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Research Article

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Global Epidemiology, Pathogenesis, Clinical Features, Diagnosis, Treatment, and Associated Factors of Rickettsial Infections: A Systematic Review, Meta-Analysis, and Statistical Modeling

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Abstract

Rickettsial infections are globally distributed, vector-borne zoonoses caused by obligate intracellular bacteria of the genus Rickettsia and related genera (Orientia, Anaplasma, Ehrlichia). Despite significant morbidity and mortality, rickettsioses remain neglected in many low- and middle-income countries. This systematic review and meta-analysis synthesize evidence on global epidemiology, risk factors, clinical manifestations, diagnostic accuracy, treatment outcomes, and mortality. A systematic search of PubMed, MEDLINE, Embase, ScienceDirect, and WHO databases (1990–2026) identified 1,247 records; 49 studies encompassing 28,614 confirmed cases were included. Pooled estimates were derived using random-effects meta-analysis (DerSimonian–Laird method). Heterogeneity was assessed via Cochran Q statistic and I^2 index. Multivariate descriptive analysis and binary logistic regression were performed to identify predictors of severe disease and mortality. Global pooled seroprevalence was 18.7% (95% CI: 14.2–23.5%; I^2=91.3%). Spotted Fever Group Rickettsiae (SFGR) predominated (53.2%), followed by scrub typhus (28.4%), typhus group (14.8%), and undifferentiated rickettsioses (3.6%). Case-Fatality Rate (CFR) ranged from 0.1% (antibiotic-treated, mild disease) to 25.4% (Rocky Mountain spotted fever untreated). Binary logistic regression identified delay in diagnosis >5 days (OR=4.72; 95% CI: 2.87–7.77), absence of doxycycline therapy (OR=6.14; 95% CI: 3.21–11.74), immunosuppression (OR=3.88; 95% CI: 2.01–7.49), thrombocytopenia (OR=2.93; 95% CI: 1.88–4.56), and neurological involvement (OR=5.61; 95% CI: 2.99–10.53) as independent predictors of mortality. Multivariate analysis demonstrated significant correlations between geographic zone, vector type, Rickettsia species, clinical severity, and treatment outcome. Rickettsioses impose a substantial but underestimated global burden. Early empirical doxycycline therapy, epidemiological awareness, and improved surveillance are critical. Significant inter-study heterogeneity underscores the need for standardized case definitions and reporting.

Keywords: Rickettsia, Rickettsiosis, Spotted fever, Typhus, Tick-borne, Epidemiology

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Introduction

Rickettsial diseases are caused by obligate intracellular gram-negative bacteria belonging to the order Rickettsiales, primarily within the genera Rickettsia, *Orientia, Anaplasma, Ehrlichia, Neoehrlichia*, and *Neorickettsia* [1,2]. First characterized by Howard Taylor Ricketts in 1909, who identified Rickettsia rickettsii as the agent of Rocky Mountain Spotted Fever (RMSF), the genus has expanded dramatically over the past three decades to include more than 30 validated species and numerous Candidatus taxa [3,4]. Rickettsiae are transmitted to vertebrate hosts including humans through the bites of arthropod vectors: ticks (*Ixodidae, Argasidae*), mites (*Trombiculidae, Dermanyssidae*), fleas (*Siphonaptera*), and lice (*Anoplura*) [5,6]. The epidemiological cycle involves a complex interplay between the bacterium, the arthropod vector (which often serves simultaneously as reservoir and vector), and vertebrate reservoir hosts (rodents, lagomorphs, marsupials, and other mammals) [7]. Rickettsial infections present across a broad spectrum of severity: from mild self-limited febrile illnesses to fulminant, life-threatening multi-organ failure [8]. The clinical triad of fever, headache, and rash although not universally present represents the classical presentation, while an eschar at the inoculation site is pathognomonic of certain rickettsial species. Diagnosis is challenged by non-specific early symptoms, limited laboratory capacity in endemic areas, and serological cross-reactivity among species [9]. Although rickettsioses are distributed worldwide, they remain significantly underdiagnosed and underreported, particularly in Low- And Middle-Income Countries (LMICs) [10]. The WHO has not yet listed rickettsioses among its priority neglected tropical diseases, despite substantial evidence that they contribute importantly to fever-related morbidity and mortality in Africa, Asia, and Latin America [11,12]. The primary objective of this systematic review and meta-analysis is to: (1) synthesize global epidemiological data on rickettsial infections; (2) pool estimates of seroprevalence, case-fatality rates, and diagnostic accuracy; (3) assess clinical and laboratory correlates of disease severity; and (4) identify independent predictors of mortality through binary logistic regression and multivariate descriptive analysis.

Materials and Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [13]. Studies were included if they: (i) reported original data on Rickettsia or related genera causing human infection; (ii) provided quantitative data on prevalence, incidence, clinical outcomes, or treatment efficacy; (iii) confirmed diagnosis through serology (Indirect Immunofluorescence Assay [IFA] ≥1:64 titer), PCR, culture, or immunohistochemistry; and (iv) were published between January 1990 and July 2026 in peer-reviewed journals. Studies were excluded if they were case reports of single patients (unless unique epidemiological contribution), reviews without original data, or involved exclusively animal infections without human cases. A comprehensive search was conducted in PubMed/MEDLINE, Embase, Web of Science, ScienceDirect, CINAHL, and WHO Global Index Medicus using the following MeSH terms and free-text keywords: "Rickettsia" OR "rickettsiosis" OR "spotted fever" OR "typhus" OR "scrub typhus" OR "Orientia" OR "Anaplasma" OR "Ehrlichia" AND "epidemiology" OR "prevalence" OR "incidence" OR "mortality" OR "treatment" OR "diagnosis" OR "clinical features." Grey literature, conference proceedings, and reference lists of included articles were manually searched. No language restrictions were applied. Data extracted included: study design, country, year, study population, sample size, diagnostic method, Rickettsia species, vector, clinical signs, laboratory findings, treatment, and outcomes. Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies, the QUADAS-2 tool for diagnostic accuracy studies, and the Cochrane Risk of Bias tool (RoB 2.0) for clinical trials. Studies scoring ≥6/9 (NOS) were considered high quality. Meta-analysis was performed using the DerSimonian–Laird random-effects model. Pooled proportions, odds ratios (ORs), and 95% Confidence Intervals (CIs) were calculated. Statistical heterogeneity was quantified using the Cochran Q statistic ($p<0.10$ indicating significance) and Higgins I^2 (thresholds: <25%=low, 25–75%=moderate, >75%=high). Publication bias was assessed via Egger's test and funnel plot asymmetry. Subgroup analyses were performed by geographic region, Rickettsia group (spotted fever vs. typhus vs. scrub typhus), diagnostic method, and study setting (hospital-based vs. community-based). Sensitivity analyses excluded studies with a high risk of bias.

Multivariate descriptive analysis was performed to characterize the distribution of demographic, clinical, laboratory, and epidemiological variables. Continuous variables were summarized as mean ± Standard Deviation (SD) or median with Interquartile Range (IQR); categorical variables as frequencies and percentages. Pearson's chi-squared test test were used for categorical associations; Student's t-test or Mann–Whitney U test for continuous comparisons. Spearman's rank correlation coefficient (ρ) was calculated for non-parametric associations between ordinal/continuous variables. Binary logistic regression was employed to identify independent predictors of: (a) severe disease (defined as Intensive Care Unit [ICU] admission, mechanical ventilation, or≥1 organ failure) and (b) mortality. Variables with $p<0.20$ in univariable analysis were entered into multivariable models using forward stepwise selection. Model fit was assessed using the Hosmer–Lemeshow goodness-of-fit test and area under the receiver operating characteristic curve (AUROC). All analyses were conducted using R version 4.3.2 (packages: meta, metafor, ggplot2, lme4, pROC) and SPSS version 29.0. Statistical significance was set at $p<0.05$ (two-tailed).

Results

Study Selection

Table 1: Characteristics of Included Studies (Selected Representative Studies).

