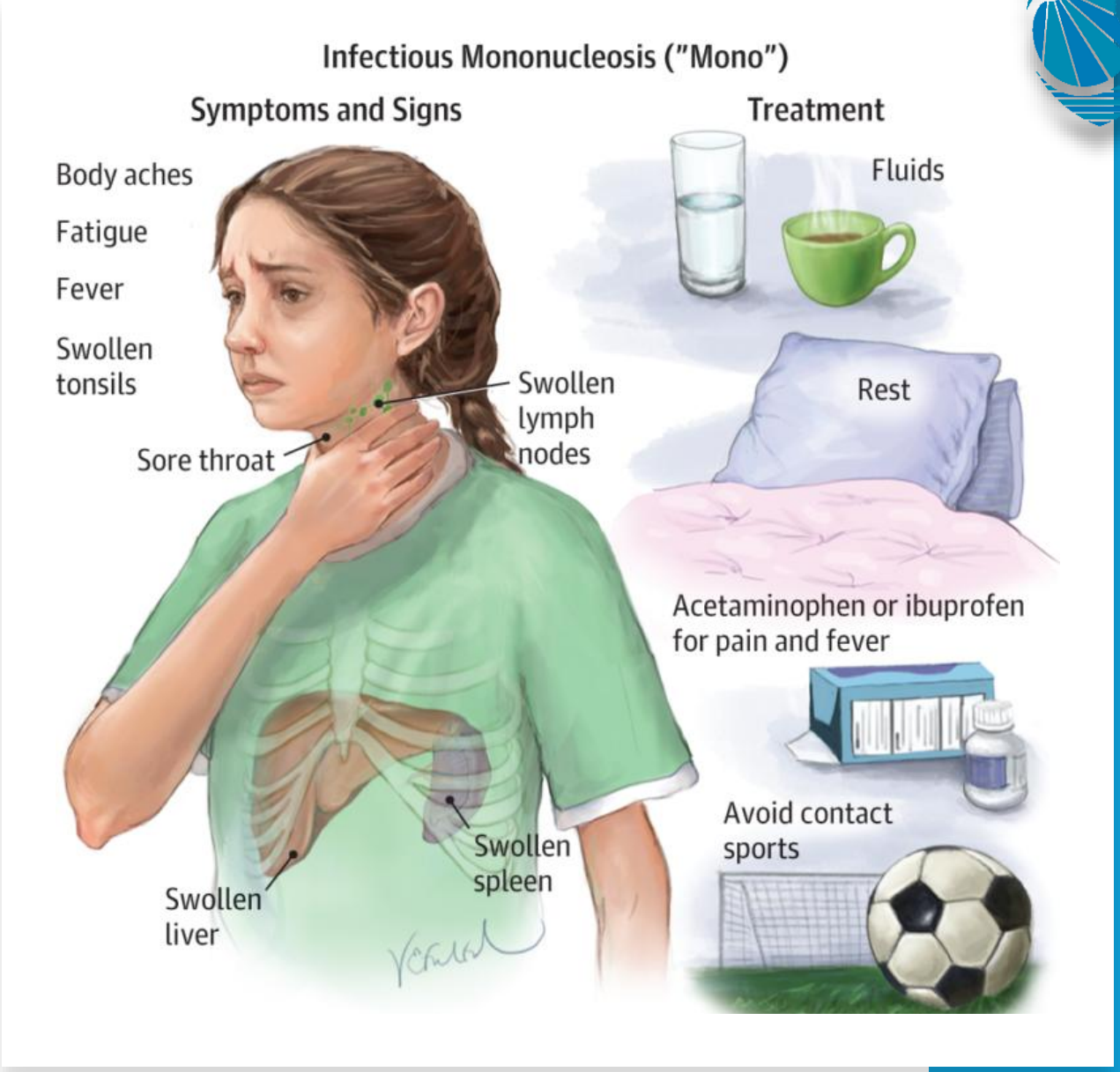
Infections of Lymphocytes (2)

University of Jordan
Malik Sallam, M.D., Ph.D.
School of Medicine
Department of Pathology, Microbiology and Forensic Medicine

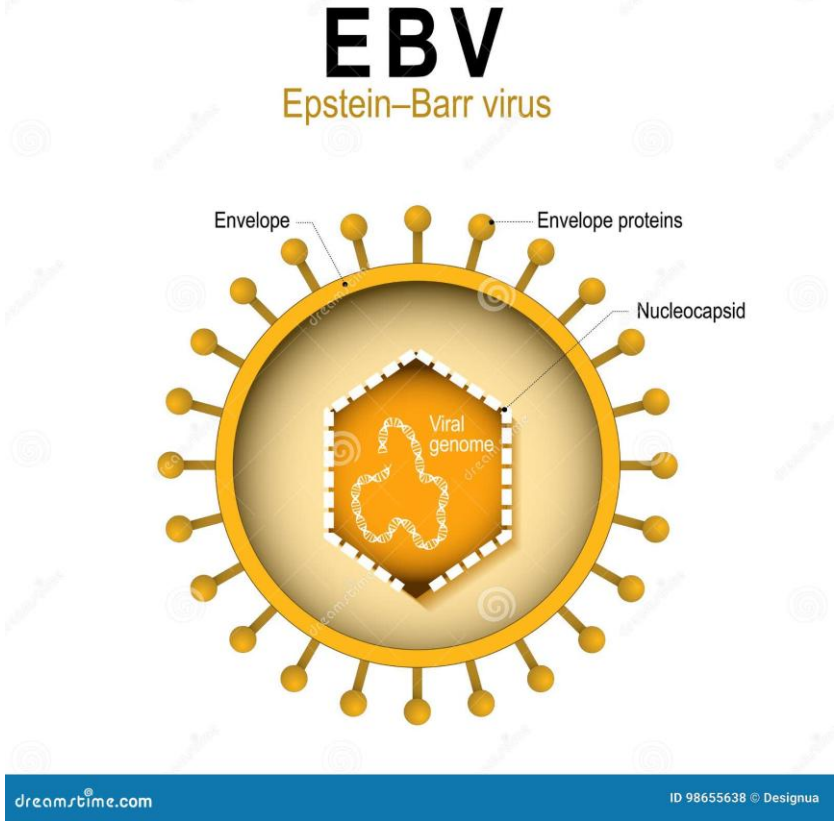
Infectious mononucleosis – Mononucleosis like illness

