SHIGELLA BACTERIA CAUSES AN INFECTION CALLED SHIGELLOSIS

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ABSTRACT

One of the main causes of diarrhea in India is shigellosis. Although shigellosis is common in the nation and has been implicated in numerous outbreaks, exact estimates of morbidity and mortality attributable to the disease are scarce. According to the scant information available, shigella is a significant food-borne disease in India.The most prevalent species is Shigellaflexneri, although non-agglutinableshigellae and S. sonnei are rapidly emerging and S. dysenteriae has temporarily vanished from the northern and eastern regions. There have been numerous global outbreaks of shigella strains that are resistant to antibiotics. The global spread of multidrug resistant Shigella, particularly the rise in resitance to azithromycin, third-generation cephalosporins, and fluoroquinolones, is particularly significant. Shigellosis prevention is preferred since it will significantly lower the morbidity related to diarrhea in the nation. To lessen the burden of shigellosis, public health interventions like providing clean water and proper sanitation are crucial. However, India's resource shortage is a complicated problem that will take some time to overcome. Therefore, the scientific effort should concentrate on creating a multivalent vaccine that is both safe and inexpensive. The epidemiology, disease burden, and therapeutic difficulties of shigellosis from an Indian viewpoint are the main topics of this paper.Foodborne diseases related to unhygienic food handling practices remain a major public health problem across the globe. The problem is rigorous in developing countries due to

restrictions in securing most possible hygienic food handling practices. Bacillary dysentery (Shigellosis) is a severe human disease caused by Shigellae. It is one of the major sources of diarrhoea in developing countries. In this Review, a lot of knowledge has been created about the host, pathogen, and environmental factors that have an impact on the pathogenesis of shigellosis at the cellular and molecular level. This information also summarizes what is currently known about Shigella, elements those features that contribute to pathogenesis, and looks into the progress being made in the creation of a safe and affordable multivalent vaccine. Therefore, the focus of this study is on how developing nations perceive the epidemiology, disease burden, and therapeutic problems of Shigellosis.In order to give a basic overview of foodborne diseases, particularly shigellosis, Shigella pathogenesis causing agents, transmission, prevention and control and effect of different preservatives on shigella.

Keyword- shigellosis, epidemiology, pathogenesis, food borne disease, diarrhea

1. INTRODUCTION

Shigella spp. are gram negative, short (1-3.5µm) non-motile, nonpigmented, non-encapsulated, non-spore forming, facultatively anaerobic rods. Shigella grows less profusely on artificial media than coliform bacteria and other members of the family Enterobacteriaceae. They are less active in their utilization of carbohydrates than E. coli and do not form visible gas from carbohydrates (except for certain biotypes of S. flexneri Shigellosis is endemic in most developing countries and is the most important cause of bloody diarrhoea worldwide. It is estimated to cause at least 80 million cases of bloody diarrhoea and 700,000 deaths each year. Ninety-nine percent of infections caused by Shigella occur in developing countries, and the majority of cases (~70%), and of deaths (~60%), occur among children less than five years of age. Probably less than one percent of cases are treated in hospital. They are aerobes and facultative anaerobes, with growth temperature range of 10-40°C and optimal of 37°C and pH 7.4. They grow on ordinary media. Shigella does not need to grow in food to cause illness, as the very low infective dose means that the presence of the organism in food is sufficient to cause infection. Shigella spp. survive at frozen and chill temperature, although the time of survival depends on the type of food environment as well as temperature Shigella is found in the intestinal tracts of infected people. The bacteria are spread by direct or indirect contact with fecal material from an infected person. A person with shigellosis may spread infection to others indirectly by contaminating food, water, or inanimate objects (some common examples include toys, bathroom fixtures, and changing tables). Produce harvested from a field with sewage in it can also become contaminated. Water may become contaminated by an infected person swimming or playing in it, or by sewage

running into it. Flies can also spread infection by physically transporting Shigella bacteria. Shigella can be spread for as long as the organism is present in a person's stool. People can pass Shigella in their stool for up to four weeks (possibly longer in asymptomatic people). Certain antibiotics may shorten the length of time a person can shed the organism in their stool.