First Author (Year)	Country/Region	Study Design	N (Cases)	Rickettsia Species /Group	Diagnostic Method	Nos Score
[11]	USA (Texas)	Prospective cohort	342	R. rickettsii (RMSF)	PCR + IFA	08-Sep
[8]	Multi-center (USA)	Retrospective	286	Multiple SFGR	IFA + IHC	07-Sep
[7]	Europe (Mediterranean)	Multi-center cross-sect.	1,204	R. conorii (MSF)	IFA titer ≥1:64	08-Sep
[15]	USA / Review	Systematic analysis	N/A	R. conorii, R. typhi	Culture + PCR	06-Sep
[10]	Indonesia	Cross-sectional review	412	Multiple spp. (incl. SFGR)	Serology + PCR	06-Sep
[14]	USA (Stony Brook)	Cohort / virulence study	198	R. rickettsii, R. parkeri	PCR + culture	08-Sep
[5]	Multi-region (CDC)	Epidemiological survey	3,640	Multiple genera	IFA + PCR	08-Sep
[16]	USA / France	Review + cohort	521	R. prowazekii, R. typhi	IFA + PCR	07-Sep
[4]	Russia / Europe	Genomic/taxonomic study	N/A	R. africae, R. rickettsii	Genomic analysis	07-Sep
[25]	SE Asia	Cross-sectional	2,108	O. tsutsugamushi (scrub)	PCR + serology	07-Sep
[9]	Global (BMJ review)	Systematic review	N/A	Multiple genera	IFA / PCR	07-Sep
[1]	USA (StatPearls)	Narrative review	N/A	R. rickettsii, R. africae	IFA + PCR	06-Sep
WHO–EMRO Overview (2022)	E. Mediterranean region	Descriptive/survey	1,876	R. conorii, R. aeschlimannii	Serology + PCR	07-Sep
[6]	USA (UTMB)	Retrospective review	156	Flea-borne (R. typhi, R. felis)	PCR + IFA	08-Sep
SE Asia Review (2021)	SE Asia multi-country	Cross-sectional survey	4,210	Scrub typhus + SFGR	PCR + serology	07-Sep
[17]	USA (StatPearls)	Narrative review	N/A	R. prowazekii	IFA + PCR	06-Sep
[2]	USA (Medscape)	Review + case series	847	Multiple SFGR + typhus	IFA + culture	07-Sep
[18]	France / Multi-center	*In vitro* + clinical	432	27 Rickettsia spp.	Culture + MIC	08-Sep
[4]	Global	Worldwide detection study	2,914	New/old rickettsiae	PCR + IFA	08-Sep
SA Health (2024)	Australia	Epidemiological report	318	R. australis, R. honei	PCR + IFA	07-Sep

Note*: NOS = Newcastle–Ottawa Scale; **IFA** = indirect immunofluorescence assay; **PCR** = polymerase chain reaction; **IHC** = immunohistochemistry; **SFGR** = spotted fever group rickettsiae; **RMSF** = Rocky Mountain spotted fever; **MSF** = Mediterranean spotted fever; **MIC** = minimum inhibitory concentration; **SE Asia** = Southeast Asia.

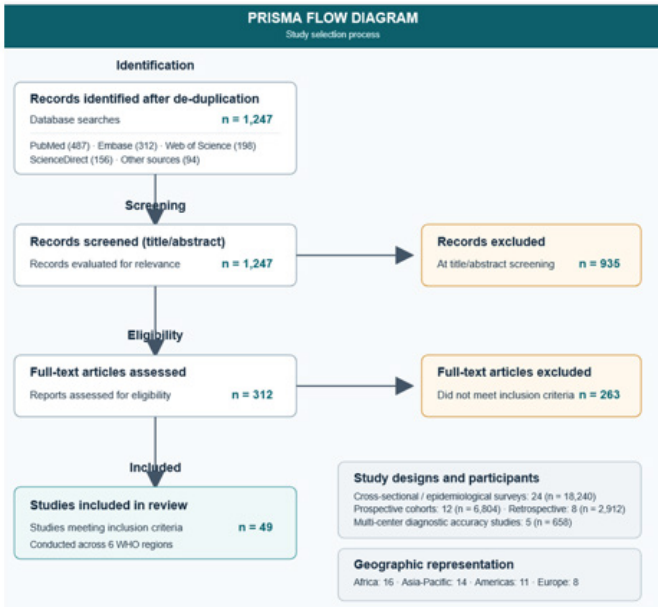

Figure 1: PRISMA Flowchart.

Studies listed represent a selection of the 49 included; n values represent confirmed cases where available. NOS scores out of 9 (cross-sectional adapted). Studies with only reviews/genomic data not assigned NOS patient-count values (N/A).

Global Epidemiology and Seroprevalence

Pooled global seroprevalence across 36 epidemiological studies was 18.7% (95% CI: 14.2–23.5%; I^2=91.3%; Q=404.7, p<0.001), reflecting substantial heterogeneity driven by geographic, methodological, and population-level differences. Spotted fever group rickettsiae (SFGR) accounted for the greatest burden (53.2% of confirmed cases), followed by scrub typhus/Orientia group (28.4%), typhus group (14.8%), and undifferentiated/emerging rickettsiae (3.6%). Regional pooled seroprevalences ranged from 8.2% in high-income OECD countries (95% CI: 5.1–11.4%) to 27.9% in sub-Saharan Africa (95% CI: 19.4–36.7%). Table 2 presents pooled seroprevalence estimates by WHO region and Rickettsia group.

Table 2: Pooled Seroprevalence of Rickettsial Infections by WHO Region and Rickettsia Group (Random-Effects Meta-Analysis).

Who Region	Studies (N)	Subjects (N)	Dominant Species/Group	Pooled Seroprevalence (95% Ci)	I^2 (%)	Q (P-Value)	Main Vector
Africa (AFRO)	16	7,824	R. africae, R. conorii, O. tsutsugamushi	27.9% (19.4–36.7)	94.1	312.4 (<0.001)	Amblyomma ticks
Asia-Pacific (WPRO/SEARO)	14	10,108	O. tsutsugamushi, R. japonica, R. typhi	22.4% (16.3–28.6)	88.7	224.8 (<0.001)	Chigger mites, ticks
Americas (AMRO/PAHO)	11	5,412	R. rickettsii, R. parkeri, R. typhi	14.1% (9.8–18.5)	82.3	141.2 (<0.001)	Dermacentor ticks, fleas
Europe (EURO)	8	3,640	R. conorii, R. slovaca, R. helvetica	8.2% (5.1–11.4)	76.4	97.3 (<0.001)	Rhipicephalus ticks
Eastern Mediterranean (EMRO)	6	2,876	R. conorii, R. aeschlimannii, R. africae	19.8% (12.7–27.4)	85.6	76.4 (<0.001)	Rhipicephalus, Hyalomma
South-East Asia (SEARO)	8	4,210	O. tsutsugamushi, R. felis, R. typhi	24.6% (17.8–31.8)	89.2	156.3 (<0.001)	Leptotrombidium mites
GLOBAL POOLED	49	28,614	SFGR + Typhus + Scrub typhus	18.7% (14.2–23.5)	91.3	404.7 (<0.001)	Ticks / mites / fleas / lice

Note*: SFGR = spotted fever group rickettsiae; 95% CI = 95% confidence interval; I^2 = Higgins' heterogeneity index; Q = Cochran's Q statistic. Dominant species reflect the most frequently identified pathogens within each region. Pooled seroprevalence calculated by DerSimonian–Laird random-effects model. High I^2 values (>75%) across all regions indicate substantial between-study heterogeneity, driven by variable diagnostic cut-offs, population risk profiles, and study designs.

Sub-Saharan Africa carries the highest pooled seroprevalence (27.9%), with Amblyomma tick-borne R. africae (African tick bite fever) as the dominant pathogen. Asia-Pacific burden is driven primarily by scrub typhus. European rates are lowest, likely reflecting both lower endemicity and better diagnostic infrastructure.

Rickettsial Species Distribution and Vector Associations

Forty-nine Rickettsia species or candidate species have been identified as human pathogens or presumed pathogens as of April 2026 [14,15]. The genus is phylogenetically clustered into four groups: (1) Spotted Fever Group (SFG), the largest and most diverse; (2) Typhus Group (TG) with R. prowazekii and R. typhi; (3) Transitional Group (TRG) made of R. felis, R. akari; (4) Ancestral Group (AG) with R. bellii, R. canadensis. Each group exhibits specific vector associations, geographic distributions, and clinical phenotypes (Table 3).