- Infectious mononucleosis classically presents with fever, lymphadenopathy, and pharyngitis.
- The term was coined to describe pharyngeal illness with lymphocytosis and atypical mononuclear cells. EBV was later identified as the primary cause.
- Mononucleosis-like syndromes can occur with CMV, HIV, HHV-6, and toxoplasmosis.



Mononucleosis - Etiology

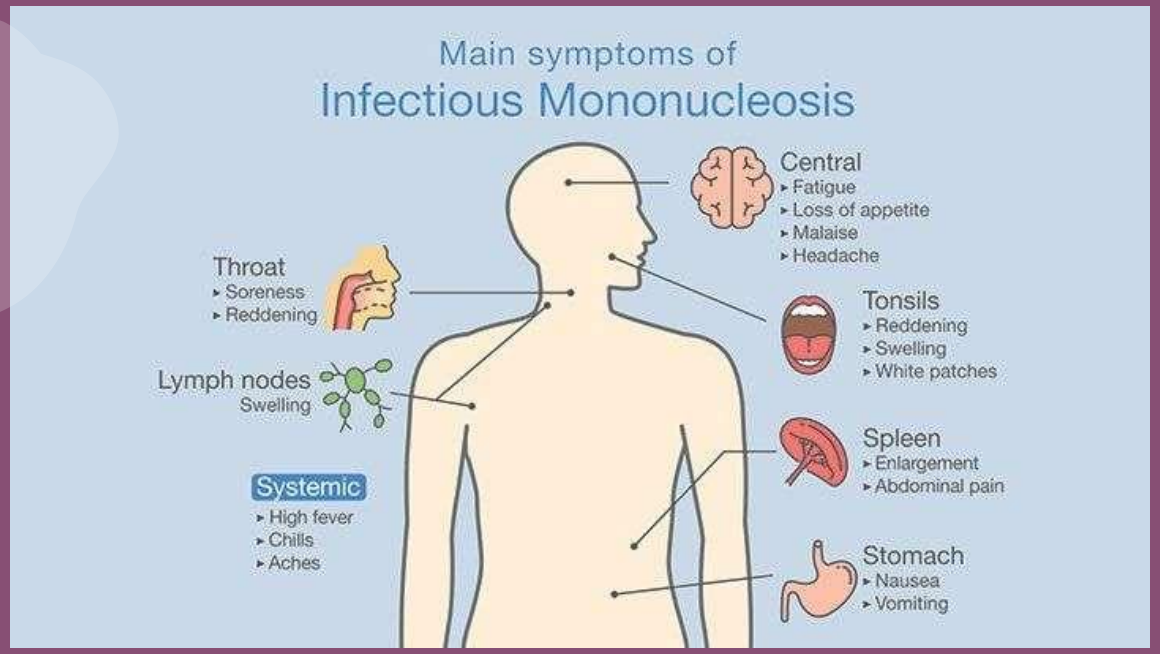
- EBV, a herpesvirus spread mainly via salivary contact, is the classic cause of mononucleosis.
- Oral shedding can persist for up to 6 months after illness onset.
- EBV infects B lymphocytes via the CD21 (CR2) receptor, leading to lymphocytosis and **atypical lymphocytes**.
- Mononucleosis-like illness may also be caused by CMV, HIV, HHV-6, and toxoplasmosis.



Mononucleosis – Epidemiology and Pathophysiology

- Up to 95% of adults worldwide are seropositive for EBV; infection is most common in adolescents (15-24 years).
- Often called the “kissing disease” due to transmission via **saliva**; adults are usually immune due to prior exposure.
- EBV enters via the oropharynx, replicates, and infects B lymphocytes in lymphoid tissue.
- Infection spreads through the lymphatic system, triggering antibody production.

