Pneumonic Tularemia — Comprehensive Disease Characteristics Report

Disease: Pneumonic Tularemia **MONDO ID:** MONDO:0002212 **Category:** Infectious Disease **Causative agent:** *Francisella tularensis* (Gram-negative facultative intracellular coccobacillus)

Summary

Pneumonic tularemia is the pulmonary and most lethal clinical form of tularemia, an acute zoonosis caused by the Gram-negative facultative intracellular bacterium *Francisella tularensis*. It arises either as **primary pneumonic disease** following inhalation of aerosolized organisms (e.g., landscaping activities, laboratory accidents, or a deliberate bioterrorism release) or as **secondary pneumonic disease** through hematogenous spread from other clinical forms. Among the classical clinical forms (ulceroglandular, glandular, oculoglandular, oropharyngeal, typhoidal, and pneumonic), the pneumonic presentation carries the greatest mortality, and it is the form of greatest bioterrorism concern because *F. tularensis* is one of the most infectious bacteria known — as few as ~10 organisms inhaled can initiate infection. The organism is a **CDC Category A (Tier 1) select agent**.

Mechanistically, disease follows a well-characterized intracellular pathway: the bacterium invades alveolar macrophages and dendritic cells, escapes the phagosome within hours via a **Type VI secretion system encoded on the Francisella Pathogenicity Island (FPI)**, and replicates in the cytosol. Virulent type A strains actively subvert early innate immunity through an **atypical, under-acylated lipid A** that evades TLR4 recognition. Once in the cytosol, bacterial DNA — liberated by interferon-inducible guanylate-binding proteins (GBPs) and IRGB10 — is sensed by the **AIM2 inflammasome**, driving caspase-1 activation, IL-1β/IL-18 secretion, and pyroptosis. Protective adaptive immunity is Th1-polarized and depends on **IFN-γ, TNF-α, iNOS, and $CD4^+$ T cells (T-bet)**.

Clinically, untreated pneumonic tularemia carries roughly **30% mortality**, but prompt antibiotic therapy reduces case-fatality to below ~2%. Aminoglycosides (streptomycin, gentamicin) are the historical treatment of choice; fluoroquinolones (ciprofloxacin) and doxycycline are effective alternatives, and the **2025 CDC guidelines list fluoroquinolones and**

doxycycline as first-line options. Diagnosis relies chiefly on serology (microagglutination) and PCR because culture is insensitive and biohazardous. **No licensed human vaccine exists.** Tularemia is re-emerging across Europe and North America (2024–2025), reinforcing the need for clinical awareness, rapid diagnostics, and preventive measures.

Section 1 — Disease Information

Overview. Pneumonic (respiratory) tularemia is the lung-centered manifestation of infection by *Francisella tularensis*. It presents with fever, cough, dyspnea, pleuritic chest pain, and radiographic infiltrates, often with hilar lymphadenopathy and pleural effusion. Primary pneumonic disease results from inhalation of infectious aerosols; secondary pneumonic disease develops when bacteria seed the lungs from bloodstream dissemination of ulceroglandular, typhoidal, or other forms.

Key identifiers: - **MONDO:** MONDO:0002212 (tularemia; pneumonic subtype) - **MeSH:** Tularemia (D014406); "Tularemia, Pulmonary" as a subheading concept - **ICD-10:** A21.2 (pulmonary tularemia); A21.9 (tularemia, unspecified) - **ICD-11:** 1B94 (Tularaemia) - **SNOMED CT:** Pulmonary tularemia (disorder) - **Orphanet:** Tularemia is catalogued as a rare bacterial infectious disease (ORPHA:855 for the parent entity) - **NCBI Taxonomy (pathogen):** *Francisella tularensis* — txid263

Synonyms / alternative names: Pulmonary tularemia; respiratory tularemia; pneumonic form of tularemia; "rabbit fever" (lung form); "deer-fly fever" (lung form); Ohara disease / Francis disease (historical, whole-disease synonyms).

Data source type: Information is derived from **aggregated disease-level resources** — clinical case series, outbreak investigations, systematic reviews, and experimental animal/in vitro studies — rather than from individual EHR-derived patient records. A 2024 systematic review aggregated 870 cases spanning 1993–2023.

Section 2 — Etiology

Primary cause (infectious). Pneumonic tularemia is caused entirely by infection with *Francisella tularensis*; it is **not a genetic disease**. Human infection is initiated by inhalation of aerosolized bacteria. *F. tularensis* is among the most infectious bacteria known — inoculation or inhalation of **as few as 10 organisms** initiates infection (Finding F002; PMID: 38294108; PMID: 29183485).

