Journal of Medical and oral biosciences
ISSN (Online): 3007-9551
ISSN (Print): 3007-9543

JMOB
Open Access DOAJ

IRAQI
Academic Scientific Journals

Type: Narrative Review article
Publish online: 01 / 03 / 2026

Virulence Factors and Pathogenic Mechanisms of *Salmonella enterica Serovar Typhi*: A Narrative Review

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OPEN ACCESS

ARTICLE INFO

Received: 05 /01 /2026
Revised: 04 / 02/ 2026
Accepted: 16 / 02 / 2026
Publish online: 01 / 03 / 2026
Plagiarism percentages at publication: 18 %

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CITATION

Hadeer F. Hamoodi, Mays A. Mahdi, Al-Shaikhli Nawfal Haitham. (2026). Virulence Factors and Pathogenic Mechanisms of *Salmonella enterica Serovar Typhi*: A Narrative Review : A Narrative Review. JMOB. 3;(1): 01-20. https://doi.org/10.58564/jmob.122

Abstract

Typhoid fever caused by Salmonella enterica serovar Typhi (S. Typhi), remains a major public health concern, particularly in low- and middle-income countries. The pathogenic success of *S. Typhi* is driven by a sophisticated array of virulence factors that enable host colonization, immune evasion, systemic dissemination, and long-term persistence. Key determinants include Type III Secretion Systems (T3SS), the Vi capsular polysaccharide, *Salmonella* pathogenicity islands (SPIs), lipopolysaccharide (LPS), and multiple secreted effector proteins. This review aims to summarize the major virulence factors of *S. Typhi* and elucidate the molecular mechanisms underlying host–pathogen interactions, immune modulation, systemic infection, and chronic persistence. It further seeks to highlight recent advances in molecular pathogenesis and genomics that inform vaccine development and novel therapeutic strategies. A comprehensive review of current literature was conducted, focusing on molecular, genetic, and genomic studies of *S. Typhi* virulence. Peer-reviewed articles addressing T3SS function, SPIs, capsular and surface antigens, intracellular survival strategies, and host immune responses were analyzed to integrate current knowledge on *S. Typhi* pathogenicity. In conclusions: the coordinated action of *S. Typhi* virulence factors enable efficient invasion, immune evasion, and systemic spread, while specific determinants support survival within host macrophages and persistence in the gallbladder, leading to chronic carriage. Advances in genomics and molecular pathogenesis have deepened understanding of host–pathogen interactions and revealed promising molecular targets for vaccine design and innovative therapeutics. A thorough understanding of *S. Typhi* pathogenic mechanisms is essential for improving typhoid fever prevention, treatment, and control strategies, particularly in endemic regions where the disease burden remains high.

Keywords: Pathogenicity, typhoid fever, *Salmonella Typhi*, virulence factors, type III secretion system.

Introduction

Salmonella species are Gram-negative, oxidase-negative, catalase-positive, non–spore-forming rods belonging to the family Enterobacteriaceae. They are facultative anaerobes and, with the exception of *Salmonella pullorum* and *Salmonella gallinarum*, most species are motile by means of peritrichous flagella. Salmonella is widely distributed in the environment and is capable of infecting a broad range of hosts, including humans and animals, where it causes diverse clinical diseases (1).As facultative intracellular pathogens, Salmonella species can invade and survive within various host cell types, leading to clinical manifestations ranging from self-limiting gastroenteritis to bacteremia and enteric fever. Diarrhea is the most common symptom of salmonellosis; however, in certain cases, infection may progress to septicemia. Disease severity depends on several factors, including the infecting strain, infectious dose, host age, immune status, underlying medical conditions, and the composition of the normal intestinal microbiota (2). More than 2,600 serovars of *Salmonella enterica*, the species most commonly associated with human disease, have been identified (3). Based on their role in human infections, Salmonella serovars are broadly classified into *non-typhoidal Salmonella (NTS)* and *typhoidal Salmonella* (TS). The typhoidal serovars—*Salmonella enterica serovar Typhi* (*S. Typhi*), *S. Paratyphi*, and *S. Sendai*—are human-restricted pathogens responsible for typhoid and paratyphoid fever (4). These serovars possess distinctive virulence determinants, including the Vi capsular polysaccharide and typhoid toxin, which are associated with disease development and immune evasion (5) (Figure. 1).

