Salmonella Gastroenteritis (MONDO:0005950): A Comprehensive Disease Characterization

Summary

Salmonella gastroenteritis is a self-limited, foodborne zoonotic enterocolitis caused chiefly by **non-typhoidal *Salmonella enterica* (NTS)** serovars — predominantly **S. Typhimurium** and **S. Enteritidis** — and represents one of the leading bacterial causes of diarrheal illness worldwide. The disease is fundamentally an **infectious**, not a genetic, entity: the initiating lesion is ingestion of *Salmonella* in contaminated food or water, and the causal chain runs from bacterial invasion of the distal ileal/cecal/colonic epithelium through host inflammasome activation and neutrophilic colitis to inflammatory-secretory diarrhea. A defining mechanistic insight, established across multiple lines of evidence in this investigation, is that *Salmonella* does not merely tolerate host inflammation but actively **exploits it** — inflammation oxidizes luminal thiosulfate to **tetrathionate**, which the pathogen uses as a respiratory electron acceptor to outcompete the fermentative resident microbiota and bloom in the gut lumen.

Clinically, most immunocompetent patients present with **diarrhea (~96%)**, **fever (~62–66%)**, **abdominal pain (~32–42%)**, **vomiting (~34%)**, and less often **bloody diarrhea (~19%)**, after an incubation period of roughly **6–72 hours** (dose-dependent), and recover spontaneously within **2–7 days** with **oral/IV rehydration alone**. Antibiotics do not shorten uncomplicated illness and may prolong fecal carriage; they are therefore reserved for severe disease and high-risk hosts. A distinct and dangerous **invasive NTS (iNTS)** branch causes bacteremia and extraintestinal focal infection (mycotic aortitis, endovascular infection, osteomyelitis, meningitis) in the very young, the elderly, and immunocompromised hosts — especially those with **HIV, malaria, malnutrition, anemia, sickle cell disease, or inborn errors of the IL-12/IL-23/IFN-γ axis**. iNTS carries a case-fatality rate of ~15–25% and is concentrated in sub-Saharan Africa, where the multidrug-resistant **S. Typhimurium ST313** lineage drives epidemics.

This report synthesizes **19 confirmed findings** drawn from **94 reviewed papers**, organized against the 15-section disease-characterization template. Because Salmonella gastroenteritis is an infectious disease, several template sections designed for Mendelian genetic disorders (causal genes, pathogenic variants, inheritance patterns) are **not applicable in the classical sense** and are reframed around *host susceptibility genetics* and *bacterial virulence genetics*, which are the biologically meaningful analogues.

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1. Disease Information

Overview. Salmonella gastroenteritis is an acute inflammatory enterocolitis of the distal small bowel and colon caused by non-typhoidal serovars of the Gram-negative facultative intracellular bacterium *Salmonella enterica* subsp. *enterica*. It is the enteric-limited form of non-typhoidal salmonellosis, distinct from enteric (typhoid/paratyphoid) fever caused by the host-restricted serovars Typhi and Paratyphi.

Key identifiers. - **MONDO:** MONDO:0005950 (Salmonella gastroenteritis / salmonella food poisoning) - **MeSH:** Salmonella Infections; Salmonella Food Poisoning - **ICD-10:** A02.0 (Salmonella enteritis); ICD-11: 1A07 (Enteritis due to *Salmonella*) - **SNOMED CT:** Salmonella gastroenteritis - **NCBI Taxonomy:** *Salmonella enterica* (txid28901); serovar Typhimurium, serovar Enteritidis - OMIM/Orphanet: not a Mendelian disease; no primary OMIM entry (host susceptibility loci discussed in Section 4/9).

Synonyms: non-typhoidal salmonellosis, Salmonella enterocolitis, Salmonella food poisoning, NTS gastroenteritis.

Data source type. The knowledge in this report derives predominantly from **aggregated disease-level resources** — epidemiological surveillance (GBD, CDC, WHO), clinical cohort studies, systematic reviews, and mechanistic model-organism/in-vitro experiments — rather than from individual EHR-level patient records.

The leading global role of NTS is well documented: *"Bacterial pathogens cause approximately 10-15% of episodes, most often Shigella, nontyphoidal Salmonella (NTS) Campylobacter and Shiga toxin-producing Escherichia coli (STEC)"* (PMID: 35165210), and *"Salmonella enterica serovar Enteritidis (S. Enteritidis) is a commonly reported pathogen which adapts to multiple hosts and causes critical disease burden at a global level"* (PMID: 39855357). *(Finding F001)*

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2. Etiology

Primary cause — infectious. The disease is caused by ingestion of viable *Salmonella enterica* NTS serovars. S. Typhimurium and S. Enteritidis are the most common serovars worldwide.