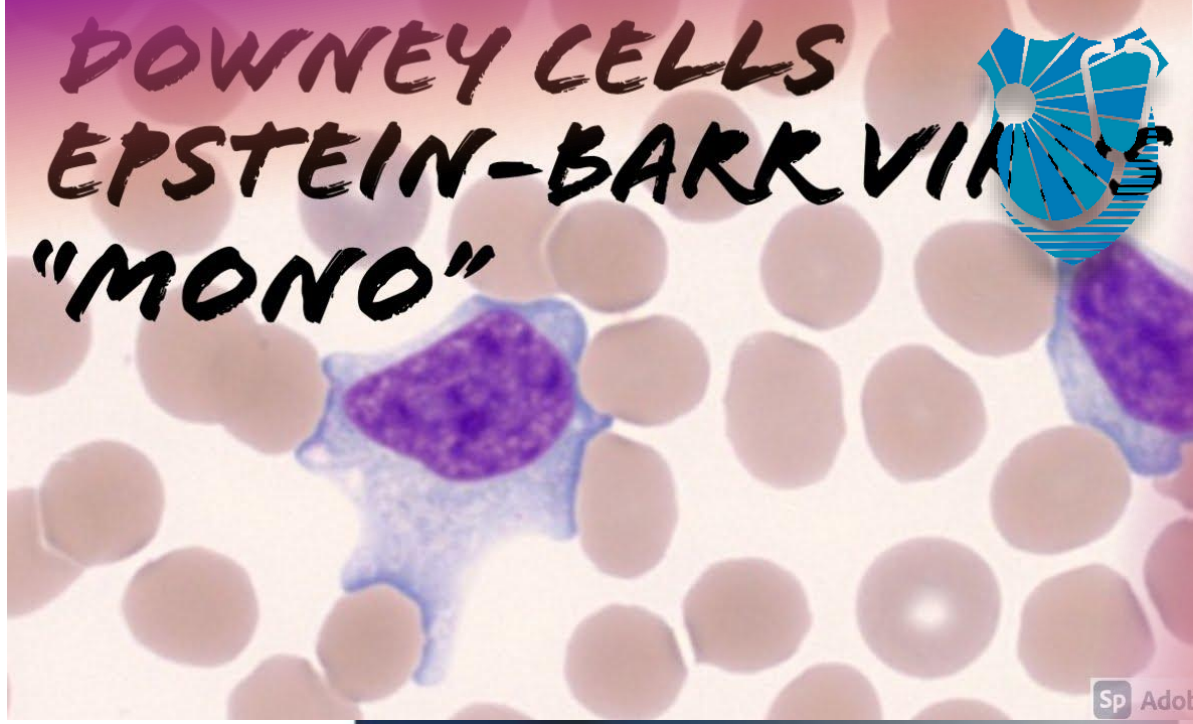
Mononucleosis – Clinical Features

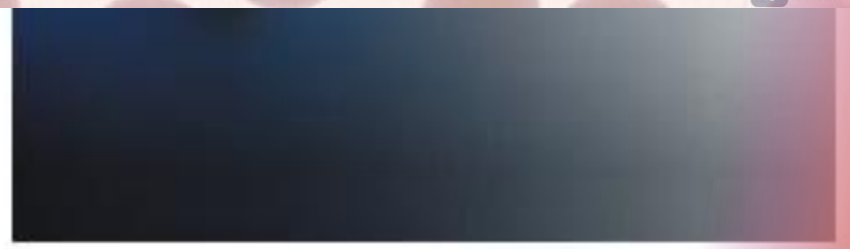


- Classic triad: fever, pharyngitis (often with tonsillar exudates), and lymphadenopathy (commonly posterior cervical). Additional features: headache, malaise, fatigue (can persist for months).
- Splenomegaly occurs in up to 50% of cases; petechiae on the palate and a maculopapular rash may be seen.
- Incubation is long (3-6 weeks).
- Most patients recover without sequelae.

Mononucleosis – Diagnosis and Management

- Lab findings: lymphocytosis (>50%), atypical lymphocytes (>10%), leukocytosis, and possible thrombocytopenia.
- Monospot (heterophile antibody) test is used to screen followed by EBV VCA IgM detection by ELISA.
- Supportive care is mainstay: antipyretics, anti-inflammatory, hydration, rest, and good nutrition.







Human T-cell lymphotropic virus type 1 (HTLV-1)

HTLV-1, a human retrovirus, infects ~10 million people; 1-5% develop adult T-cell leukemia/lymphoma (ATL).

Transmission: **breastfeeding, sexual contact, blood transfusion**; endemic in Japan, Caribbean, Africa, Middle East, Central/South America.

Presentation: lymphadenopathy, hepatosplenomegaly, skin lesions, opportunistic infections.

ATL subtypes: acute, lymphoma, chronic, smoldering; aggressive forms have <1-year survival, while chronic/smoldering types have a better prognosis.

Adult T-cell leukemia (ATL)

Adult T-cell leukemia (ATL) is primarily caused by HTLV-1 infection, which often remains asymptomatic.

