Enteric Gram-negative bacterial infections of the Gastrointestinal tract

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Gram-Negative Enterobacteriaceae Causing Gastrointestinal Infections

- Enterobacteriaceae family members are **ubiquitous** organisms and are part of the normal intestinal flora of most animals, including humans.
- Some organisms (e.g., *Salmonella* serotype Typhi, *Shigella* species, *Yersinia pestis*) are **always associated with human disease.**
- Others (e.g., *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*) are members of the normal commensal flora that can cause **opportunistic infections.**
- Other commensal organisms can become pathogenic when they acquire virulence genes (e.g., *E. coli*).

Janda JM, Abbott SL. 2021. The changing face of the family Enterobacteriaceae (order: "Enterobacterales"): new members, taxonomic issues, geographic expansion, and new diseases and disease syndromes. Clin Microbiol Rev 34:e00174-20. https://doi.org/10.1128/CMR.00174-20.

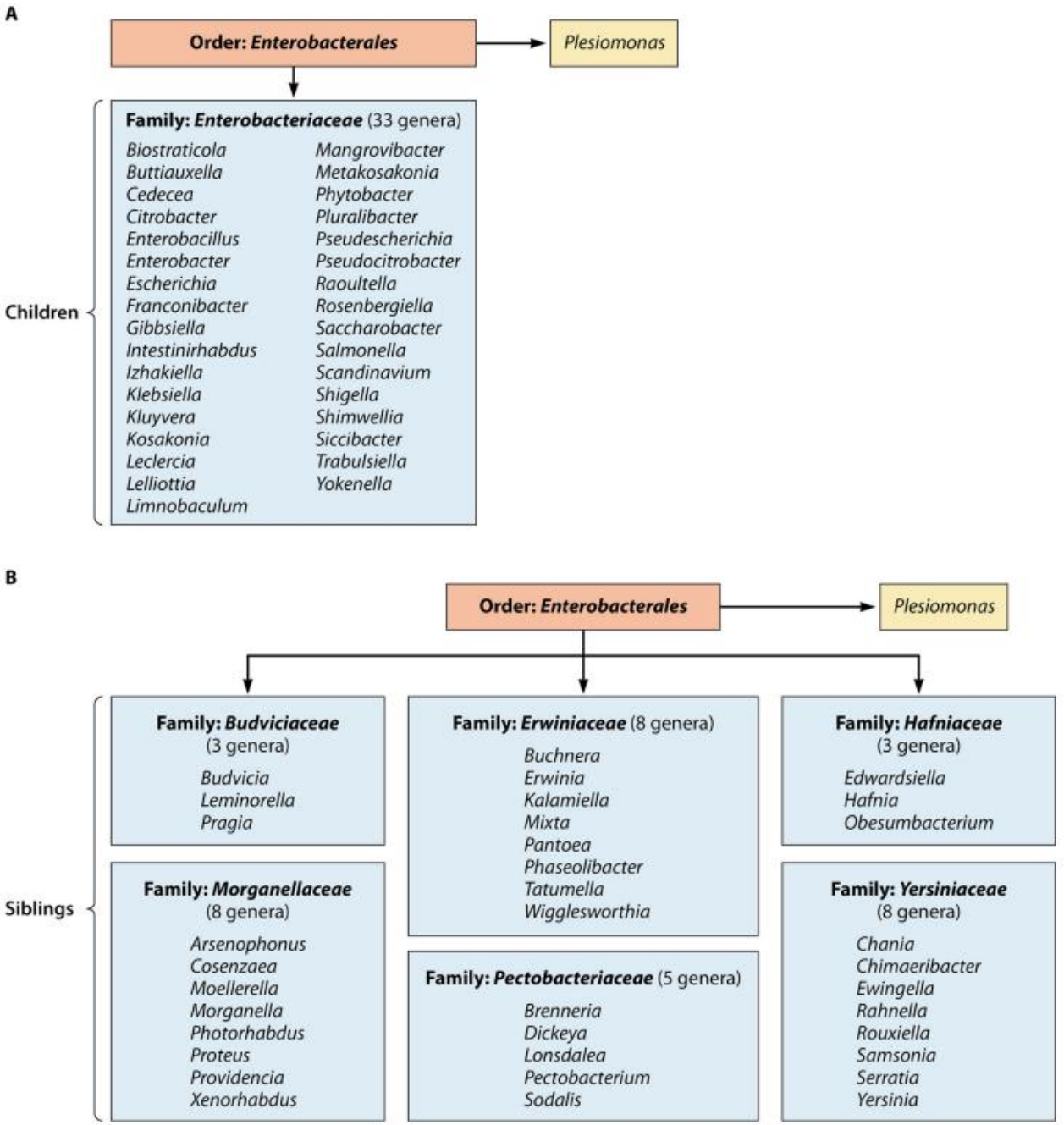


FIG 1 Proposed classification of current members of the family *Enterobacteriaceae* according to Adeolu et al. (98). (A) Revised family *Enterobacteriaceae*; (B) six newly proposed families for inclusion in the order *Enterobacterales*.

