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Salmonella Pathogenicity Islands and Their Clinical Implications: A Comprehensive Review

Asmaa, Elsayed Mohammed*; Ahmed, Gaber Hassanein and Abd Elfattah, I. El-Zanaty*****

*Department of Bacteriology, Animal Health Research Institute, Agriculture Research Center (ARC), Sohag, Egypt.

**Maxillofacial Head and Neck Surgery Unit, Department of General Surgery, Oncological and Laparoscopic Surgery, Faculty of Medicine, Sohag University, Sohag.

***Avian Pathology unit, Poultry Disease Diagonsis and Research Departement, Animal Health Research Institute (AHRI), Agriculture Research Center (ARC), Egypt.

Review Article

Corresponding author:
Asmaa Elsayed Mohammed
E.mail: dr_asmaa_lab@yahoo.com

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Abstract

Salmonella Pathogenicity Islands (SPIs) are essential genomic regions that encode virulence factors, enabling Salmonella species to invade host cells, evade immune responses, and establish infections. Among the well-characterized SPIs; SPI-1 and SPI-2 play a crucial job in bacterial invasion and intracellular subsistence, respectively, while other SPIs, as SPI-3, SPI-4, and SPI-7, responsible for biofilm formation, systemic dissemination, and chronic carriage. Understanding SPIs has significant clinical implications, particularly in vaccine development, anti virulence therapy, antimicrobial resistance, food safety, host-pathogen interactions and immune modulation. This review explores the pathogenic mechanisms of SPIs, their clinical significance, and emerging therapeutic approaches aimed at mitigating Salmonella infections. SPIs are essential for Salmonella virulence, enabling invasion, intracellular survival, and immune evasion. Their study provides crucial insights into bacterial evolution, infection mechanisms, and therapeutic interventions. SPIs are attractive targets for developing vaccines, anti virulence therapies, and diagnostic tools.

Keywords: *Salmonella Pathogenicity Island, Virulence, Vaccine, antimicrobial resistance.*

Introduction

Salmonella is a typical member belongs to Enterobacteriaceae family. It is a Gram-negative, rods, non-spore-forming bacterium, frequently 0.7-1.5 µm width x 2.5 µm length in size. All *Salmonellae* are motile by peritrichate flagellae with the non motile exceptions, *Salmonella* Gallinarum and *Salmonella* Pullorum **Saeed, Hasoon, and Mohammed (2013)**. It is a facultative intracellular pathogen responsible for foodborne concerns and systemic infections, causing as many as 1.3 billion cases of illness annually. Its virulence is largely attributed to a variety of virulence factors that are responsible for the organism's pathogenicity **Fierer and Guiney (2001)**. Salmonella is antigenically distinguishable by agglutination reactions with homologous antisera. Antigenic variations are

relied on the antigens divergence on the bacterial cell surface. The most important antigens are the somatic or outer membrane antigen (O) and the flagella antigen (H), which in numerous Salmonella cultures, there are switching between the two flagellar types; H1 and H2 expression. In addition, scarce strains exhibit the capsular antigen (Vi). Generally, the integration of these antigens defining the antigenic formula, allows distinction of each Salmonella serotype **Zhang *et al.* (2015)**.

Salmonella infections are acquired through the ingestion of contaminated food or water. To reside an infection in the host gut, Salmonella utilizes a suite of substantial virulence components which constitute the organism's pathogenicity. These components may comprise multiple fimbrial adhesins, phase-variable flagella, polymorphic surface carbohydrates, and well-structured mechanisms which facilitate invasion and survival of the pathogen in host macrophages and other body cells **Helaine *et al.* (2010)**.