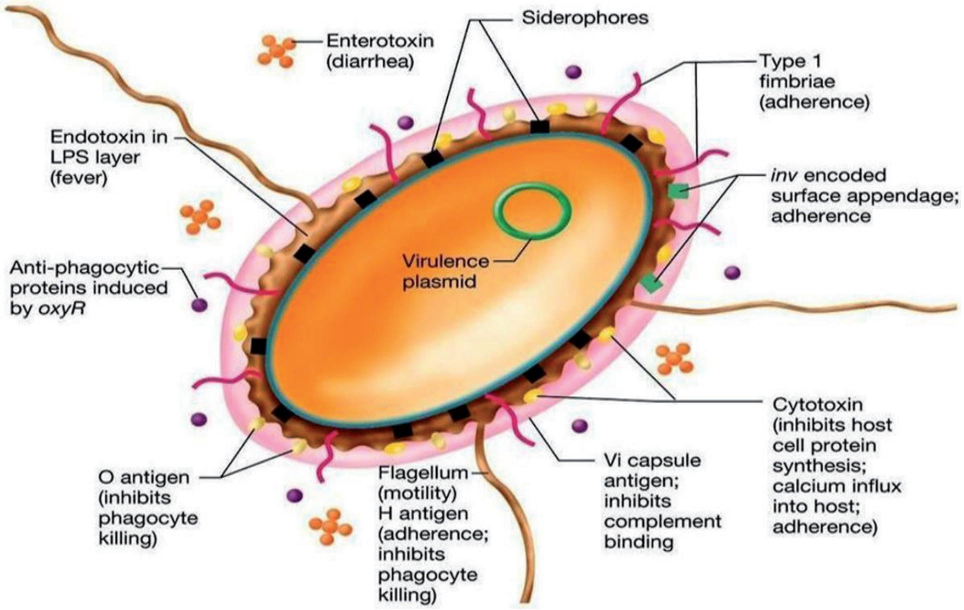


Figure 1: *Salmonella* virulence factors (12)

In contrast, *non-typhoidal Salmonella serovars* have a broader host range and are primarily associated with gastroenteritis. Although NTS infections are generally self-limiting and confined to the intestinal mucosa, some serovars harbor virulence genes that enable invasion of epithelial cells and survival within phagocytic cells (6). Both *typhoidal* and *non-typhoidal Salmonella* rely on two type III secretion systems (T3SS-1 and T3SS-2), encoded by *Salmonella* pathogenicity islands, which are essential for bacterial invasion, intracellular survival, and dissemination (7). Following ingestion, *S. Typhi* penetrates the intestinal epithelium and disseminates to systemic organs such as the liver, spleen, bone marrow, and gallbladder. Clinical manifestations of typhoid fever, including sustained fever, headache, abdominal pain, myalgia, and constipation or diarrhea, typically appear 10–14 days after exposure (8). Infection with *S. Paratyphi A* produces similar but often milder symptoms (9). Although appropriate antibiotic therapy reduces mortality, a proportion of infected individuals develop a chronic carrier state. Approximately 3–5% of patients continue to shed *S. Typhi* for prolonged periods following recovery, often without clinical symptoms. During chronic carriage, *S. Typhi* and *S. Paratyphi A* persist in the gallbladder, serving as a long-term reservoir for transmission (10). Because *typhoidal Salmonella serovars* are restricted to humans, asymptomatic carriers play a critical role in the maintenance and spread of typhoid fever (11). The aim of this study is to describe and summarize the major virulence factors of *Salmonella enterica serovar Typhi*, with particular emphasis on factors involved in host invasion, immune evasion, systemic dissemination, and persistence within the human host. This study also seeks to provide an overview of virulence determinants associated with chronic carriage, especially gallbladder colonization, to enhance understanding of *Salmonella* pathogenicity and support future strategies for disease prevention and control.

Virulence factors of *Salmonella typhi*

The synthesis of toxins (LPS endotoxin, enterotoxin, and cytotoxin), colonization, adhesion, and invasion, as well as survival inside the host cells, are all stages of infection that are influenced by *S. Typhi* virulence factors (13) (Table.1).

Table.1: Summary of Key Virulence Factors in *Salmonella typhi* Pathogenesis(14)

Stage	Virulence Factor	Primary Function
Adherence	Fimbriae & H Antigen	Movement and attachment to host cells.
Invasion	T3SS-1	Forceful entry into M Cells.
Protection	Vi Antigen	Shielding against the host immune system.
Survival	T3SS-2	Living and replicating inside Macrophages.
Toxicity	Endotoxin (LPS)	Induction of fever and systemic inflammation.

Vi Antigen (Capsular Polysaccharide)

One important virulence component unique to *Salmonella enterica serovar typhi* (and to a lesser extent *C. Paratyphi* and *Citrobacter freundii*) is the Vi antigen, also known as the virulence antigen. *S. typhi* differs from other *Salmonella serovars* in that it biosynthesizes the virulence capsular polysaccharide (Vi), a crucial virulence component during infection (15). Felix and Pitt made the initial discovery of the Vi antigen (16) . Vi antigen is a linear homopolymer composed of α-1-4-linked N-acetyl galactosaminuronate (GalNAcA); it has a molecular mass of more than 200 kDa and 60–70% of its monomeric units are O acetylated at the C-3 position (17). It is usually found in *Citrobacter freundii* (*C. freundii*), *Salmonella dublin* (*S. Dublin*), *Salmonella Typhi*, and *Salmonella paratyphi C* (*S. paratyphi C*). It is an antigen that has been demonstrated to trigger an immunological response in rabbits and increases *S. Typhi* pathogenicity in mice. According to in vitro research, Vi is antiopsonic and antiphagocytic, decreases the amount of *S. Typhi*-induced tumor necrosis factor α (a sign of activation) secreted by human macrophages, and raises the organism's resistance to oxidative death (15). By protecting bacterial outer structures especially LPS O-antigen from complement and antibody attack, Vi capsule offers serum resistance (18). Although it prevents neutrophil phagocytosis, it can increase macrophage uptake by attaching to the DC-SIGN receptor and inducing an anti-inflammatory reaction (19). Vi expression is synchronized with reduced flagellar and SPI-1 T3SS activity through tviA, which decreases early inflammatory signals and acts as a covert tactic during epithelial invasion. According to Lee *et al.* (20), the genes that produce the Vi capsule include the viaB locus within *Salmonella* pathogenicity island (SPI-7), which also encodes a type IVB pilus and the type III secretion system (T3SS) effector SopE. Genes involved in Vi production (tviBCDE), regulation (tviA), export, and retention on the bacterial cell surface (21). While TviA downregulates flagellar and SPI-1 genes in high osmolarity conditions (22), it is a positive regulator that promotes expression of the viaB locus. Vi expression is elevated in tissues during systemic dissemination, where it inhibits antibody-mediated activation of neutrophil responses, while it is downregulated in the colon, where flagella and SPI-1 contribute to invasion of epithelial cells (23). Because TviA-mediated suppression of flagellin expression limits NAIP's ability to recognize flagellin, macrophage pyroptosis and IL-1β secretion are decreased. Vi has been shown to bind cell surface prohibitin, which reduces inflammation by producing IL-8 and MPK signaling(24) . One feature of *S. Typhi* infection that sets it apart from *S. Typhimurium* infection is low levels of neutrophil influx, which is caused by reduced TLR5- and TLR4-mediated release of IL-8 (25) .

