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Original Article

Evaluation of Oral Doxycycline, Azithromycin, or Sequential Doxycycline-Azithromycin Treatment for Scrub Typhus

Weizhen Wang, Yuqing Dong and Hanchen Liu.

Department of Infectious Diseases, The 970th Hospital of the People's Liberation Army, Yantai, Shandong 264000, China.

Competing interests: The authors declare no competing interest.

Abstract. ***Background*: Scrub typhus is a leading cause of febrile illness across the Asia–Pacific region. Doxycycline is the first-line therapy, with azithromycin as an alternative; sequential treatment (doxycycline followed by azithromycin) is used for nonresponders. However, comparative real-world effectiveness for sequential therapy remains uncertain.**

***Methods*: We conducted a single-center, non-interventional target-trial emulation at the 970th Hospital of the People's Liberation Army (January 2023 - June 2025). Consecutive patients ≥12 years receiving oral doxycycline, azithromycin, or sequential doxycycline/azithromycin treatment were included. The primary outcome was 48-hour defervescence sustained ≥24 h without antipyretics. Secondary outcomes were time to defervescence, Day 5 failure, complications, length of stay, 28-day mortality, and safety. Confounding was addressed using inverse probability weighting (generalized boosted models). The confirmatory comparison (doxycycline vs azithromycin) was limited to non-pregnant initiators (pregnancy excluded due to structural non-overlap) to satisfy positivity. The sequential pathway was explored descriptively with time-varying and 48-hour landmark analyses.**

***Results*: We analyzed 512 patients (doxycycline 206, azithromycin 208, and sequential 98). Crude 48-hour defervescence was 82.0%, 78.8%, and 66.3%, respectively. In the confirmatory inverse probability of treatment weighting (IPTW) analysis, doxycycline vs azithromycin showed no difference (adjusted RR 1.03, 95% CI 0.95–1.12; p=0.34). Weighted time-to-event analysis was concordant (aHR 1.08, 95% CI 0.96–1.21; p=0.20). Secondary outcomes were similar between monotherapies (Day-5 failure aRR 0.83, 95% CI 0.56–1.24; complications aRR 0.94, 95% CI 0.66–1.33; median length of stay 5 [IQR 4–7] days in both; 28-day mortality 1.6% overall). The sequential switch group had lower crude 48-hour defervescence, consistent with escalation after early non-response. Pairwise causal contrasts involving the sequential pathway were not presented due to structural bias.**

***Conclusions*: Oral doxycycline and azithromycin demonstrated comparable effectiveness and safety for early defervescence in routine care. Inferior crude outcomes with sequential therapy likely reflect clinical escalation. Multi-center validation and randomized trials are warranted.**

Keywords: Scrub typhus; Doxycycline; Azithromycin; Sequential therapy; Observational cohort; Target-trial emulation; Inverse probability weighting; Defervescence; Real-world evidence.