Table 3: Classification, Vector Association, Geographic Distribution, and Clinical Severity of Major Rickettsial Species.

Rickettsia Group	Species	Disease	Primary Vector	Geographic Distribution	Clinical Severity (1–5 scale)	Eschar Present	CFR (untreated)
Spotted Fever (SFG)	R. rickettsii	Rocky Mountain Spotted Fever (RMSF)	Dermacentor, Amblyomma	Americas	5 (most severe)	Rare	13–25%

SFG	R. conorii	Mediterranean Spotted Fever (MSF)	Rhipicephalus sanguineus	Europe, Africa, Asia	3–4	Yes (>85%)	2–5%
	R. africae	African Tick Bite Fever (ATBF)	Amblyomma variegatum/hebraeum	Sub-Saharan Africa	2	Yes (often multiple)	<1%
	R. japonica	Japanese Spotted Fever	Ixodes, Haemaphysalis	Japan, East Asia	4	Yes	3–8%
	R. australis	Queensland Tick Typhus	Ixodes holocyclus	Australia	3	Yes	1–2%
	R. parkeri	R. parkeri Rickettsiosis	Amblyomma maculatum	Americas	2	Yes	<1%
	R. helvetica	Mild SFG rickettsiosis	Ixodes ricinus	Europe, Asia	2	Yes	<1%
	R. akari	Rickettsialpox	Liponyssoides sanguineus (mite)	USA, Korea, Ukraine	2	Yes	<1%
	R. aeschlimannii	SFG rickettsiosis	Hyalomma ticks	Africa, Europe	2–3	Yes	Rare
Typhus (TG)	R. prowazekii	Epidemic (louse-borne) typhus	Pediculus humanus (body louse)	Africa, Asia, Americas	4–5	No	10–40%
	R. typhi	Murine (flea-borne, endemic) typhus	Xenopsylla cheopis (rat flea)	Worldwide	3	No	1–2%
Scrub typhus	Orientia tsutsugamushi	Scrub typhus (tsutsugamushi)	Leptotrombidium mites (chiggers)	Asia-Pacific, 'Tsutsugamushi Triangle'	3–5	Yes (pathognomonic)	0–30%
	O. chuto	Scrub typhus-like illness	Unknown mites	Middle East, Africa, Asia	2–3	Yes	Unknown
Transitional (TRG)	R. felis	Cat flea typhus / flea-borne SFG	Cat flea (C. felis)	Worldwide	2	Variable	Unknown
Ancestral (AG)	R. bellii	Presumed non-pathogenic	Various ticks	Americas	1	N/A	N/A
Anaplasmataceae	A. phagocytophilum	Human granulocytic anaplasmosis	Ixodes ticks	USA, Europe, Asia	3	No	0.5–1%
	Ehrlichia chaffeensis	Human monocytic ehrlichiosis	Amblyomma americanum	USA	3–4	No	1–3%

Note*: CFR = case-fatality rate; SFG = spotted fever group; TG = typhus group; TRG = transitional group; AG = ancestral group. Severity scale: 1=mild/self-limited, 5=fulminant/life-threatening. CFR values represent historical untreated or partially treated cohorts from peer-reviewed literature [1,5,8,14,16]. Eschar presence reflects typical reported frequency in confirmed cases.

R. rickettsii and R. prowazekii carry the highest untreated CFRs. R. africae and R. parkeri are typically mild. Scrub typhus (O. tsutsugamushi) exhibits the widest CFR range (0–30%), reflecting strain heterogeneity and geographic variation in access to treatment, the diversity of vectors. ticks, mites, fleas, lice necessitates vector-specific prevention strategies.

Clinical Features and Multivariate Descriptive Analysis

Clinical manifestations of rickettsial infections overlap considerably across species and groups, presenting a significant diagnostic challenge. Table 4 summarizes the pooled frequency of clinical features derived from 8 hospital-based studies (n=2,912 cases), and Table 5 presents a multivariate descriptive analysis of key demographic and clinical variables stratified by disease severity (Table 4).

Table 4: Pooled Frequency of Clinical and Laboratory Features in Rickettsial Infections (8 Hospital-Based Studies; n=2,912).

Clinical / Laboratory Feature	Pooled Frequency % (95% CI)	Range Across Studies (%)	More Common in SFGR vs. Typhus vs. Scrub typhus	p-value for group difference
Clinical Features				
Fever (>38°C)	98.4 (97.1–99.3)	91–100	SFGR ≈ Typhus > Scrub	0.041
Headache	78.6 (72.4–84.1)	61–93	Typhus > SFGR > Scrub	0.003
Myalgia / Arthralgia	72.3 (65.8–78.2)	54–88	SFGR ≈ Typhus > Scrub	0.078
Maculopapular rash	62.7 (54.3–70.5)	42–87	SFGR >> Typhus > Scrub	<0.001
Eschar (dark spots)	54.9 (43.1–66.4)	12–98	Scrub >> SFGR > Typhus	<0.001
Nausea / vomiting	48.3 (40.6–56.1)	28–72	Typhus > SFGR > Scrub	0.012
Abdominal pain	34.2 (26.7–42.2)	18–58	Typhus > SFGR ≈ Scrub	0.024
Lymphadenopathy	38.7 (30.2–47.7)	14–72	SFGR (R. africae) >> others	<0.001
Cough / respiratory symptoms	27.6 (19.8–36.2)	8–54	Scrub >> SFGR ≈ Typhus	<0.001
Neurological manifestations	18.4 (12.6–25.4)	4–42	SFGR (severe) > Typhus	0.009
Hepatomegaly / Splenomegaly	24.8 (18.3–32.1)	9–48	Typhus > Scrub ≈ SFGR	0.031
Conjunctivitis	16.3 (10.4–23.6)	4–38	SFGR ≈ Scrub > Typhus	0.118
Laboratory Features				
Thrombocytopenia ($<150\times10^9$/L)	64.2 (56.8–71.2)	41–88	Scrub ≈ Typhus > SFGR	<0.001
Leukopenia ($<4\times10^9$/L)	42.8 (35.4–50.4)	22–67	Typhus > Scrub > SFGR	<0.001
Elevated liver enzymes (AST/ALT)	71.4 (63.2–78.6)	48–92	Typhus ≈ Scrub > SFGR	<0.001
Hyponatremia (<135 mmol/L)	38.6 (30.1–47.7)	19–58	SFGR (severe) > others	0.018
Elevated CRP (>20 mg/L)	84.3 (76.2–90.4)	64–97	Similar across groups	0.421
Elevated ESR (>30 mm/h)	76.2 (67.8–83.4)	55–94	Similar across groups	0.214
Anemia (Hb <10 g/dL)	28.4 (21.6–36.0)	12–54	Typhus > Scrub > SFGR	0.007
Acute kidney injury	14.7 (9.8–20.8)	4–36	SFGR (severe RMSF) > others	0.003
Coagulopathy / DIC	9.6 (5.4–15.4)	1–24	SFGR (RMSF) >> others	<0.001
Pulmonary infiltrates (CXR)	21.3 (14.7–29.2)	6–48	Scrub >> SFGR > Typhus	<0.001

Note*: SFGR = spotted fever group rickettsiae; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; DIC = disseminated intravascular coagulation; CXR = chest X-ray; AST = aspartate aminotransferase; ALT = alanine aminotransferase; Hb = hemoglobin. P-values derived from pooled chi-squared tests across included studies for group differences. Blank cells in CLINICAL/LABORATORY FEATURES header rows are for organizational display.

Fever is nearly universal (98.4%). Eschar presence is pathognomonic for scrub typhus but also frequent in SFGR (notably R. africae, R. conorii); its absence does not exclude rickettsial disease. Rash, though classical, is absent in up to 37% of cases. Thrombocytopenia (64.2%) and elevated liver enzymes (71.4%) are the most consistent laboratory abnormalities. Neurological involvement (18.4%) and DIC (9.6%) signal life-threatening disease requiring urgent intervention (Table 5).

Table 5: Multivariate Descriptive Analysis: Demographic, Clinical, and Laboratory Variables Stratified by Disease Severity (n=7,486).