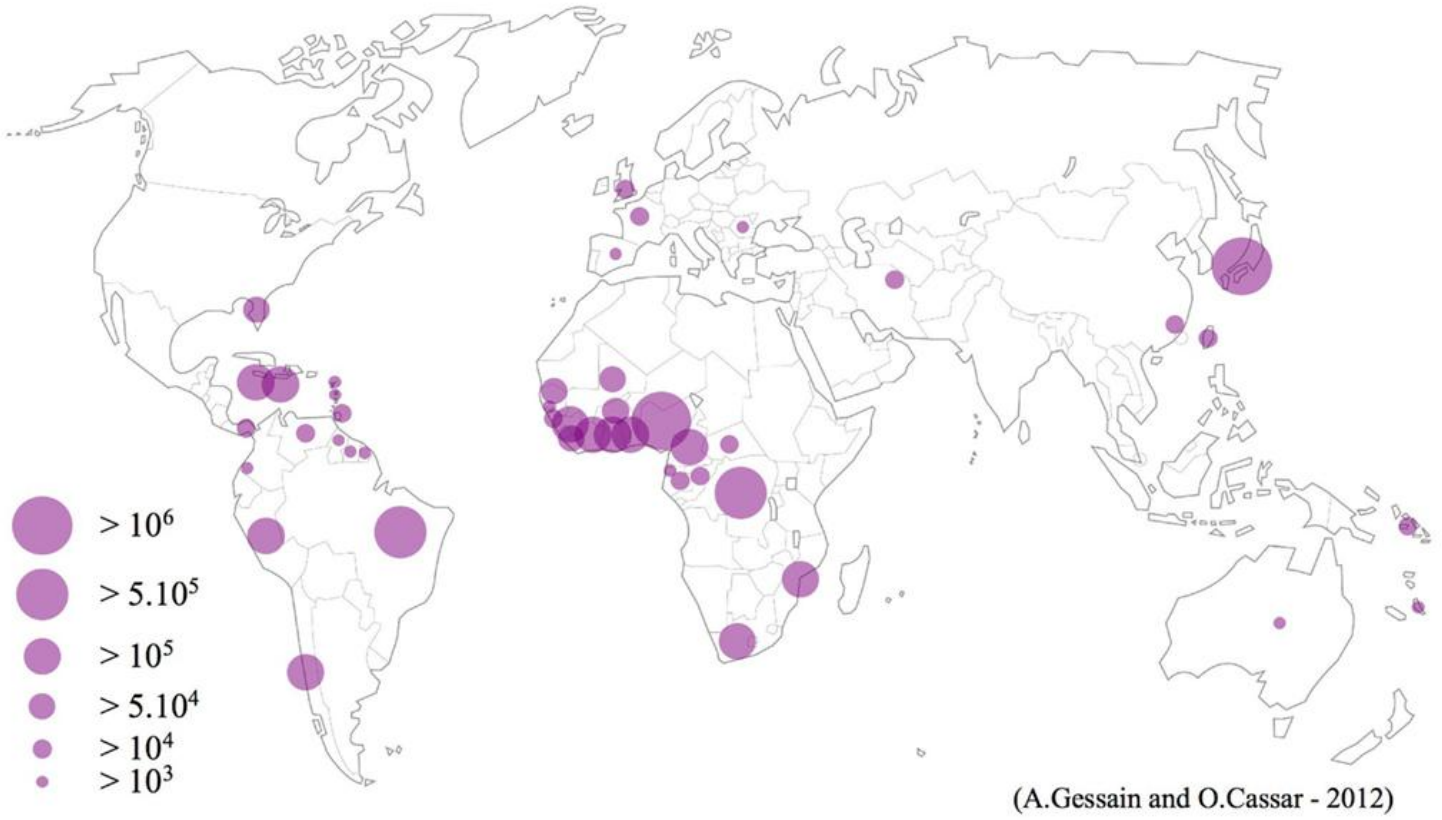
Two viral oncoproteins: Tax and HBZ play key roles in disease development and progression.

Tax drives neoplastic transformation by initiating uncontrolled T-cell proliferation.

HBZ is expressed on all malignant cells and supports leukemic cell proliferation and persistence.

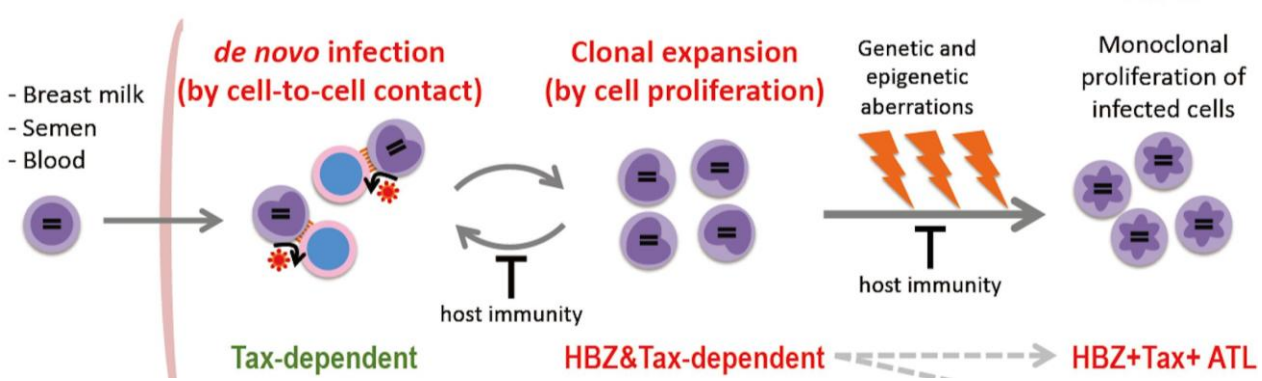
HTLV-1 Epidemiology

- Prevalence is highest in southwestern Japan, the Caribbean, West Africa, northeast Iran, and Central/South America.
- There is a slight male predominance among cases.
- HTLV-1 and ATL are rare in North America (incidence 0.06 per 100,000).
- In Japan, annual incidence is 60 per 100,000 carriers with about 1,000 deaths each year.



ATL Pathophysiology

- HTLV-1 infects CD4+ T cells, causing transformation via viral proteins *Tax* (trans-acting viral regulatory protein) and *HBZ* (HTLV-1 basic leucine zipper protein).
- Tax drives T-cell activation while HBZ sustains chronic infection and neoplastic growth.
- Hypercalcemia is common due to cytokine release, leading to lytic bone lesions and increased bone turnover.



Source: Yasunaga J (2020) Strategies of Human T-Cell Leukemia Virus Type 1 for Persistent Infection: Implications for Leukemogenesis of Adult T-Cell Leukemia-Lymphoma. Front. Microbiol. 11:979

ATL Diagnosis & Management

- Screening: ELISA is used to detect HTLV-1 antibodies in serum or plasma.
- Confirmation: Western blot or PCR that detects proviral DNA and confirms infection, especially in indeterminate or early cases.
- Common lab findings: Hypercalcemia (70%) and renal dysfunction in advanced disease.
- Prognosis: Aggressive types (acute, lymphomatous, or chronic with poor features) have median survival in months. Therapy choice depends on subtype.