Salmonella Pathogenicity Islands

Pathogenicity Island (PI) is a particular genetic element that occurs as an independent and distinct segment within the bacterial chromosome. All PIs share a few prevalent merits such as their absence in a closely related nonpathogenic species or reference strains, also, often comprising large DNA regions (10-200 kB) that involve genes which frequently enhance bacterial virulence **Hentschel and Hacker (2001)**. These genes present within the chromosome or on plasmids either as units of sole, or a few number (islets) or large cassettes composed of sets of genes and operons (PIs). Accordingly, PIs typically house excessive genes clusters that dictate a specific virulence phenotype, which is commonly expressed at a particular time through the course of infection. Thus, for numerous enteric bacteria, a sole PI can alter a naturally naive microorganism into a pathogen one **Helaine *et al.* (2010)**.

Salmonella Pathogenicity Islands (SPIs) are horizontally gained genomic sites that encode various virulence factors enabling infection, colonization, and immune evasion. SPIs are large genomic segments (typically 10–50 kb) integrated into tRNA genes or other conserved regions of the Salmonella genome. SPIs have a very crucial role through the infection process, as they provide components for the type III secretion system (T3SS) or the effector proteins injected through it, enabling bacteria to colonize, invade the host's mucosal lining, and mediate systemic infection **Hensel (2004)**.

SPIs are frequently introduced into tRNA genes and commonly have lower GC content '37 - 47%' than the remaining of the bacterial chromosome 'about 52%'. Thus, SPIs have probably been gained by horizontal transfer from plasmids or phage of uncertain origin besides they are greatly conserved between the various Salmonella serotypes **Kombade and Kaur (2021)**. Consequently, SPIs are recognized via the diverse G-C content and codon employ of the island linked to the genome backbone. SPIs are frequently found in close proximity to tRNA genes and/or insertion sequences **Lin *et al.* (2021)**.

Seventeen SPIs had been recognized in Salmonella enterica serovars. A minimum of five pathogenicity islands; 'SPI-1 through SPI-5', are present in the scope of *S.* enterica serovars, while the complete S. Typhi genome possess five more islands with properties indicative of SPIs **(Vernikos and Parkhill 2006)**. There are nearly two hundreds genes involving those present in chromosomal SPI-1 to SPI-5 that are substantial for Salmonella virulence.

Interestingly, all *S.* enterica serovars possess SPI-1 and SPI-2 which considered the two major pathogenesis elements that encode type III secretion systems (T3SSs) which are primarily responsible for Salmonella infection and invasion inside host's body **Lou *et al.* (2019)**.

***Salmonella* Pathogenicity Islands-1**

SPI-1 is a 40-kb chromosomal cluster located at centisome 63 in *S. enterica.* It located near *the fhlA gene* and is crucial for the host cells invasion and inducement of macrophage apoptosis. It carries virulence elements which are implemented in Salmonella pathogenicity; adhesion, invasion, and toxigenicity (**Tambassi *et al.* 2025)**. SPI-1 comprises a minimal of 37 genes, which encode various constituents of T3SSs, including its regulators and secreted effectors that provide Salmonella isolates the capability to colonize and invade the cells lin-

ing the intestine and then proceed to deliver their virulence proteins into the host cell's cytosol **(Golubeva *et al*. 2012 and Lu *et al.* 2022)**. Additionally, **Altier (2005)** mentioned other SPI-1 encoded proteins, termed as effector proteins, that have the ability of converting eukaryotic cell structure. In close proximity to intestinal epithelial cells, Salmonella utilizes its needle complex to introduce secreted proteins into the cell cytoplasm. These proteins then alter the cell's cytoskeletal structure, specifically actin filaments, causing the cell to engulf the bacterium through macropinocytosis **(Que *et al.* 2013)**.

SPI-1 secretion apparatus is implemented in the oral infection and its mutants expose reduced virulence in oral infection models but do not affect the virulence of systemic infection models. Also it employs a prime role in induction of gastroenteritis via facilitating the colonization of the intestinal epithelium and promoting the host immunity to initiate inflammatory responses **Lerminiaux *et al.* (2020)**.

Structural genes (T3SS apparatus): *invA, invB, invC, invG, invH* and *prgH, prgI, prgJ, prgK*: form the needle complex

Effector proteins *sipA, sipB, sipC, sopE, sopE2, sopB (sigD), sopA, avrA*. These effectors manipulate host actin for uptake and inflammation.

