is endemic in many developing countries and also occurs in epidemics causing considerable morbidity and mortality. Among the four species of *Shigella*, *Shigella dysenteriae type 1 (Sd1)* is especially important because it causes the most severe disease and may occur in large regional epidemics. Major obstacles to the control of shigellosis include the ease with which *Shigella* spreads from person to person and the rapidity with which it develops antimicrobial resistance (WHO, 2005).

Salmonellosis is an infectious disease of humans and animals caused by organisms of the two species of Salmonella; *Salmonella enteric* and *S. bongori* (Grimont and Weill, 2007). Clinical syndromes caused by *Salmonella* infection in humans are divided into typhoid fever, caused by *Salmonella typhi* and *Salmonella paratyphi*(Gordon, 2008).

General characteristics of genus Shigella and Salmonella

The cells of the *Shigella* species are Gram-negative bacilli , nonmotile, non-spore-forming, facultative anaerobic rods(Feng,2003) *Shigellae* are differentiated from the closely related *Escherichia coli* on the basis of pathogenicity, physiology (failure to ferment lactose or decarboxylate lysine) and serology. They are generally catalase positive and oxidase and lactose negative. They ferment sugars, usually without forming gas. The strains grow between 7 and 46^0C, with an optimum at 37^0C and and pH 4.5. The genus is divided into four serogroups with over 2,500 identified multiple serotypes (Thomas and Gerald, 2000).

Salmonella species are Gram-negative, flagellated, non-sporeforming, facultative anaerobic bacilli characterized by O, H, and Vi antigens belongs to the family *Enterobacteriaceae.* Currently, there are over 2,500 identified serotypes of *Salmonella* (Foley and Lynne, 2008). *Salmonella typhi is one of the member and* its diagnostic identification can be attained by growth on MacConkey and EMB agars, and the bacteria is strictly non-lactose fermenting. Flowers (1988) and D'Aoust(1989) reported that *Salmonellae* form gas while growing in media containing glucose. They are mesophilic, with optimum growth temperature between 35 and 37^0C, but generally have a growth range of 5 to 46^0C. They are killed by pasteurization temperature and time, sensitive to low pH (4.5 or below), and do not multiply at an *Aw* of 0.94, especially in combination with a pH of 5.5 and below. The cells survive in frozen and dried states for a long time.

Epidemiology

Shigellosis is a global human health problem. Annually, there are 165 million cases of shigellosis resulting in 1.1 million deaths in the developing world with high morbidity and mortality (99%) (WHO, 2006 and Michael *et al*., 2008). Of these 1.1 million deaths due to Shigella, 69% are in children aged less than five years (Kotloff, 1999 and WHO, 2006). It is endemic in most developing countries where substandard hygiene and unsafe water supplies, in densely populated areas and institutions (Shane *et al*., 2003 and Gupta 2004). Humans are the only natural hosts for Shigella. The most frequently reported factor associated with the involvement of the infected worker was bare hand contact with the food followed by failure to properly wash hands, inadequate cleaning of processing or preparation equipment or utensils, cross-contamination of ready-to-eat foods by contaminated raw ingredients. In United States and Europe, children in day-care centers, migrant workers, travelers to developing countries and individuals in custodial institutions are infected most often (WHO, 2001).

Salmonellosis is a worldwide health problem. Approximately 95% of cases of human salmonellosis are associated with the consumption of contaminated products such as meat, poultry, eggs, milk, seafood, and fresh produce (Foley and Lynne, 2008). Risk factors for salmonellosis include gastric hypoacidity, recent use of antibiotics, extremes of age, and immunosuppressive conditions (Shelobolina *et al*., 2004 and Crum-Cianflone, 2008). With an estimated 16–33 million cases of typhoid fever annually resulting in 216,000 deaths in endemic areas, the World Health Organization identifies typhoid as a serious public health problem. Its incidence is highest in children and young adults between 5 and 19 years old (WHO.2007).