General Properties of Enterobacteriaceae

- Enterobacteriaceae are **moderate-sized non spore forming Gram-negative, facultative anaerobic rods.**
- All members ferment glucose, reduce nitrate, and are catalase positive, but they are oxidase negative.
- Most members grow readily on nonselective (e.g.blood agar) and selective (e.g.MacConkey agar) media, which is important for stool and blood culture diagnosis.
- Selective and differential media, such as **MacConkey agar**, help separate lactose fermenters from non-lactose fermenters.

- *Escherichia coli, Klebsiella, and Enterobacter* are usually lactose fermenters, whereas *Salmonella, Shigella, Yersinia, and Proteus* are usually non-lactose fermenters.
- Biochemical identification may include carbohydrate fermentation, indole production, urease activity, citrate use, motility, and hydrogen sulfide production.
- Most Enterobacteriaceae are motile (coated with flagella), with the exception of some common genera (e.g., *Klebsiella, Shigella, Yersinia*).
- Modern laboratories often use automated identification systems, MALDI-TOF MS, molecular assays, and culture-based susceptibility testing.

Antigenic Structure of Enterobacteriaceae

O, K, and H antigens

- The **O antigen** (somatic) is the outer polysaccharide component of lipopolysaccharide and is useful for serologic classification.
- The **K antigen** is the capsular polysaccharide antigen and can contribute to immune evasion and virulence.
- The **H antigen** is the flagellar antigen and is present in motile organisms.
- Serotyping remains important for organisms such as ***Salmonella***, ***Shigella***, and some diarrheagenic ***E. coli*** strains.
- Antigenic variation of these antigens helps these organisms evade host immune responses and complicates epidemiologic classification.

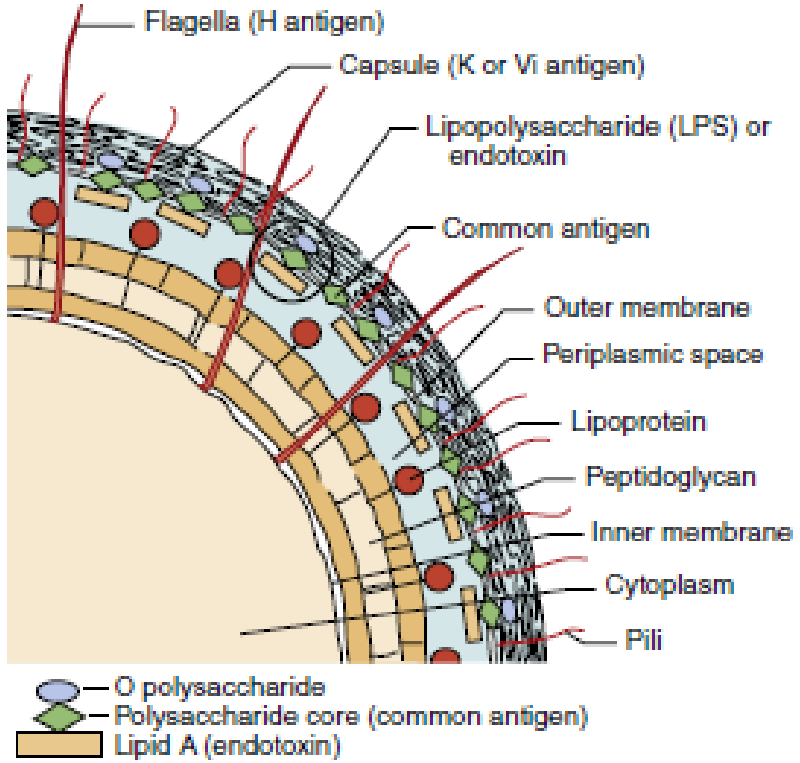


Fig. 25.2 Antigenic structure of Enterobacteriaceae cell wall.

Major Virulence Factors

- Many Enterobacteriaceae are harmless colonizers, but pathogenic strains acquire virulence genes that allow them to attach, invade, produce toxins, or survive host defenses.
- **Endotoxin**, or lipid A of lipopolysaccharide, is shared by aerobic Gram-negative rods and can trigger fever, inflammation, shock, and disseminated intravascular coagulation.
- **Capsules** protect organisms from phagocytosis and may interfere with complement-mediated killing.
- **Adhesins** allow organisms to bind host epithelial surfaces and are essential for colonization of the intestinal tract.
- **Exotoxins**, including enterotoxins and Shiga toxins, explain many of the diarrheal syndromes caused by these organisms.
- Antimicrobial resistance and resistance to serum killing.

Escherichia coli

- *E. coli* is the most common and important member of the genus *Escherichia*.
- This organism is associated with a variety of diseases, including gastroenteritis and extraintestinal infections.
- The strains of *E. coli* that cause gastroenteritis are subdivided into a number of groups: enterotoxigenic, enteropathogenic, enteroaggregative, Shiga toxin–producing, and enteroinvasive E. coli (EIEC).
- *Escherichia* strains possess specialized virulence factors : adhesins and exotoxins.