Regulatory genes: *hilA, hilC, hilD, invF*: master transcriptional regulators. *hilD* acts as the central activator, responding to environmental signals **(Que *et al.* 2013)**.

Salmonella Pathogenicity Islands-2

SPI-2 is a DNA segment of 40 -kb settled between centisomes 30 and 31and is defined to encode a 2nd TTSS. It locates between ssa and ssr genes. It is close near to the tRNA gene and holds genes needed for replication within macrophages and thereby systemic infection **(Kim *et al.* 2022)**. Unlike SPI-1, which acts early in infection, SPI-2 T3SS becomes active later, enabling Salmonella to survive and replicate inside host cells, comprising epithelial cells and macrophages **(Pico-Rodríguez *et al.* 2024)**.

Deficiency of SPI-2 genes leads to minimizing of virulence and loss of the ability to colonize the splenic cells of infected animals. **León-Montes *et al.* (2022)** described the inability of SPI2 mutants to disseminate in the mesenteric lymph nodes, spleen or liver in spite of colonization of the Peyer's patches in orally infected mice.

It is mentioned that after phagocytosis, Salmonella keeps inside the engulfing phagosomes, which are transformed to compose the Salmonella-containing vacuole (SCV). Despite the possibility that SPI-1 effectors contribute to the early stages of SCV maturation, SPI-2 effectors are thought to manage the bulk of this process, due to the rapid down-regulation of SPI-1 genes post-internalization **(Brawn *et al.* 2007)**.

SPI-2 particularly assists in bacterial replication within the SCV. It is substantial for survival and persistence inside SCV and keeps vesicle transport inside the host cell conditioning sufficient furnish in the vesicle. Moreover, Salmonella growth within the vesicles is guarded from bactericidal substances **(Lawrence *et al.* 2021)**. SPI-2 is implemented in the restraint of numerous diverse performances such as fusion between lysosomes and SCV, escape from macrophage killing, accumulation of cholesterol around the SCV and keeping of the SCV membrane **(Thurston and Holden 2023)**.

Structural genes (T3SS apparatus): *ssaB, ssaC, ssaD, ssaE, ssaG, ssaH, ssaJ, ssaK.*

Effector proteins *sseF, sseG, sseJ, sifA, pipB2, sopD2*: mediate SCV formation and immune evasion

Regulatory genes *ssrA, ssrB*: Two-component regulatory system (SPI-2 specific). Additional control via *PhoP/PhoQ* and *OmpR/EnvZ* systems **León-Montes *et al.* (2022)**.

Salmonella Pathogenicity Islands-3

SPI-3 sequences reveal variability among the *Salmonella* spp. The right terminal portion of this 17-kb island is found in all species however a four-gene cluster located in the center is limited to certain subspecies. It locates near

thrW tRNA gene. Its functions are magnesium transport, macrophage survival and systemic infection. SPI-3 holds 10 genes, involving the *mgtCB* operon, which is needed for survival of Salmonella inside macrophages and enables the organism to grow in low-magnesium circumstances. Assessment of the G-C content in SPI3 exhibits a mosaic structure, and therefore it seems to have evolved in a multistep operation **(Salam *et al.* 2023)**.

Genetic Components of SPI-3 *mgtC* promotes survival in magnesium-limited phagosomes. *misL* encodes an autotransporter adhesin for epithelial binding. *MarT* is a transcriptional activator that regulates SPI-3 genes **(Jayaweera *et al.* 2021)**.