Typhoid fever, also called enteric fever, is a common worldwide disease, caused by bacterium *Salmonella typhi*, serotype typhi (Giannella,1996). Paratyphoid fever which is caused by *S. paratyphi* is also a systemic disease and its presenting symptoms are similar to those of typhoid fever, but they are milder and the case fatality rate is much lower. *S. typhi* is a multi-organ pathogen that inhabits the lympathic tissues of the small intestine, liver, spleen, and bloodstream of infected humans (WHO, 2003). Today, outbreaks of typhoid

fever occur most often in developing countries with poor sanitary systems and lack of antibiotics, in refugee camps or in overwhelmed areas with a high population density, putting travelers to Asia, Latin America, and Africa in a high risk group. The disease is less common in North America, an estimated 500 cases are reported each year in the United States, 70% occurring in travellers returning from endemic areas(Sharma and Sharma, 1992; USCDCP, 2001 and Lakshmi, 2006).Typhoid fever is more common in children and young adults than in olders(Threlfall and Ward, 2001). Typhoid fever is a disease occurring more commonly among people after travel to, or residence in, developing countries where sanitation is poor and where there is faecal contamination of food and water (Edelman and Levine, 1986).

The morbidity of typhoid fever is more severe among infected patients with immune suppression, biliary and urinary tract abnormalities and the like (Cohen, *et al.*, 1987). The mortality with severe typhoid fever is up to 32% depending on the country studied (Hoffman, *et.al,* 1984; WHO,2007).

Microbiology, Mode of spread and Virulence factors

There are four Shigellae species (serogroups) are defined on the basis of serologic or biochemical reactions, namely, *Shigella dysenteriae*, serogroup A; *Shigella flexneri*, serogroup B; *Shigella boydii*, serogroup C; and *Shigella sonnei*, serogroup D that cause shigellosis, and all but *S. sonnei* have more than one genetically distinct subtype (serotype) (von Seidlein, 2006).

Several studies showed that species classification has important therapeutic implications because the species differ in both geographic distribution and antimicrobial susceptibility (Finkelstein *et al.* , 2002 and Ashkenazi *et al.* 2003).

Species	**Serogroup**	**Serotypes**	
S. dysenteriae	A	1 – 12	most common, with outbreaks
S. flexneri	B	1 – 6 (with 15 subtypes)	developing countries
S. boydii	C	1-18	
S. sonnei	D	1	developed countries*

Table 1: Species and serogroups of Shigella (Sourse: Thomas and Gerald, 2000).
(*Edwards. 1999; Prado, 1999; Ashkenazi *et al.* ,1993; Yurdakok *et al*.,1997and Kotloff, 1999).

Shigellosis is initiated by ingestion of *shigellae* usually via fecal-oral contamination, via direct person to- person contact, and via food, water, and inanimate objects (WHO, 2001). Only a small number of ingested bacteria are required to produce illness. An early symptom, diarrhea (possibly elicited by enterotoxins and/or cytotoxin), may occur as the organisms pass through the small intestine. The hallmarks of shigellosis are bacterial invasion of the colonic epithelium and inflammatory colitis. These are interdependent processes amplified by local release of cytokines and by the infiltration of inflammatory elements. Colitis in the rectosigmoid mucosa, with concomitant malabsorption, results in the characteristic sign of bacillary dysentery: scanty, unformed stools tinged with blood and mucus. The disease is communicable as long as an infected person excretes the organism in the stool, which can extend up to four weeks from the onset of illness. Secondary attack rates, the number of exposed persons developing the disease within one to four days following exposure to the primary case (Park, 2005), can be as high as 40% among household contacts (Sur,2004). Flies especially *Musca domestica*, are also considered to play an important role in the spread of *Shigella* (Dupont *et al.,* 1989).

Shigella dysenteriae type 1 produces severe disease and may be associated with life-threatening complications. Shiga toxin, encoded chromosomally and found mainly in *S. dysenteriae* serotype 1, is a potent protein-synthesis inhibitor that targets primarily the vascular endothelium (Sandvig, 2001; Thorpe, 2001 and Bitzan and te Loo, 2003). Shiga toxin mediates the severe complication of hemolytic-uremic syndrome (Ray and Liu, 2001 and Bitzan and te Loo, 2003). In addition, Shiga toxin might play a role in the increased duration and severity of the diarrhea caused by *S. dysenteriae* serotype 1 (Faruque *et al.,* 1998 and Edwards, 1999). Moreover, *Shigella* enterotoxin 1 (ShET1) and ShET2, which are produced by several *Shigella* strains, were also found to induce fluid secretion into the intestine, thus accounting for the watery phase of diarrhea (Schroeder and Hilbi, 2008).