During infection, *S. Typhi* employs a variety of virulence characteristics that set it apart from *nontyphoidal Salmonella* (*NTS*). *S. Typh*i promotes invasion by secreting a pool of effectors into host cells via the SPI-1 T3SS. Effectors particular to *S. Typhi*, such as t1865, are likely linked to pathogenesis. The presence of bile, oxygen availability, and fever-like temperatures (42°C) cause *typhoidal* and *nontyphoidal Salmonella* to regulate SPI-1 T3SS differently. The Vi antigen, which is expressed by *S. Typhi*, prevents complement activation and antibody binding. It also prevents TLR4 and TLR5 from recognizing lipopolysaccharide and flagellin, which reduces downstream TLR-mediated signaling. TviA regulates the production of Vi via inducing expression of the viaB gene, which encodes Vi. The presence of cytosolic flagellin and SPI-1 T3SS components is reduced by TviA, which adversely controls flagellar and SPI-1-associated genes, hence decreasing recognition by NAIP receptors. Pyroptosis is induced and the NLRC4 inflammasome is diminished as a result. The typhoid toxin, which is produced when *S. Typhi* is intracellular, is another virulence factor linked to *typhoidal Salmonella*. When it binds to Neu5Ac-terminated receptors on target cells, it can cause G2/M cell cycle arrest and/or cell death. It is exported from the SCV in vesicles into the extracellular environment. Typhoid toxin causes a decrease in the number of neutrophils in the blood (26) (Figure.2).

Somatic O antigen (cell wall Ag or LPS)

The oligosaccharide component of LPS is represented by the thermostable somatic O antigen, which is found in the bacterial cell's outer membrane. On the chromosome, the genes that produce O antigen are often arranged in a cluster between the *galF* and *gnd* genes. The variations among different O antigen types are explained by genetic variability within this gene cluster (28) (Figure.3). The 'L' layer (OMP) may also contain antigenic outer membrane proteins. Porin (OMP F and OMP C) and non-porin (OMP F and OMP C) molecules are examples of outer membrane proteins. Porin proteins are pore-forming channels that help create pores that are employed for solute absorption, while non-porin proteins are structural proteins (29). Patients with typhoid fever have a good antibody response to all of these antigens, which are highly immunogenic. The somatic antigens, which are hydrophilic and heat stable, are the side chains of repeated sugar units that protrude from the bacterial cell wall surface and the lipopolysaccharide layer. For serological diagnostics, it is employed (17,30). Using gene transfer, genotypic research revealed that Salmonella possesses roughly 60 somatic antigens (31). *Salmonella* can be divided into several serotypes according to these antigens and certain antisera. The three cell surface antigens of *Salmonella* are, in short, the O (cell-wall somatic), H (flagellar), and K (capsular) antigens. The somatic O antigen is thermostable, but the flagellar antigen is a thermolabile protein (32). A heat-sensitive carbohydrate known as the K antigen is also present in some *Salmonella* serovars. *Salmonella* is unique among the Enterobacteriaceae in that it has two different H antigens: phase 1 (specific) and phase 2 (non-specific) flagella antigens (31).

