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The mechanisms of virulence and antimicrobial resistance in *Salmonella enterica* serovar Typhi: A systematic review

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Abstract

Salmonella enterica serovar Typhi is the etiologic agent of typhoid fever which is responsible for about 21,600 deaths annually, a large proportion of which is reported in developing countries. The organism is capable of evading the host defense mechanism to establish pathogenesis and this is enabled by the presence of specific virulence genes clustered in regions over the chromosome known as *Salmonella* Pathogenicity Island (SPI). Typhoid fever could be fatal therefore it requires effective antibiotic therapy. Strains which are antibiotic resistant could lead to increased mortality rates due to failure of routinely used antibiotics. This review gives an insight into the molecular mechanisms of virulence and antibiotic resistance so as to enhance more effective disease management and control.

Keywords: *Salmonella enterica serovar Typhi, Enteric fever, Antibiotic resistance, Pathogenicity islands, Plasmids*

1. Introduction

Salmonella is a gram-negative, non-capsulated, non-spore forming rod that is motile with peritrichous flagella and possess outer coat antigens (Shahane *et al*., 2007). It is facultatively anaerobic with an optimum temperature and pH range of 37 °C and 6.5-7.5 respectively.

The major niche of *Salmonella* serovars is the intestinal tract of man and farm animals. Soil, feed, bedding, litter and faecal matter are the major sources of contamination in farms (Hoelzer *et al*., 2011; and Madoroba *et al*., 2016). They are common contaminants of a wide range of foods such as vegetables, water, milk, eggs, meat and meat products and thus considered as primary sources of food borne infection globally (Scallan *et al*., 2011; and Jajere *et al*., 2014).

Salmonella causes salmonellosis and enteric fever which is characterized by nausea, abdominal pain, diarrhoea and sometimes fever that result in morbidity and in some instances mortality in animals and man (Madoroba *et al*., 2016).

Salmonellae form a complex group of bacteria consisting of two species and six subspecies and 2,579 serovars (Malorny *et al*., 2011; and Hanning and Andino, 2015). Several species of this important group are pathogenic producing infections in many animal hosts and man. The genus *Salmonella* is comprised of two species, *S. bongori* and *S. enterica*. *S. enterica* is further subdivided into six subspecies each represented by roman

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numerals and a name: I, ssp. enterica; II, ssp. salamae; IIIa, ssp. arizonae; IIIb, ssp. diarizonae; IV, ssp. houtenae and VI, ssp. indica which are differentiated by biochemical characteristics and genomic phylogeny (Brenner *et al*., 2000; Perkins, 2009; and Kroft, 2017). Of the over 2,500 recognized serotypes, more than 1,500 are of subspecies I and associated with warm-blooded animals (Guibourdenche *et al*., 2010). *S. enterica* subspecies I strains are responsible for 99% of all reported human *Salmonella* infections in the United States (Eng *et al*., 2015; and Centers for Disease Control and Prevention, 2013). Serotyping, which utilizes variation of phase I (H1) and phase II (H2) flagellar and somatic lipopolysaccharide (O) antigens on the surface of bacterial cells, is commonly used to distinguish strains.

Salmonella enterica is a rod-shaped, flagellate, facultative aerobic, gram-negative bacterium and is a species of the genus *Salmonella*. *S. enterica* has serovars Typhi, Paratyphi, Enteritidis, Typhimurium and Choleraesius. A number of these serovars are serious human pathogens. Among more than 2,300 closely-related *Salmonella* serovars recognized, *S. enterica* serovar Typhi and Paratyphi are pathogenic exclusively for humans, and cause systemic infections and typhoid fever respectively whereas others such as *S. enterica* serovar Typhimurium cause gastroenteritis (Zhang *et al*., 2008). *S. enterica* serovar Typhimurium is frequently associated with gastroenteritis in humans, whereas this serovar causes a systemic typhoid-like disease in susceptible mice (Forest *et al*., 2010). There are two major groups of *S. enterica* that cause disease in humans: the systemic (typhoid fever) group and the non-typhoidal salmonellae group. Typhoid fever is mainly caused by *S. enterica* serovar Typhi (*Salmonella* Typhi), a host-adapted serovar that is specific for humans. Non-typhoidal salmonellae are generally associated with gastroenteritis, which rarely develops into an invasive infection.