Virulence genes of this organism are coded on both chromosomes and plasmids. The severe irritation that is responsible for the bloody diarrhea is caused partly by LPS in its outer membrane, as well as a Shiga Toxin (an A-B toxin), produced by this organism, which acts as a cytotoxin, causing cell necrosis and ulceration, (Acheson, 1991 and Yavzori *et al.,* 2002). The Shiga toxins work by inhibiting protein synthesis in the host cells and cause cell death. After entering a cell, the Shiga toxin acts as an N-glycosidase, cleaving several nucleobases from the RNA that comprises the ribosome, thereby halting protein synthesis (Dutta *et al.,* 2004).

Pathogenesis

Shigellosis is an acute invasive enteric infection and it is clinically manifested by diarrhoea that is frequently mucoid or bloody and can lead to death. It is a disease limited to humans and certain other primates (Pozsgay, *et al*, 2006 and Phalipon and Sansonetti ,2007). Shigellosis is highly communicable of the bacterial diarrheas.

Experiments in volunteers have demonstrated that shigellosis is unique among bacterial enteropathogens in that fewer than 200 viable cells can readily produce the disease in healthy adults. The reasons for this low-dose response are not completely clear. One possible explanation is that virulent *Shigella* can withstand the low pH of gastric juice therefore gastric acids will have little effect on destroying them (Smith, 1987 and Flowers,1988). *Shigella* infections are almost always limited to the gastrointestinal tract; bloodstream invasion is quite rare (Jawetz *et al.,* 2003 and Mandell *et al.,* 2005).

Shigella causes disease by invading and replicating in cells lining the colonic mucosa. Structural gene proteins mediate the adherence of the organisms to the cells, as well as their invasion, intracellular replication, and cell-to-cell spread. *Shigella* species appear unable to attach to differentiated mucosal cells; rather, they first attach to and invade the M cells located in Peyer's patches. Then, secretion of proteins into epithelial cells and macrophages is mediated. These proteins induce membrane ruffling on the target cell, leading to engulfment of the bacteria. *Shigella* lyse the phagocytic vacuole and replicate in the host cell cytoplasm. With the rearrangement of actin filaments in the host cells, the bacteria are propelled through the cytoplasm to adjacent cells, where cell-to-cell passage occurs. In this way, *Shigella* organisms are protected from immune-mediated clearance. *Shigella*e survive phagocytosis by inducing programmed cell death **(apoptosis).** This process this in turn destabilizes the integrity of the intestinal wall and allows the bacteria to reach the deeper epithelial cells (Murray *et al.,* 2005). Following host epithelial cell invasion and penetration of the colonic mucosa, *Shigella* infection is characterized by degeneration of the epithelium and inflammation of the lamina propria. This results in desquamation and ulceration of the mucosa, and subsequent leakage of blood, inflammatory elements and mucus into the intestinal lumen. Patients suffering from *Shigella* infection will therefore pass frequent, scanty, dysenteric stool mixed with blood and mucus, since, under these conditions, the absorption of water by the colon is inhibited (Todar, 2009).

According to WHO (2005), *S. dysenteriae* type 1 differs from other *Shigella* in four important ways:

- it produces a potent cytotoxin (Shiga toxin);
- it causes illness that is more severe, more prolonged, and more frequently fatal than is illness caused by other *Shigella*;
- resistance to antimicrobials occurs more frequently than among other *Shigella*; and
- it causes large, often regional, epidemics, frequently with high attack rates and high case fatality rates.

Salmonella typhi has a combination of characteristics that make it an effective pathogen. This species contains an endotoxin typical of Gram negative organisms, as well as the Vi antigen which is thought to increase virulence. It also produces and excretes a protein known as “invasin” that allows non-phagocytic cells to take up the bacterium, where it is able to live and replicate intracellularly. It is also able to inhibit the oxidative burst of leukocytes, making innate immune response ineffective.

Human beings become infected with *S .typhi* through ingestion of faecal contaminated food, milk, or water. 1–5% of infected people become chronic carriers by harbouring *S. typhi* in the gall bladder, despite antibiotic therapy (WHO, 2003). The inoculum size and the type of vehicle in which the organisms are ingested greatly influence both the attack rate and the incubation period. Epidemiological data suggest that waterborne transmission of *S. typhi* usually involves small inocula, whereas foodborne transmission is associated with large inocula and high attack rates over short periods. For foodborne salmonellosis, an individual generally has to consume ca. 10^{5-6} cells; however, for some virulent strains, ingestion of fewer cells can cause the disease. Strains sensitive to gastric acidity generally need more cells to establish in the intestine and cause the disease; conversely, acidresistant strains may require fewer cells to cause the disease.