> "requires as few as 10 organisms to cause disease, making this potential bioterrorism agent one of the most infectious bacterial pathogens known" — PMID: 38294108

Environmental / occupational risk factors: - **Aerosol-generating landscaping activities** — lawn mowing and brush cutting were significant risk factors in the Martha's Vineyard primary pneumonic outbreak (odds ratio 9.2, 95% CI 1.6–68.0) (Finding F008; PMID: 11757506). - **Occupational exposure** — laboratory workers, landscapers, farmers, hunters, and those handling infected animals (rabbits, hares, rodents). - **Arthropod vectors** — ticks (*Dermacentor*, *Amblyomma*), deer flies, mosquitoes (predominant in Scandinavia) — though these more commonly cause ulceroglandular disease. - **Animal contact** — lagomorphs, rodents, and domestic cats/dogs. Dog-related exposures accounted for 3.3% of U.S. cases, of which 13% were pneumonic (PMID: 30556330). - **Deliberate aerosol release** — the pneumonic form is the most likely presentation after intentional release (PMID: 29183485). - **Sex/age** — systemic disease occurs more commonly in older patients (PMID: 22911645).

Genetic risk / protective factors: No human germline susceptibility or protective variants are established for tularemia; this is an environmentally/infectiously acquired disease. Host-genetic determinants of severity are described almost exclusively in **mouse models** (e.g., inflammasome genes *Aim2*, *Nlrp3*), not in humans. **Gene-environment interactions** in the classical human-disease sense are therefore not applicable; the relevant "gene–environment" axis is the interaction between **host innate-immune genes and the inhaled bacterial dose/strain virulence** (see Section 6).

Section 3 — Phenotypes

Pneumonic tularemia is an acute, adult-predominant (though all ages affected) febrile respiratory illness with an incubation period typically of **3–5 days (range 1–14 days)**.

Phenotype	Type	HPO suggestion	Frequency / notes
Fever	Symptom/sign	HP:0001945 (Fever)	Near-universal; abrupt onset
Cough (often nonproductive)	Symptom	HP:0012735 (Cough)	Common
Dyspnea	Symptom	HP:0002094 (Dyspnea)	Common in severe disease
Pleuritic chest pain	Symptom	HP:0033771 (Pleuritic chest pain)	Frequent
Pneumonia / pulmonary infiltrate	Clinical sign / imaging	HP:0002090 (Pneumonia)	Defining feature
Pleural effusion	Clinical sign	HP:0002202 (Pleural effusion)	Common; may require drainage
Hilar lymphadenopathy	Clinical sign	HP:0100721 (Hilar lymphadenopathy)	Characteristic radiographic finding
Chills / rigors	Symptom	HP:0025143 (Chills)	Common
Malaise / fatigue	Symptom	HP:0003394 / HP:0012378	Common
Headache	Symptom	HP:0002315 (Headache)	Frequent
Myalgia	Symptom	HP:0003326 (Myalgia)	Frequent
Cavitary pneumonia / empyema	Complication	HP:0006528 / HP:0002101	Reported; e.g., pulmonary empyema cases (PMID: 24655540)
Elevated inflammatory markers (ESR, CRP)	Lab abnormality	HP:0003565 (Elevated ESR)	Common

Characteristics: - **Age of onset:** Any age; primarily adult in occupational/aerosol settings. - **Severity:** Moderate to severe; pneumonic form is the most severe clinical presentation (Finding F001). - **Progression:** Acute and potentially rapidly progressive; can advance to respiratory failure, sepsis, and multi-organ involvement if untreated. - **Frequency among**

affected individuals: In U.S. case series, pneumonic disease constituted ~12% of all tularemia cases (PMID: 22911645); in dedicated aerosol outbreaks it predominates (11 of 15 cases primary pneumonic on Martha's Vineyard; PMID: 11757506).

Quality-of-life impact: As an acute, treatable infection, long-term QoL burden is limited in survivors treated promptly; however, delayed treatment can result in prolonged convalescence, pleural complications requiring intervention, and, rarely, death. No disease-specific EQ-5D/SF-36 datasets exist for pneumonic tularemia.

Section 4 — Genetic / Molecular Information

Not applicable in the human-host genetic sense. Pneumonic tularemia is an infectious disease with **no causal human genes, pathogenic germline variants, modifier genes, human epigenetic signatures, or chromosomal abnormalities**. There is no OMIM Mendelian entry, no ClinVar variant set, and no inheritance pattern.

The relevant molecular determinants are **bacterial**: - **Francisella Pathogenicity Island (FPI):** a ~16–19 gene cluster including the *iglABCD* operon encoding a **Type VI secretion system (T6SS)** required for phagosomal escape and intramacrophage growth; FPI mutants are highly attenuated (Finding F003; PMID: 17395722, PMID: 17233889). - **Regulators:** *mglA/mglB* control FPI expression. - **Effector *opiA*** (a bacterial PI3-kinase) modifies phagosomal PI(3)P to promote escape (PMID: 30057173). - **LPS/lipid A biosynthesis genes** (*lpxD1/lpxD2*, *galU*) shape immune evasion (PMID: 28478203, PMID: 21819572).