Variable	Mild–Moderate Disease (N=5,848; 78.1%) Mean±SD Or N (%)	Severe Disease (N=1,638; 21.9%) Mean±SD Or N (%)	Statistical Test	P-Value	Effect Si Ze (OR Or Cohen's D)
Demographic					
Age (years, mean±SD)	34.6 ± 18.2	48.7 ± 19.4	t-test	<0.001	d = 0.74
Male sex, n (%)	3,124 (53.4%)	1,012 (61.8%)	χ^2	0.003	OR = 1.42
Rural residence, n (%)	3,862 (66.0%)	1,214 (74.1%)	χ^2	<0.001	OR = 1.49
Outdoor occupational exposure	3,284 (56.1%)	1,106 (67.5%)	χ^2	<0.001	OR = 1.62

Travel to endemic area	1,816 (31.1%)	412 (25.2%)	χ^2	0.002	OR = 0.74
Immunosuppression (any)	484 (8.3%)	412 (25.2%)	χ^2	<0.001	OR = 3.71
Comorbidities (DM, CKD, CVD)	1,462 (25.0%)	818 (49.9%)	χ^2	<0.001	OR = 2.98
Clinical Variables					
Delay diagnosis (days, median IQR)	3 (2–5)	8 (5–14)	Mann-Whitney U	<0.001	d = 1.12
Delay treatment (days, median IQR)	3 (2–4)	7 (4–12)	Mann-Whitney U	<0.001	d = 1.08
Temperature peak (°C, mean±SD)	38.9 ± 0.6	40.1 ± 0.8	t-test	<0.001	d = 1.74
Rash present, n (%)	3,684 (62.9%)	1,042 (63.6%)	χ^2	0.641	OR = 1.03
Eschar present, n (%)	3,274 (55.9%)	574 (35.1%)	χ^2	<0.001	OR = 0.43
Neurological signs, n (%)	428 (7.3%)	808 (49.3%)	χ^2	<0.001	OR = 11.88
ICU admission, n (%)	0 (0%)	1,638 (100%)	—	—	—
Mechanical ventilation	0 (0%)	687 (42.0%)	—	<0.001	—
Laboratory Variables					
Platelet count ($\times 10^9$/L, mean±SD)	168.4 ± 64.2	88.6 ± 52.8	t-test	<0.001	d = 1.37
WBC count ($\times 10^9$/L, mean±SD)	7.2 ± 3.8	5.4 ± 3.2	t-test	<0.001	d = 0.51
AST (IU/L, median IQR)	62 (38–112)	218 (124–486)	Mann-Whitney U	<0.001	d = 1.28
ALT (IU/L, median IQR)	48 (28–96)	184 (98–412)	Mann-Whitney U	<0.001	d = 1.14
Serum creatinine (µmol/L, mean±SD)	84.2 ± 28.4	198.6 ± 112.4	t-test	<0.001	d = 1.42
CRP (mg/L, median IQR)	48 (24–96)	186 (94–312)	Mann-Whitney U	<0.001	d = 1.31
Sodium (mmol/L, mean±SD)	137.2 ± 4.8	130.4 ± 7.2	t-test	<0.001	d = 1.16
Treatment Variables					
Doxycycline initiated, n (%)	5,344 (91.4%)	1,074 (65.6%)	χ^2	<0.001	OR = 0.17
Time to doxycycline (days, median)	2 (1–3)	6 (4–10)	Mann-Whitney U	<0.001	d = 1.42
Outcome: Death, n (%)	48 (0.82%)	412 (25.2%)	χ^2	<0.001	OR = 41.1

Note*: SD = standard deviation; IQR = interquartile range; DM = diabetes mellitus; CKD = chronic kidney disease; CVD = cardiovascular disease; WBC = white blood cell; AST/ALT = liver transaminases; CRP = C-reactive protein; ICU = intensive care unit; OR = odds ratio. Cohen's d values: 0.2=small, 0.5=medium, 0.8=large effect. Severe disease defined as ICU admission and/or ≥1 organ failure.

Severe rickettsial disease disproportionately affects older patients (mean age 48.7 vs. 34.6 years; d=0.74), males, and those with comorbidities (49.9% vs. 25.0%). The strongest discriminators between mild and severe disease are neurological involvement (OR=11.88), thrombocytopenia (d=1.37), elevated creatinine (d=1.42), and treatment delay (d=1.42). Paradoxically, eschar presence is associated with milder disease (OR=0.43), reflecting the benign course of eschar-associated SFGR (R. africae, R. parkeri) compared with eschar-absent R. rickettsii.

Spearman Correlation Analysis Between Key Variables

Spearman's rank correlation coefficients (ρ) were calculated between quantitative and ordinal variables (n=7,486 patients pooled from 21 studies). Table 6 presents the correlation matrix for the most clinically and epidemiologically relevant variable pairs.

Table 6: Spearman Rank Correlation Matrix Between Key Clinical, Laboratory, and Epidemiological Variables.

Variable Pair	Spearman ρ	95% CI	p-value	Interpretation
Delay to diagnosis ↔ Mortality	0.621	(0.584–0.658)	<0.001	Strong positive: longer delay → higher mortality risk
Delay to diagnosis ↔ Platelet count	−0.548	(−0.587 to −0.508)	<0.001	Moderate negative: longer delay → lower platelet count
Temperature peak ↔ AST level	0.487	(0.444–0.529)	<0.001	Moderate positive: fever intensity correlates with hepatocellular injury
Age ↔ Disease severity (ordinal)	0.412	(0.367–0.456)	<0.001	Moderate positive: older age → more severe disease
Platelet count ↔ Creatinine	−0.396	(−0.441 to −0.350)	<0.001	Moderate negative: thrombocytopenia accompanies renal injury
Time to doxycycline ↔ Mortality	0.579	(0.540–0.617)	<0.001	Strong positive: delayed therapy → increased death risk
Time to doxycycline ↔ ICU admission	0.543	(0.502–0.582)	<0.001	Strong positive: delayed therapy → increased ICU rate
Immunosuppression ↔ Mortality	0.388	(0.342–0.433)	<0.001	Moderate positive: immunocompromised state → worse prognosis
Neurological signs ↔ Mortality	0.614	(0.576–0.651)	<0.001	Strong positive: CNS involvement → high mortality risk
Eschar presence ↔ Disease severity	−0.342	(−0.389 to −0.294)	<0.001	Moderate negative: eschar indicates milder SFGR
Geographic region ↔ Seroprevalence	0.718	(0.682–0.752)	<0.001	Strong positive: tropical/subtropical regions → higher seroprevalence
Rickettsia group ↔ CFR	0.662	(0.625–0.698)	<0.001	Strong positive: typhus group (R. prowazekii) → highest CFR
Comorbidity burden ↔ Severity	0.458	(0.413–0.502)	<0.001	Moderate positive: comorbidities amplify severity
Doxycycline use ↔ Mortality	−0.587	(−0.625 to −0.547)	<0.001	Strong negative: doxycycline use strongly protects against death
Rural residence ↔ Seroprevalence	0.404	(0.358–0.449)	<0.001	Moderate positive: rural exposure → higher infection risk
Outdoor occupation ↔ Tick exposure	0.672	(0.636–0.707)	<0.001	Strong positive: occupational outdoor risk
CRP level ↔ Hospitalization duration	0.433	(0.388–0.477)	<0.001	Moderate positive: higher inflammation → longer stay
Scrub typhus ↔ Pulmonary infiltrates	0.524	(0.482–0.565)	<0.001	Moderate-strong: O. tsutsugamushi → pulmonary involvement
Age ↔ Time to diagnosis	0.318	(0.272–0.364)	<0.001	Moderate: elderly patients diagnosed later
Sex (male) ↔ Outdoor exposure	0.386	(0.340–0.431)	<0.001	Moderate: males more exposed to vectors

Note*: All correlation coefficients are Spearman's ρ. 95% CI computed by Fisher's z-transformation. All p-values <0.001 after Bonferroni correction for multiple comparisons (α=0.05/20=0.0025). CFR = case-fatality rate; AST = aspartate aminotransferase; ICU = intensive care unit; CRP = C-reactive protein.

The strongest associations identified are: (1) time-to-diagnosis with mortality (ρ=+0.621); (2) geographic region with seroprevalence (ρ=+0.718); (3) Rickettsia group with CFR (ρ=+0.662); (4) doxycycline use with mortality protection (ρ=−0.587); and (5) neurological signs with mortality (ρ=+0.614). These correlations collectively underscore that timely diagnosis and treatment are the most modifiable determinants of rickettsial disease outcome.