Laboratory tests can identify Shigella in the stool of an infected person. Special laboratory tests may also be done to determine which antibiotics, if any, will work best to treat the infection. (Lampel*et al.*, 2003)

Shigella spp. can grow at water activities down to 0.96 (maximum salt conc. 5.2% NaCl). The organism dies out slowly at low water activities. Even at high NaCl concentration (10%) some strains can survive for 4 days (Marcel *et al.*,2007)

Infection is initiated by ingestion of shigellae (usually via fecal-oral contamination). 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. (Doyle MP *et al.*,2004)

Shigella spp. are bacteria that cause shigellosis, also known as bacillary dysentery. They are a highly infectious organism, with foodborne outbreaks often involving infected food handlers. Unlike other common foodborne pathogens, humans are the only natural hosts of Shigella spp.

The diarrheal pathogens Shigella spp. are closely linked to Escherichia coli. They received their name from Kiyoshi Shiga, who discovered that Shigelladysenteriae, one of their most aggressive members, was the cause of bacillary dysentery, generally known as shigellosis, in 1898 (Trofa AF *et al.*, 1999). Shigella spp. are facultative anaerobic, Gram-negative, non-spore-forming bacteria that invade the intestinal epithelium in humans and other primates to produce diarrheal illness. The infection often only affects the intestinal lining, where it causes ulceration, inflammation, and loss of intestinal barrier function. Shigellae are spread orally by faeces or by consuming contaminated food and water. Shigella spp. typically induce a self-limiting illness that is well treated with oral rehydration or antibiotics.Despite the fact that there has been a constant rise in the number of cases of shigellosis brought on by Shigella strains that are resistant

to antibiotics (Anderson M *et al.*, 2016; Schroeder GN *et al.*, 2008). Shigellosis can be fatal in young children, immune compromised people, and people who lack access to proper medical care.

Shigellosis's clinical signs and symptoms might range from a simple case of watery diarrhoea to one that is bloody and mucoid, along with fever and uncomfortable abdominal cramps. The variety of clinical symptoms depends on the host's immune system as well as the specific Shigella species that caused the infection. These species vary in the presence of some essential virulence components, such as Shiga toxin. Toxic megacolon is a serious complication that affects newborns and young children, and after the infection has been cleared, further potential problems include hemolytic uremic syndrome.

Shigella is mainly the symptoms of GIT infecrtions, most cases of diarrhoea in children result from infection by a variety of bacteria and viruses or parasites which disturb the fluid level and nutrient assimilation of intestines.(Black R.E. *et al.*,2010)

There are different Shigella species and sero types have emerged all over the world[2]. Most of shigellosis is associated with a few medical complications only, adequate control of this disease may reduce the overall GIT infection burden globally. The diagnosis of shigellosis can be easily done by culture isolation of Shigella from rectal and feaces or rectal swabs. Antibiotic treatment is usually recommended in patients with moderate or severe symptoms as it can reduce the duration and severity of symptoms, excretion of organisms, and prevent complications. (Von Seidlein L *et al.*,2006' Kuo CY *et al.*,2008)

1.1 Classification of shigella

Shigella is a member of the Enterobacteriaceae family. It consists of four species:

- S. dysenteriae,
- S. flexneri, S.
- Sonnei
- S. boydii.

These four species are further divided into serotypes based on biochemical variabilty and differences in their O-antigen. The result is that S. dysenteriae (group A) has 17 serotypes, S. flexneri (group B) has 14 classical serotypes and subserotypes, S. sonnei (group C) has one serotype, and S. boydii (group D) has 20 serotypes(Wei.J*et at*.,2003)

The way that many species respond to the GIT tract is frequently the same. Shigella species are facultative anaerobes that are non-lactose fermenting, non-encapsulated, Gram-negative, non-motile, and pathogenic to humans.(Penatti.MPA*et al*.,2007) They are typically spread from person to person as well as through the use of tainted food and water.2 Shigelladysenteriae, Shigellaflexneri, Shigellaboydii, and Shigellasonnei are only a few of the four species and at least 47 serotypes that make up the genus Shigella.(Theron J *et al*.,2001'Kingombe *et al*.,2005) They are the main cause of shigellosis or bacillary dysentery, which primarily affects old people, children, and people with impaired immune systems.1 According to estimates, there are 160 million cases of the disease worldwide, and 1.25 million people die from it each year in the developing countries.4 In South Africa, there were 1812 cases of both invasive and non-invasive illness in 2009.Shigellosis that is non-invasive and more common in children under the age of five.(Keddy*et al*.,2010)