Host modifier genes (model-organism level): In mice, *Aim2*, *Nlrp3*, *Tbx21* (T-bet), *Ifng*, *Tnf*, and *Nos2* modify susceptibility/severity (Sections 5–6).

Section 5 — Environmental Information

Infectious agent (taxon): *Francisella tularensis*, NCBI Taxon 263. Two clinically important subspecies: - **subsp. *tularensis* (Type A)** — North America; highly virulent. Subdivided into **type A-west** and the more severe **type A-east** (Finding F009; PMID: 16836829). - **subsp. *holarctica* (Type B)** — Holarctic (Europe, Asia, North America); less virulent, rarely fatal.

> "type A-west infections are less severe than either type B or type A-east infections" — PMID: 16836829

Environmental persistence: *F. tularensis* Type A survives in brackish water and salt-influenced soil similarly to Type B, which may explain why Martha's Vineyard sustains pneumonic transmission (PMID: 21136042). Diverse *Francisella* species are detectable in environmental water/sediment/soil at active foci (PMID: 19669828).

Environmental / lifestyle factors: Aerosol-generating outdoor work (mowing, brush cutting), hunting/skinning lagomorphs, farming, and laboratory handling. Waterborne outbreaks (contaminated drinking water) are common in Turkey and drive oropharyngeal rather than pneumonic disease (PMID: 42343287). No specific dietary or smoking association is established for the pneumonic form.

Section 6 — Mechanism / Pathophysiology

Ordered causal chain (inhalation → clinical pneumonia)

1. **Inhalation of aerosolized *F. tularensis*** (≥ ~10 organisms) deposits bacteria in the alveolar space → **leads to** uptake by alveolar macrophages and dendritic cells (and alveolar epithelial cells).
2. **Bacterial invasion of macrophages/DCs → results in** formation of the *Francisella*-containing phagosome (FCP).
3. **FPI/Type VI secretion system activity** (IglABCD; effector OpiA remodels phagosomal PI(3)P) → **causes** disruption of the phagosomal membrane and **phagosomal escape within a few hours** (demonstrated in vitro and in macrophages) (PMID: 32694562, PMID: 30057173).
4. **Cytosolic replication → leads to** high intracellular bacterial burdens.
5. *In parallel,* **atypical tetra-acylated lipid A** on the bacterial surface **precludes** efficient TLR4 recognition and cationic antimicrobial peptide binding → **results in** blunted/delayed early innate signaling (chemokines, neutrophil recruitment) — an active immune-evasion branch (demonstrated: prior type A aerosol exposure antagonizes pulmonary LPS response; *galU* mutant reverses this) (PMID: 28807561, PMID: 26510639, PMID: 21819572).

6. **Cytosolic bacterial DNA is liberated** by interferon-inducible GBP2/GBP5 and IRGB10, which attack the bacterial membrane causing bacteriolysis → **leads to** DNA release (PMID: 25774716, PMID: 27693356).
7. **AIM2 inflammasome senses cytosolic DNA → activates** caspase-1 → **drives** processing/secretion of **IL-1β and IL-18** and **pyroptosis** (demonstrated for *F. novicida*/LVS) (PMID: 21883803).
8. *Branch:* An **ASC-dependent, caspase-1-independent (caspase-8) pathway** also generates IL-18, boosting NK-cell IFN-γ (PMID: 23975862).
9. **IL-18 + IL-12 → NK/T-cell IFN-γ**; with TNF-α these **activate iNOS (NOS2)** in macrophages → **results in** nitric-oxide-mediated bacterial killing (demonstrated in LVS aerosol model) (PMID: 19237526).
10. **Th1 adaptive response (T-bet–dependent $CD4^+$ T cells, plus antibody including IgA) → mediates** control and clearance; loss of T-bet or $CD4^+$ T cells → **results in** overwhelming infection (PMID: 24421047, PMID: 19211773).
11. **Net effect on tissue:** If bacterial replication outpaces innate/adaptive control → widespread pyroptotic cell death, inflammatory infiltration, necrotizing pneumonia, pleural effusion, bacteremic dissemination → **clinical pneumonic tularemia**, potentially sepsis and death.