Depending on the size of the inoculum ingested and the health and immune status of the person, the incubation period of *S. typhi* ranges from 5 to 21 days. In volunteers who ingested 10^9 and 10^8 pathogenic *S. typhi* in 45 ml of skimmed milk, clinical illness appeared in 98% and 89% respectively. Doses of 10^5 caused typhoid fever in 28% to 55% of volunteers, whereas none of 14 persons who ingested 10^3 organisms developed clinical illness. (Hornick,*et al.,* 1970; Pearson and Guerrant, 2000).

Pathogenic *salmonellae* ingested in food can survive passage through the gastric acid barrier and invade the mucosa of the small and large intestine and produce toxins. Invasion of epithelial cells stimulates the release of pro-inflammatory cytokines which induce an inflammatory reaction. The acute inflammatory response causes diarrhea and may lead to ulceration and destruction of the mucosa. The bacteria can disseminate from the intestines to cause systemic disease. According to Rodriguez *et al. (*1986) and MacLennan *et al*. (2004), the pathogenesis of enteric fever depends on the ingested inoculum size of *S typhi*, the virulence of the strain such as possession of a complete lipopolysaccharide coat, the presence of the Vi antigen, and the production and excretion of a protein (invasion), the host’s immune response and previous exposure, and local protective factors. Numerous extra-intestinal complications can occur with S *typhi* infection, including the involvement of the central nervous system (3–35%), cardiovascular system (1–5%), pulmonary system (1–86%), bone and joints (1%), hepatobiliary system (1–26%), genitourinary system (<1%), and others (Pearson and Guerrant, 2000 and Su, *et al.,* 2004). Study by Threlfall and Ward (2001) showed that a chronic carrier state is established in an

estimated 1 -5% of cases.

Garcia-del Portillo, *et al.* (1993) and Foster (1993) showed that once ingested, *S .typhi* is able to survive exposure to gastric acid in the stomach before passage into the small intestine. *S .typhi* possess a two-stage inducible acid tolerance system that allows the bacterium to survive in conditions of severe low pH stress (pH 3·3). The first stage involves the production of an inducible pH homeostasis system functional at external pH values below 4·0, and the second stage involves the synthesis of acid shock proteins that are essential for pH 3·3 acid tolerance.

In the small intestine, *S .typhi* penetrates the intestinal mucosa via M cells that overlie the ileal

Peyer's patches (Kohbata *et al.*, 1986). *S. typhi* are then taken up by mononuclear cells in the intestinal lymphoid tissue, which may lead to dissemination via the lymphatic system or the haematogenous route. This intracellular bacterium multiplies in reticuloendothelial cells and macrophages located in the lymph nodes, liver, spleen, and bone marrow during the asymptomatic incubation phase of typhoid fever. Once a threshold level of *S .typhi* is reached, the bacteria are released into the blood, initiating a continuous secondary bacteraemia with secretion of cytokines by macrophages during the symptomatic phase of typhoid fever(MacLennan *et al.,*2004). This secondary, and persistent, bacteraemia seeds additional organs, which results in extra-intestinal infectious complications.

Pathogenesis of extra-intestinal infections by *S .typhi*

Central nervous system involvement with *S .typhi* infection occurs in 3–35% of patients. Green and Cheesbrough (1993), Dutta *et al*.(2001) and WHO (2003) reported that central nervous system manifestations include encephalopathy, meningitis (12%), transient Parkinsonism, motor neuron disorders, ataxia, cerebral abscesses, cerebral oedema, seizures, and Guillain–Barre syndrome.

Cardiac problems caused by *S .typhi* infection, such as myocarditis and endocarditis, occur in 1–5% of cases(Schneider *et al.*, 1976; Kamili *et al.*, 1996; Ghadage and Bal, 2001; Khan *et.al,* 2003). Pericarditis and arteritis occur in less than 1% of cases. Most patients with cardiac infectious complications have underlying cardiac abnormalities such as existing valvular abnormalities, rheumatic heart disease, or congenital heart defects. Respiratory symptoms of typhoid fever, such as cough, occur in 11–86% of cases. Studies by Dutta *et al.* (2001) and Su *et al.* (2004) indicated patients with pulmonary manifestations of typhoid fever often have underlying lung abnormalities, a previous history of lung infection, sickle cell anemia, alcohol abuse, diabetes, or immunosuppression with HIV/AIDS. Patients may present with fever, chills, cough (with or without productive sputum), pleuritic pain, coarse crackles and bronchial breathing on auscultation, diarrhoea, and leucopenia.