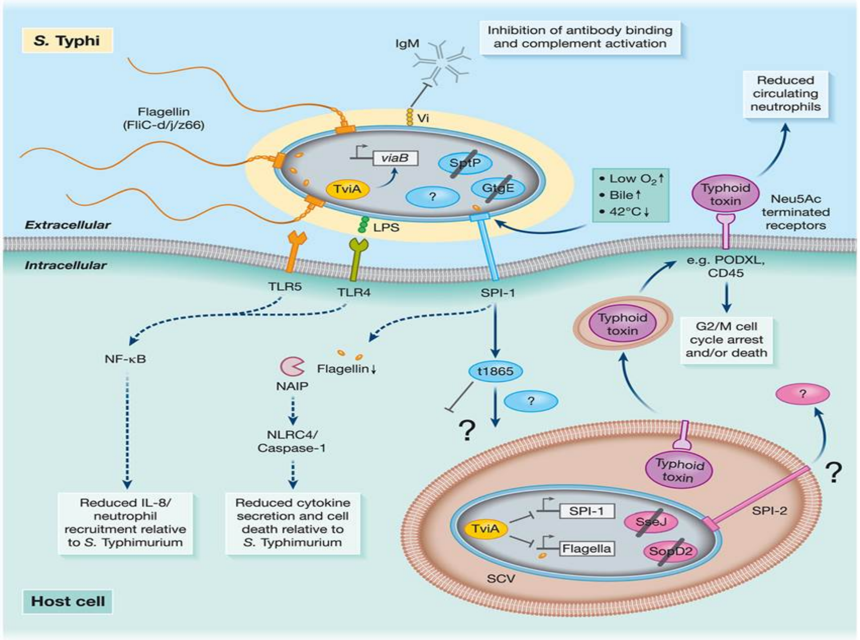
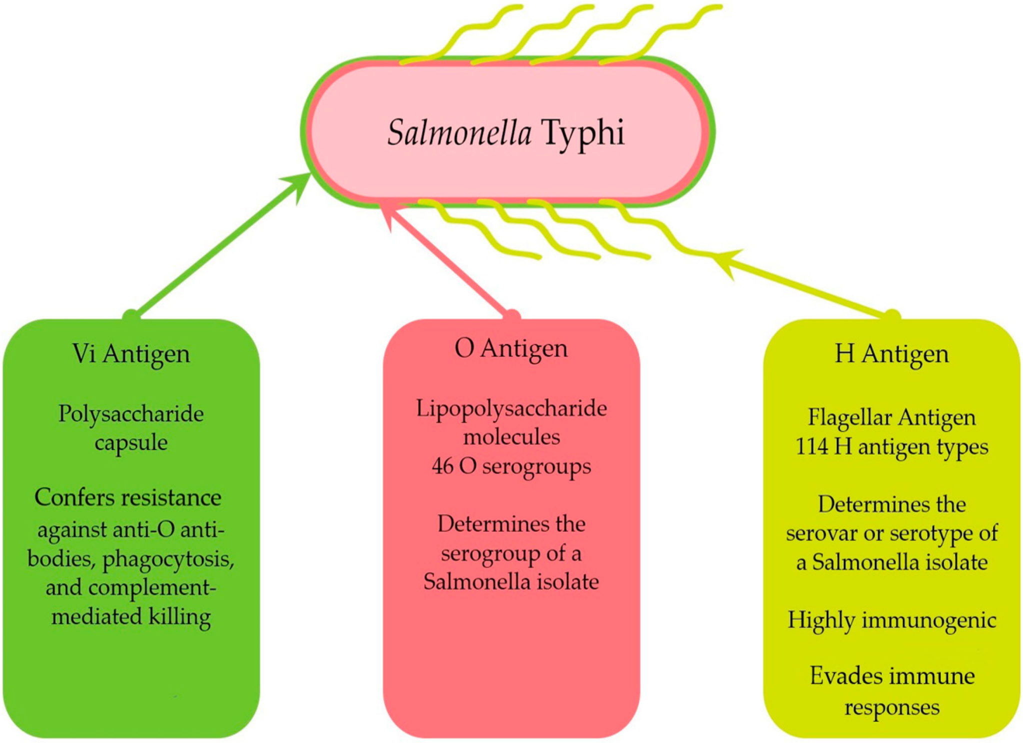


Figure 2: Molecular pathogenesis of *Salmonella typhi* (27) https://www.creative-diagnostics.com/molecular-mechanism-of-*Salmonella-typhi*-pathogenesis.htm

Flagella (H antigen)

In addition to contributing to pathogenicity, flagella are made up of two genes that code for flagellar proteins (Figure.4). These genes are important activators of the innate immune system through toll-like receptor 5 (TLR5) and neuronal apoptosis inhibitory protein (NAIP) receptor recognition of monomeric flagella. Phase 1 and phase 2 are the two types of H antigen that can exist (32). The flagella filament, of which polymerized flagellin is the main component, makes up the complex structure known as the flagellum. Flagella are a crucial antigen that initiates innate immune responses and facilitates bacterial movement (33). Tvi A, a transcriptional regulator linked to the viaB locus on SPI-7 in *S. Typhi*, has been shown to partially downregulate the expression of *S. Typhi* flagellin during invasion of intestinal epithelial cells. Notably, this regulator is typically absent in *Salmonella serovars* that cause gastroenteritis (23,34). *S. Typhi* can then undermine the innate immune system by reducing inflammasome activation in infected phagocytes as a result of this downregulation. As was previously mentioned, *S. Typhi* but not *S. Typhimurium* up-regulates SPI-1 gene expression and flagellin synthesis in experimental culture conditions supplemented with 3% bile (35). This finding could potentially clarify how the flagellar filament contributes to the development of S. Typhi biofilms on gallstones (36).