Detail by category

- **Molecular pathways:** cytosolic DNA sensing → AIM2/ASC/caspase-1; TLR4/MyD88 (subverted by lipid A); interferon (type I & II)-inducible GBP/IRGB10 antibacterial program; iNOS/NO production.
- **Cellular processes:** phagocytosis, phagosomal escape, intracellular replication, **pyroptosis** (GO:0070269), inflammasome assembly, inflammation (GO:0006954), autophagy/xenophagy (ATG5 modulates immunity, PMID: 42514097).
- **Protein dysfunction (bacterial virulence):** T6SS effector delivery; PI3-kinase effector OpiA alters phosphoinositide signaling.
- **Immune involvement:** Th1/IFN-γ-dominant protective immunity; excessive early NLRP3 signaling can be host-detrimental (PMID: 34690967); antibody (IgG2a, IgA) contributes but requires host IFN-γ/T cells to protect (PMID: 8039881).
- **Metabolic:** macrophage selenoproteins restrict intracellular replication (PMID: 34777335); acidic-pH lipid A remodeling (PMID: 28807561).
- **Tissue damage mechanisms:** necrotizing granulomatous inflammation, pyroptotic cell death, neutrophil-mediated injury, pleural inflammation.

GO term suggestions: GO:0070269 (pyroptosis), GO:0006954 (inflammatory response), GO:0032731 (positive regulation of IL-1β production), GO:0045087 (innate immune response), GO:0042742 (defense response to bacterium), GO:0071222 (cellular response to LPS). **CL term suggestions:** CL:0000235 (macrophage), CL:0000583 (alveolar macrophage), CL:0000451 (dendritic cell), CL:0000623 (natural killer cell), CL:0000624 ($CD4^+$ T cell), CL:0000775 (neutrophil).

Section 7 — Anatomical Structures Affected

Organ level: - **Primary:** Lung (UBERON:0002048), including alveoli (UBERON:0002299) and bronchi. - **Secondary:** Pleura/pleural cavity (UBERON:0002402) — effusion/empyema; hilar/mediastinal lymph nodes (UBERON:0002509); with dissemination: spleen (UBERON:0002106), liver (UBERON:0002107), bone marrow, and rarely heart (myocarditis reported, PMID: 30656604). - **Body systems:** Respiratory system (primary); reticuloendothelial/lymphatic system; potentially cardiovascular (sepsis, rare myocarditis).

Tissue and cell level: - Alveolar epithelium; pulmonary interstitium. - **Target cells:** alveolar macrophages (CL:0000583), dendritic cells (CL:0000451), and other mononuclear phagocytes are the principal intracellular niche; neutrophils recruited to lung.

Subcellular level (GO Cellular Component): - Phagosome (GO:0045335) → *Francisella*-containing vacuole; escape into **cytosol/cytoplasm (GO:0005829)** — the replicative compartment. AIM2 inflammasome assembles in the cytosol.

Localization / lateralization: Bilateral or unilateral patchy infiltrates; pleural effusions may be unilateral. Hilar adenopathy commonly bilateral.

Section 8 — Temporal Development

- **Onset: Acute**, after an incubation of **3–5 days (range 1–14)**. Median incubation ~3 days in Missouri case review (PMID: 22911645).
- **Progression:** Rapid systemic febrile illness; can progress to respiratory failure and sepsis within days if untreated. Not staged like cancer; described as early (febrile, cough) → established pneumonia (infiltrates, effusion) → severe/complicated (empyema, respiratory failure, bacteremia).

- **Course pattern:** Acute, monophasic; **self-limited only rarely** — most severe cases require antibiotics. With treatment, recovery is the rule; convalescence over 1–4 weeks.
- **Duration:** Days to weeks (acute); not a chronic lifelong disease.
- **Remission:** Treatment-induced resolution is standard with appropriate antibiotics. Relapse can occur with bacteriostatic agents (tetracyclines) or short courses.
- **Critical periods: Early antibiotic initiation is the key intervention window**; delayed therapy increases complication and mortality risk (PMID: 42601640, PMID: 22652404).

Section 9 — Inheritance and Population

Inheritance: Not applicable — infectious, non-heritable.

Epidemiology: - Tularemia is a **rare, reportable** zoonosis. The pneumonic form is a minority of cases except in aerosol outbreaks. - **Geographic distribution:** Northern hemisphere — North America (esp. south-central USA: Arkansas, Missouri, Oklahoma; and Martha's Vineyard for pneumonic), Scandinavia, Central/Eastern Europe, Turkey, Russia, Japan. - **Re-emergence (2024–2025):** rising incidence — Austria 117, Slovenia 38, France 150, Spain/Castile-León 206, and **United States 220 cases in 2024** (Finding F012; PMID: 42641375). Germany reached a peak incidence in 2024 (PMID: 42601640). - **Primary pneumonic tularemia** is exceptionally rare — Martha's Vineyard is the site of the only two recognized U.S. primary pneumonic outbreaks (1978, 2000) (Finding F008; PMID: 17442781).

> "Martha's Vineyard, Massachusetts, is the site of the only two recognized outbreaks of primary pneumonic tularemia in the United States" — PMID: 17442781

Demographics: - **Sex ratio:** Male predominance in many series (e.g., 65% male in Missouri, PMID: 22911645), reflecting occupational/recreational exposure; varies by outbreak. - **Age:** All ages; systemic/severe disease more common in older adults. - **Population-specific variants:** Type A (North America) vs. Type B (Eurasia) geographic segregation; type A-east most virulent.