Environmental / lifestyle risk factors. - **Contaminated food and water** — poultry, eggs, dairy, beef, and produce are principal vehicles (Section 5, 12). - **Gastric acid suppression.** Gastric acid is a key host defense barrier. A population case-control study (6,414 cases vs 50,000 controls) found current PPI use raised bacterial gastroenteritis risk **RR 2.9 (95% CI 2.5–3.5)**, rising to **RR 5.0** with a doubled PPI dose, while H2-receptor antagonists showed no significant effect: *"Current use of PPIs was associated with an increased risk of bacterial GE compared with nonuse, regardless of the treatment duration (RR, 2.9; 95% confidence interval [CI], 2.5-3.5)"* (PMID: 18054750). A systematic review confirmed *"PPIs appear to increase susceptibility to the following bacterial enteropathogens: Salmonella, Campylobacter jejuni, invasive strains of Escherichia coli"* (PMID: 21999643). *(Finding F011)* - **Age extremes** (infants, elderly), **immunocompromise** (HIV), **malaria, malnutrition, anemia, sickle cell disease** — chiefly risk factors for the invasive branch (Section 8/9).

Host genetic risk factors. Inborn errors of the **IL-12/IL-23/IFN-γ axis** (Mendelian Susceptibility to Mycobacterial Disease, MSMD; >17 genes) predispose to severe/recurrent NTS. *"Mendelian susceptibility to mycobacterial disease is a rare clinical condition... Other infections such as salmonellosis and candidiasis are also reported"* (PMID: 28865061); *"Autosomal recessive complete IL-12Rβ1 deficiency is the most frequent genetic etiology of MSMD"* (PMID: 29995221). Relevant genes: **IL12B, IL12RB1, IFNGR1, IFNGR2, STAT1, IL23R**. In mouse models, **Slc11a1 (NRAMP1)** genotype strongly controls Salmonella susceptibility. *(Finding F010)*

Protective factors. Intact gastric acid barrier; a healthy, competitive gut microbiota (Section 6); defined-microbiota administration is protective in animal models (Section 15).

Gene–environment interaction. Susceptibility emerges from the intersection of host immune-genetic status (IL-12/IFN-γ axis, HIV, hemoglobinopathy) and environmental exposure (ingested dose, acid suppression). This interaction is most consequential for the invasive branch.

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3. Phenotypes

The clinical phenotype is well characterized in pediatric cohorts:

Phenotype	Frequency	HPO term	Source
Diarrhea	~95–96%	HP:0002014	P 36449648 P 27668899
Fever	~61–66%	HP:0001945	P 36449648 P 27668899
Abdominal pain	~32–42%	HP:0002027	P 36449648 P 27668899
Vomiting	~34%	HP:0002013	P 27668899
Bloody diarrhea	~19%	HP:0025085	P 36449648
Dehydration (moderate/severe)	~16%	HP:0001944	P 27668899
Loss of appetite	~7%	HP:0004396	P 27668899
Malaise	~7%	HP:0033834	P 27668899
Elevated CRP / leukocytosis / elevated ESR	common (lab)	HP:0011227 / HP:0001974	P 27668899

An Istanbul pediatric cohort (n=172) reported: *"The most common clinical symptoms were diarrhea (n = 166, 96.5%), fever (n = 113, 65.7%) and abdominal pain (n = 73, 42.4%). Bloody diarrhea was seen in 19.2% of patients"* (PMID: 36449648). A second cohort (n=67) corroborated: *"The presenting symptoms were diarrhoea (95.5%), fever (61.1%), vomiting (34.3%), abdominal pain (32.8%), loss of appetite (7.4%) and malaise (7.4%)"* (PMID: 27668899). *(Finding F015)*

- **Phenotype type:** predominantly symptoms/clinical signs (diarrhea, fever, pain) plus laboratory abnormalities (elevated CRP/ESR, leukocytosis).
- **Age of onset:** any age; pediatric predominance in reported cohorts (median age ~59 months).

- **Severity:** mild-to-moderate and self-limited in immunocompetent hosts; variable.
- **Progression:** acute, episodic, self-limited.
- **Quality of life:** transient; acute illness confines patients for days (dose-dependent bed confinement, Section 8), with generally full recovery. Post-infectious reactive arthritis (Section 11) can cause lasting morbidity.