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Introduction. Scrub typhus, caused by the bacterium *Orientia tsutsugamushi*, belonging to a genus distinct from Rickettsia, but a member of the family Rickettsiaceae, is transmitted through the bite of infected chiggers.[1] It is a significant public health concern in endemic regions such as rural Asia, the Pacific Islands, and parts of Australia.[1,2] The disease is particularly prevalent in rural and suburban areas, with notable incidence in agricultural communities.[3,4] Epidemiologically, scrub typhus exhibits a seasonal pattern, often peaking during the post-monsoon months from September to January.[4,5] The most affected demographic includes individuals aged 19-64 years, although younger populations are also significantly impacted.[6,7] Clinically, scrub typhus typically presents as an acute febrile illness with symptoms such as fever, headache, myalgia, and, in some cases, a characteristic eschar at the site of the chigger bite.[1,8,9] Other common symptoms include skin rash, body aches, and gastrointestinal disturbances such as vomiting.[3,5] Complications can be severe, involving multi-organ dysfunction, acute respiratory distress syndrome, acute kidney injury, and hepatic involvement.[4,6,7] Laboratory findings often reveal thrombocytopenia, leukocytosis, and elevated liver enzymes.[3,9] The mortality rate varies, with some studies reporting up to 6%.[5] Early diagnosis and treatment with doxycycline can significantly improve outcomes.[3,9] Despite the availability of effective antibiotics, challenges such as drug resistance and limited access to healthcare in rural areas persist.[1,2] Current guidance supports oral doxycycline as first-line therapy for suspected scrub typhus, with azithromycin as an acceptable alternative. Early IV therapy, preferably doxycycline plus azithromycin, improves outcomes in severe disease.[10] Scrub typhus, caused by *Orientia tsutsugamushi*, remains a leading cause of acute undifferentiated fever in endemic regions, where oral doxycycline is widely used as first-line therapy and oral azithromycin is a common alternative, particularly for patients for whom doxycycline is unsuitable. A sequential doxycycline/azithromycin switch is often used in non-responders under routine care. Despite broad uptake of these strategies, comparative real-world evidence remains limited and may be confounded by differences in baseline severity, timing of antibiotic administration, and clinical decision pathways. Our objective was to compare the real-world effectiveness and safety of oral doxycycline, oral azithromycin, and sequential doxycycline/azithromycin within a single center using bias-aware observational methods grounded in target-trial emulation. We prespecified 48-hour defervescence (sustained ≥24 hours without antipyretics) as the primary clinical endpoint and hypothesized no clinically meaningful difference between initial doxycycline and initial azithromycin on this outcome. Outcomes among patients receiving sequential therapy would largely reflect greater baseline acuity or early non-response rather than intrinsic regimen effects, necessitating careful adjustment and sensitivity analyses to minimize confounding and immortal-time bias.

Methods

Study design and oversight. We conducted a single-center, non-interventional, retrospective cohort study that emulated key features of a target trial to compare the real-world use of oral doxycycline, oral azithromycin, and a sequential doxycycline/azithromycin strategy for scrub typhus without altering clinical care. The protocol, case report forms, and a time-to-stamped statistical analysis plan were finalized before analysis and received institutional review board approval. This study was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Ethics Committee of the 970th Hospital of the People's Liberation Army, which waived the requirement for informed consent because the analysis was retrospective, used de-identified, routinely collected data, and posed no more than minimal risk to participants. All data were anonymized before analysis.

Setting and participants. The study took place at the 970th Hospital of the People's Liberation Army in a scrub-typhus–endemic region and analyzed consecutive inpatients and emergency admissions from January 2023 through June 2025. We classified cases as confirmed when PCR from blood or eschar was positive, or when IgM ELISA met a locally validated high-titer cutoff or seroconversion occurred on ELISA/IFAT. Cases with a compatible syndrome in an endemic setting, with eschar but without confirmatory testing, were considered probable for descriptive analyses. Because single-sample serology can reflect past exposure, our confirmatory analyses were robust to restricting to PCR and/or four-fold IFA rise.[11]

Eligibility required age ≥12 years; a clinical diagnosis of scrub typhus supported by at least one laboratory modality (IgM ELISA, IFA with a four-fold rise when available, or PCR from whole blood or eschar) or a classic compatible syndrome with an eschar in the endemic setting while confirmatory testing was pending; and receipt of one of the oral regimens as first active anti-rickettsial therapy. Exclusions were primary intravenous anti-rickettsial therapy, initiation of antibiotics >14 days after fever onset, and death or transfer within 12 hours of the first dose because outcomes could not be ascertained; pregnancy was not an exclusion, but, because no pregnant participants received doxycycline, it produced structural non-overlap and was handled as described under Statistical analysis. Time zero was defined as the time of administration of

the first active oral dose for suspected or confirmed scrub typhus.