Enterotoxigenic *E. coli* (ETEC)

- ETEC is one of the most common causes of bacterial diarrheal disease in developing countries and a major cause of traveler's diarrhea.
- It is usually acquired by ingestion of contaminated food or water.
- Disease is mediated by bacterial attachment to the small bowel by colonization factors followed by production of enterotoxins.
- The diarrhea is usually watery and non-bloody, with abdominal cramps, nausea, and sometimes low-grade fever.
- ETEC causes disease without prominent tissue invasion, which explains the absence of dysentery in typical cases.

ETEC Toxins

- ETEC produces **heat-labile toxin, heat-stable toxin, or both**.
- Heat-labile toxin is functionally similar to cholera toxin and increases intracellular cyclic AMP.
- Heat-stable toxin increases cyclic GMP and promotes intestinal fluid secretion; more commonly responsible for severe disease.
- Both mechanisms result in impaired absorption and increased secretion of water and electrolytes into the intestinal lumen.
- Clinically, this produces watery diarrhea that can resemble mild cholera but is usually self-limited.

Enteropathogenic *E. coli*

- EPEC is an important cause of diarrhea in infants, especially in developing countries.
- Posses a cluster of virulence genes located on a chromosomal pathogenicity island called the locus of enterocyte effacement (LEE).
- It causes disease by attaching to enterocytes and producing attaching and effacing lesions.
- These lesions are associated with loss of microvilli and disruption of normal absorptive function.
- transmitted by fecal-oral exposure to contaminated surfaces or food products.
- The diarrhea is usually watery and may be prolonged in infants.
- Most infections resolve after a few days; persistent diarrhea requiring hospitalization can occur.
- Unlike ETEC, EPEC disease is mainly due to epithelial injury and altered absorption rather than classic enterotoxin production.

Enteroaggregative E. coli

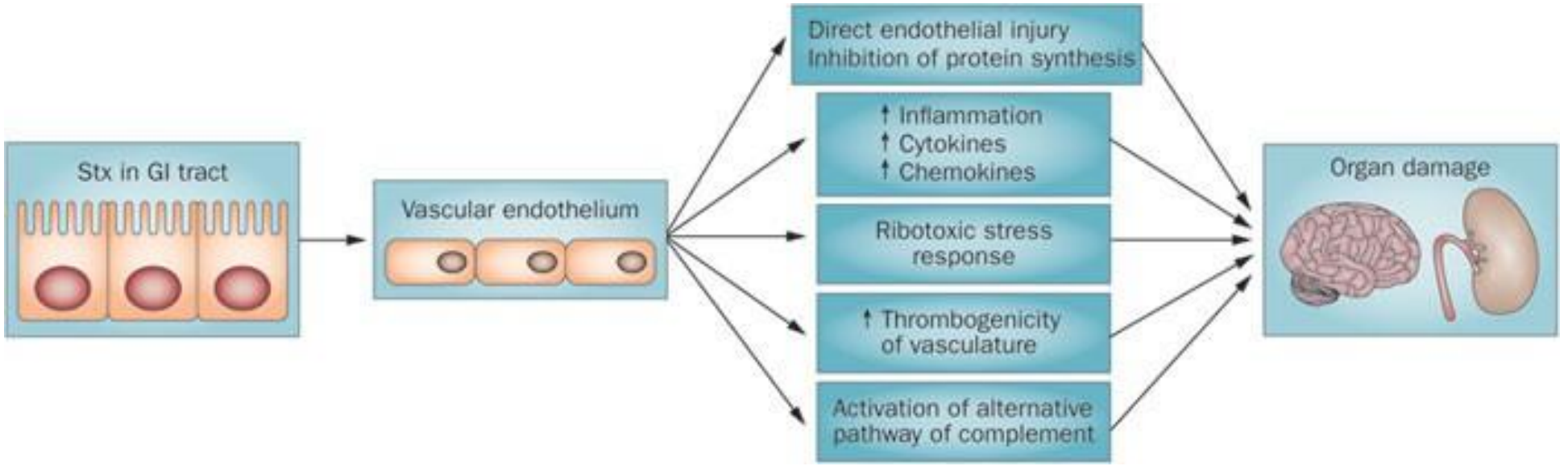
- **EAEC** is associated with acute or persistent diarrhea, especially in children and immunocompromised patients.
- It adheres to intestinal epithelial cells in an aggregative, stacked-brick pattern.
- EAEC may produce mucus biofilm, inflammatory injury, and toxins that contribute to prolonged disease.
- The clinical illness is commonly watery diarrhea, often with fever, nausea, vomiting, and abdominal pain
- EAEC is important because its chronicity can contribute to nutritional compromise and growth effects in vulnerable children.

