

Tularemia During Pregnancy: A Systematic Review of Treatment and Outcomes

Shannon Fleck-Derderian¹, Katharine M. Cooley¹, Camryn Scheets², Dana Meaney-Delman³, Christina Nelson¹

¹National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Fort Collins, CO

²Texas A&M University, College Station, TX

³National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA

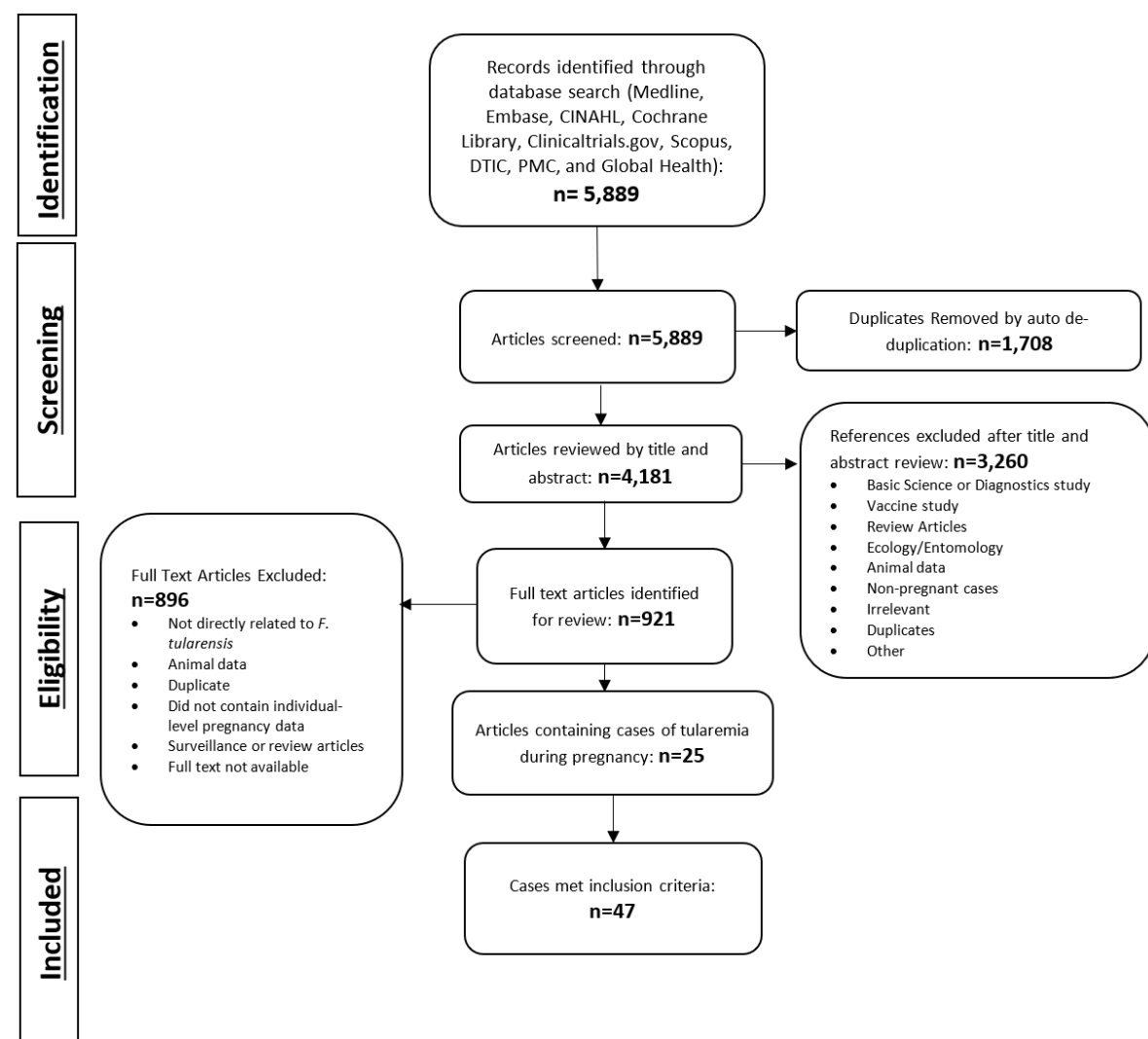
Background

- Tularemia is caused by *Francisella tularensis*, a gram-negative coccobacillus transmitted to humans by tick or other arthropod bites, direct contact with infected animals, and ingestion or inhalation of infectious particles.
- F. tularensis* is endemic throughout the Northern Hemisphere and is a Tier 1 bioterrorism agent.
- Depending on the clinical form of tularemia, clinical manifestations can include fever, skin ulcer, lymphadenopathy, pharyngitis, or pneumonia.
- Aminoglycosides (gentamicin and streptomycin), fluoroquinolones (ciprofloxacin), and tetracyclines (doxycycline) are considered effective for treating tularemia.
- Data on tularemia during pregnancy are lacking but could inform best practices for clinical care.
- Objective:** Examine maternal, fetal, and neonatal outcomes associated with *F. tularensis* infection during pregnancy to better understand clinical disease and management.

Methods

- We searched 9 literature databases and consulted tularemia subject matter experts to identify articles published on tularemia during pregnancy.
- Articles that reported tularemia during pregnancy and either maternal or fetal outcome were included (Figure 1).
- Data was abstracted using Microsoft Access and Excel databases.
- We abstracted information related to the clinical features of tularemia, maternal antimicrobial treatment, maternal and fetal morbidity and mortality, and evidence for maternal-fetal transmission of *F. tularensis*.

Figure 1. PRISMA Flow Diagram of Search Results and Articles Selected



Results

Our search identified 5,889 articles, of which 25 were eligible for inclusion and described a total of 47 cases of tularemia in pregnant women.

Description of Pregnant Patients with Tularemia:

- Cases occurred from 1930-2021; the majority (55%) were reported after 2000.