Organ system involved	**Prevalence**	**Risk factors**	**Complications**
Central nervous system	3–35%	Residence in endemic region, malignancy, endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, and osteomyelitis of the skull	Encephalopathy, cerebral oedema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia, seizures, Guillain–Barre syndrome, psychosis
Cardiovascular system	1–5%	Cardiac abnormalities, eg. existing valvular abnormalities, rheumatic heart disease, or congenital heart defects	Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
Pulmonary system	1–6%	Residence in endemic region, past pulmonary infection, sickle cell anaemia, alcohol abuse, diabetes, HIV infection	Pneumonia, empyema, bronchopleural fistula
Bone and joint	<1%	Sickle cell anaemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, those at extremes of age, and steroid use	Osteomyelitis, septic arthritis
Hepatobiliary system	1–26%	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, haemoglobinopathy	Cholecystitis, hepatitis,hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
Genitourinary system	<1%	Urinary tract, pelvic pathology, and systemic abnormalities	Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
Soft tissue infections	least cases reported	Diabetes	Psoas abscess, gluteal abscess, cutaneous vasculitis
Haematological	least cases reported		Haemophagocytosis syndrome

Table 2: Extra-intestinal infectious complications of typhoid fever caused by Salmonella enterica serotype Typhi (Source: Su *et al.* 2004)

Toxins

Following ingestion of *Salmonella* cells, the pathogens invade mucosa of the small intestine, proliferate in the epithelial cells, and produce a toxin, resulting in an inflammatory reaction and fluid accumulation in the intestine.

The ability of the pathogens to invade and damage the cells is attributed to the production of a thermostable cytotoxic factor. Once inside the epithelial cells, the pathogens multiply and produce a thermolabile enterotoxin that is directly related to the secretion of fluid and electrolytes. Production of the enterotoxin is directly related to the growth rate of the pathogens(Hornick *et al.,*1970; Pearson and Guerrant, 2000).