Vi Antigen

Polysaccharide capsule

Confers resistance against anti-O antibodies, phagocytosis, and complement-mediated killing

O Antigen

Lipopolysaccharide molecules
46 O serogroups

Determines the serogroup of a Salmonella isolate

H Antigen

Flagellar Antigen
114 H antigen types

Determines the serovar or serotype of a Salmonella isolate

Highly immunogenic

Evades immune responses

Figure 3: Description of antigens of *Salmonella Typhi* (28)

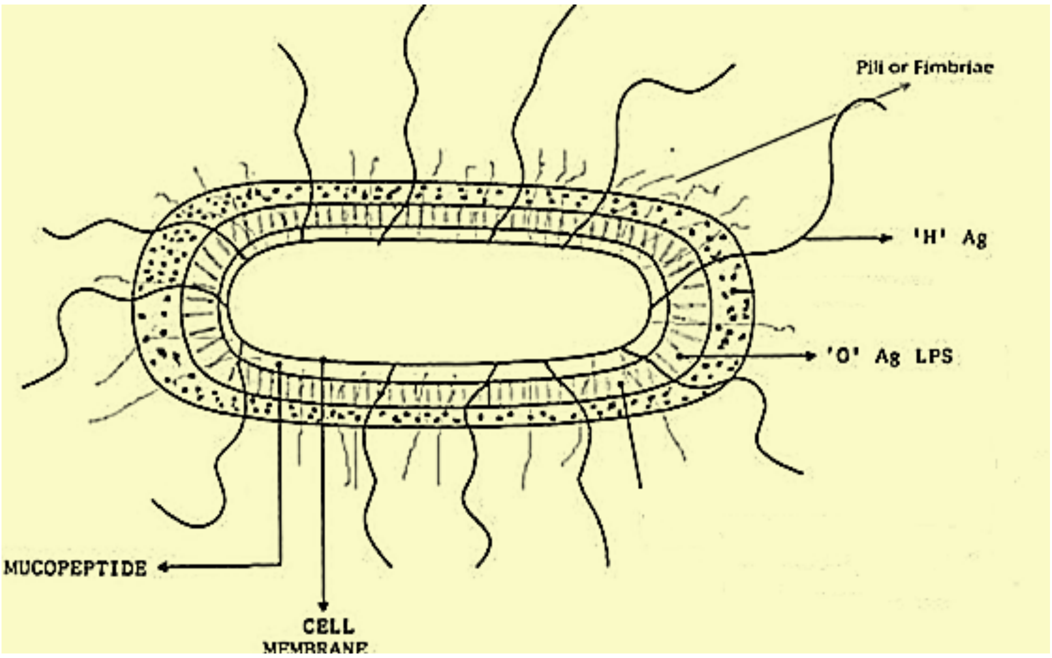


Figure 4: Somatic O, flagella H antigen of *Salmonella* (37)

Adhesins and Fimbriae

A variety of virulent elements, including as flagella, plasmids, capsules, and secretion systems, are implicated in *Salmonella* pathogenicity. With the help of these diverse virulence factors, Salmonella has produced a large number of fimbrial adhesins that allow it to connect to the host cell in a variety of ways, sometimes leading to infection (38). When describing the non-flagellar filamentous apparatus, the Latin word fimbria (meaning fibers) is preferred (39). Fimbriae are extracellular projections that range in length from 0.5 to 10 µm and breadth from 2 to 8 nm. Usually, they have a role in adhesion as well as a variety of other processes, such as bacterial aggregation, intestinal persistence, biofilm formation, and contact with macrophages (40) .*Salmonella typhi* gene (STG) genes, which are found in the intergenic region of *serovar typhi* in vitro. It was found that one of six fimbriae found in *S. typhi* but absent in *S. typhi murium* plays a part in epithelial cell death and cellular invasion. By evading the innate immune system by penetrating Peyer patches cells, the Stg (*Salmonella typhi* gene) operon has been found The majority of fimbriae are not well expressed in the lab, and their functional redundancy complicates research on them. Nonetheless, fimbriae are thought to be essential components in comprehending *Salmonella* pathogenesis. The chaperone–usher (CU) pathway, the extracellular nucleation–precipitation (N/P) pathway, and, similar to the type II secretion system, a unique mechanism for type IV (T4) fimbriae are among the several assembly pathways for Salmonella fimbrial adhesins. These three kinds of assembly paths result in the various fimbriae (42).

In several bacteria, fimbriae have been found to be a significant virulence factor. Numerous host cell receptors, which are involved in many crucial aspects of Salmonella pathogenesis, they are susceptible to binding by Salmonella fimbriae (43) . Fimbriae are a possible antigen for creating salmonellosis vaccines because of their abundance in the extracellular matrix (44). Fimbriae are also crucial for *Salmonella* identification using several molecular methods (45). Fimbrial genes allow for the differentiation of *Salmonella* species from non-Salmonella species. Furthermore, distinct patterns of fimbrial genes help distinguish between various *Salmonella serovars*. Fimbriae play a significant role in the creation of novel therapeutic medications to treat Salmonella infections. Additional knowledge about fimbriae could provide fresh perspectives on the pathophysiology of Salmonella (46).