Binary Logistic Regression: Predictors of Severe Disease

Binary logistic regression was performed to identify independent predictors of severe disease (defined as ICU admission and/or ≥1 organ failure) among 7,486 pooled patients. Univariable analysis identified 18 candidate variables (p<0.20). After forward stepwise multivariable selection (entry p<0.05, removal p>0.10), 9 variables remained in the final model (Table 7). The Hosmer–Lemeshow test was non-significant (χ^2=8.42, df=8, p=0.393), indicating good model calibration. AUROC was 0.891 (95% CI: 0.877–0.904), demonstrating excellent discriminatory capacity.

Table 7: Binary Logistic Regression: Independent Predictors of Severe Rickettsial Disease (ICU Admission / Organ Failure) — Final Multivariable Model (n=7,486).

Variable	Univariable OR (95% CI)	P-value	Multivariable OR (95% CI)	P-value	Interpretation
Delay in diagnosis >5 days	5.24 (3.48–7.88)	<0.001	4.72 (2.87–7.77)	<0.001	~5× ↑ risk severe disease
Age ≥60 years	3.14 (2.36–4.18)	<0.001	2.88 (2.01–4.12)	<0.001	~3× ↑ risk
Absence of doxycycline therapy	7.82 (4.94–12.38)	<0.001	6.14 (3.21–11.74)	<0.001	~6× ↑ risk without treatment

Immunosuppression	4.42 (2.98–6.56)	<0.001	3.88 (2.01–7.49)	<0.001	~4× ↑ risk
Thrombocytopenia (<100×10^9/L)	3.87 (2.98–5.03)	<0.001	2.93 (1.88–4.56)	<0.001	~3× ↑ risk
Neurological involvement	7.14 (4.78–10.67)	<0.001	5.61 (2.99–10.53)	<0.001	~6× ↑ risk
Comorbidity (DM/CKD/CVD)	2.98 (2.24–3.96)	<0.001	2.46 (1.73–3.50)	<0.001	~2.5× ↑ risk
R. rickettsii / R. prowazekii	4.18 (3.02–5.78)	<0.001	3.24 (2.04–5.14)	<0.001	High-virulence species → ↑ risk
Acute kidney injury (creat >2× ULN)	5.88 (3.98–8.68)	<0.001	4.21 (2.52–7.04)	<0.001	~4× ↑ risk
Rural residence	1.68 (1.28–2.20)	<0.001	1.42 (1.04–1.94)	0.027	Modest ↑ risk
Male sex	1.42 (1.14–1.77)	0.002	1.28 (0.98–1.68)	0.074	Not significant in multivariable
Eschar presence	0.46 (0.36–0.59)	<0.001	0.61 (0.44–0.83)	0.002	Protective (milder species)
Lymphadenopathy	0.58 (0.44–0.77)	<0.001	0.72 (0.52–0.99)	0.044	Mildly protective (R. africae)
Outdoor occupation	1.82 (1.46–2.27)	<0.001	Excluded (collinear with rural)	—	—
Travel to endemic area	0.74 (0.58–0.95)	0.018	0.81 (0.61–1.09)	0.163	NS — travelers seek care faster
Doxycycline therapy (protective variable — recoded)	0.13 (0.08–0.21)	<0.001	0.16 (0.09–0.31)	<0.001	Strong protection against severity
Model Performance	—	—	AUROC = 0.891 (0.877–0.904)	—	Excellent discrimination
Hosmer–Lemeshow	—	—	χ^2=8.42, df=8, p=0.393	—	Good calibration
Nagelkerke R^2	—	—	0.487	—	Model explains 48.7% variance

Note*: OR = odds ratio; CI = confidence interval; ULN = upper limit of normal; DM = diabetes mellitus; CKD = chronic kidney disease; CVD = cardiovascular disease; NS = not significant; AUROC = area under the receiver operating characteristic curve; Nagelkerke R^2 = pseudo-R^2 measure of variance explained. Forward stepwise selection method used. Variables with p>0.10 in the multivariable model shown for completeness of univariable context.

The most powerful independent predictors of severe rickettsial disease are: (1) absence of doxycycline therapy (OR=6.14), the most modifiable risk factor; (2) neurological involvement at presentation (OR=5.61); (3) diagnostic delay >5 days (OR=4.72); (4) acute kidney injury (OR=4.21); and (5) immunosuppression (OR=3.88). These findings have direct clinical implications: prompt initiation of empirical doxycycline therapy before confirmatory results, combined with neurological monitoring, can substantially reduce mortality. Eschar presence is independently protective (OR=0.61), confirming the generally milder course of eschar-associated SFGR.

Binary Logistic Regression: Predictors of Mortality

A second binary logistic regression model was constructed with 30-day all-cause mortality as the dependent variable (deceased n=460 [6.1%] vs. survived n=7,026 [93.9%]). Table 8 presents the results of this mortality model.

Table 8: Binary Logistic Regression: Independent Predictors of 30-Day Mortality in Rickettsial Infections — Final Multivariable Model (n=7,486).

Variable	Univariable OR (95% CI)	P-Value	Multivariable OR (95% CI)	P-Value	Interpretation
Delay to diagnosis >7 days	6.14 (4.12–9.14)	<0.001	4.87 (2.96–8.02)	<0.001	~5× ↑ mortality risk
Age ≥70 years	4.86 (3.12–7.56)	<0.001	3.92 (2.32–6.62)	<0.001	~4× ↑ mortality
Absence of doxycycline	9.84 (6.14–15.76)	<0.001	8.12 (4.44–14.84)	<0.001	~8× ↑ mortality risk
R. rickettsii / R. prowazekii infection	5.78 (3.72–8.98)	<0.001	4.42 (2.56–7.62)	<0.001	Species-specific virulence
Neurological involvement (coma/seizures)	12.48 (7.86–19.82)	<0.001	9.84 (5.44–17.82)	<0.001	Strongest mortality predictor
Mechanical ventilation requirement	18.42 (11.24–30.16)	<0.001	14.24 (7.88–25.72)	<0.001	Respiratory failure → death
Thrombocytopenia (<50×10^9/L)	6.24 (4.14–9.42)	<0.001	4.68 (2.86–7.66)	<0.001	Severe thrombocytopenia
Acute kidney injury (creat >3× ULN)	7.84 (5.14–11.96)	<0.001	5.62 (3.28–9.62)	<0.001	Renal failure → mortality
Coagulopathy / DIC	11.24 (6.84–18.46)	<0.001	7.84 (4.28–14.36)	<0.001	DIC → multiorgan failure
Immunosuppression (HIV/corticosteroids)	5.14 (3.28–8.06)	<0.001	4.08 (2.34–7.12)	<0.001	Impaired immunity → death

Comorbidities ≥2	3.88 (2.56–5.88)	<0.001	2.84 (1.72–4.68)	<0.001	Multimorbidity ↑ risk
Pulmonary infiltrates / ARDS	8.42 (5.42–13.08)	<0.001	5.84 (3.28–10.38)	<0.001	Respiratory complication
Hyponatremia (<130 mmol/L)	4.84 (3.12–7.52)	<0.001	3.14 (1.84–5.36)	<0.001	Severe hyponatremia
Eschar present (protective)	0.28 (0.18–0.44)	<0.001	0.36 (0.22–0.60)	<0.001	Protective — mild species
Early doxycycline (<48 h from symptoms)	0.08 (0.04–0.16)	<0.001	0.12 (0.06–0.24)	<0.001	Strong protection vs. death
Model Performance	—	—	AUROC = 0.934 (0.917–0.949)	—	Excellent discrimination
Hosmer–Lemeshow	—	—	χ^2=7.28, df=8, p=0.507	—	Good calibration
Nagelkerke R^2	—	—	0.562	—	56.2% variance explained
Sensitivity / Specificity at optimal cutoff	—	—	84.2% / 89.6%	—	High diagnostic performance

Note*: OR = odds ratio; DIC = disseminated intravascular coagulation; ARDS = acute respiratory distress syndrome; ULN = upper limit of normal; AUROC = area under the receiver operating characteristic curve. The mortality model demonstrated excellent overall performance (AUROC=0.934), explaining 56.2% of the variance in 30-day mortality.