Shiga Toxin-Producing E. coli

- **STEC**, also called verocytotoxin-producing *E. coli* (VTEC) or enterohemorrhagic *E.coli (***EHEC)**, when associated with hemorrhagic colitis, is an important cause of bloody diarrhea.
- Disease is strongly associated with Shiga toxins, especially Stx1 and Stx2.
- Important reservoirs include cattle, and transmission may occur through undercooked beef, unpasteurized products, contaminated fruits and vegetables, or person-to-person spread.
- The most common serotype associated with sever human disease is O157:H7.
- The illness often begins with abdominal cramps **and watery diarrhea that can progress to bloody diarrhea and hemorrhagic colitis.**
- **Fever may be absent or low-**grade, which can help distinguish STEC from some invasive bacterial dysenteries.

STEC Complications and Management

- The most feared complication of STEC infection is **hemolytic uremic syndrome**, especially in children younger than 10 (5-10%) and older adults - STX2 preferentially.
- HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.
- Resolution of symptoms occurs in uncomplicated disease after 4 to 10 days in most untreated patients; however, death can occur in 3% to 5% of patients with HUS, and severe sequelae (e.g., renal impairment, hypertension, CNS manifestations) can occur in as many as 30% of HUS patients.
- Antibiotics and antimotility agents are generally avoided when STEC infection early intravenous fluids may reduce renal failure risk in children with STEC O157 infection.
- Diagnosis requires detection of Shiga toxin or Shiga toxin genes, often combined with culture for epidemiologic investigation.



Trachtman, H., Austin, C., Lewinski, M. et al. Renal and neurological involvement in typical Shiga toxin-associated HUS. Nat Rev Nephrol 8, 658–669 (2012). https://doi.org/10.1038/nrneph.2012.196

Enteroinvasive *E. coli*

- **EIEC** causes an invasive diarrheal illness resembling shigellosis.
- It invades and replicates within colonic epithelial cells initially producing watery diarrhea.
- A minority progress to dysenteric form with fever, abdominal cramps, tenesmus, and bloody or mucoid diarrhea.
- EIEC is less commonly identified than other diarrheagenic *E. coli* pathotypes in routine clinical practice.
- Its pathogenesis is important because it shows that not all *E. coli* diarrhea is toxin-mediated or watery.

TABLE 25.3 Gastroenteritis Caused by *Escherichia coli*

Organism	Site of Action	Disease	Pathogenesis	Diagnosis
ETEC	Small intestine	Traveler's diarrhea; infant diarrhea in developing countries; watery diarrhea, vomiting, cramps, nausea, low-grade fever	Plasmid-mediated, ST and LT enterotoxins that stimulate hypersecretion of fluids and electrolytes	Most U.S. outbreaks caused by ST-producing strains; commercial immunoassays available for detecting ST in clinical specimens and cultures; PCR assays used with clinical specimens
EPEC	Small intestine	Infant diarrhea in developing countries; watery diarrhea and vomiting, nonbloody stools; believed to be rare in United States	Plasmid-mediated A/E histopathology, with disruption of normal microvillus structure resulting in malabsorption and diarrhea	Characteristic adherence to HEp-2 or HeLa cells; probes and amplification assays developed for the plasmid-encoded bundle-forming pili and gene targets on the "locus of enterocyte effacement" pathogenicity island
EAEC	Small intestine	Infant diarrhea in developing and probably developed countries; traveler's diarrhea; persistent watery diarrhea with vomiting, dehydration, and low-grade fever	Plasmid-mediated aggregative adherence of rods ("stacked bricks") with shortening of microvilli, mononuclear infiltration, and hemorrhage; decreased fluid absorption	Characteristic adherence to HEp-2 cells; DNA probe and amplification assays developed for conserved plasmid
STEC	Large intestine	Initial watery diarrhea followed by grossly bloody diarrhea (hemorrhagic colitis) with abdominal cramps; little or no fever; may progress to hemolytic uremic syndrome	STEC evolved from EPEC; A/E lesions with destruction of intestinal microvilli, resulting in decreased absorption; pathology mediated by cytotoxic Shiga toxins (Stx1, Stx2), which disrupt protein synthesis	Screen for O157:H7 with sorbitol-MacConkey agar; confirm by serotyping; immunoassays (ELISA, latex agglutination) for detection of the Stx toxins in stool specimens and cultured bacteria; DNA amplification assays developed for Stx genes
EIEC	Large intestine	Rare in developing and developed countries; fever, cramping, watery diarrhea; may progress to dysentery with scant bloody stools	Plasmid-mediated invasion and destruction of epithelial cells lining colon	Sereny (guinea pig keratoconjunctivitis) test; plaque assay in HeLa cells; probes and amplification assays for genes regulating invasion (cannot discriminate between EIEC and *Shigella*)

A/E, Attachment/effacement; *DNA*, deoxyribonucleic acid; *EAEC*, enteroaggregative *E. coli*; *EIEC*, enteroinvasive *E. coli*; *ELISA*, enzyme-linked immunosorbent assay; *EPEC*, enteropathogenic *E. coli*; *ETEC*, enterotoxigenic *E. coli*; *LT*, labile toxin; *PCR*, polymerase chain reaction; *ST*, stable toxin; *STEC*, Shiga toxin–producing *E. coli*.