Exposure definitions and treatment strategies. Exposures reflected observed strategies at time zero and comprised doxycycline monotherapy (100 mg twice daily), azithromycin monotherapy (500 mg once daily for 3–5 days, including single-dose use at clinician discretion), or sequential doxycycline/azithromycin, which was operationalized strictly as a switch or add-on to oral azithromycin occurring 2–5 days (48–120 hours) after doxycycline initiation, permitted a short dual-oral overlap ≤24 hours based on medication timestamps to allow a clinical hand-off, and was not assigned at time zero. Overlap >24 hours was classified as oral combination therapy and not considered sequential. To prevent immortal time bias, the confirmatory analysis classified patients by initial regimen at time zero (doxycycline vs. azithromycin) for all primary inferences, whereas the sequential pathway was analyzed only using time-varying exposure and 48-hour landmark methods and presented as an association.

Outcomes and temperature harmonization. The primary outcome was defervescence within 48 hours of the first active oral dose, defined as an oral-equivalent temperature <38.0 °C sustained for ≥24 hours without antipyretics. Temperature harmonization used a priori conversion rules: oral readings were used directly; axillary readings were adjusted by +0.5 °C to obtain oral equivalents; rectal readings were adjusted by −0.5 °C; tympanic readings were treated as oral equivalents if device calibration was documented. If antipyretics were administered, temperature measurements obtained in the subsequent six hours were not considered in establishing sustained defervescence. Secondary outcomes included time-to-defervescence (hours) censored at discharge or day 7 (whichever occurred first), Day-5 clinical failure (persistent oral-equivalent ≥38.0 °C or the need to change or add an anti-rickettsial agent), a composite of in-hospital complications (shock or vasopressors, respiratory failure including ARDS or need for supplemental oxygen or ventilation, acute kidney injury per KDIGO, hepatitis defined as ALT or AST >5× the upper limit of normal, and clinician-documented encephalitis or myocarditis), intensive care unit admission, hospital length of stay, 28-day all-cause mortality, treatment-related adverse events (gastrointestinal intolerance, transaminitis, photosensitivity, and QTc ≥500 ms among azithromycin recipients), and 28-day relapse or readmission for a recurrent compatible illness requiring retreatment.

Covariates and data sources. Baseline covariates at time zero included demographics, pregnancy status, comorbidities, days of fever before antibiotics, prior outpatient antibiotics, clinical features (eschar, rash, Glasgow Coma Scale, and qSOFA), vital signs, laboratory values (complete blood count and platelets, creatinine and estimated glomerular filtration rate, bilirubin, ALT/AST, and C-reactive protein), chest imaging findings, ward or ICU location, concomitant antimicrobials, and laboratory-confirmed coinfections (dengue, malaria, leptospirosis, enteric fever). Data were abstracted from the electronic health record into standardized forms with explicit definitions; temperatures were captured at 8–12-hour intervals, and antipyretic administrations were timestamped to adjudicate sustained defervescence.

Statistical analysis. Analyses followed the preregistered SAP and targeted the average treatment effect (ATE) for the confirmatory comparison of doxycycline versus azithromycin in non-pregnant initiators, because positivity was violated in the full cohort. For this contrast, we estimated binary inverse probability of treatment weights (IPTW) via generalized boosted models (GBM) with 5,000 trees, interaction depth 2, learning rate 0.01, bag fraction 0.5, and early stopping based on minimizing the mean absolute post-weighting SMD across covariates. Stabilized weights were used and truncated at the 1st and 99th percentiles. For descriptive three-group summaries and any exploratory contrasts involving the sequential pathway, we estimated a multinomial generalized propensity score with the same GBM tuning. Balance was assessed using absolute SMDs, with a target $|SMD|<0.10$. The primary endpoint was analyzed using IPTW-weighted log-binomial regression to estimate adjusted risk ratios (RRs) and risk differences (RDs), with 95% confidence intervals (CIs). Time to defervescence was analyzed using IPTW-weighted Cox models with Schoenfeld residual checks, and weighted Kaplan–Meier curves with numbers at risk were used to provide medians and interquartile ranges. Binary secondary outcomes used IPTW-weighted log-binomial or robust Poisson models, and length of stay used IPTW-weighted quantile regression at the 50th percentile, with negative binomial regression in sensitivity. All tests were two-sided. No multiplicity adjustment was applied to the sole confirmatory primary test, and Benjamini–Hochberg FDR control was used for multiplicity across secondary endpoints. Sequential-pathway estimates were time-varying or 48-hour landmark by design and are reported only as an association.