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4. Genetic/Molecular Information

Salmonella gastroenteritis is **not a Mendelian human genetic disease**, so "causal genes," "pathogenic variants," and germline classification per ACMG do not apply in the standard sense. The biologically meaningful genetics fall into two categories:

A. Host susceptibility genes. - **IL12B, IL12RB1, IFNGR1, IFNGR2, STAT1, IL23R** (MSMD axis) — loss-of-function variants cause severe/disseminated salmonellosis. Documented variants include biallelic **IL12RB1 C291Y** (absent IFN-γ production) and an **IL12B frameshift c.527_528delCT (p.S176Cfs*12)** (PMID: 29995221). Functional consequence: loss of IFN-γ–dependent macrophage killing of intracellular *Salmonella*. *(Finding F010)* - **SLC11A1 (NRAMP1)** — divalent-cation transporter at the phagosomal membrane; genotype controls Salmonella susceptibility in mouse models (multiple *Ity* QTL mapped). - **HLA-B27** — a major susceptibility allele for the post-infectious complication reactive arthritis (Section 11). *(Finding F004)*

B. Bacterial virulence genes (the true "molecular drivers" of disease): - **SPI-1 (Salmonella Pathogenicity Island 1)** T3SS and effectors **SipA, SipB, SipC, SopB, SopE2** — drive epithelial invasion and inflammation. - **SPI-2** — intracellular survival/systemic spread. - Regulators **hilD, hilC, rtsA, hilA** control SPI-1 expression.

No epigenetic host mechanisms, chromosomal abnormalities, or germline/somatic variant frameworks are applicable to this infectious disease.

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5. Environmental Information

Infectious agent. *Salmonella enterica* subsp. *enterica*, NTS serovars — chiefly **Typhimurium** and **Enteritidis**; also **S. Choleraesuis** (swine-associated, invasive), **S. Dublin** (cattle-adapted), and reptile-associated serovars (S. Poona, S. Paratyphi B var Java, S. Agbeni, S. Cotham).

Transmission — zoonotic, fecal-oral. *"Human infection occurs by fecal-oral transmission through ingestion of contaminated food, milk, or water (inter-human or zoonotic transmission)"* (PMID: 31321641). Reptile reservoirs are an increasing source: *"Reptile-associated outbreaks of human Salmonella infections are increasing in Canada, coinciding with a rise in the popularity of reptiles as pets"* (PMID: 41017027), with documented pet-turtle→child transmission of S. Poona confirmed by identical genomic fragment patterns. *(Finding F012)*

Lifestyle/environmental factors. Consumption of undercooked poultry/eggs, raw dairy, contaminated produce, and contaminated water; contact with reptiles/amphibians and livestock. **Multidrug resistance** is rising (e.g., nalidixic acid resistance 97.67% in a Chinese S. Enteritidis collection).

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6. Mechanism / Pathophysiology

Ordered causal chain

1. **Ingestion** of *Salmonella* in contaminated food/water → bacteria transit the stomach (gastric acid is a barrier; acid suppression **increases risk**, F011) → **reach the distal ileum, cecum, and colon**.
2. Bacteria access the mucosa via **two portals**: (a) **M cells** of the follicle-associated epithelium over Peyer's patches, via the **GP2–FimH** receptor interaction; and (b) **direct invasion of enterocytes** via the SPI-1 T3SS. → *leads to* epithelial entry.
3. **SPI-1 T3SS** injects effector proteins (**SipA, SopE2, SopB, SipB, SipC**) into host cells → *results in* cytoskeletal rearrangement and bacterial internalization (membrane ruffling/ macropinocytosis).
4. **SipB binds and activates caspase-1** → *results in* cleavage of pro-IL-1β to mature IL-1β (inflammasome activation).
5. Effector activity + inflammasome → *drives* **massive neutrophil recruitment** into the cecal/ colonic lumen and lamina propria → acute neutrophilic colitis (SPI-1/invA-dependent).
6. **SopB (inositol phosphatase)** activity → *causes* fluid/electrolyte secretion → **secretory-inflammatory diarrhea** (cell death itself is *not required* for enteritis — an inferred but experimentally supported branch point).
7. Host inflammation → *generates* reactive oxygen/nitrogen species that **oxidize luminal thiosulfate to tetrathionate** → *enables Salmonella* anaerobic respiration of **ethanolamine**

(host-derived) → **luminal growth advantage** over the fermentative microbiota → sustained bloom and transmission. *(Finding F007)*

8. **Branch — invasive (iNTS):** in immunocompromised/susceptible hosts (HIV, malaria, malnutrition, anemia, sickle cell, IL-12/IFN-γ axis defects), bacteria that survive within macrophages (via SPI-2) → *lead to* **bacteremia** (~5% of NTS gastroenteritis) → **extraintestinal focal infection** (~40% of bacteremias): mycotic aortitis, endovascular infection, osteomyelitis, meningitis. *(Findings F008, F013)*

Detail

Molecular pathways & effectors (F002). The SPI-1 T3SS is *"a syringe-like protein injection apparatus that translocates bacterial effector proteins into host cells and is essential for epithelial invasion and early stages of pathogenesis"* (PMID: 41212225). An in-vivo neonatal-mouse study showed *"the critical but redundant role of SopE2 and SipA for enterocyte invasion, prerequisite for transcriptional stimulation and mucosal translocation in vivo"* (PMID: 29522566). Pharmacologic T3SS inhibition (Xanthotoxol, downregulating *hilD/hilC/rtsA/hilA*) reduces epithelial invasion without affecting bacterial growth.

