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Virulence and Pathogenicity of Major Bacterial Pathogens Tome 2: Gram-Negative Pathogens

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1. *Salmonella enterica subsp. enterica serovar* Typhi

This chapter examines *Salmonella enterica subsp. enterica serovar Typhi* (*S. Typhi*), a human-restricted, Gram-negative invasive enteric pathogen that causes typhoid fever (enteric fever). Emphasis is placed on mechanisms that couple mucosal invasion to systemic dissemination, the genetic architecture of key virulence determinants and mobile elements, and the ways antimicrobial resistance and vaccination reshape transmission at the population level (Parry et al., 2002; Crump et al., 2019; Dyson et al., 2019).

1.1 Epidemiology and Transmission Dynamics

Typhoid fever is a systemic invasive bacterial infection caused by *S. Typhi*, a host-restricted member of the Enterobacterales that is transmitted primarily by the faecal–oral route through contaminated water or food and through direct hand-to-mouth transfer in settings with inadequate sanitation (Parry et al., 2002; Crump et al., 2019). Unlike non-typhoidal *Salmonella*, which are typically zoonotic, *S. Typhi* persists in humans as both acute infections and longer-term carriage states that sustain community transmission in endemic regions (Crump et al., 2019).

Global disease burden remains substantial. The World Health Organization estimates that, as of 2019, typhoid fever causes approximately 9 million cases annually and about 110,000 deaths, with highest incidence in parts of South Asia and sub-Saharan Africa where access to safe water and sanitation is limited and rapid urbanisation amplifies exposure risk (World Health Organization, n. d.). These estimates align with modeling-based syntheses that highlight spatial heterogeneity in incidence and the importance of improving laboratory-confirmed surveillance to reduce uncertainty in national burden estimates (Crump et al., 2019).

Transmission is shaped by the interplay of pathogen shedding, environmental survival, and host susceptibility. During acute disease, *S. Typhi* is shed intermittently in stool and, less consistently, in urine; shedding may begin before diagnosis and continue during early convalescence, enabling household

and community spread even where symptomatic cases receive treatment (Crump et al., 2019). A minority of infected individuals progress to chronic carriage—often defined as persistence of shedding for ≥ 12 months—creating a durable reservoir that can maintain transmission chains in the absence of recognized outbreaks (Gonzalez-Escobedo et al., 2011; Gunn et al., 2014).

Human infectious dose varies with gastric acidity and buffering, consistent with the need for *S. Typhi* to survive gastric transit before reaching the small intestine. In a modern controlled human infection model, escalating oral doses delivered with sodium bicarbonate were used to achieve an attack rate of approximately 60–75% in typhoid-naïve adults, demonstrating that inocula in the range of 10^3–10^4 colony-forming units (CFU) can produce reproducible infection under buffered conditions (Waddington et al., 2014). Such models provide quantitative anchors for vaccine efficacy testing and for mechanistic immunology, but their generalizability is constrained by volunteer selection, controlled exposure routes, and standardized challenge strains (Waddington et al., 2014).

Epidemiologic inference depends heavily on diagnostic ascertainment. Blood culture is the conventional reference standard for confirming typhoid fever, yet sensitivity is limited by low-level bacteraemia, prior antibiotic exposure, and small blood volumes, biases that systematically undercount incidence in routine surveillance (Parry et al., 2002; Crump et al., 2019). Consequently, contemporary transmission analyses increasingly integrate culture confirmation with pathogen genomics (whole-genome sequencing, WGS) to resolve transmission networks, identify importation events, and link antimicrobial-resistance determinants to specific lineages (Wong et al., 2015; Dyson et al., 2019).

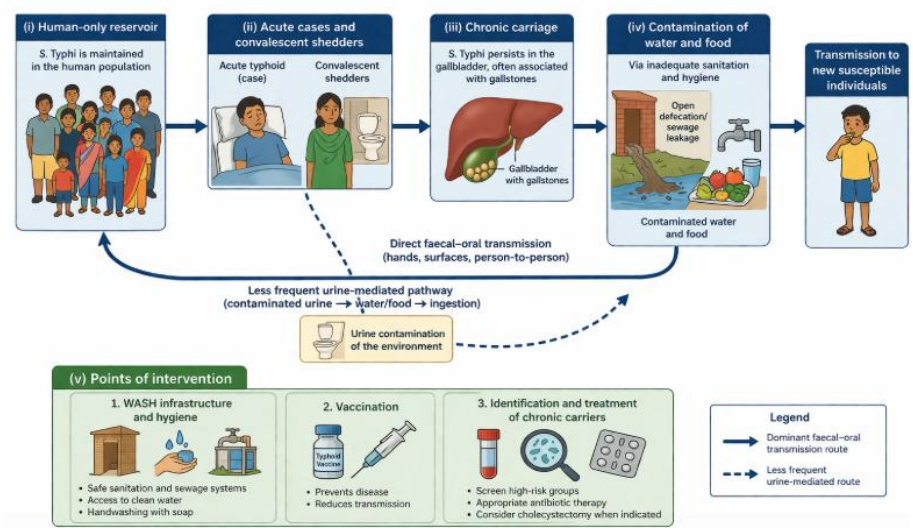

Figure 1.1. Transmission ecology of *S. Typhi* in endemic settings (Crump et al., 2019).