Sensitivity and subgroup analyses. We performed an as-treated analysis reclassifying exposure at the time of regimen change. A time-varying exposure analysis that updated treatment status at azithromycin start so that person-time before the switch contributed to the initial regimen and person-time after the switch contributed to the sequential pathway, and a 48-hour landmark analysis

conditioning on being alive and still at risk at 48 hours to minimize immortal-time bias for the primary endpoint. Prespecified subgroup analyses of the confirmatory contrast examined baseline severity (qSOFA ≥2 vs <2), days of fever before therapy (≤5 vs >5), age (≥60 vs <60 years), and laboratory-confirmed coinfection using interaction terms. Pregnancy could not be estimated because no pregnant participants received doxycycline. Weighting diagnostics included the post-weighting effective sample size (ESS), empirical weight distribution, and overlap of propensity scores; for the confirmatory contrast the post-weighting ESS was ~362, the median stabilized weight was 0.98 (IQR 0.72–1.21), the 99th percentile weight was 3.9, and the maximum after truncation was 5.8, with no mass near zero and adequate overlap of estimated propensity scores.

Analyses were performed in R (version 4.4) using established libraries for GBM weighting, survey-weighted estimation, survival analysis, and multiple imputation.

Results. Between January 2023 and June 2025, 589 patients were screened, 77 were excluded for prespecified reasons (primary intravenous therapy, delayed antibiotic start >14 days, death/transfer within 12 hours, non–scrub typhus diagnosis, or declined/no consent), and 512 were included in the analytic cohort: 206 received initial doxycycline, 208 received initial azithromycin, and 98 met the sequential doxycycline/azithromycin definition with dual-oral overlap ≤24 hours (**Figure 1**). For the confirmatory monotherapy contrast, the non-pregnant analysis set comprised all 206 doxycycline recipients and 173 azithromycin recipients; sequential-pathway analyses were conducted with time-varying and 48-hour landmark methods.

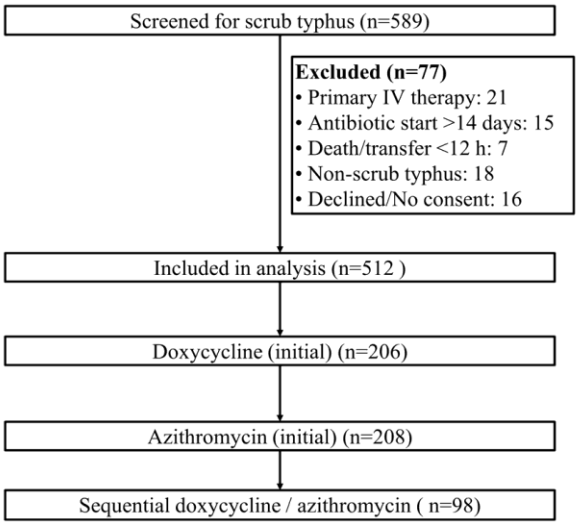

Figure 1. Study flow diagram for observational cohort. Screened n=589, excluded n=77, included n=512 (doxycycline 206; azithromycin 208; sequential 98). Reasons for exclusion (with counts) are prespecified.

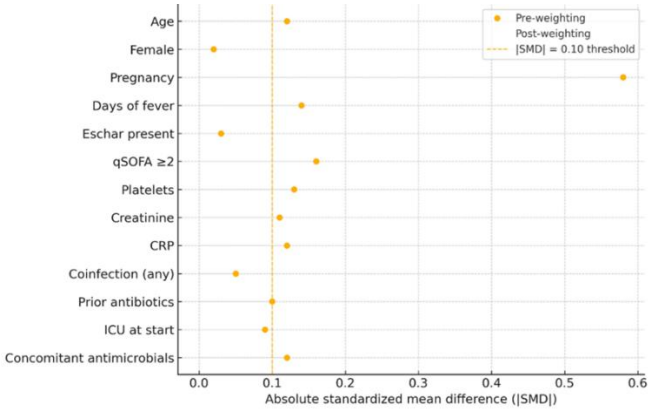

Figure 2. Covariate balance (Love plot). Absolute standardized mean differences (|SMD|) pre- vs post-weighting for three-group summaries; pregnancy remains >0.10 post due to structural non-overlap (no pregnant participants received doxycycline) and therefore cannot be balanced by weighting, while all other covariates approach balance.