Primary Effusion Lymphoma

- Rare, aggressive B-cell lymphoma that localizes to serous body cavities (pleural, peritoneal, pericardial) without a solid mass.
- Caused by HHV-8 (KSHV); often coinfected with EBV (~80%) and seen mostly in immunocompromised patients (e.g., HIV or transplant recipients).
- HIV/AIDS and Severe Immunosuppression are the most common setting; chronic T-cell depletion promotes HHV-8 activation
- Prognosis: Poor, even with aggressive therapy.
- Treatment: multi-agent chemotherapy protocols.

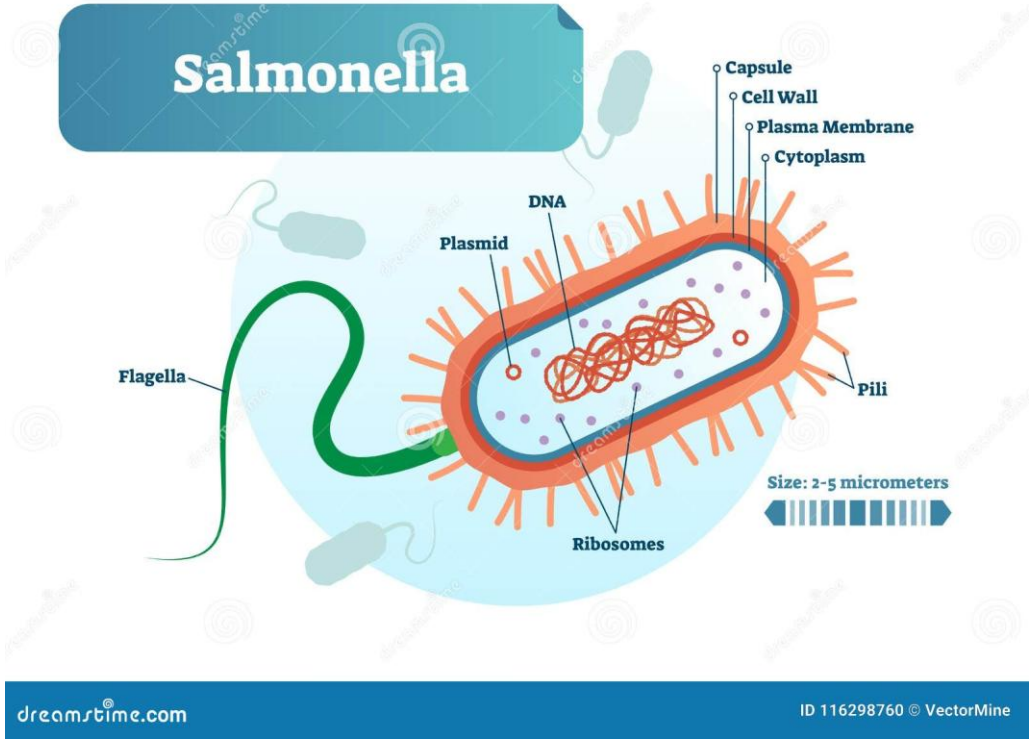
Typhoid Fever

- Caused by *Salmonella enterica* serotypes Typhi and Paratyphi (A, B, C) and is transmitted via the fecal-oral route (the "5 Fs": food, flies, fingers, feces, fomites).
- Causes more than 9 million cases and more than 100,000 deaths/year globally; most common in low- and middle-income countries lacking clean water and sanitation.