1.2 Molecular Mechanisms of Virulence

S. Typhi pathogenesis reflects a coordinated program of adhesion, epithelial invasion, and intracellular survival. Following ingestion, bacteria traverse the intestinal mucus layer and engage the epithelium via fimbrial and non-fimbrial adhesins, after which invasion is driven by a type III secretion system (T3SS-1) encoded primarily on *Salmonella* pathogenicity island 1 (SPI-1), which injects effector proteins that remodel actin and promote membrane ruffling and bacterial uptake (Parry et al., 2002; Dyson et al., 2019). Although much mechanistic detail derives from comparative work in *Salmonella* Typhimurium, the core SPI-1 architecture is conserved, and invasion-associated phenotypes in *S. Typhi* remain T3SS-dependent in human epithelial models (Parry et al., 2002).

After translocation across the intestinal barrier, *S. Typhi* disseminates systemically by surviving and replicating within phagocytes. Intracellular persistence occurs in a membrane-bound compartment termed the *Salmonella*-containing vacuole (SCV), whose biogenesis and maturation are controlled by a second secretion apparatus (T3SS-2) encoded on SPI-2; this system delivers effectors that modulate vesicular trafficking, limit

antimicrobial effector access, and support replication in the reticuloendothelial system, particularly liver, spleen, and bone marrow (Parry et al., 2002; Parkhill et al., 2001).

A defining virulence determinant of *S. Typhi* is the Vi (virulence) capsular polysaccharide, an O-acetylated N-acetylgalactosaminuronic acid polymer encoded within the viaB locus on SPI-7. Expression of Vi contributes to serum resistance and dampens intestinal inflammation by masking surface pathogen-associated molecular patterns and by interacting with innate immune recognition pathways (Wilson et al., 2011; Parkhill et al., 2001). Vi is tightly regulated in response to environmental cues encountered during infection, enabling the pathogen to balance invasion-associated phenotypes with immune evasion (Dyson et al., 2019).

At the level of genetic control, virulence gene expression is integrated through global regulators and two-component systems that sense osmolarity, pH, Mg2+ limitation, and antimicrobial peptides. Systems such as PhoP/PhoQ and OmpR/EnvZ influence outer membrane remodeling, stress resistance, and expression of SPI-associated regulons, thereby linking intracellular survival to environmental sensing (Dyson et al., 2019). In parallel, SCV-localized transcriptional programs coordinate expression of distinct intracellular effectors—including the typhoid toxin discussed below—whose timing is constrained by vacuolar localization and host cell trafficking (Fowler & Galán, 2017).

Experimental dissection of these mechanisms typically relies on isogenic mutants and quantitative infection assays. Invasion is classically measured using polarized epithelial monolayers and a gentamicin-protection protocol in which extracellular bacteria are killed with aminoglycoside while intracellular bacteria are enumerated by CFU after host-cell lysis; rigorous controls include non-invasive mutants (e. g., SPI-1 secretion-defective strains), cytotoxicity monitoring, and verification of gentamicin activity against the inoculum (Parry et al., 2002). Intracellular survival is quantified in macrophage-like cell lines or primary human monocyte-derived macrophages by time-course CFU and microscopy, with major sources of error including variable multiplicity of infection, host-cell activation state, and differences in vacuolar acidification between models (Parry et al., 2002).

As summarized in Table 1.1, the major virulence determinants of *S. Typhi* comprise secretion systems, immune-modulating surface polymers, and lineage-specific islands that collectively support invasion, intracellular replication, and systemic spread (Parkhill et al., 2001; Wong et al., 2015).

Table 1.1. Core virulence determinants of *S. Typhi* and their genetic loci.