Unweighted baseline characteristics were broadly similar for the two monotherapies, while the sequential pathway had modestly longer pre-treatment fever duration and higher acuity markers. Median days of fever before antibiotics were 4 (IQR 3–6) for both monotherapy groups and 5 (IQR 4–7) for the sequential group, and qSOFA ≥2 occurred in 10.2%, 10.6%, and 18.4% of doxycycline, azithromycin, and sequential patients, respectively (**Table 1**). Pregnancy clustered in the azithromycin group (16.8%) and was absent with doxycycline, creating structural non-overlap; the confirmatory doxycycline vs azithromycin analysis therefore excluded pregnancy and achieved post-weighting |SMD|<0.10 across modeled covariates with satisfactory overlap (**Figure 2**). Weighting diagnostics for the confirmatory contrast showed a post-weighting ESS of approximately 362 and a well-behaved weight distribution after truncation at the 1st and 99th percentiles, supporting stable estimation.

Crude 48-hour defervescence occurred in 82.0% (169/206) with initial doxycycline, 78.8% (164/208) with initial azithromycin, and 66.3% (65/98) in the sequential pathway (**Table 2**). The confirmatory IPTW analysis in the non-pregnant set showed no difference between initial doxycycline and initial azithromycin in the probability of 48-hour defervescence defined as oral-equivalent <38.0 °C sustained ≥24 hours without antipyretics (adjusted RR 1.03, 95% CI 0.95–1.12; p=0.34; adjusted RD +2.4%, 95% CI −3.8% to +8.7%; p=0.44), yielding no estimable number-needed-to-treat because the RD confidence interval crossed zero (**Table 2**). Patients who switched before 48 hours remained in their initial regimen for the primary ITT-like endpoint, whereas in the time-varying analysis, their person-time contributed to the initial regimen until azithromycin initiation and to the sequential pathway thereafter. A 48-hour landmark analysis restricted to patients alive and still at risk at 48 hours produced concordant inferences.

Table 1. Baseline characteristics by regimen.

Characteristic	Doxycycline (n=206)	Azithromycin (n=208)	Sequential (n=98)	SMD (D vs A)	Weighted p (3-group)
Age (years), median (IQR)	46 (33–60)	47 (34–61)	49 (36–63)	0.03	0.58
Female, n (%)	96 (46.6%)	98 (47.1%)	47 (48.0%)	0.01	0.97
Pregnant, n (%)	0 (0.0)	35 (16.8)	3 (3.1)	0.58	<0.001
Days of fever before antibiotics, median (IQR)	4 (3–6)	4 (3–6)	5 (4–7)	0.04	0.04
Eschar present, n (%)	132 (64.1%)	133 (63.9%)	59 (60.2%)	0.00	0.71
qSOFA ≥2, n (%)	21 (10.2%)	22 (10.6%)	18 (18.4%)	0.01	0.06
Platelets (×109/L), median (IQR)	142 (98–196)	144 (100–198)	135 (92–184)	0.03	0.29
Creatinine (mg/dL), median (IQR)	1.02 (0.84–1.28)	1.00 (0.83–1.26)	1.08 (0.89–1.34)	0.05	0.18
CRP (mg/L), median (IQR)	38 (20–68)	39 (21–70)	46 (26–78)	0.02	0.07
Coinfection, n (%)	19 (9.2%)	20 (9.6%)	13 (13.3%)	0.01	0.39
Prior outpatient antibiotics, n (%)	32 (15.5%)	29 (13.9%)	19 (19.4%)	0.04	0.31
ICU at start, n (%)	5 (2.4%)	6 (2.9%)	6 (6.1%)	0.03	0.11
Concomitant antimicrobials at start, n (%)	28 (13.6%)	31 (14.9%)	21 (21.4%)	0.04	0.10

Table 2. Primary endpoint (48-hour defervescence sustained ≥24 h without antipyretics).