Salmonella spp

- ***Salmonella*** are Gram-negative, facultative anaerobic rods within Enterobacteriaceae.
- Clinically, *Salmonella* infections are divided into **non-typhoidal Salmonella gastroenteritis** and **typhoidal Salmonella enteric fever**.
- Non-typhoidal *Salmonella* commonly causes foodborne gastroenteritis.
- ***Salmonella* Typhi** and ***Salmonella* Paratyphi** cause enteric fever, a systemic febrile illness.
- This classification is essential because gastroenteritis and enteric fever differ in pathogenesis, clinical course, diagnosis, treatment, and prevention.

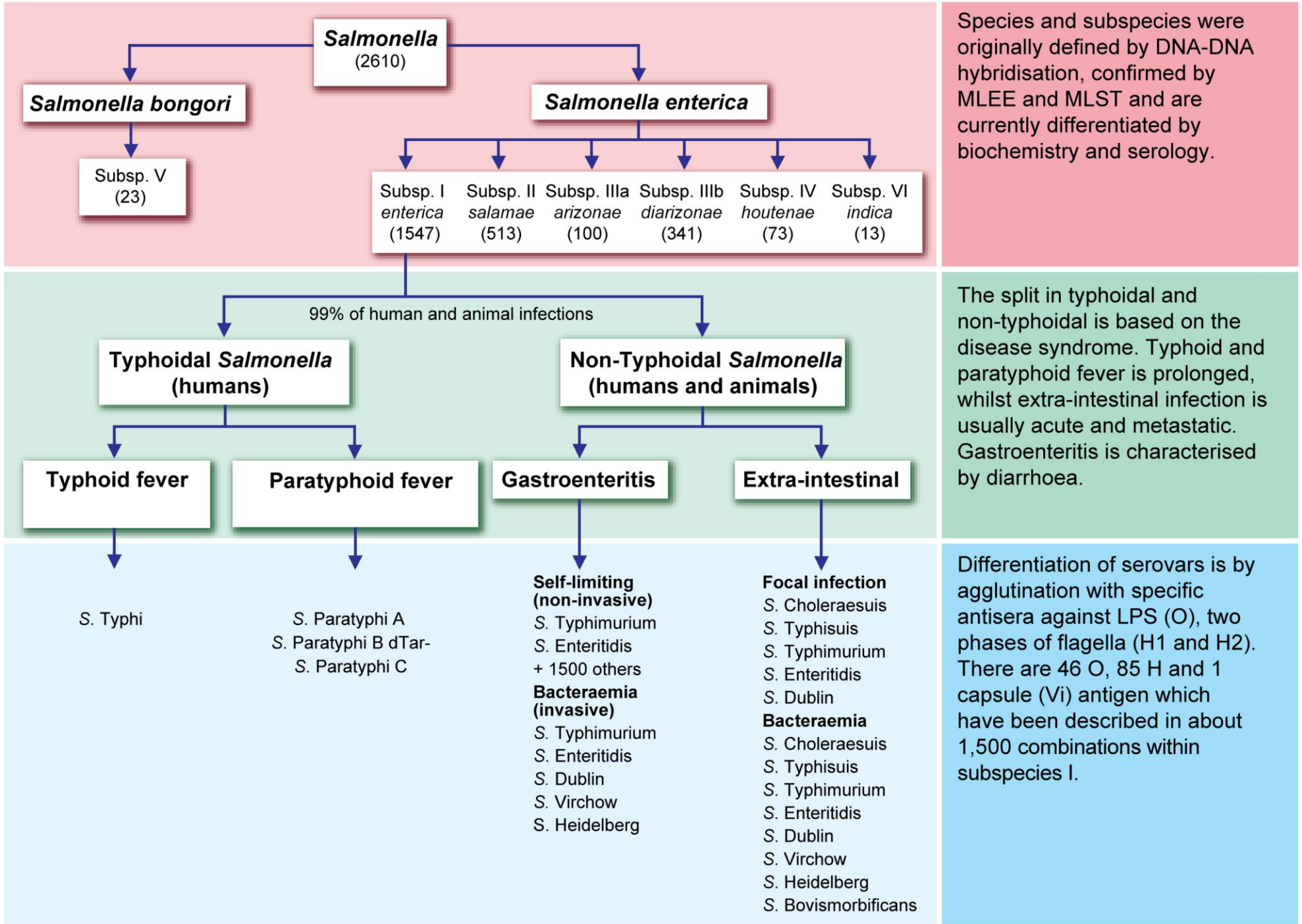


Figure 1. General overview of the current classification of *Salmonella enterica*. Source: https://journals.plos.org/plospathogens/article/figure?id=10.1371/journal.ppat.1002776.g001