- Cases were reported from 8 different countries: Turkey (n=20), United States (n=18), France (n=3), Kosovo (n=2), Austria (n=1), Czech Republic (n=1), Italy (n=1), and Slovakia (n=1).
- Among cases with information on the clinical form of tularemia available, the most common forms were (Figure 2):
 - Oropharyngeal (n=13/23; 57%)
 - Ulceroglandular (n=5/23; 22%)
 - Glandular (n=3/23; 13%)
 - Oculoglandular (n=2/23; 9%)
- Laboratory evidence of *F. tularensis*:
 - Confirmed: 4 (9%)
 - F. tularensis* isolated or 4-fold change in serologic titer
 - Probable: 33 (70%)
 - F. tularensis* detected (not isolated) in clinical specimen or single positive serologic titer
 - No lab testing done or missing: 10 (21%)
- Among 34 patients with known trimester of infection, 47% occurred during the 2nd trimester of pregnancy (Table 2).
- 19 (40%) pregnant patients received at least one antimicrobial effective against *F. tularensis* (Figure 3; Table 1).
 - No maternal deaths were reported among treated or untreated pregnancies.

Fetal and Neonatal Outcomes:

- 4 intrauterine fetal deaths (IUFDs) occurred (Table 2):
 - 3 in untreated pregnancies
 - 1 in which the mother received an antimicrobial not considered effective for tularemia (amoxicillin)
- No spontaneous abortions (SABs) or neonatal deaths were reported.
- Among the 34 live births:
 - 2 were preterm
 - 1 case of hydranencephaly was identified; this infant later died at 4 months of age
 - Mother had flu-like illness in 3rd month of pregnancy; single positive serologic titer; history of alcohol abuse throughout 1st trimester
 - Cannot prove causation due to limited information and presence of confounders

Maternal-Fetal Transmission:

- Previously unknown whether *F. tularensis* can be transmitted from mother to fetus during pregnancy.
- Maternal-fetal transmission considered likely for 1 case:
 - 30-year-old U.S. woman infected with ulceroglandular tularemia in 1945
 - Infected during 8th month of pregnancy; IUFD 29 days after illness onset
 - No maternal antimicrobial treatment
 - Single positive titer in cord blood (1:2,560)
- Fetal autopsy showed gram-negative coccobacilli consistent with *F. tularensis* identified in placental villi and macrophages in the spleen.