Entry portal (F014). M cells are the avid uptake portal: *"GP2 interacts with FimH, a major component of the type 1 pilus on the outer membrane of a subset of gram-negative enterobacilli such as E. coli and Salmonella enterica"* (PMID: 21468225), and RANKL-driven M-cell differentiation confers *"avid uptake of Salmonella and Yersinia organisms"* (PMID: 19828638).

Inflammasome & neutrophils (F003). *"Large numbers of luminal neutrophils were observed in the ceca of WT-infected, but not in invAmut or ssaRmut infected mice"* (PMID: 21327114); *"SipB binds and activates caspase-1, which in turn activates the proinflammatory cytokine interleukin-1beta through cleavage"* (PMID: 11402005) — and in bovine ileal loops the *sopB* mutant was attenuated for fluid secretion, showing effectors, not host cell death, drive enteritis.

Metabolic exploitation of inflammation (F007). *"By inducing intestinal inflammation, S. Typhimurium sidesteps nutritional competition and gains the ability to use an abundant simple substrate, ethanolamine, which is provided by the host"* (PMID: 21969563) — the tetrathionate-respiration mechanism is the mechanistic centerpiece of NTS colonization.

Suggested ontology terms. GO biological processes: GO:0006954 (inflammatory response), GO:0044406 (adhesion to host), GO:0052192 (movement in host), GO:0097202 (activation of cysteine-type endopeptidase/caspase-1), GO:0009410 (response to xenobiotic). Cell types (CL):

CL:0000584 (enterocyte), CL:0000682 (M cell of gut), CL:0000775 (neutrophil), CL:0000235 (macrophage). Chemical entities (CHEBI): tetrathionate (CHEBI:48889), ethanolamine (CHEBI:16000).

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7. Anatomical Structures Affected

- **Primary organs (Organ level):** distal small intestine (**ileum**, UBERON:0002116), **cecum** (UBERON:0001153), and **colon** (UBERON:0001155) — the digestive system.
- **Secondary/complication organs:** bloodstream, **aorta** (mycotic aortitis, UBERON:0000947), bone (osteomyelitis), meninges (meningitis), gallbladder (carriage), pancreas (rare acute pancreatitis) — in invasive disease.
- **Body systems:** digestive (primary); cardiovascular, skeletal, and nervous (invasive complications); immune.
- **Tissue level:** intestinal **epithelium** (follicle-associated epithelium and villous enterocytes); lamina propria (neutrophil infiltration).
- **Cell populations:** enterocytes (CL:0000584), M cells (CL:0000682), neutrophils (CL:0000775), macrophages (CL:0000235), goblet cells (depleted in colitis).
- **Subcellular compartments (GO CC):** *Salmonella*-containing vacuole (GO:0020005 symbiont-containing vacuole), host plasma membrane (GO:0005886), actin cytoskeleton (GO:0015629), inflammasome (GO:0061702).
- **Localization/lateralization:** bilateral/diffuse mucosal involvement of the distal bowel; not lateralized.

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8. Temporal Development

Onset. Acute; incubation period **~6–72 hours** (median ~12–38 h across outbreaks). Dose-dependent: a classic S. Enteritidis outbreak (n=169) showed *"As dose increased, median incubation period decreased (37 h in the low exposure group v. 21 h in the medium exposure group v. 17.5 h in the high exposure group, P = 0.006)"* (PMID: 8119352) — with higher doses also producing more vomiting, greater weight loss, more stools, and longer bed confinement. *(Finding F018)*

Progression & duration. Self-limited; median duration ~1–5 days (typically 2–3): *"Median incubation period was 19 h (range: 3-26 h). Median duration of illness was 5 days (range: 1-11 days)"* (PMID: 21824356). Convalescent fecal shedding can persist for weeks.

Course pattern. Acute, episodic, self-limited in immunocompetent hosts. **Critical window for intervention:** early rehydration prevents complications; for invasive disease, early susceptibility-matched antibiotics on day 0–1 improve survival (Section 12).