Plasmid

A large, low copy number plasmid containing virulence genes is carried by some *Salmonella*. It is unknown how virulence plasmids contribute to the intestinal stage of the infection, but they are necessary to cause systemic illness. Although the size of *Salmonella* virulence plasmids varies from 50 to 90 kb, they always share a 7.8 kb region, or SPV, which is essential for bacterial proliferation in the reticuloendothelial system (47). Plasmids containing virulence and antibiotic resistance genes are present in *S. enterica* serovar *Typhi*. The *spv* operon, which is crucial for systemic infection, is shared by the virulent plasmids, which range in size from 50 to 90 kb (48). According to Guiney and Fierer (49), the *spv* genes seem to have a significant role in the growth of bacteria inside host cells during extraintestinal infections. *SpvRABCD* genes are found in a genetic locus known as *Salmonella* plasmid virulence, which is present in these virulence plasmids. According to reports, the virulence of the host is significantly increased when *spv* genes are present. The genes producing serum resistance (*traT*) and fimbriae (*pef-*

BACDI) are additional virulence genes found on virulence plasmids (50) .Certain virulence plasmids seem to have a complete set of transfer (*tra*) genes that enable the plasmids to be conjugated to other strains, potentially enhancing the virulence of the recipients, even if the majority of virulence plasmids are not self-transmissible (51).The *pef* genes that code for the plasmid-encoded fimbriae are also present in the virulence plasmid. These genes have been demonstrated to be involved in the adhesion to crypt epithelial cells and the induction of a proinflammatory response (52); however, it is unclear if they would also be involved in the adhesion to plant tissue or other environmental surfaces. Whether the *pef* or *fae* fimbrial structures encoded in the *pSV* aid in the adhesion to plant tissues and other potential Salmonella hosts, including invertebrate animals, is an intriguing question. Nevertheless, no research has been done on this topic, necessitating the use of isogenic strains that either have or do not have the *pSV* (53).

Typhoid Toxin (Cytolethal Distending Toxin)

Endotoxins are high-molecular weight complexes of lipopolysaccharides (LPS), the main component of bacterial cell walls, and have been found to play a significant role in the pathogenicity of Gram-negative bacterial infections. They are also known as enterotoxins because they are strong mediators of a variety of pathophysiological effects in humans, primarily in the gasterointestinal tracts. These toxic behaviors, along with many beneficial ones linked to immunostimulation, include lethal toxicity, pyrogenicity, and tissue necrotizing activity (54). Gram-negative bacteria emit this heat-stable poisonous material when their cell membranes are disrupted. Previous research has examined the function of endotoxins in bacterial pathogenesis and their chemical characterization as lipopolysaccharide (LPS) (55). In terms of chemistry, LPS is made up of a hydrophilic polymer that is covalently bound to a hydrophobic lipid component known as lipid A, which serves as an anchor for the molecules in the outer membrane (OM) (56).The significant role endotoxins play in human disease states has sparked interest in examining the pathogenicity of the bacteria that produce them (54). It has been discovered that lipopolysaccharide plays a significant role in immune system activation, which results in a non-specific inflammatory immunological response (57).

The potential of *S. Typhi* and *S. Paratyphi A* to cause typhoid fever in humans has been better understood since the discovery of the typhoid toxin. Experimental animals have demonstrated that typhoid toxin has a significant role in coordinating the clinical manifestations of acute typhoid. The nearly identical copies of the toxin-encoding genes found in the genomes of *S. Typhi* and *S. Paratyphi A* provide more proof that typhoid toxins play a part in acute typhoid fever. It has also been suggested that typhoid toxin plays a significant role in chronic asymptomatic infection, a complicated process that allows the virus to evade removal from the gallbladder (58).

The CtdB gene, which is specific to the *S. Typhi* serotype and encoded on SPI-11, is one of the key virulence factors that *S. Typhi* produces: cytolethal distending toxins (CDTs). According to Johnson *et al.*, (2018) (59), the toxin is mostly expressed when S. Typhi is intracellular, contained within a *Salmonella*-containing vacuole, and discharged into the extracellular area. The gene for the cytolethal distending toxin cdtB codes for toxins that cause infected cells to undergo apoptosis (60).Following export, typhoid toxin actively works through autocrine and paracrine mechanisms to intoxicate both infected and uninfected cells (61).