Pathogenesis

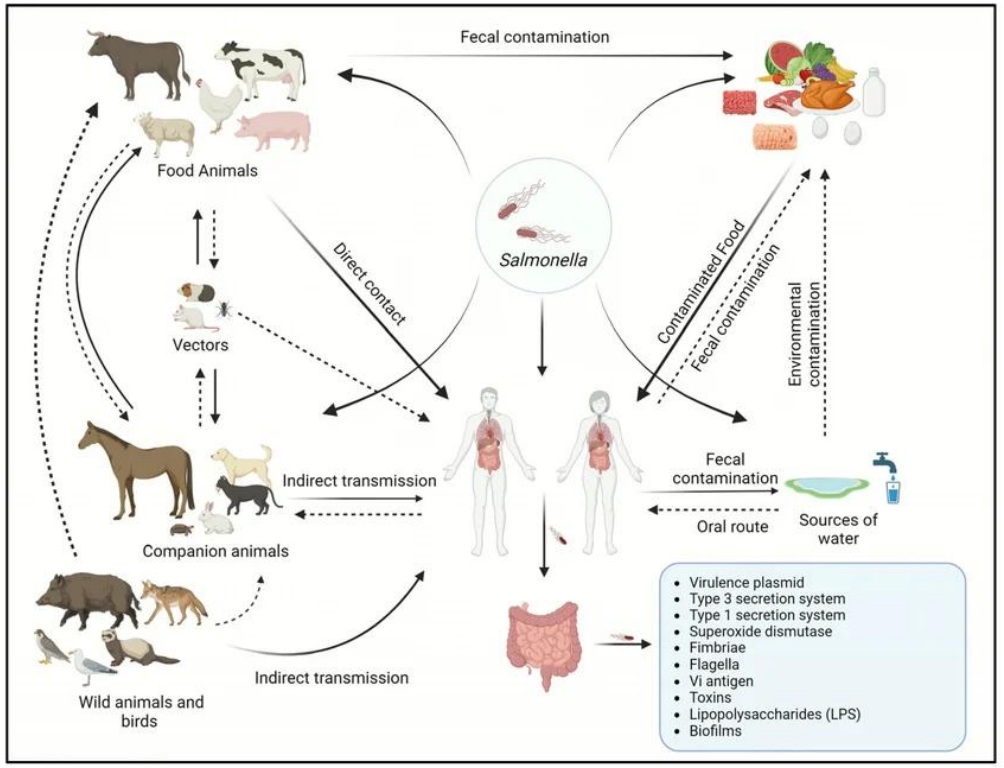
- *Salmonella* infection begins after ingestion of contaminated food or water, or feco-oral spread in children .
- The bacteria pass through the stomach and invade the intestinal mucosa, especially through M cells over Peyer patches.
- *Salmonella* can survive within macrophages, allowing dissemination beyond the intestine in some infections.
- Non-typhoidal *Salmonella* usually causes localized intestinal inflammation, whereas typhoidal strains are adapted for systemic spread.
- Endotoxin and inflammatory responses contribute to fever and systemic manifestations.

Epidemiology

- *Salmonella* can colonize virtually all animals, including poultry, reptiles, livestock, rodents, domestic animals, birds, and humans.
- Serotypes such as *Salmonella* Typhi and *Salmonella* Paratyphi are highly adapted to humans and do not cause disease in nonhuman hosts.
- *Salmonella* Typhi and *Salmonella* Paratyphi can survive in the gallbladder and establish chronic carriage (chronic colonization).
- *Salmonella* Typhi infections occur when food or water contaminated by infected food handlers is ingested.
- The infectious dose for *Salmonella* Typhi infections is low (unlike other serovars), so person-to-person spread is common.