Chronic branch (model). Chronic murine infection produces persistent intestinal fibrosis (TGF-β1, CTGF, IGF-I upregulation; type I collagen deposition peaking day 21, present to day 70) — an inferred correlate of rare human chronic sequelae (F005).

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9. Inheritance and Population

Epidemiology. NTS is a leading foodborne diarrheal pathogen. Global estimates place non-typhoidal salmonellosis at **~90+ million gastroenteritis cases/year**. GBD 2021 estimated **509,976 (95%UI 413,361–606,167) incident iNTS cases** in 2021: *"GBD 2021 estimated 509976...incident cases of iNTS worldwide in 2021, with the most cases and highest age-standardized rate (ASR) in Western Sub-Saharan Africa"* (PMID: 40168434). Foodborne bacterial pathogens (incl. NTS) caused *"an estimated 364,500 deaths from diarrheal diseases (age-standardized death rate, ASDR 3.63/100,000)"* (PMID: 42241982) and 24.6M DALYs in 2021. *(Finding F016)*

Inheritance. Not applicable — infectious, not heritable. *Host susceptibility* traits (MSMD axis) follow autosomal-recessive inheritance; HLA-B27 (reactive arthritis) is a co-dominant HLA allele.

Population demographics. - **Age distribution:** skews to young children; iNTS peaks *"early in the second year of life, declining before the age of 3 years"* (PMID: 40684736) and in the <1-year group by GBD. Elderly are at high risk of invasive vascular complications. - **Sex ratio:** slight male predominance in pediatric cohorts (M:F ~55:45). - **Geographic distribution:** global; invasive burden concentrated in **sub-Saharan Africa and South Asia** (78.7% of DALYs). S. Typhimurium ST313 drives African epidemics.

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10. Diagnostics

Stool culture remains the gold standard, increasingly supplemented by **multiplex PCR gastrointestinal panels** (BioFire FilmArray GI, QIAstat-Dx), which detect ~23 pathogens in ~80 minutes with markedly higher yield: *"QGP demonstrated a higher pathogen detection rate (42.3%; 2,033/4,801) than stool culture (12.6%; 255/2,018) and O&P examination (6.3%; 63/986)"* (PMID: 42153668), with >98% negative and near-100% positive agreement. In a Saudi pediatric cohort, Salmonella was the most common pathogen detected (22.1%). *(Finding F009)*

Test	Role	Performance / Note
Stool culture	Gold standard; enables serotyping & susceptibility	Detection ~12.6% yield; slower
Multiplex PCR GI panel	Rapid syndromic diagnosis	42.3% yield; ~80 min turnaround
Blood culture	Essential for invasive disease	iNTS *"presentation... is often with fever alone, so clinical diagnosis is impossible without blood culture confirmation"* (PMID: 30657108)
Inflammatory markers (CRP, ESR, WBC)	Support bacterial etiology	Elevated in bacterial AGE
CT angiography / FDG-PET	Detect mycotic aneurysm/ endovascular focus	For complicated bacteremia

Differential diagnosis: other bacterial enteritides (Shigella, Campylobacter, STEC, Yersinia), viral gastroenteritis (rotavirus, norovirus), C. difficile, inflammatory bowel disease. Multiplex panels aid discrimination but require clinical correlation given asymptomatic carriage.

11. Outcome / Prognosis

Immunocompetent hosts. Excellent prognosis; self-limited recovery in 2–7 days, negligible mortality.

Invasive NTS. High morbidity and mortality. A systematic review of Africa (1966–2014) found *"NTS have been responsible for up to 39% of community acquired blood stream infections in sub-Saharan Africa with an average CFR of 19%"* (PMID: 28056035). In DR Congo children <5, *"overall in-hospital case fatality was 25.1% (60/239)"* with 60% extensively drug-resistant (PMID: 41429348). *(Findings F008, F013)*

Complications. - **Bacteremia:** ~5% of NTS gastroenteritis; **~40% of bacteremias develop extraintestinal focal infection** — *"Approximately 5% of patients with NTS gastroenteritis develop bacteremia and the incidence of extra-intestinal focal infection in NTS bacteremia is about 40%"* (PMID: 31321641). NTS causes ~40% of all infective aortitis; reported fatal cases include ruptured mycotic abdominal aortic aneurysm and aortoesophageal fistula (S. Choleraesuis). *(Finding F013)* - **Reactive arthritis (post-infectious).** A major sequela strongly linked to HLA-B27: in a hospitalized cohort (n=63), *"HLA-B27 was present in 88%"* (PMID: 9370874); in a 592-person outbreak, *"HLA-B27 was present more frequently in those who developed Salmonella infection than in healthy controls (OR 3.0)"* (PMID: 18528961). HLA-B27+ patients had higher ESR and were the only ones to develop sacroiliitis; 8/50 progressed to chronic spondyloarthropathy at 5–22 yr follow-up. *(Finding F004)* - Toxic megacolon/intestinal perforation (pediatric, rare).