Conclusions

- IUFD and preterm birth have been documented in untreated pregnancies with tularemia.
- Possible evidence of *F. tularensis* in placental and fetal tissues might suggest that tularemia is transmissible from mother to fetus in the absence of effective antimicrobial treatment.
- Further research is needed to establish whether these outcomes were attributable to the infection.
- Prompt recognition and treatment of tularemia during pregnancy is critical to minimize the risk of adverse outcomes.

Figure 2. Primary Clinical Form of Tularemia Among Pregnant Patients

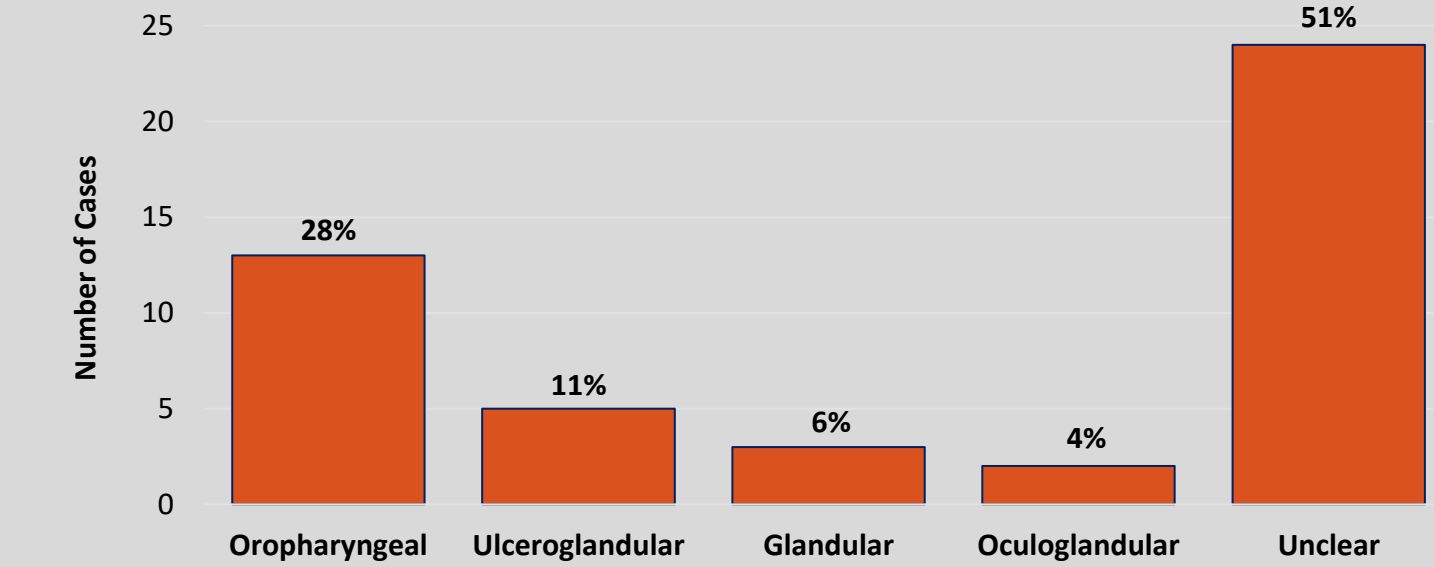


Figure 3. Antimicrobial Treatment of Tularemia Among Pregnant Patients

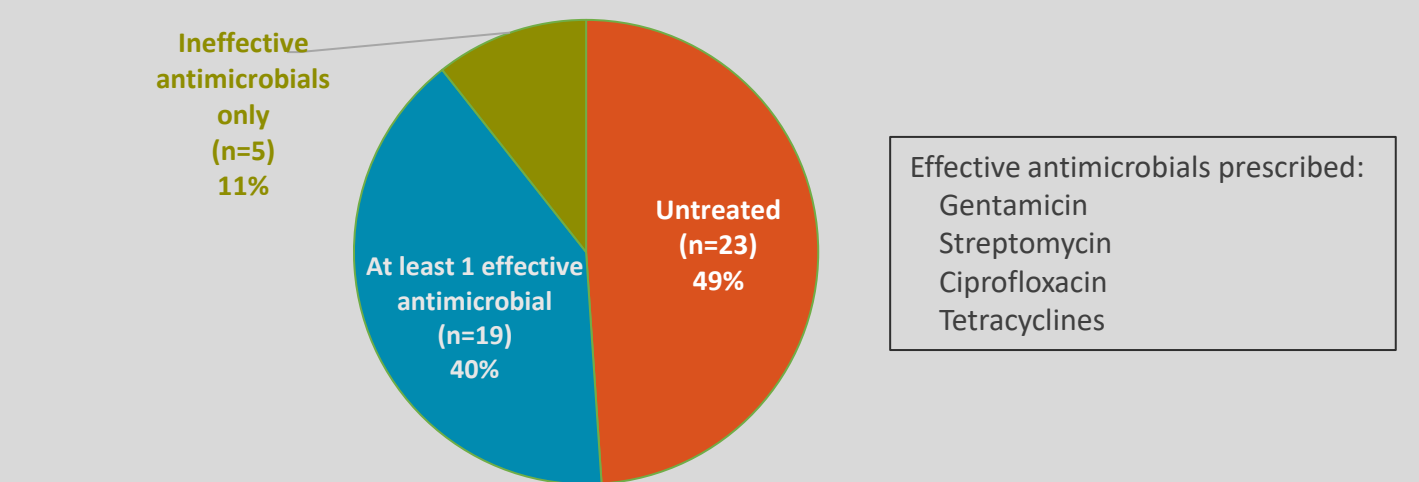


Table 1. Maternal and Pregnancy Outcomes of Pregnant Patients with Tularemia, by Antimicrobial Treatment Received¹

Treatment	Maternal fatalities among those who received n (%)	Fetal demise among those who received n (%)	Live births – full term and unspecified timing n (%)	Live births – preterm n (%)
Untreated (n=23)	0 (0%)	3 (13%)	18 (78%)	2 (9%)
Effective Antimicrobials (n=19)	0 (0%)	0 (0%)	11 (58%)	0 (0%)
Gentamicin (n=13)	0 (0%)	0 (0%)	8 (62%)	0 (0%)