Salmonella Pathogenicity Islands-4

SPI4 is a 25-kb DNA insertion, settled at centisome 92 and surrounded by ssb and soxSR which are genes encoding the single stranded DNA binding protein and regulation of superoxide response respectively. Also, SPI4 has a mosaic structure and its boundaries have transcriptional terminator structure and a putative tRNA-like gene. It locates between *STM2000* and *STM2020* genes **(Kombade and Kaur 2021)**. Its function is adhesion to epithelial cells. It encodes eighteen genes proposed to be needed for intra-macrophage survival, also it comprises 6 open reading frames (ORF), termed siiA to siiF **(Main-Hester *et al.* 2008)**. It mediates attachment to and invasion of ileac mucosa in cattle but not in chickens and pigs, probably in integration with the SPI-1 T3SS. It has been thought to employ a role in the invasion of epithelial cells lines. It holds genes for apoptosis and toxin synthesis; cytotoxin **(Medvedev *et al.* 2024)**.

Genetic Components of SPI-4 *siiE*: Giant non -fimbrial adhesin (~6000 aa). *siiABCDEF*: Type I secretion system for exporting SiiE. Facilitates intimate attachment to host cells (often works with SPI-1) **(Kombade and Kaur 2021)**.

Salmonella Pathogenicity Islands-5

SPI5 is 7.6 kb. It is settled at centisome 25 on the *Salmonella* chromosome and has been recognized in a broad divergence of *Salmonella enterica* spp., involving *Salmonella Typhimurium*, although it seems to be not present in other enteropathogenic bacteria **(Jayaweera *et al.* 2021)**. It locates near *tRNA-Leu-Xaa.* Its function is to aid inflammatory response and fluid secretion. It constitutes a cluster of genes that encode multiple proteins termed T3SS effector **(Alarcón Navas *et al.* 2024)**. Also, SPI5 encodes proteins that are related to enteropathogenesis; chloride and fluid secretion as well as neutrophil recruitment and induction of inflammation **(Ma *et al.* 2022)**. Genes that located on the virulence plasmid may be needed for growth of the bacterium inside host macrophages and are required for extended survival **(Dos Santos *et al.* 2021)**.

SPI-5 hold pipB, pipD and sopB genes that encode proteins affect secretory responses through enteritis. sopB is placed into the host cytosol, where it initiates inflammatory response by attracting neutrophils to the locations of infection as well as altering ion balances within cells, leading to increase fluid secretion in intestinal mucosa and consequent diarrhea. this gene
mediates cytoskeleton remolding and bacterial entry by altering signal transduction via synthesis of second messengers and plays a crucial role in the triggering of secretory pathways **(Medvedev *et al.* 2024)**. Other proteins, such as SipA, SopA, SopD, and SopE2 have been proposed to play a role in Salmonella gastroenteritis. On the other hand, the effector proteins such as SipA, SipC, and SopB can interact with the actin cytoskeleton, and induce a process named membrane ruffling, which is the formation of outward protrusions on the host cell membrane **(Smereczańska *et al.* 2023)**.

Genetic Components of SPI-5 *sopB (sigD* have dual role in SPI-1 and SPI-5; induces fluid secretion**.** *pipA, pipB, pipC* involved in epithelial cell responses **(Dos Santos *et al.* 2021)**.

Clinical Implications of *Salmonella* Pathogenicity Islands.

Grasping the job of SPIs in Salmonella pathogenesis has significant clinical implications, particularly in the development of vaccines, targeted therapies, and antimicrobial resistance

strategies. Below are some key areas where SPIs influence clinical outcomes and disease management **(Marcus *et al.* 2000)**.

Vaccine Development
SPIs play a crucial role in designing live-attenuated vaccines. Deleting or inactivating specific SPI genes can weaken Salmonella without eliminating its ability to stimulate an immune response **(Xiong *et al.* 2010)**.

Live-attenuated Salmonella vaccines: they have been developed by deleting SPI-1 or SPI-2 genes, reducing the bacteria capability to invade and survive in host cells while still inducing protective immunity. These vaccines have shown promise in protecting versus typhoid fever as well as non-typhoidal Salmonella infections **(Huang *et al.* 2024)**.

SPI-7 and *Vi* Capsule-Based Vaccines: specifically, *Salmonella Typhi*, the etiological agent of typhoid fever, harbors SPI-7, which encodes polysaccharide capsule (*Vi*). So the Typhoid Vi-conjugate vaccine (TCV) targets this capsule, providing long-lasting immunity **(Wang *et al* . 2023)**.