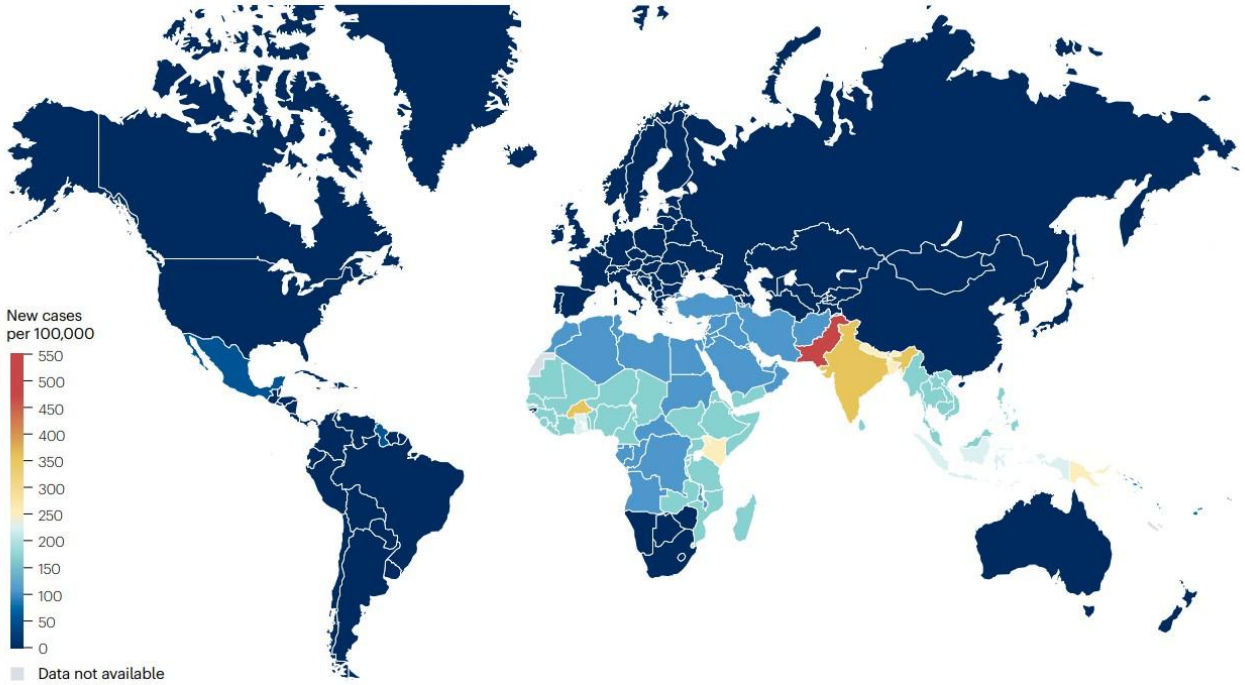


Typhoid Fever – Etiology

- Causative agents: *Salmonella enterica* serovars Typhi and Paratyphi (A, B, C) which are human-restricted pathogens transmitted by the fecal-oral route.
- Belong to the *Enterobacteriaceae* family.
- Other species: Non-typhoidal *Salmonella* (NTS) usually causes gastroenteritis but rarely invasive disease in immunocompromised hosts.



Typhoid Fever – Epidemiology



Source: Meiring, J.E., Khanam, F., Basnyat, B. et al. Typhoid fever. Nat Rev Dis Primers 9, 71 (2023)

- Humans are the only natural host.
- Endemic areas: Highest burden in South Asia, sub-Saharan Africa, and parts of the Middle East due to limited WASH (Water, Sanitation, and Hygiene).
- Risk factors in endemic countries: poor sanitation, unsafe water, crowding, malnutrition. In non-endemic countries: travel to endemic regions or food prepared by carriers.

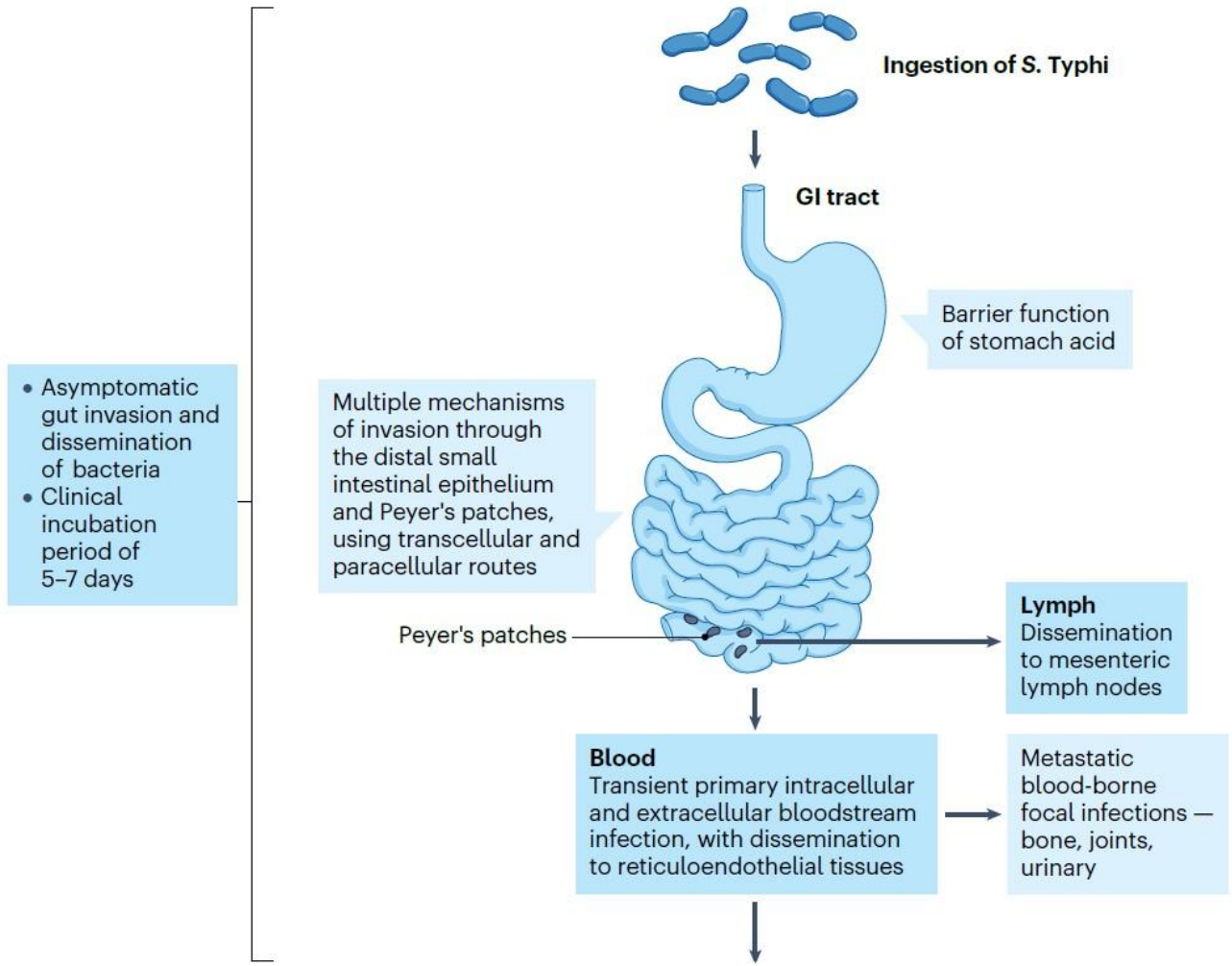
Typhoid Fever – Epidemiology

- The disease more severe in immunocompromised (HIV, steroid therapy, malaria, sickle cell anemia).
- Gastrointestinal factors: Low stomach acid (achlorhydria), antacid use, or altered gut flora from antibiotics increase susceptibility.
- Nutrition & genetics: Malnutrition weakens mucosal defense; certain HLA class II variants linked to resistance or susceptibility.
- Immunity: Natural infection provides incomplete protection — reinfections can still occur.