Non-Typhoidal Salmonella Gastroenteritis

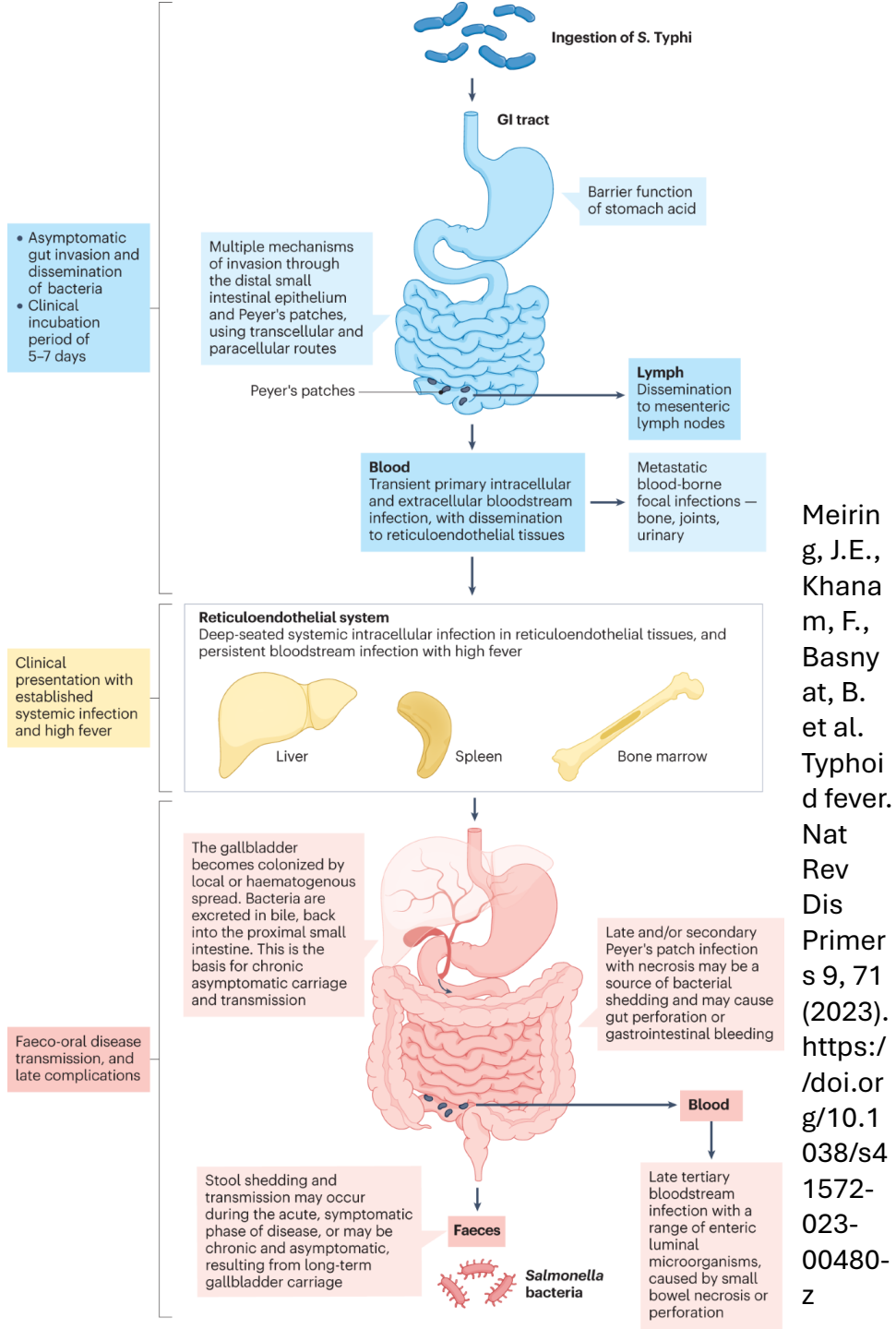
- Non-typhoidal *Salmonella* gastroenteritis is commonly associated with contaminated poultry, eggs, meat, reptiles, and cross-contaminated foods.
- Symptoms usually include non-bloody diarrhea, abdominal cramps, fever, nausea, and vomiting.
- The incubation period is commonly hours to a few days, and illness is often self-limited.
- Stool may be inflammatory, and bacteremia can occur, especially in infants, older adults, and immunocompromised patients.
- Most uncomplicated cases are treated with fluids and supportive care, while antibiotics are reserved for severe disease or high-risk patients.



Salmonellosis: An Overview of Epidemiology, Pathogenesis, and Innovative Approaches to Mitigate the Antimicrobial Resistant Infections - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Transmission-cycle-of-Salmonella-between-animals-and-humans_fig1_377410958

Enteric Fever

- Enteric fever is caused by ***Salmonella* Typhi** and ***Salmonella* Paratyphi A,B,C (Typhoid and Paratyphoid fever respectively).**
- The disease is endemic in Africa, south Asia and Latin America.
- It is acquired by ingestion of food or water contaminated with human feces.
- The bacteria pass through the cells lining the intestines and are engulfed by macrophages. They replicate after being transported to the liver, spleen, and bone marrow.
- The illness is systemic and typically presents 10-14 days after ingestion with sustained fever, headache, malaise, and sometimes rose-colored spots, followed by GI symptoms.
- Typhoid fever often produces fever lasting more than three days and may reach 39 to 40°C.
- Diagnosis is often by blood culture early in disease, while stool culture may become positive later.



Meiring, J.E., Khanam, F., Basnyat, B. et al. Typhoid fever. Nat Rev Dis Primers 9, 71 (2023). https://doi.org/10.1038/s41572-023-00480-z

Diagnosis, Treatment, and Prevention

Clinical and public-health approach

- Stool culture is useful for suspected non-typhoidal *Salmonella* gastroenteritis.
- Blood culture is important when enteric fever or invasive Salmonella infection is suspected.
- Antimicrobial susceptibility testing is important because resistance affects treatment choices.
- First-line treatments often include ciprofloxacin (for susceptible strains), azithromycin, or ceftriaxone.
- Prevention includes safe food handling, cooking poultry and eggs thoroughly, avoiding cross-contamination, and proper sanitation.
- Typhoid prevention also includes safe water, sanitation, identification of carriers, and vaccination for travelers to endemic regions.