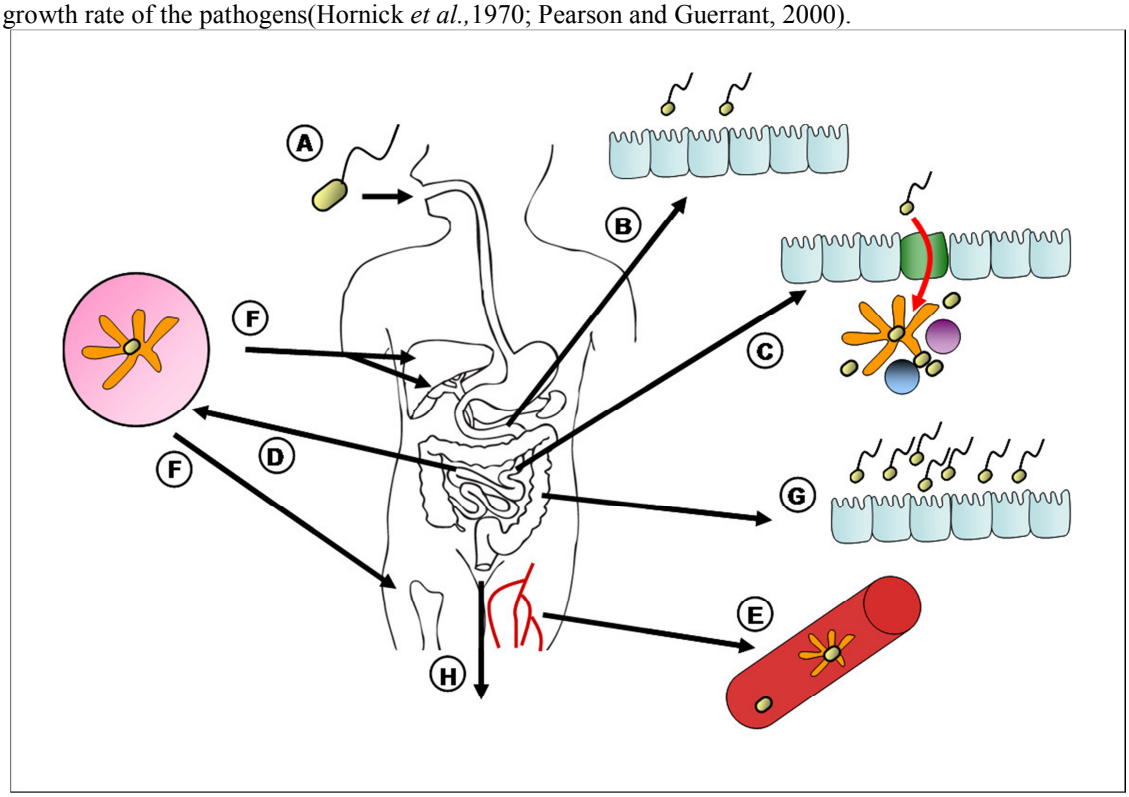

Figure: 1. The lifestyle of *Salmonella* typhi in the human host and implications for diagnostics. (Source: Baker, *BMC Infectious Diseases*, 2010).

A: For *S. typhi* infection, the organism normally enters the human host through oral ingestion of an infectious dose.

B: *S. typhi* does not replicate in large numbers in the intestine and shedding may be sporadic and limited.

C: Invasion occurs through the terminal ileum, perhaps a short time after ingestion, M cells may be the preferred portal of entry.

D: *S. typhi* is transferred to monocytic cells and is trafficked to the reticulo-endothelial system, potentially in a semi-dormant state.

E: *S. typhi* re-emerges at an unknown time from the reticulo-endothelial system, possibly as the acquired immune response is activated, and re-enters the blood stream in low numbers.

F: *S. typhi* seeds into the liver, the gall bladder and the bone marrow where it can reside and may be detected for months or years.

G: *S. typhi* can enter into the bile duct and be shed sporadically, potentially in high numbers into the environment via the intestine.

Clinical features

Shigellosis typically evolves through several phases and manifestations of Shigella infection vary with the infecting species, the age of the host, the presence of risk factors and the specific immune status of the host. Clinical presentations of shigellosis are watery diarrhea occurring in younger children and associated with a shorter duration of illness and with more vomiting and dehydration and dysentery with stool blood and abdominal pain. These different presentations may reflect two mechanisms in the pathogenesis of shigellosis or different stages of the disease. The most useful signs and symptoms for the diagnosis of shigellosis were stool with blood and abdominal pain in all patients and the absence of watery diarrhea and vomiting in patients over one year old. Simple visual inspection of stool for blood correctly identified 44% of all patients infected with *Shigella* (Stoll *et al*., 1982).

The incubation period is 1 to 4 days, but may be as long as 8 days with S. dysenteriae (Levine *et al.,* 1973). The clinical manifestation of shigellosis ranges from an asymptomatic illness to bacteraemia and sepsis. Symptoms include fever, diarrhoea and/or dysentery with abdominal cramps and ineffectual and painful straining at stool or in urinating (Niyogi, 2005). Shigellosis may be associated with mild to life-threatening complications, such as rectal prolapse, arthralgia (painful joints), arthritis, intestinal perforation, and toxic mega

colon (extreme inflammation and distension of the colon), central nervous disorders, convulsions, enteropathy (protein-losing disease of the intestines), electrolyte imbalance of salts, and sepsis (Ozuah, 1998; Sur, 2004 and WHO2005b). Haemolytic uraemic syndrome (a complication resulting in kidney failure, bleeding, and anaemia) and leukemoid reaction (blood findings resembling leukaemia) complicate infection due to *S. dysenteriae* type 1 and may be fatal.

Diagnosis

The most useful signs and symptoms for the diagnosis of shigellosis are stool with blood and abdominal pain in all patients and the absence of watery diarrhea and vomiting in patients over one year old (Stoll *et al*., 1982). Routine microscopy of fresh stool is a simple screening test that is cheap, rapid, and easy to perform; and visualization of numerous poly-morphonucleocytes suggests a bacterial aetiology. Definite diagnosis of shigellosis can only be made by stool culture (WHO, 2005a). However, Shigella species die rapidly in unfavourable environments and stool culture should ideally be supplemented by attempts to identify Shigella DNA using polymerase chain reaction (PCR) (von Seidlein 2006).