Typhoid Fever – Pathophysiology

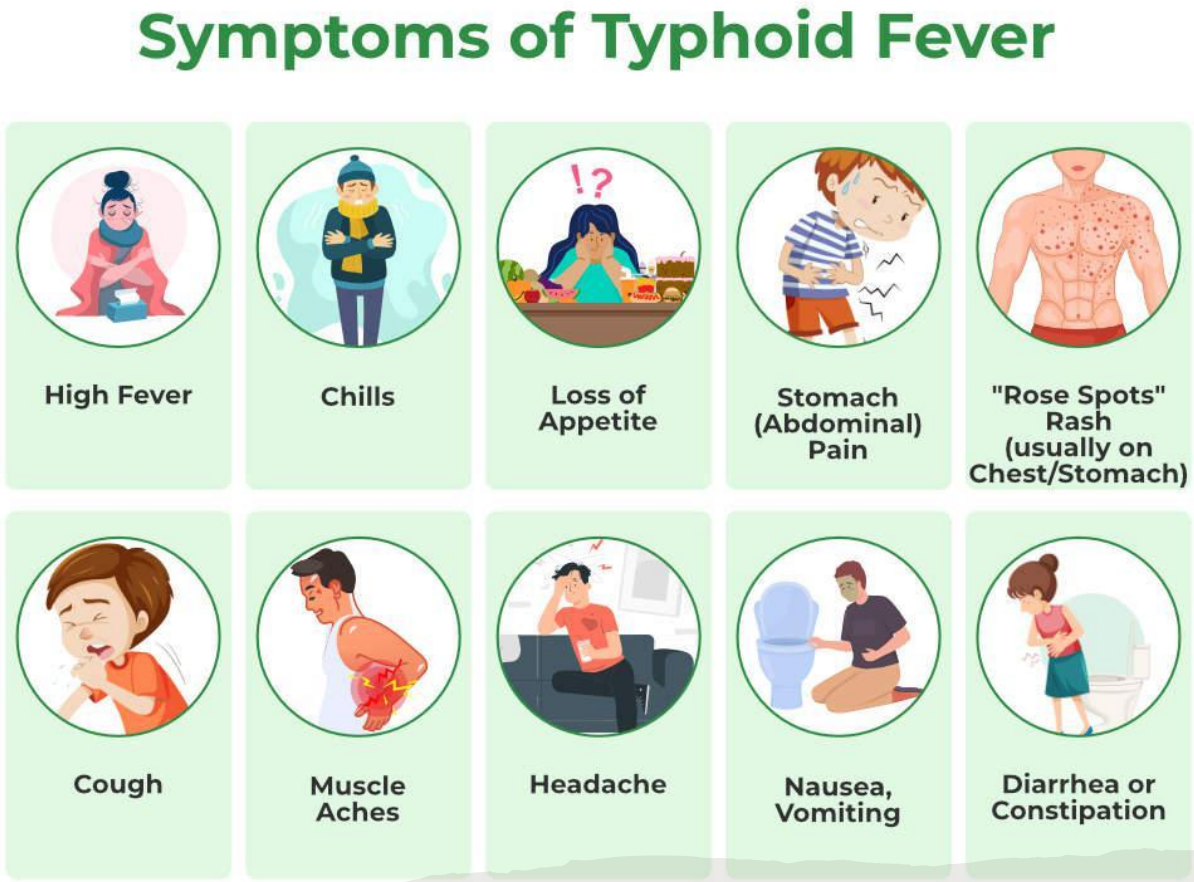
- S. Typhi and S. Paratyphi enter through the fecal-oral route, survive gastric acid, and invade the small intestinal epithelium (via M cells of Peyer's patches).
- Bacteria are taken up by **macrophages and B cells** multiplying **intracellularly**, and spread to the mesenteric lymph nodes, liver, spleen, and bone marrow, leading to **bacteremia**.
- Infection triggers endotoxin release, causing fever and inflammation; necrosis of Peyer's patches may result in intestinal perforation or bleeding.
- Vi antigen (capsular polysaccharide) aids in immune evasion. Pathogenicity islands encode proteins for adhesion, invasion, intracellular survival, and antimicrobial resistance. Intracellular persistence explains the carrier state and chronic infection (e.g., **gallbladder colonization**).

Typhoid Fever – Pathophysiology



Typhoid Fever – Clinical Features

- Incubation: 6-30 days followed by a gradual onset with a stepwise rise in fever, fatigue, malaise, headache, abdominal pain; relative bradycardia (**Faget sign**).
- GI: Constipation (early) followed by diarrhea (later), may be “pea-soup” in color. Abdominal pain, distension, tenderness.
- Hepatosplenomegaly is common.
- Rose spots: faint pink maculopapular rash on trunk (seen in 25%)



Typhoid Fever – Clinical Features

- Neuropsychiatric: delirium ("typhoid state") in severe disease.
  Children: diarrhea, vomiting, febrile seizures.
  Immunocompromised: may present with severe sepsis or extraintestinal foci (osteomyelitis, myocarditis, meningitis).
- Complications (3^{rd}-4^{th} week):

✓Intestinal perforation or bleeding (Peyer's patch necrosis).

✓Septic shock, encephalopathy, hepatitis, myocarditis, abscesses.