Streptomycin (n=1)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Ciprofloxacin (n=6)	0 (0%)	0 (0%)	6 (100%)	0 (0%)
Tetracyclines (n=2)	0 (0%)	0 (0%)	1 (50%)	0 (0%)
Ineffective Antimicrobials (n=11)	0 (0%)	1 (9%)	10 (91%)	0 (0%)
Amoxicillin (n=6)	0 (0%)	1 (17%)	5 (83%)	0 (0%)
Azithromycin (n=3)	0 (0%)	0 (0%)	2 (67%)	0 (0%)
Cephalosporins (n=4)	0 (0%)	0 (0%)	4 (100%)	0 (0%)

¹Column totals within and across groups are >47 since some patients received multiple antimicrobial classes.

Table 2. Maternal and Pregnancy Outcomes of Pregnant Patients with Tularemia, by Trimester of Infection

	All Cases (n=47)	Timing of Infection				Unknown (n=13)
		Before pregnancy (n=3)	1 st Trimester (n=9)	2 nd Trimester (n=16)	3 rd Trimester (n=6)	
Maternal Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pregnancy Loss						
SAB ¹	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IUFD ²	4 (9%)	1 (25%)	1 (25%)	1 (25%)	1 (25%)	0 (0%)
Live Birth	34 (72%)	2 (6%)	6 (18%)	14 (41%)	5 (15%)	7 (21%)
Neonatal Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infant Death	1 (2%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)

¹SAB: spontaneous abortion. ²IUFD: intrauterine fetal death.

CONTACT INFO

Shannon Fleck-Derderian, MPH
LGV5@cdc.gov

Authors have no financial relationships to disclose.