Prognostic factors: host immune status, age extremes, ingested dose, serovar, antimicrobial susceptibility, presence of endovascular/prosthetic material, severe anemia.

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12. Treatment

Core principle. Uncomplicated Salmonella gastroenteritis is managed with **rehydration alone**; antibiotics are **reserved for severe/high-risk cases and invasive disease**. European ESPID/ESPGHAN guidance: *"There is no argument to treat moderate salmonella gastroenteritis or carriage. However, the severe cases and those occurring in high risk patient must be treated (ciprofloxacin or ceftriaxone)"* (PMID: 19000862). Antibiotics do not shorten uncomplicated illness and may prolong carriage. *(Finding F017)*

Treatment	Class / NCIT-type	Indication
Oral/IV rehydration & electrolytes	Supportive care (NCIT: Fluid Replacement)	All patients — mainstay
Ciprofloxacin	Fluoroquinolone (NCIT: Ciprofloxacin)	Severe/high-risk, invasive
Ceftriaxone / cefotaxime	3rd-gen cephalosporin (NCIT: Ceftriaxone)	Severe/invasive, pediatric
Azithromycin	Macrolide (NCIT: Azithromycin)	Alternative
Subcutaneous IFN-γ	Immunomodulator	MSMD-associated disseminated salmonellosis

High-risk groups warranting therapy: infants <3 months, elderly, immunocompromised (HIV, MSMD), hemoglobinopathy, and patients with prosthetic/endovascular grafts.

Susceptibility-guided therapy is critical for invasive disease. In DR Congo children, *"susceptibility-matched third-generation cephalosporin treatment on hospital day 0-1 had better 14-day in-hospital survival"* (PMID: 41429348); with extensive drug resistance in 60% of isolates, empiric mismatches worsen outcomes.

No gene, cell, or RNA-based therapies apply. Surgical intervention (graft excision, aneurysm repair) is required for endovascular complications.

13. Prevention

Primary prevention centers on food and water safety. *"Proper food and water treatment, better sanitary facilities, public awareness campaigns, and adherence to food safety laws are all part of prevention measures"* (PMID: 38021876). Key measures: safe food handling/cooking (poultry, eggs), pasteurization, hand hygiene, reptile-contact precautions, and One Health surveillance of animal reservoirs and antimicrobial resistance. *(Finding F006)*

Vaccination. No licensed human NTS vaccine exists. Candidates in preclinical/animal development include: - Live attenuated strains — e.g., ΔmanA ΔsteD (RAST002): *"Protective efficacy was assessed through challenge studies, demonstrating up to 80% protection against the homologous strain"* (PMID: 41398587) (60–80% heterologous). - Outer-membrane vesicle (OMV) vaccines. - Probiotic-derived antimicrobial peptides.

Prevention levels. Primary — food/water safety, (future) vaccination, gastric-acid preservation (avoid unnecessary PPIs in at-risk patients). Secondary — early rehydration and diagnosis. Tertiary — susceptibility-guided antibiotics and surveillance for endovascular complications in bacteremic patients. Public-health: sanitation, health education, livestock/reptile reservoir control.

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14. Other Species / Natural Disease

Salmonella gastroenteritis is fundamentally **zoonotic**, with broad animal reservoirs.

- **Taxonomy:** *Salmonella enterica* subsp. *enterica* (NCBI txid59201); serovars Typhimurium, Enteritidis, Dublin, Choleraesuis.
- **Reservoir species:** poultry and eggs, cattle, pigs (S. Choleraesuis), and reptiles/amphibians (turtles, snakes, bearded dragons).
- **Natural disease in animals. S. Dublin is a cattle-adapted (host-restricted) serovar** causing bovine salmonellosis (systemic disease, abortion, calf enteritis) and serving as a reservoir for human invasive NTS. WGS links human isolates to dairy-cattle isolates and interstate cattle movement (PMID: 42742664; PMID: 42308994). Salmonella is detectable in bovine deep-tissue lymph nodes (~10.8% pooled prevalence) and cow milk (~9.56%), providing zoonotic exposure routes. *(Finding F019)*
- **Comparative pathology:** broad-host-range serovars (Typhimurium, Enteritidis) dominate human sporadic gastroenteritis, whereas host-adapted serovars (Dublin–cattle, Choleraesuis–swine) tend toward invasive disease.
- **Zoonotic transmission:** reptile-associated salmonellosis with serovar-specificity (S. Paratyphi B var Java–snakes; S. Agbeni–turtles; S. Cotham/Chester/Tennessee–bearded dragons) is well documented and rising (PMID: 41017027). *(Finding F012)*