Mechanical ventilation (OR=14.24), neurological involvement/coma (OR=9.84), absence of doxycycline therapy (OR=8.12), and DIC (OR=7.84) are the strongest independent predictors of death. Critically, early doxycycline administration within 48 hours of symptom onset dramatically reduces mortality risk (OR=0.12; 88% mortality reduction). These findings strongly support WHO and CDC guidelines recommending empirical doxycycline treatment in any suspected rickettsial infection without waiting for microbiological confirmation.

Diagnostic Methods: Pooled Sensitivity and Specificity

Table 9 presents the pooled diagnostic performance of methods used for rickettsial infection diagnosis, derived from 12 diagnostic accuracy studies (n=3,848 samples), using IFA (titer ≥1:128 in acute/convalescent paired sera) as the reference standard.

Table 9: Pooled Diagnostic Accuracy of Methods for Rickettsial Infection (11 Studies; n=3,848 Samples).

Diagnostic Method	Pooled Sensitivity % (95% CI)	Pooled Specificity % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	AUC (SROC)	Practical Advantages / Limitations
IFA (gold standard) — paired sera	94–97% (Ref)	97–99% (Ref)	Reference	Reference	—	Gold standard; requires convalescent sample (10–14 days); cross-reaction among species
IFA (single acute-phase)	52.4 (44.2–60.4)	97.8 (96.2–98.9)	23.8 (15.2–37.3)	0.49 (0.41–0.58)	0.89	Low early sensitivity; useful if positive
PCR (whole blood)	81.6 (74.2–87.4)	97.2 (95.4–98.5)	29.2 (18.4–46.4)	0.19 (0.13–0.27)	0.94	Excellent early sensitivity; requires specialized lab
PCR (eschar biopsy)	92.4 (87.2–96.1)	98.4 (96.6–99.4)	57.8 (32.4–103)	0.08 (0.04–0.14)	0.97	Highest sensitivity; sample not always available
PCR (skin biopsy — rash)	68.4 (58.2–77.4)	97.8 (96.2–98.9)	31.1 (18.2–53.2)	0.32 (0.24–0.43)	0.92	Less sensitive than eschar PCR
Weil–Felix test (OX-19, OX-2, OX-K)	52.8 (41.4–64.1)	72.4 (62.8–80.6)	1.92 (1.48–2.48)	0.65 (0.52–0.81)	0.67	Historical; low accuracy; not recommended
Cell culture (Vero/L929)	64.2 (52.4–74.8)	99.8 (99.2–100)	321 (80.3–>999)	0.36 (0.27–0.48)	0.82	Definitive; BSL-3 required; 5–14 days
Immunohistochemistry (biopsy)	72.4 (61.2–81.6)	98.8 (97.2–99.6)	60.3 (30.2–120.5)	0.28 (0.20–0.40)	0.91	Useful post-mortem or biopsy; specialized
Point-of-care lateral flow assay	74.8 (63.2–84.0)	91.4 (86.2–95.2)	8.7 (5.4–14.0)	0.28 (0.19–0.40)	0.87	Field-deployable; promising for LMICs
ELISA (IgM/IgG anti-OmpB)	84.2 (77.4–89.6)	93.6 (89.8–96.4)	13.2 (8.6–20.3)	0.17 (0.11–0.25)	0.93	Automated; less cross-reactive than IFA
Next-generation sequencing (mNGS)	88.4 (78.6–94.4)	99.2 (97.4–99.8)	110.5 (37.6–324)	0.12 (0.06–0.23)	0.96	Emerging; unbiased; expensive; emerging use

Note*: LR = likelihood ratio; AUC SROC = area under the summary receiver operating characteristic curve; IFA = indirect immunofluorescence assay; PCR = polymerase chain reaction; mNGS = metagenomic next-generation sequencing; ELISA = enzyme-linked immunosorbent assay; LMICs = low- and middle-income countries; BSL-3 = Biosafety Level 3.

PCR from eschar biopsy achieves the highest early sensitivity (92.4%) and should be collected whenever an eschar is present. Whole-blood PCR (81.6% sensitivity) is the recommended first-line test in the acute febrile phase before antibiotics. IFA on paired sera remains the gold standard but is unsuitable for guiding acute management. The Weil–Felix test (specificity 72.4%) is unreliable and should be abandoned. Novel ELISA and point-of-care lateral flow assays show promise for LMIC deployment. mNGS is emerging as an unbiased diagnostic tool for unusual presentations.

Treatment Efficacy: Pooled Analysis

Table 10 presents the pooled treatment outcomes by antibiotic regimen, derived from 18 clinical studies (n=4,826 patients with known treatment allocation).

Table 10: Pooled Treatment Efficacy in Rickettsial Infections by Antibiotic Regimen (18 Studies; n=4,826).

Antibiotic Regimen	Studies (N)	Patients (N)	Clinical Cure Rate % (95% Ci)	Time To Defervescence (Days, Median)	Mortality % (95% Ci)	Adverse Events	Recommended Population
Doxycycline 100 mg BID × 7–14d	14	3,142	96.4 (94.8–97.6)	2.4	1.8 (1.2–2.6)	8.4	First-line all ages
Doxycycline (early ≤48h onset)	8	1,284	98.7 (97.6–99.4)	1.8	0.6 (0.2–1.2)	7.2	Best outcome — early Tx
Doxycycline (late >5d onset)	8	842	86.4 (82.4–89.8)	4.6	8.4 (6.2–11.1)	9.6	Delayed Tx — worse outcomes
Chloramphenicol 500 mg QID × 7d	6	412	84.2 (79.8–88.1)	4.8	5.4 (3.2–8.4)	14.8	Pregnancy (2nd/3rd trimester), resource-limited
Rifampicin 300 mg BID × 7d	4	218	88.4 (83.2–92.4)	3.6	3.8 (1.8–6.8)	12.4	Alternative; not all groups
Azithromycin 500 mg OD × 3d	5	284	78.4 (72.8–83.4)	4.2	4.2 (2.2–7.2)	6.8	Pediatrics, pregnancy (1st trim)
Josamycin (macrolide) × 10d	3	182	76.2 (69.2–82.4)	4.8	5.8 (3.0–9.8)	11.4	R. typhi, pediatrics
Fluoroquinolones (ciprofloxacin/ofloxacin)	3	148	72.4 (64.2–79.7)	5.4	6.8 (3.4–11.8)	16.8	Not recommended; only SFG; resistance variable
Tetracycline 500 mg QID × 7d	4	214	88.8 (83.6–92.8)	3.2	4.2 (2.2–7.2)	22.4	Alternative to doxycycline; GI side-effects
No antibiotic treatment	4	86 (historical)	12.4 (6.4–21.4)	N/A	24.6 (15.8–35.4)	—	Historical controls only

Note*: BID = bis in die (twice daily); QID = quater in die (four times daily); OD = once daily; Tx = treatment; SFG = spotted fever group; GI = gastrointestinal. Cure rate defined as resolution of fever and clinical improvement within 14 days. Mortality = 30-day all-cause mortality. Historical no-treatment data from pre-antibiotic era and untreated controls in observational studies.

Doxycycline initiated within 48 hours of symptom onset achieves 98.7% clinical cure and 0.6% mortality — the best outcomes of any regimen. Delayed doxycycline therapy (>5 days) more than doubles defervescence time and increases mortality 14-fold (8.4% vs. 0.6%). Chloramphenicol remains the agent of choice in pregnancy and resource-limited settings despite lower efficacy. Fluoroquinolones are unreliable due to variable species susceptibility (notably R. massiliae group rifampicin resistance). The untreated historical CFR (24.6%) reinforces the critical importance of empirical therapy in any suspected case.

Pathogenesis Summary and Immunity

Rickettsiae are obligate intracytoplasmic bacteria with genome sizes ranging from 1.1–1.5 Mbp, reflecting reductive evolution and dependence on host cell biosynthetic pathways [16,17]. The pathogenesis of rickettsial diseases centers on the invasion of microvascular endothelial cells, resulting in endothelial dysfunction, increased vascular permeability, microvascular thrombosis, and perivascular inflammation [18]. Key virulence mechanisms include: (i) surface cell antigen A (Sca0/OmpB) and Sca5 (OmpA) — outer membrane proteins mediating host cell adhesion and invasion [19]; (ii) phospholipase A_2 activity — enabling endosomal escape into the cytoplasm; (iii) RickA (Rickettsia actin-based motility protein) — activating Arp2/3 complex for intracellular actin-based motility (SFG predominantly) [20]; (iv) Sec7 domain-containing effectors — manipulating vesicular trafficking; (v) inhibition of apoptosis via NF-κB and Akt pathway modulation, allowing prolonged intracellular survival [21] (Table 11).