S. enterica serovar Typhi is the causative agent of typhoid fever which is a systemic, life threatening disease of humans (Galan, 2016). *S. enterica* serovar Typhi is transmitted through contaminated food and water. Following ingestion of contaminated food or and water, the bacteria spread from the intestine via blood to the

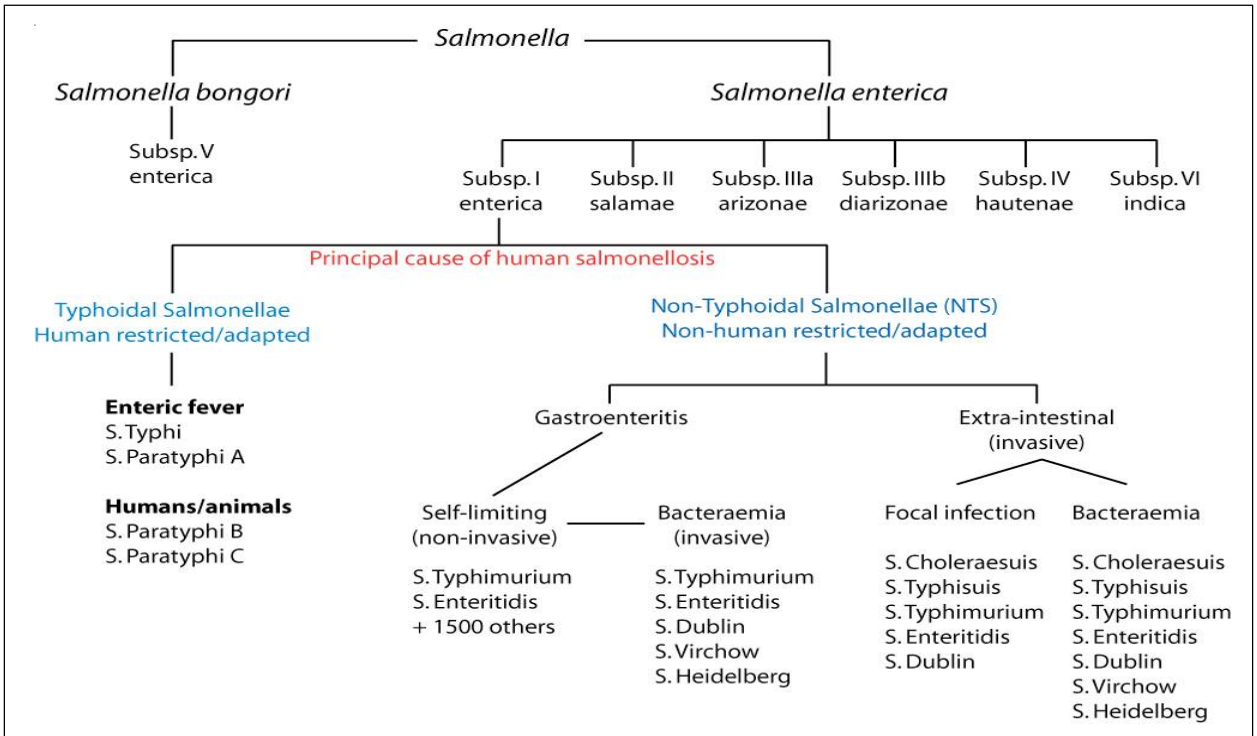

Figure 1: Classification and diseases of *Salmonella* species (Perkins, 2009)

intestinal lymph nodes, liver and spleen where they multiply (Kaur and Jain, 2012). A significant percentage of normal animals harbor *Salmonella* in their intestinal tracts (Jajere *et al*., 2014).

S. enterica serovar Typhi is a gram-negative, rod-shaped, flagellated bacterium whose only reservoir is the human body (Crump *et al*., 2015). It is the etiologic agent of an enteric fever called typhoid fever and considered a public health problem in the world (Fallah *et al*., 2016). They are intracellular pathogens with the ability of systemic spread and can also populate the intestinal lumen, causing diseases such as typhoid fever, blood infections and food borne gastroenteritis, depending on the host-pathogen-pairing.

As estimated, 16 to 22 million cases and about 21,600 deaths occur annually due to typhoid, most of which are reported in developing countries caused by consumption of unsafe drinking water and contaminated food.