Salmonella Pathogenicity Islands (SPIs) and type III Secretion System

The genetic factors known as virulence genes, which are found in the SPI, are what allow *S. Typhi* to infect the host (61). According to Liaquat *et al.,*(62) pathogenicity islands are unique genetic elements found on the chromosomes of pathogenic bacteria. Either the bacterial chromosome or sizable virulence-associated plasmids contain the pathogenicity island. SPIs are DNA segments that have been obtained from other bacteria through horizontal gene transfer; non-pathogenic strains lack them (63).The nucleotide composition of SPI differs from that of the core genome, and they are frequently linked to tRNA genes and mobile genetic elements such as transposons, IS elements, or phage genes. According to Vernikos and Parkhill (64),SPIs have been found in *S. enterica* serovar *Typhi* thus far. Additionally, the SPIs generate and release a protein called invasion, which enables the bacterium to be taken up by non-phagocytic cells and live intracellularly. Additionally, it can prevent leukocytes from undergoing an oxidative burst, which renders the innate immune response ineffective (65). The SPI contains clusters of *Salmonella* virulence components, including adhesion, invasion, and toxin genes (66).As of right now, at least sixty 60 virulence genes linked to SPIs have been mapped, and each one has a distinct purpose. Some help the pathogen colonize in order to evade the host's defenses, while others are in charge of the pathogen's internal growth. SPI-1, SPI-2, SPI-3, SPI-4, SPI-5, SPI-6, SPI-7, SPI-8, SPI-9, SPI-10, SPI-15, SPI-16, and SPI-17 are the SPIs for *S. enterica* serovar *Typhi.* The most researched are SPI-1 and SP1-2, which encode the genetic material for a huge number of proteins known as the type III secretion system (T3SS) and are exclusively accountable for pathogenicity. T3SS is encoded on SP1 and SP2, respectively, and comes in two varieties: T3SS-1 and T3SS-2. When it comes to interactions with the host during pathogenesis, both T3SSs are involved. T3SS-1 aids in the crossing of epithelia and promotes the invasion of non-phagocytic cells. In numerous eukaryotic cell types found in the many organs that are accessed during the course of a systemic infection, T3SS-2 is necessary for bacterial reproduction (67). T3SS-1 and T3SS-2 are necessary for *Salmonella* to initially infiltrate the intestinal epithelium and then endure in tissue phagocytes. T3SS-1 is primarily in charge of invasion, which is mediated by actin polymerization and reorganization and results in bacterial engulfment and membrane ruffling. It causes intestinal irritation as well. Both SPIs appear to be crucial for distinct phases of *S. enterica* serovar *Typhi*'s infectious life cycle.SPI-1 makes it possible for *S. enterica* serovar *Typhi* to start the infection and infiltrate the gastrointestinal system in order to spread throughout the host. It is believed that the genes expressed by this area are crucial during the intestinal epithelial invasion stage. A number of proteins (effector molecules) that mediate cytoskeletal reorganization and aid in the invasion of epithelial cells are encoded by genes found in SPI-1. Type III secretion system (T3SS-1), which is made up of many operons, translocate these effector molecules into the host cells (68).

It has been shown that intestinal epithelium's low oxygen and high osmotic pressure trigger SP1-1 expression by controlling transcriptional activators. T3SS-1, an injection-like structure that injects effector proteins into the host, is encoded by SPI-1 (69). SPI-1 effector proteins seek to take over the cytoskeleton, giving Salmonella a point of entry. *SpoE* and *SipA* are two instances of effector proteins that are encoded by SPI-1. Rho GTPases are a class of GTPases that *SopE* activates to cause Arp2/3-dependent actin polymerization. Actin filaments are directly bound and stabilized by *SipA* .When combined, they create membrane ruffling, which increases Salmonella's site of entrance. Effectors function by stabilizing actin, which ruffles membranes and allows Salmonella to enter (70). SPI-1–mediated invasion in *Salmonella* is regulated by the master transcriptional activator HilA, which is controlled by HilD and HilC in response to environmental cues such as pH and osmolarity (71). *HilC* and *HilD* relieve H-NS repression at the *hilA* promoter, leading to activation of SPI-1 genes and the transcription factor InvF (72). Following host cell invasion, intracellular acidification triggers the EnvZ/OmpR system, which activates the SPI-2 regulator *ssrAB*. OmpR also suppresses the CadC/BA acid- neutralization system, maintaining acidic conditions required for SPI-2 effector secretion

(73). Phosphorylated SsrB induces SPI-2 gene expression and represses SPI-1 by directly inhibiting *hilA* and *hilD*, enabling the switch from invasion to intracellular survival. *HilD* uniquely links SPI-1 and SPI-2 regulation by activating both systems and counteracting H-NS repression (74). Additionally, intestinal butyrate inhibits *hilD* expression; while *Salmonella* can metabolize butyrate via β-oxidation, the absence of this pathway in *S.* Typhi may explain its reduced intestinal inflammation and distinct systemic dissemination

(75) (Figure.5).