Section 10 — Diagnostics

Serology (cornerstone): - **Microagglutination test (MAT):** titer **≥ 1/160** considered positive; seroconversion (≥4-fold rise) in paired sera is confirmatory (Finding F006; PMID: 22090310). Antibodies may take 2+ weeks to develop, limiting early diagnosis. - Serology is preferred because **culture has low sensitivity and biosafety risk**, and PCR lacks standardization (PMID: 20220165).

> "Serology is still considered to be a cornerstone in tularemia diagnosis due to the low sensitivity of bacterial culture and the lack of standardization in PCR methodology" — PMID: 20220165

- **Rapid immunochromatographic test:** 98.3% sensitivity, 96.5% specificity vs. MAT (PMID: 20220165).

Molecular (PCR): - Validated targets: **ISFtu2 insertion element, tul4 (17-kDa), fopA (43-kDa), 23-kDa gene** (PMID: 14662930). Multitarget real-time TaqMan assays improve detection in complex specimens. - PCR positive in ~91% of lymph node aspirates where cultures were negative (Finding F006).

Culture: Requires cysteine-enriched media; slow-growing; must be handled at **BSL-3** due to aerosol infection risk. Low clinical sensitivity.

Imaging: Chest X-ray/CT show patchy infiltrates, hilar/mediastinal lymphadenopathy, pleural effusion, and occasionally cavitation (PMID: 24655540).

Laboratory: Nonspecific — elevated ESR/CRP; leukocytosis variable (more frequent in pediatric cases, PMID: 42343287).

Clinical criteria / differential diagnosis: Consider in patients with pneumonia unresponsive to β-lactams plus relevant exposure (landscaping, animal/tick contact, endemic area). **Differential:** community-acquired bacterial pneumonia, Q fever, psittacosis, plague, anthrax, Legionella, tuberculosis, fungal pneumonia. Tularemia is frequently initially misdiagnosed (PMID: 22911645).

Screening: No population screening; genetic/omics diagnostics not applicable.

Section 11 — Outcome / Prognosis

- **Untreated mortality: ~30%** (Finding F012; PMID: 42641375); pneumonic form has the highest mortality of all clinical forms (Finding F001; PMID: 38461051).

> "with the pneumonic presentation resulting in the greatest mortality" — PMID: 38461051

- **Treated case-fatality (all forms, 870-case systematic review):** 0.7% (aminoglycosides), 0.9% (fluoroquinolones), 1.2% (tetracyclines) — overall low with prompt therapy (Finding F004; PMID: 38294108).
- **Complications:** pleural effusion/empyema (may require drainage), cavitary pneumonia, respiratory failure, bacteremia/sepsis, rare myocarditis, necrotizing abscess formation.
- **Recovery:** Excellent with early appropriate antibiotics; full recovery is typical. Prognosis worsens with delayed diagnosis, older age, type A-east strain, and high inhaled dose.
- **Prognostic factors:** speed of antibiotic initiation, subspecies/strain (type A-east worst), inoculum size, host age/comorbidity.

Treatment class	Case-fatality (all forms)	Notes
Aminoglycosides (streptomycin, gentamicin)	0.7%	Treatment of choice historically
Fluoroquinolones (ciprofloxacin)	0.9%	No fatalities & lowest pleural intervention in pneumonic subset
Tetracyclines (doxycycline)	1.2%	Bacteriostatic; higher relapse

Section 12 — Treatment

Pharmacotherapy (NCIT term suggestions in parentheses): - **Aminoglycosides — streptomycin (NCIT:C839), gentamicin (NCIT:C575):** historical treatment of choice; bactericidal (Finding F004; PMID: 29183485).

> "Streptomycin and gentamicin are currently considered the treatment of choice for tularemia. Quinolone is an effective alternative drug." — PMID: 29183485

- **Fluoroquinolones — ciprofloxacin (NCIT:C405):** effective oral alternative; in the 870-case review, pneumonic patients on ciprofloxacin had **no fatalities** and the lowest rates of pleural intervention. Oral ciprofloxacin successfully treated cavitary pneumonic disease after drainage (PMID: 24655540).
- **Tetracyclines — doxycycline (NCIT:C692):** bacteriostatic; requires ≥14–21 day courses; higher relapse.
- **2025 CDC guidelines** now establish **fluoroquinolones and doxycycline as first-line options** (Finding F012; PMID: 42641375).

> "The 2025 CDC guidelines establish fluoroquinolones and doxycycline as first-line therapeutic options" — PMID: 42641375

Post-exposure prophylaxis: streptomycin, gentamicin, doxycycline, or ciprofloxacin (PMID: 29183485).