Outcome / Contrast	Doxycycline	Azithromycin	Sequential	Model / Effect	Estimate (95% CI)	p-value
Crude 48-h defervescence — n/N (%)	169/206 (82.0%)	164/208 (78.8%)	65/98 (66.3%)	—	—	—
Three-group global (IPTW)	—	—	—	Weighted Wald	—	0.12
Primary IPTW: Doxy vs Azithro	—	—	—	Adjusted RR	1.03 (0.95–1.12)	0.34
	—	—	—	Adjusted RD	+2.4% (−3.8% to +8.7%)	0.44
	—	—	—	NNT	NE (CI crosses 0)	—
Time-to-defervescence, median (IQR), h	28 (18–44)	30 (19–48)	44 (30–60)	—	—	—
Time-to-defervescence (IPTW): D vs A	—	—	—	Adjusted HR	1.08 (0.96–1.21)	0.20
PH assumption (global Schoenfeld)	—	—	—	—	p=0.41	—

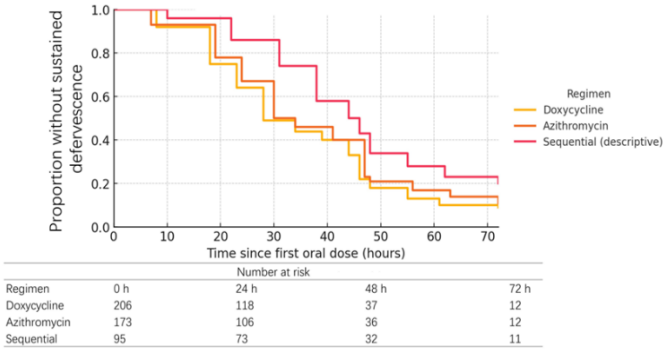

Figure 3. IPTW-weighted time to sustained defervescence (temperature <38.0 °C for ≥24 h without antipyretics) with numbers at risk. Medians: doxycycline 28 h (IQR 18–44), azithromycin 30 h (IQR 19–48), sequential 44 h (IQR 30–60). Proportional hazards not violated (global Schoenfeld p=0.41).

Suboptimal crude outcomes in the sequential group should not be interpreted as reduced regimen efficacy but rather as a marker of early non-response and regimen escalation.

IPTW-weighted Kaplan–Meier curves in the non-pregnant set showed closely overlapping trajectories for initial doxycycline and initial azithromycin, and slower resolution for the sequential pathway. Median times to sustained defervescence were 28 hours (IQR 18–44), 30 hours (IQR 19–48), and 44 hours (IQR 30–60), respectively (**Figure 3, Table 2**). The confirmatory IPTW-weighted Cox model comparing initial doxycycline with initial azithromycin yielded an adjusted hazard ratio of 1.08 (95% CI 0.96–1.21; p=0.20), and the proportional-hazards assumption was not violated on global Schoenfeld testing (p=0.41), supporting the binary endpoint.

After weighting and multiplicity control, secondary endpoints did not differ meaningfully between monotherapies: Day-5 clinical failure was 8.7% vs

Table 3. Secondary outcomes and safety (IPTW-adjusted Doxy vs Azithro).