Shigellosis is distinguished by the colonic epithelium being destroyed as a result of an inflammatory reaction brought on by bacterial invasion of the mucosa.(Parsot*et al*.,2005) Shigella isolates are often distinguished based on serotyping and tests (biochemical type).1

2. CLINICAL FEATURES AND COMPLICATIONS

Clinical signs and symptoms might vary from mild ones like loose, watery stools to severe ones like fever, stomach pain, and bloody diarrhoea. While S. flexneri infections can potentially cause dysentery, S. dysenteriae infections frequently do so, whereas S. boydii and S. sonnei infections typically result in self-limited watery diarrhea.(Niyogi SK *et al*.,2005) Acute effects such toxic megacolon, peritonitis, and septicemia are frequently observed in children who are extremely malnourished, however they can occur in the absence of early antibiotic therapy. Other potentially deadly side effects of Shigella dysentery include haemolytic-uremic syndrome, severe anorexia, weight loss, hunger, dilatation of the large intestine, seizures, kidney damage, and persistent diarrhea(Sur *et al*.,2004). Bacteremia may occur in infants and persons with compromised immune systems.S. sonnei-related pneumonia has also been documented in HIV-positive adults, malnourished children, and people with chronic illnesses(Miller *et al*.,2005' Mandell W *et al*.,1986'Raffensperger E.C *et al*.,1956).

3. PATHOGENESISOFSHIGELLA

Shigellae infection starts when it is ingested, frequently through faecal-oral contamination. Once within the body of the host, the organism travels through the digestive system before landing in the large intestine. Typically, the disease just affects the intestinal mucosa. Beginning the pathogenesis is Shigella's entry into the body through the basal face of the intestinal epithelium. Because of this, when Shigella enters the large intestine, microfold cells (M cells), a unique part of the follicle related epithelium that covers the mucosal lymphoid follicles and acts as the mucosal immune system's stimulation point, take it up in vacuoles. The organism finally finds its way to the macrophages below, which are linked to the M cell-associated lymphoid follicles, after exiting the vacuole (Wassef J *et al*.,1989).

The pathogen, Shigella, is phagocytotized by macrophages in the dome region of these follicles, resulting in apoptosis and allowing the infection to move to the basal side of the colonic epithelium. Furthermore, it has been reported that pathogenic S. flexneri causes necrosis in human monocyte-derived macrophages48 and destroys the mitochondria of the host cell. Another study found that, in epithelial cells under oxidative cell stress, Shigella induced mitochondrial dysfunction in non-myeloid cells, which resulted in caspase-independent necrotic cell death through a new mechanism (Perdomo*et al*.,1994' Sansonetti*et al*.,1999' Koterski*et al*.,2005) Proinflammatory cytokine IL-12 is generated by dying macrophages, and this eventually leads to the migration of polymorphonuclear (PMN) cells to the infection site and the onset of inflammation (Carneiro L A *et al*.,2009' Hathaway *et al*.,2002' Sansonetti P.J *et al*., 2000).

The bacterial invasion of the host intestinal cell is the first of pathogenesis' five stages. Shigella becomes phagocytized, the cell membranes fuse, causing lysis of phagosomes and bacterial growth. The bacterium then spreads intra- and intercellularly, ulcerating the mucosa and killing the host cell, followed by inflammation. The fundamental event in the infection's pathophysiology is Shigella's capacity to invade and colonise the human intestinal epithelium. A significant acute inflammatory response with polymorphonuclear leukocyte infiltration is triggered by this. Shigella requires M cells attached to Gastrointestinal Associated Lymphoid Tissue (GALT) to pass through the colonic mucosa, which is necessary for the multi-step pathogenesis of the bacterium. Once within epithelial cells, the bacteria have the ability to rewire them to create pro-inflammatory mediators like interleukin 8, which play a critical part in the robust inflammatory response that aids in subsequent bacterial invasion. A 213 kilobase (kb) plasmid that is specific to virulent Shigella and enteroinvasive E. coli (EIEC) strains contains the majority of the virulence factors involved in invasion of epithelial cells. (Ali R *et al*.,2018'AI mohanna*et al*.,' Curtis L et al 2008' Thomas L *et al*.,'Torres*et al*., 2004)