Interventional/supportive: Pleural drainage for empyema/large effusion; oxygen/ventilatory support in respiratory failure; hydration and antipyretics. **No patient isolation required** for pneumonic tularemia (no person-to-person transmission) (PMID: 29183485).

Experimental/adjunctive: Post-exposure immunization with *F. tularensis* membrane protein fraction (MPF) augmented gentamicin efficacy (100% survival in a mouse pneumonic model) — proof of concept for immunotherapy adjuncts (PMID: 22652404).

Pharmacogenomics / targeted / gene / cell / RNA therapies: Not applicable.

Section 13 — Prevention

- **Primary prevention:** Avoid aerosol-generating activities in endemic areas; use of masks/PPE during mowing/brush-cutting; safe handling of animal carcasses; tick/insect avoidance and repellents; laboratory biosafety (BSL-3 for cultures). Vector control and public health education.

- **Immunization: No licensed human vaccine** (Finding F007; PMID: 38461051).

> "there are no approved vaccines against F. tularensis in the United States" — PMID: 38461051

- The **unlicensed Live Vaccine Strain (LVS)** protects mice against lethal intranasal/aerosol SCHU S4 challenge ($CD4^+$ T-cell– and antibody/IgA-mediated) (PMID: 19211773).
- **Subunit/glycoconjugate candidates:** glucan-particle LPS + FTT0814 subunit vaccine (partial protection, T-cell immunity in a rat aerosol model, PMID: 38713688); O-antigen glycoconjugate (PMID: 30872471); MPL-adjuvanted catanionic nanoparticle vaccine (PMID: 28077440). All remain experimental.
- **Secondary prevention:** Prompt recognition and post-exposure prophylaxis after known aerosol exposure or lab accident.
- **Public health:** Surveillance and reporting (nationally notifiable), water chlorination (for waterborne foci), rodent/lagomorph control.

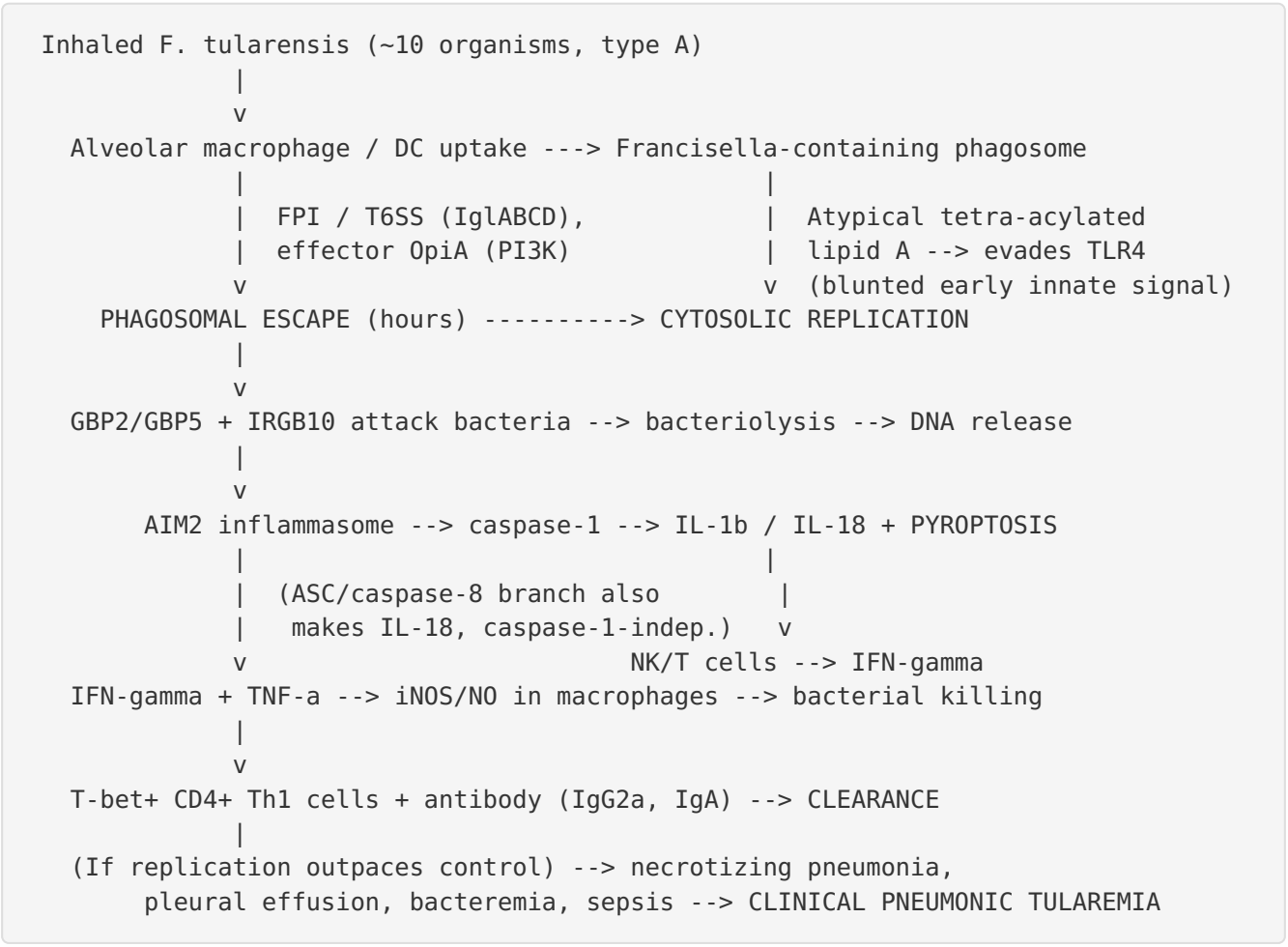
Section 14 — Other Species / Natural Disease