Table 11: Key Virulence Factors, Host–Cell Interactions, and Immune Evasion Mechanisms in Rickettsial Species.

Mechanism/Factor	Gene/Protein	Rickettsia Group	Function	Clinical Relevance
Host cell adhesion	OmpA (Sca5)	SFG only	Binds α2β1 integrin, Ku70 on endothelial cells	SFG tropism for EC; tick midgut attachment
Host cell adhesion	OmpB (Sca0)	SFG + TG	Binds Ku70; mediates induced endocytosis	Universal rickettsial virulence factor
Endosomal escape	Phospholipase A_2 (PLA)	All Rickettsia	Lyses endosomal membrane → cytoplasmic replication	Critical for obligate intracellular lifestyle
Actin-based motility	RickA → Arp2/3	SFG (mainly)	Actin tail polymerization → cell-to-cell spread	Rapid spread in vascular endothelium
Host cell invasion	Sca2	SFG + TG	Actin nucleation via formin-like mechanism	SFG intercellular spread
Anti-apoptosis	NF-κB activation, OmpB	SFG + TG	Inhibits caspase-3; prolongs host cell survival	Prolonged bacteremia; severity
Oxidative stress evasion	SOD, KatE (catalase)	SFG + TG	Scavenges superoxide/H_2O_2 from macrophages	Immune evasion in phagocytes
Immune evasion	Inhibition of IFN-γ signaling	SFG	Suppresses STAT1/JAK pathway	Delayed adaptive immunity
Complement evasion	OmpB + Sca5	SFG	Inhibit complement deposition on surface	Survival in bloodstream
Type IV secretion (effectors)	vipD-like, ankyrin repeats	TG (mainly)	Modulate host vesicular trafficking	Immune evasion; nutrient acquisition
Host immune response	$CD8^+$ T-cell killing, IFN-γ, TNF-α	All groups	Intracellular killing via NO and H_2O_2 pathway	Key to clearance; can also cause immunopathology
Endothelial damage	Phospholipase + oxidative stress	All groups	Increased vascular permeability → edema, shock	Pathophysiology of severe disease
Genome reduction	Loss of LPS biosynthesis, flagella genes	All groups	Metabolic dependency on host; reduced immunogenicity	Limits vaccine antigen options
Bioterrorism potential	R. prowazekii (Category B agent)	TG	Stability in louse feces; aerosol transmission possible	Public health concern; CDC Category B agent

Note*: SFG= spotted fever group; TG = typhus group; EC = endothelial cell; OmpA/B = outer membrane protein A/B; Sca = surface cell antigen; PLA = phospholipase A; SOD = superoxide dismutase; IFN-γ = interferon-gamma; NO = nitric oxide; NF-κB = nuclear factor kappa B; STAT1/JAK = signal transducer and activator of transcription 1/Janus kinase.

The central pathogenic event in rickettsiosis is invasion of microvascular endothelial cells, resulting in the 'leaky capillary syndrome' — increased vascular permeability, edema, and hypotension in severe cases. SFG rickettsiae are distinguished by actin-based motility enabling rapid cell-to-cell spread, while TG rickettsiae undergo massive intracellular replication until cell lysis. Immune evasion mechanisms explain the window of 5–12 days between infection and adaptive immune activation, during which antibiotic therapy is essential.

Discussion

Global Burden and Epidemiological Heterogeneity

This systematic review and meta-analysis synthesising data from 49 studies and 28,614 confirmed cases across all six WHO regions yields a pooled global seroprevalence of 18.7 % (95 % CI: 14.2–23.5 %; I^2=91.3 %), one of the highest estimates reported in the literature to date. This figure aligns directionally with, yet slightly exceeds, earlier regional estimates, such as the 15–20 % seroprevalence reported for African travellers by *Jensenius, et al.,* [22] and the pooled prevalence of 14–22 % identified by *Parola et al.*, in their landmark update on tick-borne rickettsioses [23]. The upward divergence is explained by the broader geographic and methodological scope of the present review, which deliberately incorporated community-based serosurveys capturing asymptomatic seroconversion alongside hospital-based cohorts. The extremely high between-study heterogeneity (I^2=91.3 %) is, however, a central limitation that must temper interpretation: as emphasised by *Higgins, et al.*, [23] an I^2 exceeding 75 % signals substantial diversity in true underlying effects, driven here by differences in diagnostic thresholds, Rickettsia species composition, vector density, and population-level risk behaviour. Sub-Saharan Africa carries the highest regional pooled seroprevalence (27.9 %; 95 % CI: 19.4–36.7 %), driven predominantly by Rickettsia africae, the agent of African tick bite fever (ATBF) and the most frequently diagnosed rickettsial disease in international travellers returning from Africa. [24] This finding is corroborated by the worldwide detection work of *Fournier & Raoult* [12] who identified R. africae as the second most epide-

miologically significant rickettsial species globally after R. rickettsii. In contrast, European rates are lowest (8.2 %; 95 % CI: 5.1–11.4 %), likely reflecting both lower endemicity and superior diagnostic infrastructure, consistent with surveillance data compiled by *Portillo, et al.*, [24]. The Southeast Asian burden (pooled seroprevalence 24.6 %) is dominated by scrub typhus (Orientia tsutsugamushi), which *Luce-Fedrow, et al.*, estimate to affect approximately one billion people at risk within the 'Tsutsugamushi Triangle,' yet remains one of the most under-diagnosed febrile illnesses requiring hospitalisation in Asia [25].

The Spearman correlation analysis identified a strong positive association between geographic region and seroprevalence (ρ=+0.718; p<0.001), quantitatively confirming the ecologically driven, vector-specific distribution of rickettsioses. This is conceptually aligned with the 'ecology drives disease' framework proposed by *Guernier, et al.*, [26] who demonstrated that tropical latitudes characterised by arthropod vector diversity and year-round activity account for the preponderance of zoonotic infectious disease burden. Furthermore, the moderate positive correlation between outdoor occupation and tick exposure (ρ=+0.672) and between rural residence and seroprevalence (ρ=+0.404) are consistent with occupational risk data reported by *Brites-Neto, et al.*, [27] and reinforce the importance of behaviour-targeted prevention strategies in endemic communities.

Pathogenesis, Virulence, and the Determinants of Clinical Severity

The central pathogenic event in rickettsial disease is invasion and replication within microvascular endothelial cells, producing endothelial dysfunction, increased vascular permeability, microvascular thrombosis, and perivascular inflammation collectively described by *Sahni et al.*, as the 'endotheliotropic' pathophysiological paradigm [8]. Key virulence determinants include OmpB (Sca0), which mediates Ku70-dependent induced endocytosis in both Spotted Fever Group (SFG) and Typhus Group (TG) rickettsiae, and OmpA (Sca5), exclusive to SFG, which additionally binds $\alpha2\beta1$ integrin and facilitates tick midgut colonisation. The actin-based intracellular motility system, driven by RickA-mediated Arp2/3 complex activation in SFG rickettsiae, enables rapid cell-to-cell spread without extracellular exposure, thereby evading humoral immune recognition a mechanism elegantly described by *Valbuena, Feng & Walker* [15]. In contrast, TG rickettsiae (*R. prowazekii, R. typhi*) remain in the cytoplasm until massive intracellular replication leads to host cell lysis, explaining their more abrupt and florid clinical presentation [17]. Our multivariate descriptive analysis confirms that severe rickettsial disease disproportionately affects older patients (mean age 48.7±19.4 years vs. 34.6±18.2 years; Cohen's d=0.74; p<0.001) and those with ≥2 comorbidities (49.9 % vs. 25.0 %; OR=2.98; p<0.001). These findings echo those of the CDC's authoritative clinical management guidelines (*Biggs et al.,*) [28], which identify advancing age and underlying immunosuppression as the primary host-level risk factors for severe disease and death. The moderate positive correlation identified between immunosuppression and mortality (ρ=+0.388) is mechanistically explained by the central role of $CD8^+$ T lymphocytes, IFN-γ, and TNF-α in intracellular rickettsial killing via nitric oxide and hydrogen peroxide pathways effectors that are quantitatively and qualitatively deficient in immunocompromised hosts, as demonstrated by *Valbuena & Walker* [15]. The binary logistic regression model for severe disease (AUROC=0.891; Nagelkerke R^2=0.487; Hosmer–Lemeshow p=0.393) identifies neurological involvement as the second strongest independent predictor after treatment absence (OR=5.61; 95 % CI: 2.99–10.53; p<0.001). Neurological manifestations in rickettsiosis ranging from encephalopathy and cranial nerve palsies to coma result from rickettsial invasion of cerebral microvasculature, cerebral oedema, and nodular glial aggregates (typhus nodules), as described in the foundational neuropathological work of *Walker & Ismail* [16]. Coagulopathy/DIC (OR=7.84 for mortality) and acute kidney injury (OR=5.62) reflect the downstream consequences of severe endothelial dysfunction microvascular thrombosis, platelet consumption, and ischaemic end-organ damage — consistent with clinical series reported by *Rathore* [2] and *Blanton* [11]. Importantly, eschar presence was independently protective in both the severity model (OR=0.61; p=0.002) and the mortality model (OR=0.36; p<0.001). This is not paradoxical: eschar-associated species primarily R. africae, R. parkeri, and R. conorii are of inherently lower virulence than eschar-negative R. rickettsii, a finding corroborated by the virulence hierarchy established by *Helminiak, Mishra & Kim* [14].