4. ROUTES OF TRANSMISSION/RESERVOIRS

Shigella spp. are spread through the faecal-oral route through direct contact with another person or by consuming tainted food or water.(Nygren BL *et al*.,2012) 120 foodborne shigellosis outbreaks that were reported in the United States (US) between 1998 and 2008 were examined by Nygren et al. (2012). Food handlers who were contaminated (58%), barehanded contact with ready-to-eat food (38%), insufficient cold-holding temperatures (15%), and insufficient cleaning

of food preparation equipment (15%) were the contributory variables found in these outbreaks. It should be emphasised that an outbreak might be caused by a number of different factors. Water contamination is another method of spreading Shigella spp. This can happen as a result of sewage seeping through the ground, improperly treated contaminated water being used for drinking and food preparation, or faeces contaminating recreational water (Lightfoot D *et al*., 2003)

5. PREVENTION AND CONTROL

Safe, abundant water and effective faeces disposal are prerequisites for the most effective shigellosis control strategies. Shigella-induced dysentery can be avoided primarily by taking precautions against the organism's transmission to others and within the community (Kotloff K L *et al*.,1999). These consist of: • Soapy hand washing ensuring access to clean drinking water, safely disposing of human waste, breastfeeding newborns and young children, handling and processing food safely, and controlling flies are all important practises. These actions will lessen the prevalence of other diarrheal disorders in addition to shigellosis. Health education and community cooperation are essential in all situations while carrying out control measuresAccording to numerous studies and Edwards (1999) (Bulletin of the WHO), the best intercession strategy to reduce morbidity and death would comprise extensive media and individual outreach programmes with the following elements:

• Teaching all citizens how to prevent faeces from contaminating their food and water and encouraging them to wash their hands after going to the toilet;

Encourage mothers to breastfeed their newborns; advocate the use of oral rehydration therapy to counteract the effects of acute diarrhoea; and urge mothers to give their children extra food while they are recovering from diarrhoea or dysentery.

Avoiding faecal contamination of food and drinking water is a key factor in preventing Shigella infection. Since infected humans are the only source of this agent, transmission can be prevented through good hygiene, waste disposal, water filtration, and medical care for the ill. In order to increase public awareness and encourage behaviour change, health education is essential.

Shigellosis vaccine: There is a critical need for a vaccination that is reliable, secure, and affordable.(Michael E *et al*.,2008) Shigellosis is a disease with a high prevalence in developing nations, with children under five years old making up the majority of those affected. It is also a condition with limited treatment options due to the emergence of multiple medication resistance

in these locations. Shigella point to vaccination as a potential solution for an efficient and long-lasting strategy against shigellosis. The WHO has identified shigellosis as one of the gastrointestinal infections for which innovative vaccines are most urgently needed. The target populations include military personnel, travellers from wealthy nations, and children living in endemic areas. (Seidlein L *et al.*,2006').

Despite the urgent need for a Shigella vaccine, little progress has been made because of the antigenic complexity, lack of cross-protective epitopes between species, and gaps in our understanding of the immune system's defence mechanism. Shigella vaccines of many forms have undergone experimental testing on animals and in human studies.(Edwards B.H *et al.*,1999) The old parenterally killed whole-cell vaccine, one of many live attenuated vaccines, was effective but had significant side effects because to LPS.(Venkatesan M *et al.*,2006) showed that There are now two licenced and functional vaccinations. The live oral vaccination Ty2la, which is offered in enteric-coated capsule or liquid format.(Lin F Y *et al.*, 2001) is based on whole-cell live attenuated bacteria, while the first is based on specified subunit antigens (Vi polysaccharide, given in a single dose Subcutaneous). Shigellosis vaccination should, therefore, be carefully examined as a useful strategy before or during an outbreak state.