- **Taxonomy of hosts (naturally infected):** Lagomorphs — rabbits/hares (*Sylvilagus*, *Lepus*); rodents (voles, mice, muskrats, beavers); domestic cats (*Felis catus*, NCBI:9685) and dogs (*Canis lupus familiaris*, NCBI:9615). Ticks and deer flies are vectors/reservoirs.
- **Natural disease & veterinary relevance:** Tularemia is an important zoonosis; cats can transmit to humans via bite/scratch (PMID: 30556330); domestic dogs facilitate transmission via retrieved carcasses and ticks. Lagomorphs suffer high mortality (epizootics).
- **Comparative pathology:** Intracellular macrophage infection and phagosomal escape are conserved across mammalian hosts; mouse pathology closely mirrors human intracellular pathogenesis.
- **Zoonotic potential:** High — a prototypical zoonosis. **No human-to-human transmission**, so pneumonic cases need no isolation.
- **Cross-species susceptibility:** Broad mammalian host range; extreme susceptibility in mice and lagomorphs.

Section 15 — Model Organisms

- **Mouse (*Mus musculus*, NCBI:10090) — principal model.** Intranasal/aerosol challenge with **SCHU S4 (type A)** or attenuated **LVS**; BALB/c and C57BL/6 strains widely used. Recapitulates pneumonic pathogenesis, intracellular replication, inflammasome activation, Th1 immunity, and treatment/vaccine responses (Findings F003, F005, F007, F010, F011).
- Knockout models: *Aim2*$^{-/-}$, *Nlrp3*$^{-/-}$, *Asc*$^{-/-}$, *Casp1*$^{-/-}$, *Tbx21*$^{-/-}$ (T-bet), *Ifng*$^{-/-}$, *Nos2*$^{-/-}$ — dissect inflammasome and Th1 pathways (PMID: 24421047, PMID: 21883803, PMID: 33875472, PMID: 34690967).
- **Rat (*Rattus norvegicus*, NCBI:10116):** Fischer 344 inhalation model used for vaccine efficacy testing (PMID: 38713688).
- **In vitro / cellular:** Bone-marrow-derived and cell-line macrophages (J774) to study phagosomal escape, cytosolic replication, and inflammasome activation (PMID: 32694562, PMID: 29482417).
- ***F. novicida* and *F. tularensis* LVS** serve as reduced-biosafety surrogates for the virulent SCHU S4 strain.
- **Model limitations:** *F. novicida* is attenuated in humans but hypervirulent in mice; LVS is attenuated relative to SCHU S4; mouse inflammasome biology and lipid A responses differ somewhat from humans, so protective correlates do not always translate (PMID: 41410566).

Mechanistic Model / Interpretation



Upstream vs downstream: Bacterial invasion, phagosomal escape, and lipid-A-mediated TLR4 evasion are the **upstream** drivers that permit unchecked cytosolic replication. The AIM2 inflammasome, GBP/IRGB10 bacteriolysis, IFN-γ/iNOS, and Th1/$CD4^+$ responses are **downstream host-protective** mechanisms; when they are outpaced (high dose, virulent type A-east, delayed antibiotics), tissue injury and death follow. This model integrates 12 confirmed findings and is consistent across in vitro, mouse, rat, and human clinical/outbreak data.