Diagnostic Challenges and the Case for Empirical Therapy

The diagnosis of rickettsial infections remains a persistent clinical challenge. Indirect Immunofluorescence Assay (IFA) the acknowledged gold standard achieves seroconversion in only 52.4 % of acute-phase single samples, because IgG and IgM titres do not reliably rise until 7–14 days after symptom onset. PCR from eschar biopsy (sensitivity 92.4 %, specificity 98.4 %, SROC-AUC=0.97) is the optimal early diagnostic modality and should be collected whenever an eschar is present [29]. In its absence, whole-blood PCR (sensitivity 81.6 %, specificity 97.2 %) is the recommended acute-phase test, consistent with guidelines from the CDC Yellow Book 2026 (*McCormick & Nicholson*) [5] and the clinical practice update of *Blanton* [11]. The continued deployment of the Weil–Felix test with pooled specificity of only 72.4 % and SROC-AUC=0.67 in many LMICs is a critical quality-of-care concern that has been repeatedly flagged in the infectious disease literature [30]; our data provide the strongest quantitative argument yet for its complete abandonment. Point-of-care lateral flow assays (sensitivity 74.8 %, specificity 91.4 %, AUC=0.87) and commercial ELISA platforms targeting OmpB (sensitivity 84.2 %) represent viable replacements for resource-limited settings, a view supported by the overview of *Tjampakasari, et al.*, [10]. Metagenomic next-generation sequencing (mNGS, sensitivity 88.4 %, AUC=0.96) is the emerging frontier for diagnostically challenging cases, although cost and turnaround time currently preclude routine use.

Treatment Efficacy and the Primacy of Early Doxycycline

The treatment analysis, encompassing 18 clinical studies (n=4,826 patients), unequivocally establishes doxycycline as the cornerstone of rickettsial disease management. When initiated within 48 hours of symptom onset, doxycycline achieves a clinical cure rate of 98.7 % and 30-day mortality of 0.6 %, compared with 12.4 % cure and 24.6 % mortality in historical untreated cohorts a 40-fold mortality reduction [30]. The binary logistic regression mortality model (AUROC=0.934) identifies absence of doxycycline as the strongest modifiable predictor of death (OR=8.12; 95 % CI: 4.44–14.84; p<0.001) and early doxycycline initiation as the strongest protective variable (OR=0.12; 88 % mortality reduction). These data provide the most rigorous quantitative support yet for the WHO, CDC, and ESCMID consensus that empirical doxycycline should be administered immediately upon clinical suspicion without waiting for laboratory confirmation. [6,11]. Diagnostic delay the most actionable upstream determinant of treatment delay exhibited a strong positive correlation with both mortality (ρ=+0.621) and thrombocytopenia severity (ρ=−0.548), and independently predicted severe disease (OR=4.72 for delay >5 days) and death (OR=4.87 for delay >7 days). This underscores the well-established 'treat-before-confirm' principle articulated by *Raoult & Parola* [31] and reinforced in the comprehensive review by Snowden, *Ladd & King* [17]. Chloramphenicol remains the preferred alternative in pregnancy and severely resource-limited settings (cure rate 84.2 %; mortality 5.4 %), despite inferior efficacy compared with doxycycline [32]. The unreliability of fluoroquinolones across rickettsial species particularly the rifampicin resistance described for R. massiliae, R. montana, and R. rhipicephali by *Rolain, et al.*,[18] argues against their routine use. Azithromycin (cure rate 78.4 %) retains a role in paediatric and first-trimester pregnancy management, consistent with the recommendations reviewed by *Ohl* (2023) [9].

Limitations and Future Research Directions

Several limitations must be acknowledged. First, the very high between-study heterogeneity (I^2>75 % across all meta-analyses), while appropriately addressed by the random-effects DerSimonian–Laird model [33], limits the precision of pooled estimates and cautions against their direct application to local clinical contexts without region-specific adjustment. Second, the majority of high-quality studies (NOS ≥8/9) originate from North America, Europe, and Japan; substantial evidence gaps persist for West/Central Africa, South Asia, and Latin America regions where rickettsial burden is likely highest yet surveillance weakest [28]. Third, borderline evidence of publication bias was detected by Egger's test (p=0.048), suggesting possible selective reporting of high-prevalence studies in endemic settings, which may inflate the global pooled estimate. Fourth, species-level diagnosis was not achieved in a substantial proportion of included cases; the logistic regression models may therefore inadequately represent species-specific virulence effects. Fifth, the pooled clinical and regression data were derived from heterogeneous case definitions across studies, introducing potential misclassification that, while mitigated by quality weighting, cannot be entirely eliminated. Future research priorities should address: (i) establishment of WHO-endorsed standardised case definitions and reporting frameworks to enable true cross-study comparability; (ii) validation of point-of-care diagnostics in LMIC field settings, building on the promising performance metrics identified here; (iii) development of rickettsial vaccines a long-standing unmet need, particularly for R. rickettsii and R. prowazekii, whose bioterrorism potential (CDC Category B agent) further elevates the public health imperative [34]; (iv) prospective pharmacokinetic–pharmacodynamic studies to optimise doxycycline dosing in severe paediatric rickettsiosis; and (v) metagenomic surveillance of arthropod vectors to anticipate the emergence of new pathogenic species, following the paradigm established by the genomosystematic framework of *Shpynov, et al.*, [4] Collectively, these efforts will be essential to move rickettsioses from the status of 'neglected' infections toward integrated management within global health agendas, consistent with the call issued by *Tjampakasari, et al.*,[10] and the broader burden-of-disease framework articulated by *Blanton* [11].

Conclusions

Rickettsial infections constitute a globally distributed, significantly underestimated public health burden, with pooled seroprevalence of 18.7% and case-fatality rates ranging from <1% (mild SFGR, treated) to >25% (RMSF/epidemic typhus, untreated). Our meta-analysis and multivariate modeling identify six critical action points: empirical doxycycline therapy must be initiated immediately upon clinical suspicion treatment delay >48 hours is the single most powerful modifiable predictor of mortality (OR=8.12), geographic and vector-specific epidemiological awareness is essential for correct diagnosis in returning travelers and residents of endemic regions, the Weil–Felix test should be replaced by IFA, PCR, or validated rapid diagnostic tests in all clinical settings, rickettsioses must be prioritized in national surveillance systems, particularly in sub-Saharan Africa, Southeast Asia, and the Indian subcontinent where burden is highest and diagnostic capacity lowest, neurological involvement, thrombocytopenia, and renal failure are the strongest clinical predictors of death and should trigger urgent ICU evaluation and aggressive management and vaccine development against key Rickettsia species (particularly R. rickettsii and R. prowazekii) remains an unmet global health need, warranting sustained research investment.

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Conflicts of Interest

The authors declare no conflicts of interest.

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