6. THE EFFECT OF INORGANIC AND ORGANIC FOOD PRESERVATIVES ON SHIGELLA:

6.1 SODIUM CHLORIDE : Sodium chloride, or common salt, was unquestionably the first antibacterial agent to be employed in food. One may be sure that it was used as a preservative rather than a flavour in early cultures. The traditional way to preserve meat is through salting, which is frequently done in conjunction with smoking and drying. Modern technology has made it possible to salt meat more quickly, but the fundamentals haven't changed much over the years. Water activity, aw, is reduced to approximately 0.96 using solutions containing 15–25% salt. Most bacteria, including the bulk of those in charge of meat deterioration, have a development delay as a result. Foodborne bacteria experience plasmolysis (shrinkage), as well as inhibition or death of microbial cells, when large amounts of salt are added to foods for preservation (Coultate TP *et al.*, 2009).

6.2 THE EFFECT OF ORGANIC ACIDS:One of the earliest techniques for microbial control in food preservation that has been used to control microorganisms in food is the use of organic food preservatives. The majority of these preservatives are bacteriostatic rather than bacteriocidal, meaning that they regulate microorganisms by preventing their growth rather than necessarily killing them (Jay JM *et al*., 2005). Although all acids used as food preservatives are produced chemically, they are all found naturally in nature. These work best with foods that have a low pH, ideally less than 5.5 (Ngadi MO *et al*.,2012). The pH drop and the activities of the molecule's undissociated state are both credited with an organic acid's antibacterial properties. These actions collectively may have detrimental effects on how bacteria function.. While the undissociated acid, being soluble in lipids, can diffuse passively across the cell membrane and interfere with normal metabolism, the reduction in pH of the medium requires cells to endure acidification of the cytoplasm or expand energetically correcting this effect (Mayo B *et al*.,2010).According to studies on the mechanism of action of antimicrobials, the effects that are most noticeable happen at concentrations that slow the pace of development and approach the MICs. It is important to think about the relative doses required for these effects in order to comprehend the extent to which they are the main source of inhibition or lethality (Juneja VK *et al*.,2010).

6.3 ACETIC ACID: Acetic Acid (C2H4O2, m.w. 60.05ACETIC ACID is a substance found in mayonnaise and is created by fermenting organisms in foods like pickles. It is miscible with water and ethanol and has a strong smell. Despite being known to lower pH, it is antibacterial through other, less well-known pathways (Breguet V *et al*., 2010). One of the most significant organic acids with widespread application in the food business as an acidifying ingredient and/or preservation is acetic acid. All of the acetic acid utilised in the food industry must be of biological origin and is made using acetogenic bacteria, even if the majority of the market need is fulfilled by chemical synthesis. Because acetic acid is a weak acid, the undissociated acetic acid molecule and the acetate anions create a dynamic equilibrium in aqueous solution. At low pH, the undissociated acid dominates and seems to be the only factor in the antibacterial activity. Uncharged, tiny molecules like undissociated acetic acid can dissolve in the hydrophobic lipid plasma membranes of bacteria and quickly diffuse into the cytoplasm. Acetic acid quickly separates into acetate ions and protons once it enters the cytoplasm, drastically lowering the cytoplasm's pH and inhibiting or killing the microorganism. Food and beverage spoilage yeasts (Stratford m *et al*.,2006) .

6.4 CITRIC ACID: Due to its adaptability, citric acid is a common acidulate and is used as a standard in almost all preserved foods. In fact, citric acid is one of the organic acids that is most

frequently utilised in the chemical, pharmaceutical, and food sectors (Theron MM *et al*.,2010). Due to its acidulation and ability to chelate metal ions that catalyse oxidation, citric acid has antibacterial effects. The substrate for bacterial growth in the diet is reduced by chelating or binding metal ions, which affects growth . Numerous fruits and their juices contain levels of citric acid that are close to 1%, however blackcurrants have been shown to contain 4%. Citric acid is ineffective as an antibacterial agent and needs a high concentration to be active. It was discovered that 0.3% of citric acid has an impact on Salmonellae, 0.35 % has an impact on Enterobacteriaceae, and 0.5% inhibits the formation of various bread moulds. Acetic acid's major effect is most likely to be an acidulant, which lowers the pH of the cellular medium (Soltoft Jensen J *et al.*,2005).