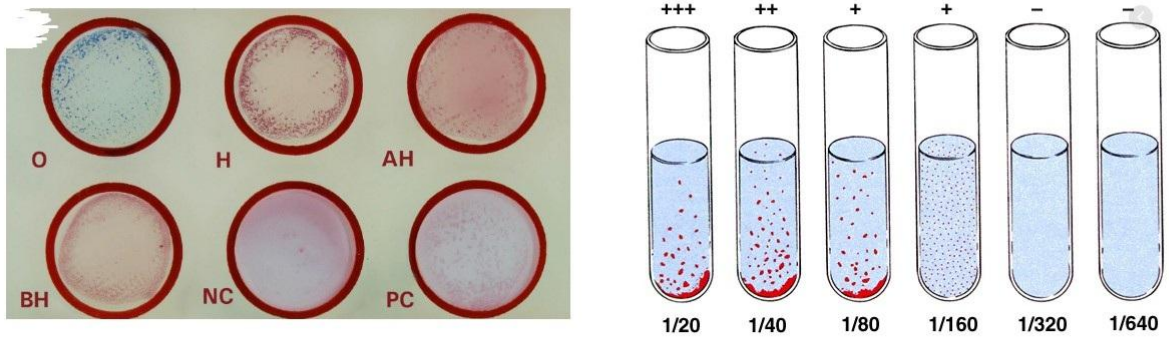
Typhoid Fever – Diagnosis

- Clinical Suspicion: Persistent fever ≥7 days without another cause in a patient from or recently in an endemic area. Must rule out malaria, dengue, and meningitis first.
- WHO: suspect if ≥3 of 7 days of fever + epidemiologic link to endemic area or contact with confirmed case.
- Laboratory Confirmation: **Culture (Gold Standard)**. Blood culture: most sensitive in 1st week (sensitivity 40–80%). Bone marrow culture: highest sensitivity (≈100%) gold standard. Stool/urine culture: positive in later stages. Allows antimicrobial susceptibility testing.



Typhoid Fever – Diagnosis

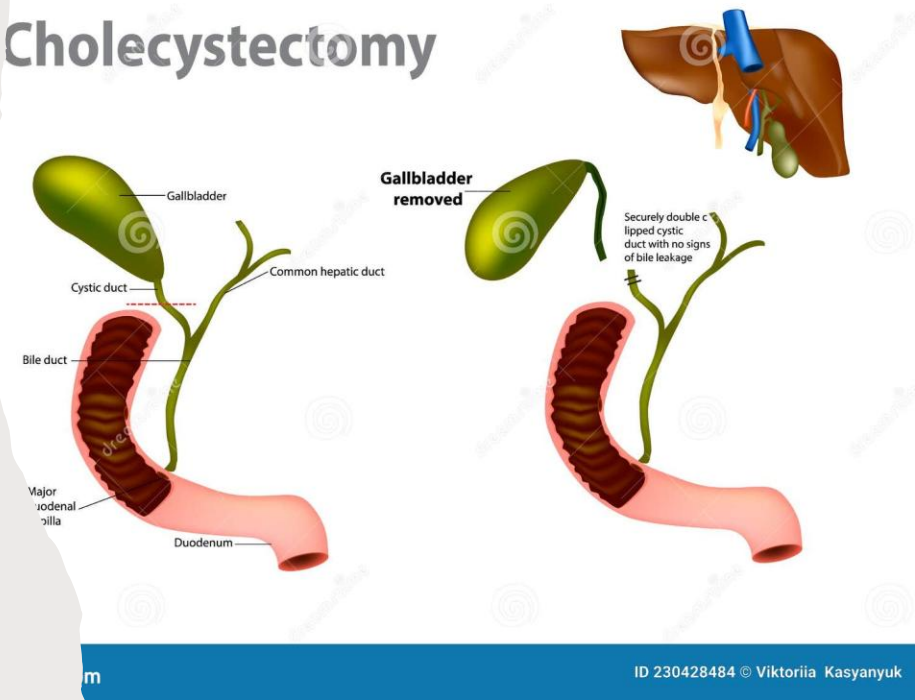
- Serology (Widal test): detects anti-O and anti-H agglutinins. However, the test has a low specificity due to cross-reactivity and prior vaccination.
- Molecular tests: PCR / Multiplex PCR to detect S. Typhi or S. Paratyphi DNA directly from blood/stool. PCR has a high sensitivity and specificity.



Typhoid Fever – Management

- Supportive care: hydration, electrolyte correction, antipyretics, nutritional support.
- For uncomplicated typhoid, the WHO recommends azithromycin as the first-line oral treatment, especially for multidrug-resistant (MDR) and extensively drug-resistant (XDR) cases, or cefixime if strains are not resistant to third-generation cephalosporins.
- For sensitive strains, ciprofloxacin is an option. For resistant infections, ceftriaxone can be used intravenously.
- Chronic carrier management: Cholecystectomy + Ciprofloxacin (if susceptible). Carriers should not handle food until cleared by negative stool cultures × 3.





Typhoid Fever – Prognosis

- Mortality (case-fatality rate CFR) in the pre-antibiotic era was 10-30%, while today the CFR with prompt therapy is < 1%.
- Early diagnosis and antibiotic treatment dramatically improves survival.
- Severe complications include intestinal perforation, hemorrhage, and encephalopathy.
- Poor prognostic factors are delayed or inadequate therapy, infection by MDR/XDR, extremes of age, malnutrition, or immunosuppression.

Typhoid Fever – Prevention



- Ensure safe water, sanitation, and hygiene (WASH)
- Practice food safety and hand hygiene
- Vaccinate using Vi polysaccharide (injectable), Ty21a (oral), or Vi-TT (conjugate) vaccine selected by age group and national recommendations.
- Identify and treat chronic carriers to prevent transmission





Thank You!