The definitive diagnosis of typhoid fever depends on the isolation of *S. typhi* from blood, bone marrow or a specific anatomical lesion. (Benavente *et al.,* 1984; Vallenas *et al.,* 1985 and Wain *et al.,* 2001) The presence of clinical symptoms characteristic of typhoid fever or the detection of a specific antibody response is suggestive of typhoid fever but not definitive. Blood culture is the mainstay of the diagnosis of this disease. Additionally, the presence of *Salmonella typhi* can be detected either by the demonstration of specific antibodies or antigen in the serum or urine. The organism may be cultured from stool or urine (Giannella, 1996 and US,1980).

Prevention and Treatment

The most effective methods for controlling shigellosis are provision of safe and abundant water and effective faeces disposal. Prevention of dysentery caused by *Shigella* relies primarily on measures that prevent spread of the organism within the community and from person to person (WHO/CDR/95.4). These include:

- hand-washing with soap,
- ensuring the availability of safe drinking water,
- safely disposing of human waste,
- breastfeeding of infants and young children,
- safe handling and processing of food, and
- control of flies.

These measures will not only reduce the incidence of shigellosis, but of other diarrhoeal diseases as well. In all cases, health education and the cooperation of the community in implementing control measures are essential.

In general, several studies and Edwards (1999), reported that the most effective intervention strategy to minimize morbidity and mortality would involve comprehensive media and personal outreach programs consisting of the following components:

- Education of all residents to actively avoid faecal contamination of food and water and to encourage hand washing after defecation;
- Encourage mother to breast feed infants;
- Promote the use of oral rehydration therapy to offset the effects of acute diarrhea;
- Encourage mothers to provide convalescent nutritional care in the form of extra food for children recovering from diarrhea or dysentery.

The key to avoiding infection by *S. typhi* is prevention of fecal contamination in drinking water and food supplies. Since the only source of this agent is infected humans, it is possible to control transmission by proper hygiene, waste management, water purification, and treatment of the sick. Health education is paramount to raise public awareness and induce behaviour change.

Vaccination

The old parenteral killed whole-cell vaccine was effective but produced strong side-effects because of LPS. Yang *et al.* (2001) revealed that two safe and effective vaccines are now licensed and available. One is based on defined subunit antigens (Vi polysaccharide, is given in a single dose Subcutaneous), the other on whole-cell live attenuated bacteria (the live oral vaccine Ty2la, available in enteric-coated capsule or liquid formulation (Lin *et al.,* 2001). Vaccination against typhoid fever before or during an outbreak situation should therefore be seriously considered as an effective tool.

Fluids &Nutrition and Antimicrobial Therapy

The mainstay of treatment of shigellosis in children is correction of the fluid and electrolyte loss, which often can be achieved by administering oral rehydration solutions (Edwards, 1999, Khan *et al*. 1999). Early feeding, even with a high-protein diet, is important, especially in developing countries, to prevent malnutrition and encourage optimal growth (Kabir *et al.* 1998). Rehydration therapy is an essential first step which can be used to correct dehydration due to diarrheas of any etiology and has greatly decreased the number of deaths due to diarrhoea.

Various antimicrobial agents are effective in the treatment of shigellosis, although options are becoming limited because of globally emerging drug resistance (Ashkenazi ,2002; Bhattacharya and Sur, 2003). Resistance of *Shigella* species to sulfonamides, tetracyclines, ampicillin, and trimethoprim-sulfamethoxazole (TMP-SMX) has been reported worldwide and these agents are not recommended as empirical therapy unless local microbiologic data suggest susceptibility (Ashkenazi *et al.,* 2003).

The World Health Organization recommends that all suspected cases of shigellosis based on clinical features be treated with effective antimicrobials (antibiotics) (WHO, 2006 and Christopher *et al.*, 2010). According to the WHO guidelines (WHO/CDR/95.3), the choice of antimicrobial drug has changed over the years as resistance to antibiotics has occurred, with different patterns of resistance being reported around the world. Evidence is insufficient to consider any class of antibiotic superior in efficacy in treating *Shigella* dysentery.

The following antibiotics are used to treat *Shigella* dysentery:

- Beta-lactams: Ampicillin, amoxicillin, third-generation cephalosporins (cefixime, ceftriaxone), and pivmecillinam (not available in the United States)
- Quinolones: Nalidixic acid, ciprofloxacin, norfloxacin, and ofloxacin
- Macrolides: Azithromycin
- Others: sulfonamides, tetracycline, cotrimoxazole, and furazolidone.