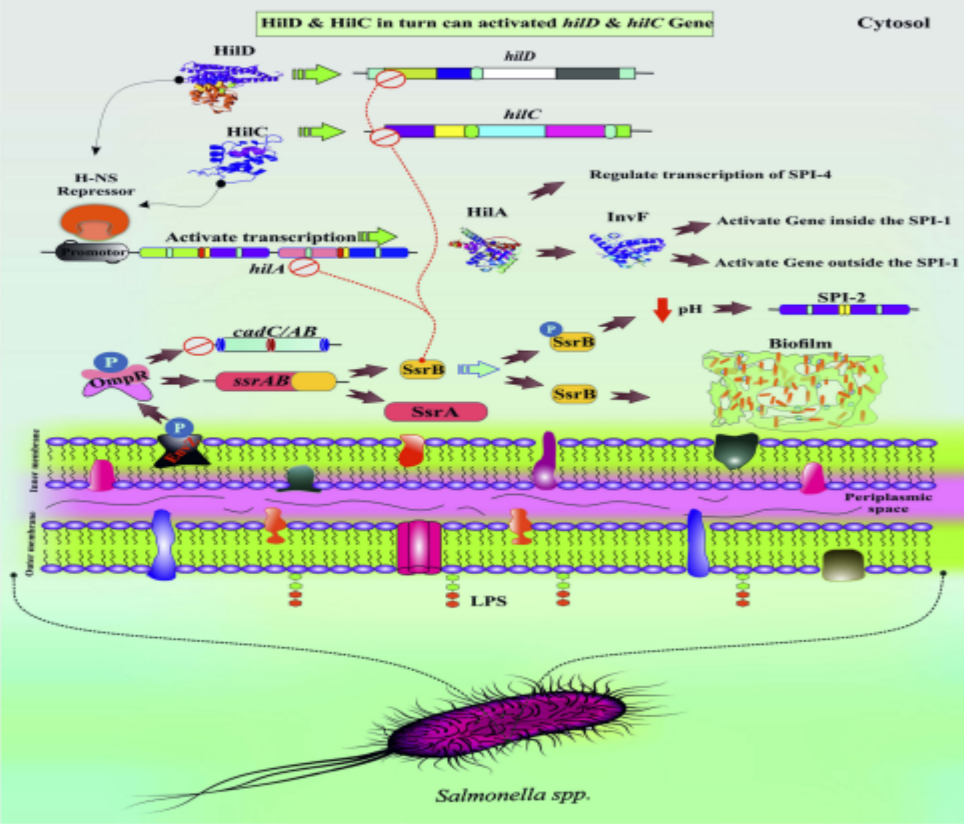


Figure. 5: Salmonella mechanisms in the regulation of pathogenic genes (75)

Salmonella eradication, antimicrobial treatment and drug resistance

First-line antibiotics, which included ampicillin, chloramphenicol, and cotrimoxazole, were traditionally used to treat enteric fever. Multi-Drug Resistant (MDR) Salmonella strains, which were resistant to these first-line antibiotics, initially appeared in the Indian subcontinent, Africa, and Southeast Asia in the 1980s, causing multiple outbreaks. Reports of resistance beginning to surface as early as the 1960s (76). When the treatment was switched to fluoroquinolones, MDR strains were more resistant to them. As a result, azithromycin and third-generation cephalosporins were prescribed instead. Cephalosporin-resistant typhoid was soon reported in isolated cases from Bangladesh (77). According to reports from all endemic nations, including the United States, the first outbreak of extensively drug-resistant (XDR) typhoid to all three first-line medicines, fluoroquinolones, and cephalosporins occurred in Pakistan in 2016 (78). Despite the rarity of azithromycin resistance, resistance inevitably develops as a result of selective antibiotic pressure. Bangladesh has produced strains of *S. Typhi* that are resistant to azithromycin. (79) . Compared to *S. Typhi*, the incidence of *S. Paratyphi* infections is double as a result of vaccination coverage. It has been discovered that the resistance profiles of *S. Paratyphi* and *S. Typhi* strains differ, despite frequently being grouped together. Compared to *S. Typhi*, *S. Paratyphi* has a reduced MDR characteristic (80). MDR *S. Paratyphi* was reported to be 2% by the Surveillance for Enteric Fever in Asia Project, however neither Bangladesh nor Nepal reported any cases (81). Increasing the minimum inhibitory concentration to fluoroquinolones may indicate that ciprofloxacin is not the best medication to use, even in cases when the occurrence of MDR strains is low (82) .

Conclusion

Numerous virulence factors that promote host invasion, intracellular survival, and systemic dispersion are what make *Salmonella* pathogenic. While the Vi capsular polysaccharide and typhoid toxin, which are traits of typhoidal serovars, aid in immune evasion, type III secretion systems expressed by *Salmonella* pathogenicity islands are essential to these activities. The capacity of typhoidal *Salmonella* to endure in the gallbladder, resulting in chronic carriage and ongoing transmission within human populations, is one of its distinguishing characteristics

Recommendation

1. Enhanced Surveillance and Genomic Studies: It is advised to continuously monitor the genome of *S. Typhi* strains in order to detect trends of antibiotic resistance and developing virulence features, particularly in endemic areas.
2. Targeted Drug Development: Future antimicrobial tactics ought to concentrate on destroying particular virulence components, including blocking the T3SS machinery or interfering with the Vi antigen's ability to function.
3. Optimizing Vaccines: Better vaccines should try to elicit strong immune responses against conserved virulence factors, such as T3SS effectors and outer membrane proteins.
4. Multidisciplinary Research: To completely map the regulatory networks of S. *Typhi* virulence and to find new treatment targets, more research combining microbiology, immunology, and systems biology is necessary.

Author’s Declarations

Acknowledgment

The authors would like to thank you everyone who agreed to be the participates in this study.

Ethics statement

Ethics statement: The authors declare that this study was conducted in accordance with the ethical standards and guidelines outlined in the journal’s “Ethics Approval” section of the author guidelines. As this work is a narrative review, formal ethical approval was not required.

Author’s Declaration

I, the undersigned author, hereby declare that the review article entitled “Key Virulence Factors and Pathogenicity of *Salmonella Typhi* Bacteria” is my original work. The manuscript has not been published previously, nor is it under consideration for publication elsewhere. All sources of information and previously published materials have been properly acknowledged. I take full responsibility for the content, analysis, and conclusions presented in this review.

Funding

The authors declare that this research received no external funding.

Competing interest’s statement

The authors declare that they have no competing interests.

Author contributions

Hadeer F. Hamoodi and Mays A. Mahd conceptualized the study, performed the data analysis, and drafted the manuscript; Hadeer F. Hamoodi and Al-Shaikhli Nawfal Haitham were responsible for data collection and contributed to data analysis; Al-Shaikhli Nawfal Haitham critically revised the manuscript and contributed to data interpretation and analysis

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