Anti-virulence Therapy:
Traditional antibiotics kill bacteria indiscriminately, leading to microbiome disruption and resistance. An alternative approach is anti-virulence therapy, which targets Salmonella pathogenicity mechanisms rather than killing the bacteria outright **(Sahler *et al.* 2018)**.

Suppression of SPI-1 and SPI-2 Function: blocking T3SS-1 and T3SS-2 that encoded by SPI-1and SPI-2 respectively thus could reduce Salmonella capability to invade and persist in host cells. Small-molecule inhibitors targeting T3SS have shown promising preclinical results **(Abdelwahab *et al.* 2022)**.

Disrupting SPI Gene Regulation: targeting regulatory networks such as PhoP/PhoQ (SPI-2 regulator) can make Salmonella more susceptible to host immunity and antibiotics **(Zaghloul and El Halfawy 2022)**.

Role of SPIs in antimicrobial resistance
Some SPIs contribute to antibiotic resistance, complicating treatment strategies.

SPI-23 in multidrug-resistant Salmonella: A recently identified SPI (SPI-23) in multidrug-resistant Salmonella enterica strains carries genes linked to resistance against aminoglycosides and β-lactam antibiotics **(Mughini-Gras *et al.* 2021)**.

Plasmid-associated SPIs and resistance gene transfer: certain SPIs can transfer antibiotic resistance elements via horizontal gene mobilization. SPI-7 in *S.* Typhi is associated with IncHI1 plasmids that carry extended-spectrum β-lactamase resistance genes. SPI-targeting drugs could reduce virulence and resistance gene spread, improving treatment outcomes. Surveillance of SPI-related resistance genes can inform antibiotic stewardship programs **Andrews *et al.* (2021)**.

Salmonella-related gastroenteritis and food safety
SPIs contribute to the severity of foodborne Salmonella infections, leading to outbreaks of gastroenteritis and systemic illness **Scallan Walter *et al.* (2021)**.

SPI-1 and SPI-2 in foodborne pathogenesis: both SPI-1 and SPI-2 allow Salmonella to survive food processing and host gut defenses, increasing the risk of severe outbreaks **Collier *et al.* (2021)**.

SPI-3 and biofilm formation in food environments: SPI-3 genes regulate biofilm production, making Salmonella more resistant to sanitizers and antibiotics in food processing facilities **Li *et al.* (2022)**.
Prevention Strategies: developing SPI-based rapid detection kits for contaminated food; targeting SPI genes, reduce Salmonella survival on food surfaces **Nieto *et al.* (2016)**.

Host-pathogen interactions and immune modulation
SPIs play a role in immune evasion and chronic infections, influencing disease severity and treatment responses **Amavisit *et al.* (2003)**.

Chronic carriers of *S.* Typhi
SPI-7 contributes to long-term carriage in the

gallbladder, making chronic carriers a reservoir for transmission **Seth-Smith *et al.* (2012)**.

SPI-2 and macrophage survival: SPI-2 effectors help Salmonella evade macrophage killing, leading to prolonged infection and relapse in immunocompromised patients **Hensel (2000)**. Identifying SPI-related biomarkers could improve diagnosis and prognosis of severe Salmonella infections **Tambassi *et al.* (2025)**. Targeting SPI-2 pathways may enhance host immune clearance in persistent infections **Kombade and Kaur (2021)**.

Conclusion

SPIs are essential for Salmonella virulence, enabling invasion, intracellular survival, and immune evasion. Their study provides crucial insights into bacterial evolution, infection mechanisms, and therapeutic interventions.

SPIs are attractive targets for developing vaccines, *anti virulence* therapies, and diagnostic tools. New research should explore combination strategies that inhibit SPI functions while enhancing host immunity. Continued surveillance of SPI-associated antibiotic resistance genes is critical for global public health.

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