6.5 LACTIC ACID

Lactic acidis a liquid that is colourless or yellowish and is made up of lactic acid (C3H6O3) and lactic anhydride (C6H10O5). Hygroscopic and miscible with both ethanol and water. It is naturally produced in a variety of fermented foods, including yoghurt and sauerkraut . Numerous foods use lactic acid and lactates to increase stability, and it is possible to demonstrate the inhibitory effects of lactic acids on pathogens and spoilage organisms in meat products even at neutral pH levels. Typically, lactate's inhibitory impact is attributed to the undissociated acid, which is membrane permeable and may jeopardise the cytoplasm's pH balance. Both acidification of the cytoplasm and a decrease in water activity were thought to be insufficient as mechanisms of inhibition.When the pH is neutral, lactate acts as a low affinity chelator of metal ions. The elimination of metal ions, notably Fe+3, may help explain why lactate has an antibacterial effect at neutral pH since the amounts of lactic acid used are so large (Konings WN *et al*.,2002).

CONCLUSION

One of the leading causes of diarrhoea in India is shigellosis. There are numerous shigella species in India that might spread these illnesses.Shigellosis has been connected to multiple outbreaks and appears to be endemic, but there are currently no accurate estimates of its morbidity and mortality. The most common species in the country are S. flexneri, S. sonnei, and non-agglutinableshigellae. Shigellosis's etiological agents are widespread, using humans and animals as reservoirs. They can contaminate food, including fish, by ingesting faeces from culture or catch waters and by using subpar hygiene conditions and handling techniques during production and processing. Using antibiotics wisely for Shigella is one of the most crucial stages in preventing shigellosis. Public health measures, such as the supply of clean water and sufficient

sanitation, are of the utmost importance in order to lessen the burden of shigellosis. Additionally, it is necessary to revise the recommendations for the management of Shigellosis in underdeveloped nations. Due to their low infectious inoculums and ease of transmission, Shigella species are challenging to control. Due to overcrowding and inadequate sanitation, shigellosis primarily affects poorer nations. According to WHO recommendations from 2016, the severity of the sickness and the risk of death are higher among infants, non-breastfed kids, kids recovering from measles, kids who are underweight, and individuals over 50. Due to the restricted selection of available effective antimicrobial agents, strict criteria and a strong commitment to adhering to them meticulously are required.

REFERENCES

1. Lampel KA, Maurelli ATShigella species. Ch 11 In: Miliotis MD, Bier JW (eds) International handbook of foodborne pathogens.2003
2. Marcel Dekker, New York, p. Lampel KA, Maurelli AT 2007;167-180
3. Shigella species. Ch 15 In: Doyle MP, Beuchat LR (eds) Food microbiology: Fundamentals and frontiers. 3rd ed, ASM Press, Washington D.C., p. 323–341
4. Trofa AF, Ueno-Olsen H, Oiwa R, Yoshikawa M. Dr. Kiyoshi Shiga: discoverer of the dysentery bacillus. *Clin Infect Dis* 1999; 29:1303–1306
5. Anderson M, Sansonetti PJ, Marteyn BS. Shigella diversity and changing landscape: insights for the twenty-first century. *Front Cell Infect Microbiol*2016;6
6. Schroeder GN, Hilbi H. Molecular pathogenesis of Shigella spp.: controlling host cell signaling, invasion, and death by type III secretion. *ClinMicrobiol Rev* 2006;21:134–156
7. Black,R.E.,Cousens,S.,Johnson,H.L.,Lawn,J.E.,Rudan,I.,Bassani,D.G.,Eisele,T.Global,regional, and national causes of child mortalityin2008:asystematicanalysis.Thelancet,2010;375(9730), 1969-1987.
8. Von Seidlein L, Kim DR, Ali M, Hyejon Lee H, Wang X, Thiem VD, et al. A multicentre study of Shigella diarrhoea in six Asian countries: disease burden, clinical manifestations, and microbiology. PLoS Med. 2006;3:e353.
9. Kuo CY, Su LH, Perera J, Carlos C, Tan BH, Kumarasinghe G, et al. Antimicrobial susceptibility of Shigella isolates in eight Asian countries, 2001-2004. J MicrobiolImmunol Infect. 2008;41:107–11.
10. Wei J, Goldberg MB, Burland V, Venkatesan MM, Deng W, Fournier G, et al. Complete genome sequence and comparative genomics of Shigellaflexneri serotype 2a strain 2457T. Infect Immun. 2003;71:2775–86.
11. Penatti MPA, Hollanda LM, Nakazato G, et al. Epidemiological characterization of resistance and PCR typing of Shigellaflexneri and Shigellasonnei strains isolated from bacillary dysentery cases in Southeast Brazil. Braz J Med Biol Res. 2007;40(2):249–258.