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15. Model Organisms

The streptomycin-pretreated mouse colitis model is the principal system recapitulating human Salmonella gastroenteritis. Streptomycin pretreatment of C57BL/6 mice before oral S. Typhimurium produces cecal/colonic colonization with acute neutrophilic mucosal inflammation, edema, epithelial damage, and goblet-cell depletion. *(Finding F005)*

- **MyD88 (TLR adaptor)** is required for full mucosal inflammation and drives fibrosis: *"they were impaired in the development of mucosal inflammation"* (PMID: 22679002).
- **Chronic model:** *"Infection led to chronic Salmonella colonization of the cecum and colon followed by edema, mucosal ulcerations, and severe transmural inflammation"* (PMID: 18325390), with persistent fibrosis.
- **Microbiota protection:** defined microbiota MET-1 protects — *"Infected mice receiving MET-1 lost less weight, had reduced serum cytokines, reduced NF-κB nuclear staining, and decreased neutrophil infiltration in the cecum"* (PMID: 26531327) — by preserving tight junctions and reducing systemic translocation without lowering intestinal CFU.

Other systems: neonatal mouse (enterocyte invasion, F002); bovine ileal loop (fluid secretion, effector dependence, F003); calf enteritis (S. Dublin); in-vitro Caco-2/Raji M-cell co-culture (M-cell translocation, F014); HeLa/epithelial invasion assays.

Model types: mammalian (mouse, calf), cellular/in-vitro (Caco-2/Raji, HeLa). **Genetic models:** MyD88−/−, Slc11a1 (Nramp1) congenic strains, IL-12/IFN-γ axis knockouts.

Phenotype recapitulation. The streptomycin mouse reproduces neutrophilic colitis, microbiota disruption, tetrathionate-driven blooming, and (chronically) fibrosis. **Limitations:** requires antibiotic pretreatment (mice are naturally colitis-resistant); the streptomycin model mimics human enterocolitis but not the human-restricted typhoid syndrome; does not fully capture human iNTS host-genetic diversity.

Mechanistic Model / Interpretation

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INGESTION (contaminated food/water) ── gastric acid barrier (down by PPIs, F011)
       |
       v
DISTAL ILEUM / CECUM / COLON
       |
  +----+------------------------------+
  v                                   v
M CELLS (GP2-FimH, F014)     ENTEROCYTES (SPI-1 T3SS: SipA/SopE2/SopB, F002)
  |                                   |
  +----------------+-----------------+
                   v
       SipB -> caspase-1 -> IL-1beta (inflammasome, F003)
                   v
       NEUTROPHIL COLITIS + SopB-driven fluid secretion (F003)
                   v
       INFLAMMATION oxidizes thiosulfate -> TETRATHIONATE
                   v
       Salmonella respires ETHANOLAMINE -> LUMINAL BLOOM (F007)
                   v
       INFLAMMATORY-SECRETORY DIARRHEA (self-limited, 2-7 d, F015/F018)
                   |
                   v (susceptible host: HIV/malaria/malnutrition/anemia/SCD/IL-12-IFNg, F008/F0
       MACROPHAGE SURVIVAL (SPI-2) -> BACTEREMIA (~5%)
                   v
       FOCAL INFECTION (~40%): mycotic aortitis, osteomyelitis, meningitis (F013)
                   |
                   v (post-infectious, HLA-B27, F004)
       REACTIVE ARTHRITIS / spondyloarthropathy
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The central, distinguishing insight is that *Salmonella* **weaponizes host inflammation**: rather than a bystander, inflammation supplies a unique anaerobic electron acceptor (tetrathionate) and nutrient (ethanolamine) that the pathogen alone can exploit, converting the host defense into a competitive advantage. This "inflammation-as-nutrient-niche" paradigm unifies the invasion (SPI-1), inflammasome, and microbiota-bloom findings into a single coherent narrative and explains why the disease is simultaneously inflammatory and self-limited in immunocompetent hosts, while diverging into a lethal invasive branch when macrophage-based control (IFN-γ axis) fails.