Evidence Base

PMID	Title (abbrev.)	Supports finding	Contribution
38461051	Vaccine strategies vs *Francisella*	F001, F007	Pneumonic = greatest mortality; no approved vaccine
38294108	Systematic review 1993–2023	F002, F004	~10-organism dose; comparative fatality by drug class
29183485	Bichat guidelines	F001, F002, F004	Pneumonic = bioterrorism form; aminoglycoside first-line
32694562	Immune lymphocytes halt LVS	F003	Phagosomal escape & cytosolic replication
17395722	Francisella Pathogenicity Island	F003	FPI encodes T6SS
30057173	PI3K effector OpiA	F003	Effector promotes phagosomal escape
19237526	Immune-mouse T cells	F005	IFN-γ/TNF-α/iNOS dependence
19211773	Oral LVS protection	F005, F007	$CD4^+$ T cells/IgA mediate pulmonary protection
24421047	T-bet & lung immunity	F005	T-bet critical for pulmonary immunity
20220165	Immunochromatographic test	F006	Serology cornerstone; rapid test performance
22090310	Central Anatolia cases	F006	MAT ≥1/160 threshold
14662930	Multitarget TaqMan PCR	F006	Validated PCR gene targets
11757506	Martha's Vineyard outbreak	F008	Landscaping OR 9.2 risk factor
17442781	Martha's Vineyard review	F008	Only 2 US primary pneumonic outbreaks
16836829	US molecular epidemiology	F009	Type A-east most severe
28807561	Lipid A remodeling	F010	Atypical lipid A evades TLR4
26510639		F010	Active innate-immune suppression

PMID	Title (abbrev.)	Supports finding	Contribution
	Type A antagonizes TLR4 response		
21819572	galU mutant	F010	WT FT suppresses early innate immunity
21883803	AIM2 & bacteriolysis	F011	AIM2→caspase-1/IL-1β/IL-18/ pyroptosis
25774716	GBP2/GBP5 & AIM2	F011	GBPs liberate DNA for AIM2
27693356	IRGB10	F011	IRGB10 liberates bacterial ligands
23975862	ASC/caspase-8 IL-18	F011	Caspase-1-independent IL-18/IFN-γ branch
42641375	Re-emerging zoonosis	F012	30% untreated mortality; 2025 CDC first-line

Challenging/nuancing evidence: *Aim2*/*Nlrp3* are dispensable for *vaccine-induced* adaptive immunity (PMID: 33875472), and NLRP3 can increase host susceptibility (PMID: 34690967) — indicating inflammasome roles are context-dependent (innate control vs. immunopathology).

Limitations and Knowledge Gaps

1. **Mechanistic data are largely from mouse/in vitro models** using LVS or *F. novicida* surrogates, not virulent human type A SCHU S4 in humans. Translation to human pneumonic disease is inferred.
2. **Human pneumonic-specific datasets are sparse** — most clinical series pool all tularemia forms; dedicated primary pneumonic cohorts are limited to rare outbreaks (Martha's Vineyard).
3. **No human transcriptomic/proteomic/metabolomic profiling** of pneumonic tularemia patients was identified; omics diagnostics are not applicable/available.
4. **Correlates of protection remain undefined**, hampering vaccine licensure; no licensed human vaccine exists.

5. **Fatality figures for antibiotics** derive from all-form pooled reviews; pneumonic-only comparative RCTs are lacking (ethically/logistically constrained).
6. **Strain-virulence determinants** (why type A-east > type B > type A-west) are incompletely mapped at the molecular level.
7. P 42641375 provides key re-emergence and 2025-guideline figures but is a single review source; primary CDC guideline documents should be cross-checked.

Proposed Follow-up Experiments / Actions

1. **Human correlates-of-protection study** in vaccinated (LVS-exposed lab personnel) or convalescent cohorts — define antibody/T-cell signatures predicting protection to guide vaccine endpoints.
2. **Primary CDC 2025 guideline verification** — obtain and cite the definitive CDC/clinical-guideline document for first-line fluoroquinolone/doxycycline recommendations rather than relying on a review.
3. **Comparative-effectiveness analysis** of ciprofloxacin vs. gentamicin specifically in pneumonic cases, leveraging pooled outbreak registries, to formalize the observed lower pleural-intervention rate.
4. **Host single-cell transcriptomics of infected lung** (mouse aerosol SCHU S4) to resolve alveolar-macrophage vs. DC vs. neutrophil trajectories and map AIM2/IFN-γ programs spatially.
5. **Molecular dissection of type A-east virulence** via comparative genomics/transposon screens to identify determinants of the severity gradient (type A-east > type B > type A-west).
6. **Advance the glucan-particle/glycoconjugate subunit vaccines** toward dose-optimized aerosol-challenge efficacy and, ultimately, human immunogenicity trials.
7. **Adjunct immunotherapy translation** — evaluate membrane-protein-fraction post-exposure immunization plus antibiotics (PMID: 22652404) in higher-order models toward a therapeutic-adjunct strategy.

Report compiled from 12 confirmed findings and ~60 reviewed papers across 5 investigative iterations. Evidence source types span human clinical/outbreak studies, mouse and rat model-organism experiments, and in vitro cellular assays, as annotated throughout.