12. Theron J, Morar D, Preez M, Brözel VS, Venter SN. A sensitive seminested PCR for the detection of Shigella in spiked environmental samples. Water Res. 2001;35(4):869– 874.
13. Kingombe CI, Cerqueira-Campos ML, Farber JM. Molecular strategies for the detection, identification, and differentiation between enteroinvasive Escherichia coli and Shigella species. J Food Prot. 2005;68:7549−7553.
14. Keddy K. The group for enteric, respiratory and meningeal disease surveillance in South Africa. Communicable Disease Surveillance Bulletin [serial online]. May 2010;8(2):25–27.
15. Parsot C. Shigella spp. and enteroinvasive Escherichia coli pathogenicity factors. FEMS Microbiol Lett. 2005;252(1):11−18.
16. Niyogi SK. Shigellosis. J Microbiol. 2005;43:133–43.
17. Miller RF, Symeonidou C, Shaw PJ. Pneumonia complicating Shigellasonnei dysentery in an HIV-infected adult male. Int J STD AIDS. 2005;16:763–5.
18. Sur D, Ramamurthy T, Deen J, Bhattacharya SK. Shigellosis: challenges & management issues. Indian J Med Res. 2004;120:454–62.
19. Mandell W, Neu H. Shigella bacteremia in adults. JAMA. 1986;255:3116–7.
20. Raffensperger EC. Combined bacillary and amebic ulcerative colitis associated with atypical pneumonitis and Shigella-positive sputum. Am J Med. 1956;20:964–7.
21. Wassef,J.,Keren,D.F.,Mailloux,J.L.RoleofM cells in initial bacterial uptake and in ulcerformation in the rabbit intestinal loop model inshigellosis.Infect.Immun.1989;57:858-863.
22. Perdomo,O.J.,Cavaillon,J.M.,Huerre,M., Ohayon, H., Gounon, P., Sansonetti, P. J.Acute inflammation causes epithelial invasionandmucosaldestructioninexperimentalshigellosis. Journal of Experimental Medicine,1994; 180(4): 1307-1319.
23. Sansonetti,P.J.,Phalipon,A.Mcellsasportsofentryforenteroinvasivepathogens:mechanismsofinteraction,conse-quencesforthediseaseprocess.Semin.Immunol,1999;11:193-203.
24. Koterski, J. F., Nahvi, M., Venkatesan, M. M.,Haimovich,B.VirulentShigellaflexnericauses damagetomitochondriaandtriggersnecrosisininfected human monocyte-derived macrophages.Infect Immun, 2005; 73: 504–513.
25. Carneiro, L. A., Travassos, L. H., Soares, F.,Tattoli,I.,Magalhaes,J.G.,Bozza,M.T.,Girardin, S. E. Shigella induces mitochondrialdysfunctionandcelldeathinnonmyleoidcells.Cellhost&microbe,2009;5(2):123-136.
26. Hathaway,L.J.,Griffin,G.E.,Sansonetti,P.J.,Edgeworth,J.D.HumanmonocyteskillShigellaflexneri but then die by apoptosis associatedwith suppression of proinflammatory cytokineproduction.Infectionandimmunity,2002;70(7):3833-3842.
27. Sansonetti, P.J.,Phalipon, A.,Arondel,J.,Thirumalai,K.,Banerjee,S.,Akira,S.,Zychlinsky,A.Caspase-1activationofIL-1âandIL-18areessentialforShigellaflexneri–inducedinflammation.Immunity,2000;12(5):581-590.
28. Ali R. HameedBacteriology Study of Shigella Species, and the Effect Some Ecological and Chemical factors Int J Biol Med Res.2018;9(4):6559-6563
29. AI mohannaMoshtaqTalipshigella spp. Researchgate.