Evidence Base

PMID	Contribution	Finding
35165210	NTS a leading bacterial diarrheal cause	F001
39855357	S. Enteritidis global burden, MDR	F001
41212225	SPI-1 T3SS essential for invasion	F002
29522566	SopE2/SipA redundant for enterocyte invasion	F002
21327114	SPI-1-dependent neutrophil recruitment	F003
11402005	SipB-caspase-1-IL-1beta; SopB fluid secretion	F003
9370874	HLA-B27 88% in reactive salmonella arthritis	F004
18528961	HLA-B27 OR 3.0 for Salmonella infection	F004
22679002	MyD88 required for mucosal inflammation	F005
18325390	Chronic mouse colitis/fibrosis model	F005
26531327	Defined microbiota protection	F005
41398587	Live attenuated NTS vaccine 80% efficacy	F006
38021876	Prevention: food/water safety	F006
21969563	Tetrathionate/ethanolamine bloom	F007
28056035	iNTS 39% of BSI, CFR 19% in Africa	F008
30657108	iNTS host risk factors; blood culture	F008/F009
40684736	iNTS age distribution	F008
42153668	Multiplex PCR yield 42.3% vs culture	F009
28865061	MSMD-salmonellosis link	F010
29995221	IL12RB1 leading MSMD defect	F010
18054750	PPI RR 2.9 for bacterial GE	F011
21999643	PPIs increase Salmonella susceptibility	F011
31321641	Fecal-oral zoonotic transmission; 5% bacteremia	F012/F013
41017027	Reptile reservoirs, serovar-specific	F012

PMID	Contribution	Finding
41429348	iNTS 25.1% CFR; susceptibility-matched Rx	F013/F017
21468225	GP2-FimH M-cell uptake	F014
19828638	RANKL/M-cell avid uptake	F014
36449648	Symptom frequencies (n=172)	F015
27668899	Symptom frequencies (n=67)	F015
40168434	GBD 2021 iNTS 509,976 cases	F016
42241982	Foodborne bacterial mortality burden	F016
19000862	Antibiotics reserved for severe/high-risk	F017
8119352	Dose-dependent incubation/severity	F018
21824356	Incubation ~19h, illness self-limited	F018
42742664	S. Dublin human-cattle WGS link	F019

Limitations and Knowledge Gaps

1. **Template–disease mismatch.** The disease-characterization template is designed for Mendelian genetic disorders. Sections on causal genes, pathogenic variant classification (ACMG/AMP), inheritance patterns, penetrance, and germline/somatic origin are **not applicable** to an infectious disease and were reframed around host susceptibility and bacterial virulence genetics.
2. **Mechanistic evidence is largely from model organisms.** The SPI-1 invasion, inflammasome, tetrathionate-bloom, and M-cell findings derive chiefly from mouse, calf, and in-vitro models; direct human intestinal mechanistic validation is limited.
3. **Symptom-frequency data** come predominantly from pediatric cohorts (Istanbul, Turkey), which may not generalize to adults or to different serovar distributions.
4. **iNTS burden and CFR** rely on regional African surveillance with heterogeneous diagnostics; global iNTS estimates carry wide uncertainty intervals.
5. **No licensed human vaccine**; efficacy data are preclinical/murine.

6. **Quality-of-life and long-term functional outcome data** (per-phenotype) are sparse for the acute self-limited illness; better characterized only for reactive arthritis sequelae.
7. **Antimicrobial resistance dynamics** (e.g., ST313, 3rd-gen cephalosporin resistance) are evolving rapidly and region-specific.

Proposed Follow-up Experiments / Actions

1. **Human mucosal validation** of the tetrathionate/ethanolamine niche using ex-vivo human intestinal organoids or biopsy-derived enteroids challenged with S. Typhimurium, measuring luminal tetrathionate and ethanolamine-utilization genes.
2. **Prospective adult and mixed-serovar cohorts** to refine symptom frequencies, complication rates, and quality-of-life metrics beyond pediatric data.
3. **Advance NTS vaccine candidates** (RAST002 live-attenuated, OMV) into early-phase human trials, prioritizing sub-Saharan African pediatric populations at highest iNTS risk.
4. **Host-genetic screening study** correlating IL-12/IFN-γ axis variants (IL12RB1, IL12B, IFNGR1/2, STAT1) and SLC11A1 genotypes with invasive-disease risk in prospective iNTS cohorts.
5. **Antimicrobial stewardship & resistance surveillance** integrated with multiplex-PCR diagnostics to guide susceptibility-matched therapy and track ST313 spread.
6. **One Health interventions** targeting the S. Dublin cattle-movement transmission network and reptile reservoirs, using WGS-based source attribution.
7. **Therapeutics targeting the inflammation-niche axis** (e.g., tetrathionate-pathway or SPI-1 T3SS inhibitors such as Xanthotoxol) as anti-virulence adjuncts that reduce microbiota disruption.

Report compiled from 19 confirmed findings across 5 investigation iterations and 94 reviewed papers. Evidence source types span human clinical cohorts/surveillance, model-organism (mouse, calf) experiments, and in-vitro cellular studies, as annotated throughout.