Virulence determinant	Primary genetic locus	Mechanistic role in pathogenesis	Representative experimental readouts
T3SS-1 (invasion apparatus)	SPI-1	Effector injection into epithelial cells; actin remodeling and uptake	Gentamicin-protection invasion assays; secretion reporter fusions (Parry et al., 2002)
T3SS-2 (intracellular survival apparatus)	SPI-2	SCV remodeling; modulation of vesicular trafficking; replication in phagocytes	Macrophage survival/replication CFU time-courses; vacuolar trafficking microscopy (Parry et al., 2002)
Vi capsular polysaccharide	viaB locus on SPI-7	Masking of surface antigens; reduced complement deposition and phagocytic clearance	Complement C3 deposition assays; CR3-dependent clearance in vivo steps (Wilson et al., 2011)
Typhoid toxin (A2B5)	Pathogenicity islet containing cdtB-pltA-pltB	Intracellularly expressed toxin; DNA damage and immune modulation	Cell-cycle arrest/DNA damage assays; toxin quantification in infected cells (Fowler & Galán, 2017; Liu et al., 2022)
Pathoadaptive envelope remodeling	fepE inactivation and related loci	Optimization of capsule-mediated immune evasion via altered O-antigen chain length	Serum resistance and complement deposition; LPS profiling (Winter et al., 2013)

Note. SPI, *Salmonella* pathogenicity island; T3SS, type III secretion system; SCV, *Salmonella*-containing vacuole; CR3, complement receptor 3. Loci and mechanisms reflect conserved principles across *Salmonella* with *S. Typhi*-specific adaptations emphasized.

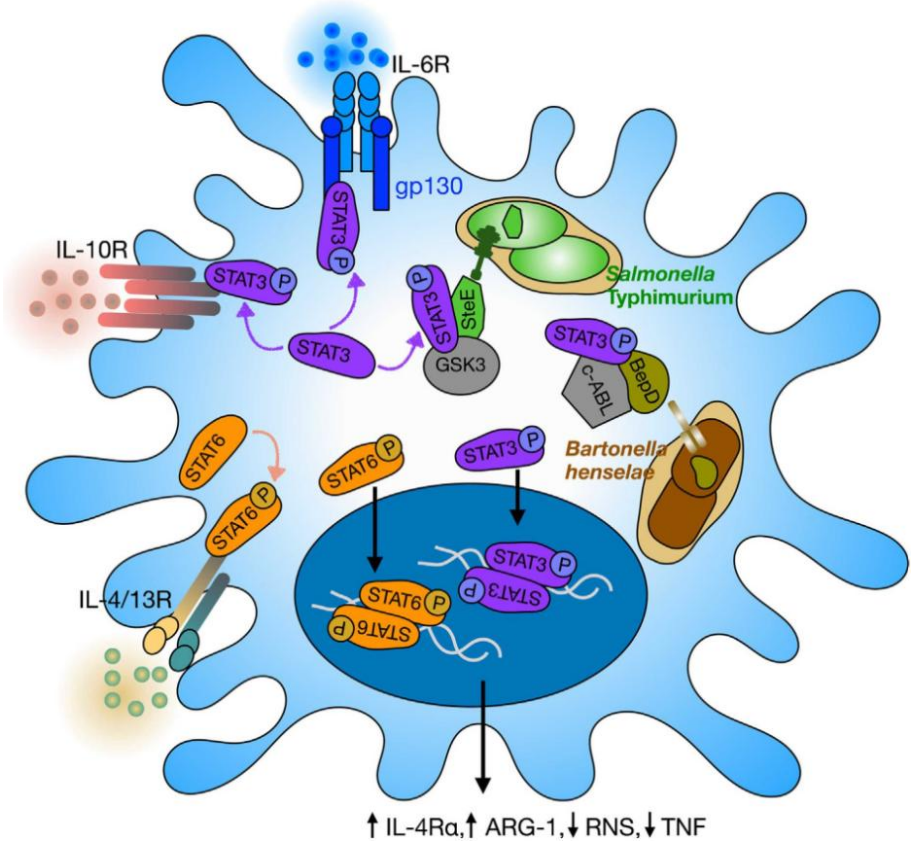

Figure 1.2. Intracellular lifecycle of *S. Typhi* and coordinated virulence expression (Parry et al., 2002; Parkhill et al., 2001; Fowler & Galán, 2017).

1.3 Host–Pathogen Interactions and Immune Evasion

The immunopathogenesis of typhoid fever reflects a balance between bacterial immune evasion and host inflammatory control. *S. Typhi* is adept at limiting early mucosal inflammation, a feature that contrasts with the robust neutrophilic enteritis often elicited by non-typhoidal *Salmonella*. This muted intestinal phenotype is partly attributable to Vi capsule expression, which reduces exposure of immunostimulatory surface structures and diminishes complement activation and opsonophagocytosis (Wilson et al., 2011; Winter et al., 2013).