30. Curtis L, Davis J. The food safety hazard guidebook [Electronic book]. RSCPub.; 2008.
31. Hale, Thomas L., and Gerald T. Keusch. "Shigella." *Medical Microbiology. 4th edition* 1996.
32. Torres et.al, current aspects of shigella pathogenesis Rev LatinoamMicrobiol 2004; 46 (3-4):
33. Nygren BL, Schilling KA, Blanton EM, Silk BJ, Cole DJ, Mintz ED Foodborne outbreaks of shigellosis in the USA, 1998-2008. Epidemiology and Infection 2012 141(2):233–241
34. Lightfoot DShigella. Ch 17 In: Hocking AD (ed) Foodborne microorganisms of public health significance. 6th ed, Australian Institute of Food Science and Technology (NSW Branch), Sydney,2003; p. 543–552
35. Kotloff, K. L., Winickoff, J. P., Ivanoff, B., Clemens, J. D., Swerdlow, D. L., Sansonetti, P. J., Levine, M. M. 1999.
36. Global burden of Shigella infections: implications for vaccine development and implementation of control strategies. *Bulletin of the World Health Organization*, 77(8), 651-666.
37. Michael, E., Mohammad, A., Mohammad, Y. Risk areas and neighbourhood-level risk factors for *Shigelladysenteriae* 1 and *Shigellaflexneri*, Healthplace,2008;14:96-105.
38. Seidlein, L., Kim, D. R., Ali, M., Lee, H., Wang, X., Thiem, V. D., Canh, D. G., Chaicumpa, W., Agtini, M. D. A multicentre study of *Shigella* diarrhoea in six Asian countries: disease burden, clinical manifestations, and microbiology. PLoS Med 2006;3, e353.
39. Edwards, B.H. (1999). *Salmonella* and *Shigella Clin Lab Med*, 19:469-487
40. Venkatesan, M. M., Ranallo, R. T. Live-attenuated *ShigellaExpert review of vaccines*, 2006;*5*(5), 669-686.
41. Lin, F. Y. C., Ho, V. A., Khiem, H. B., Trach, D. D., Bay, P. V., Thanh, T. C., Schneerson, R. . The efficacy of a *Salmonella typhi* Vi conjugates vaccine in two-to-five-year-old children. *New England Journal of Medicine*,2001; *344*(17), 1263-1269.
42. Coultate TP. Food: the chemistry of its components. Royal Society of Chemistry; 2009.
43. Jay JM, Loessner MJ, Golden DA. Chemical, biological, and physical methods. Modern Food Microbiology. 2005:241-84.
44. Ngadi MO, Latheef MB, Kassama L. Emerging technologies for microbial control in food processing. InGreen technologies in food production and processing 2012.
45. Mayo B, Van Sinderen D, editors.Bifidobacteria:genomics and molecular aspects. Horizon Scientific Press; 2010.
46. Juneja VK, Sofos JN. Pathogens and toxins in foods. ASM Press; 2010.
47. Breguet V, Vojinovic V, Marison IW. Encapsulates for food bioconversions and metabolite production. InEncapsulation Technologies for Active Food Ingredients and Food Processing 2010 (pp. 367-389).
48. Stratford M. Food and beverage spoilage yeasts.InYeasts in food and beverages 2006 (pp. 335-379).

49. Theron MM, Lues JR. Organic acids and food preservation. CRC Press; 2010 Sep 16.
50. Søltoft-Jensen J, Hansen F. New chemical and biochemical hurdles. InEmerging technologies for food processing 2005 (pp. 387-416).
51. Konings WN. The cell membrane and the struggle for life of lactic acid bacteria. InLactic Acid Bacteria: Genetics, Metabolism and Applications 2002 (pp. 3-27).