It causes a severe systemic infection; typhoid fever, which is a serious worldwide public health problem. According to the World Health Organization (WHO), the annual global burden of typhoid fever is about 11-20 million new cases per year and 1% of which are fatal. More than 90% of typhoid fever cases occurred in Asia. It is highly prevalent in Asia and Africa due to shortage of hygienic water and poor sanitation. It is also a significant travel-associated disease (Connor and Schwartz, 2005). Therefore, *S. enterica* serovar Typhi infection poses substantial global disease burden on the healthcare system in endemic countries. Typhoid fever is clinically manifested through prolonged fever, abdominal discomfort, headache, and general lethargy (Liaquat *et al*., 2018).

2. Pathogenesis of *S. enterica* serovar Typhi

The infectious dose of *S. enterica* serovar Typhi varies between 1000-1,000,000 organisms. The incubation period is usually 7 to 14 days. On ingestion, after bypassing the gastric acidity, the organisms invade the intestinal epithelium through the Peyer's patches. After penetration, they translocate to the intestinal lymphoid follicles and mesenteric lymph nodes and even to the reticuloendothelial cells of the liver and spleen where they multiply and reach the blood stream referred to as "primary blood stream invasion". The bacteria get seeded in several reticuloendothelial sites and spill over from these sites into the bloodstream causing secondary bacteraemia and the patient now begins to exhibit symptoms. The organisms are then widely disseminated into liver, spleen, bone marrow, gall bladder and Peyer's patches of terminal ileum (Raveendran *et al*., 2010). However, the initial spread of the pathogen does not evoke overt host responses, as indicated by the fact that typhoid fever has an average incubation period of two weeks (Olsen *et al*., 2003). Pathological changes in the intestine are characterized by a slow development of inflammatory infiltrates that are dominated by mononuclear cells (macrophages and dendritic cells) while neutrophils are scarce (Sterzenbach *et al*., 2013). The organism spreads to internal organs, most frequently the bone marrow, the liver and the spleen where it is found in histiocytic granulomas, known as typhoid nodules (Sterzenbach *et al*., 2013). Spread to the gall bladder or urinary bladder can lead to chronic carriage, which is important for human-to-human spread of the disease.

Symptoms of typhoid fever are non-specific, commonly including fever and a slowed heart rate (bradycardia). Splenomegaly, hepatomegaly, or rose spots are encountered less frequently (Sterzenbach *et al*., 2013). Unlike gastroenteritis, typhoid fever is not considered a diarrhoeal disease, because this symptom develops late, after the onset of fever, in only a fraction (approximately one-third) of typhoid fever patients, while the remaining individuals remain either diarrhoea free or become constipated. *Salmonella* Paratyphi A, and less frequently S. Paratyphi B and Paratyphi C, are associated with paratyphoid fever, a disease that is milder in its course but otherwise indistinguishable from typhoid fever. Together with *S. enterica* serovar Typhi, these pathogens are commonly referred to as typhoidal *Salmonella* serotypes.

3. Pathogenesis elucidated by typhoidal toxin

Once the typhoid toxin is synthesized by *S. enterica* serovar Typhi, it is secreted into the lumen of the bacteria containing vacuole by a specific and unique protein secretion system although, the full mechanism is not yet fully understood (Hodak and Galán, 2013). The typhoid toxin is then packaged into vesicle carrier intermediate and subsequently transported to the extracellular space where it can reach its target host cells via paracrine or autocrine pathways4. o target host cells is not yet fully understood but is believed to be mediated by the enzymes Rab GTPases Rab 29 and Rab 31 (Galan, 2016). Typhoid toxin cannot intoxicate the cells that produced it until it becomes extracellular thus cells lacking typhoid toxin receptors and harboring *S. enterica* serovar Typhi could serve as a toxin source while themselves are not a target of toxicity.

4. Pathogenicity of *S. enterica serovar Typhi*

4.1. Salmonella *Pathogenicity Island (SPI)*

The ability of *Salmonella* Typhi to infect the host relies on the genetic determinants called virulence genes, located in the SPI (Zishiri *et al*., 2016). Pathogenicity islands are distinct genetic components located on the pathogenic bacterial chromosomes (Liaquat *et al*., 2018). The pathogenicity island is located either on the bacterial chromosome or on large virulence-associated plasmids. SPIs are portions of DNA that have been acquired from other microorganisms by horizontal gene transfer and they are absent in non-pathogenic strains