Shigella spp

- ***Shigella*** are nonmotile highly infectious Gram-negative rods that cause shigellosis or bacillary dysentery.
- Humans are the only reservoir, and transmission occurs by fecal-oral spread.
- Shigella has a very low infectious dose, so person-to-person transmission is common.
- Outbreaks occur in childcare centers, institutions, households, and settings with poor hygiene or sanitation.
- The major species include ***S. dysenteriae, S. flexneri, S. boydii, and S. sonnei***.

Pathogenesis

- *Shigella* invades the **colonic mucosa** and spreads from cell to cell, replicating in the host cell cytoplasm, evading immune clearance.
- It survives gastric acidity better than many enteric organisms, contributing to its low infectious dose.
- Invasion causes mucosal ulceration, intense inflammation, and exudation of blood and mucus.
- The clinical result is abdominal cramps, fever, tenesmus, and frequent small-volume stools.
- **Shiga toxin**, especially from *S. dysenteriae type 1,* can contribute to severe disease and HUS.

Shigellosis

Dysentery syndrome

- Shigellosis may begin1-3 days after ingestion with **watery diarrhea** but can progress **to bloody diarrhea** with mucus.
- Cardinal features include fever, **abdominal pain, malaise, and tenesmus.**
- Abundant neutrophils, erythrocytes, and mucus are found in the stool.
- Mild disease may resolve with fluids and supportive care, but antibiotics can shorten illness and reduce transmission when indicated (ciprofloxacin, azithromycin, or ceftriaxone).
- Antimotility agents should be avoided because they may worsen invasive diarrhea.

Yersinia enterocolitica and Yersinia pseudotuberculosis

- ***Yersinia enterocolitica*** and ***Yersinia pseudotuberculosis*** can cause gastrointestinal disease in humans.
- Yersinia infections are often **zoonotic** and are associated with contaminated water and food, especially pork products.
- incubation period of 1 to 10 days (average, 4 to 6 days), and disease can last as long as 1 to 2 weeks.
- ***Y. enterocolitica*** can grow at refrigerator temperatures, which is an important food safety point.
- The organisms can invade intestinal lymphoid tissue and cause terminal ileitis and mesenteric lymphadenitis.
- Because of right lower quadrant abdominal pain, *Yersinia* infection can clinically mimic acute appendicitis in children(**pseudoappendicitis**).

Clinical Disease, Diagnosis, and Treatment

- Young children commonly present with fever, abdominal pain, and diarrhea .
- *Yersinia enterocolitis in* older children and adults may present with right lower quadrant pain and mesenteric adenitis, resembling appendicitis.
- Diagnosis may require stool culture with appropriate laboratory suspicion because Yersinia may need special culture conditions.
- Most infections are self-limited, but severe or invasive disease may require antimicrobial therapy.

Cronobacter sakazakii

- ***Cronobacter sakazakii*** *(*formerly *Enterobacter sakazakii)* is an Enterobacteriaceae member of special importance in neonates and young infants.
- Important cause of neonatal gastrointestinal and systemic infection.
- Cronobacter is naturally found in the environment and is particularly good at surviving in low-moisture, dry foods, such as powdered infant formula/milk, herbal teas, and starches.
- Infection can present as sepsis, meningitis, necrotizing enterocolitis, or severe systemic illness.
- Premature infants, low-birth-weight infants, and immunocompromised neonates are at greatest risk.
- Prevention focuses on safe preparation, storage, and handling of powdered infant formula, especially in neonatal units.

MMWR Morb Mortal Wkly Rep. 2023 Mar 3;72(9):223–226. doi: 10.15585/mmwr.mm7209a2

Cronobacter sakazakii Infections in Two Infants Linked to Powdered Infant Formula and Breast Pump Equipment — United States, 2021 and 2022

Julia C Haston [1,2,✉], Shanna Miko [1,2], Jennifer R Cope [1], Haley McKeel [1], Cynney Walters [1], Lavin A Joseph [1], Taylor Griswold [1], Lee S Katz [1], Ashley A Andújar [1], Laura Tourdot [3], Joshua Rounds [3], Paula Vagnone [3], Carlota Medus [3], JoAnn Harris [4], Robert Geist [5], Daniel Neises [5], Ashley Wiggington [6], Trey Smith [1], Monica S Im [1], Courtney Wheeler [1], Peyton Smith [1], Heather A Carleton [1], Christine C Lee [1,7,✉]

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References

- Murray PR, Rosenthal KS, Pfaller MA. Medical Microbiology. 10th ed. Philadelphia: Elsevier; 2025.
- Riedel S, Hobden JA, Morse SA, Mietzner TA, Detrick B, Alexander BD, et al. Jawetz, Melnick, & Adelberg's Medical Microbiology. 29th ed. New York: McGraw Hill; 2024.