The oral rehydration therapy is a simple way to prevent many of the deaths of diarrheal diseases in general. Supportive measures such as appropriate nutrition and blood transfusions are also important in the management of typhoid fever if indicated. More than 90% of patients can be managed at home with oral antibiotics, reliable care and close medical follow-up for complications or failure to respond to therapy (Punjabi, 2000). Where resistance is uncommon, the treatment of choice is a fluoroquinolones such as ciprofloxacin (Chinh *et al.*, 2000; Parry and Beeching, 2009 and Effa *et al.* ,2011). The fluoroquinolones attain excellent tissue penetration, kill *S. typhi* in its intracellular stationary stage in monocytes/macrophages and achieve higher active drug levels in the gall bladder than other drugs. Otherwise, a third-generation cephalosporin such as ceftriaxone or cefotaxime is the first choice (Soe and Overturf ,1987; Wallace *et al.*,1993 and Dutta *et al.*, 2001). Cefixime is a suitable oral alternative (Bhutta *et al.,* 1994 and Cao *et al.,*1999).

However, the emergence of MDR strains has reduced the choice of antibiotics in many areas. There are two categories of drug resistance: resistance to antibiotics such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole/ TMP-SMZ (MDR strains) and resistance to the fluoroquinolone drugs. Resistance to the fluoroquinolones may be total or partial (Das *et al.,* 2000; Gupta *et.al,* 2001; Dutta *et al.,* 2001 and Cooke *et al.,* 2006).

When untreated, typhoid fever persists for three weeks to a month. Death occurs in between 10% and 30% of untreated cases (WHO, 2007).

	Optimal theraupy			Alternative effective drugs		
Susceptibility	Antibiotic	Daily dose mg/kg	Days	Antibiotic	Daily dose mg/kg	Days
Fully sensitive	Fluoroquinolones Eg. Ofloxacin or ciprofloxacin	15	5-7	Chloramphenicol amoxicillin TMP-SMZ	50-75 75-100 8-40	14-21 14 14
Multidrug resistance	Fluoroquinolone or cefixime	15 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

Table:3. treatment of typhoid fever (Source: *The Indian Journal of Medical Research* 2001;113: 210-213.)

Conclusion

The epidemiology of *Shigella dysenteriae* is worldwide and the organism is responsible for bacillary dysentery. This disease is most often associated with areas of overcrowding and poor sanitation. Symptoms of dysentery due to this organism include mild to severe diarrhea, which is sometimes bloody or watery and the like. The organism penetrate the mucosal epithelial cells of the intestine and penetration causes severe irritation which is responsible for the cramps and watery, bloody diarrhea. Dehydration can become a complication. Virulence genes of this organism are coded on both chromosomes and plasmids. The severe irritation that is responsible for the bloody diarrhea is caused partly by LPS in its outer membrane, as well as a Shiga. The Shiga Toxin causes cell death by preventing protein synthesis by cleaving a specific adenine residue from RNA. Definite diagnosis of shigellosis can only be made by stool culture and PCR. This organism can be successfully treated with antibiotics such as ampicillin and ciprofloxacin. Fluids can be given to those individuals suffering from

dehydration. Since it is predominantly spread by the fecal-oral route, thoroughly washing hands, proper food handling is also an important method of prevention, as well as maintaining clean water supplies, which is highly effective.

Infection caused by *S. typhi* remains an important public health problem, particularly in developing countries. Morbidity and mortality attributable to typhoid fever are once again increasing with the emergence and worldwide spread of *S. typhi* strains that are resistant to most previously useful antibiotics. As a consequence there is renewed interest in understanding the epidemiology, diagnosis and treatment of typhoid fever and some specific aspects of its pathogenesis. Extra-intestinal infectious complications caused by *S. typhi* are uncommon. However, when *S. typhi* bacteraemia occurs virtually any organ system may be potentially involved. In general, fluorquinolones and third-generation cephalosporins are the first-line therapy for infections with *S typhi*. Alternative therapy for susceptible strains consists of ampicillin, chloramphenicol, and co-trimoxazole. More importantly, perhaps, there is much interest in the possibility of expanded roles for typhoid vaccines. Now, devise ways of using the two currently available improved typhoid vaccines, parenteral Vi polysaccharide and oral Ty21a.

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