Outcome	Doxycycline (n=206)	Azithromycin (n=208)	Sequential (n=98)	Doxy vs Azithro (IPTW)	p-value	FDR q
Day-5 clinical failure, n (%)	18 (8.7%)	22 (10.6%)	19 (19.4%)	aRR 0.83 (0.56–1.24)	0.36	0.44
Composite complications, n (%)	21 (10.2%)	23 (11.1%)	18 (18.4%)	aRR 0.94 (0.66–1.33)	0.73	0.73
Shock/vasopressors, n (%)	6 (2.9%)	7 (3.4%)	6 (6.1%)	—	—	—
ARDS/oxygen/vent, n (%)	7 (3.4%)	8 (3.8%)	7 (7.1%)	—	—	—
AKI (KDIGO), n (%)	10 (4.9%)	9 (4.3%)	7 (7.1%)	—	—	—
Hepatitis (ALT/AST >5× ULN), n (%)	7 (3.4%)	8 (3.8%)	6 (6.1%)	—	—	—
Length of stay, days, median (IQR)	5 (4–7)	5 (4–7)	6 (5–8)	aΔ(median) +0.1 (−0.3 to +0.4)	0.64	0.71
ICU admission, n (%)	6 (2.9%)	7 (3.4%)	7 (7.1%)	aRR 0.88 (0.48–1.63)	0.69	0.73
28-day mortality, n (%)	3 (1.5%)	2 (1.0%)	3 (3.1%)	aRR 1.39 (0.38–5.10)	0.62	0.71
Adverse events, n (%)	20 (9.7%)	24 (11.5%)	12 (12.2%)	aRR 0.88 (0.57–1.37)	0.58	0.70
Nausea, n (%)	12 (5.8%)	13 (6.3%)	6 (6.1%)	—	—	—
Transaminitis, n (%)	8 (3.9%)	9 (4.3%)	5 (5.1%)	—	—	—
QTc ≥500 ms, n (%)	0 (0.0)	2 (1.0%)	0 (0.0)	—	—	—
28-day relapse/readmission, n (%)	10 (4.9%)	11 (5.3%)	7 (7.1%)	aRR 0.93 (0.43–2.00)	0.86	0.86

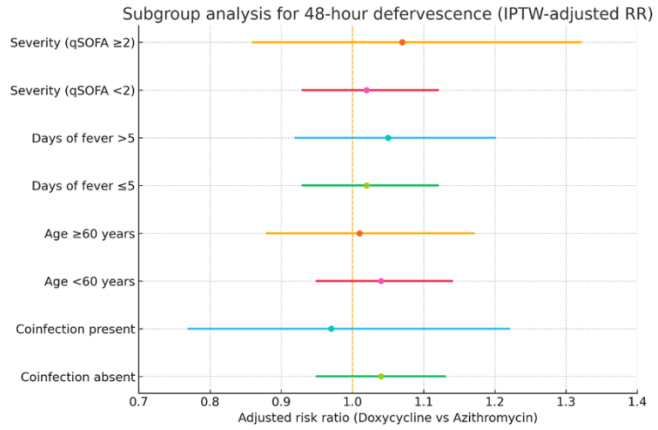

Figure 4. Subgroup analysis (Doxycycline vs Azithromycin). IPTW-adjusted risk ratios with 95% CIs by prespecified strata; pregnancy was omitted due to non-overlap (no pregnant participants received doxycycline).

10.6% (adjusted RR 0.83, 95% CI 0.56–1.24; p=0.36; FDR q=0.44); the composite complication rate was 10.2% vs 11.1% (adjusted RR 0.94, 95% CI 0.66–1.33; p=0.73; FDR q=0.73); median length of stay was 5 days (IQR 4–7) in both groups with an adjusted 50th-percentile difference of +0.1 days (95% CI −0.3 to +0.4; p=0.64; FDR q=0.71), ICU admission was uncommon (2.9% vs 3.4%; adjusted RR 0.88, 95% CI 0.48–1.63; p=0.69; FDR q=0.73), 28-day mortality was low overall at 1.6% with similar rates between monotherapies (adjusted RR 1.39, 95% CI 0.38–5.10; p=0.62; FDR q=0.71), and adverse events were infrequent and comparable, with QTc ≥500 ms recorded in 1.0% of azithromycin recipients and none with doxycycline, and 28-day relapse/readmission 4.9% vs 5.3% (adjusted RR 0.93, 95% CI 0.43–2.00; p=0.86; FDR q=0.86) (**Table 3**).

Prespecified subgroup analyses of the confirmatory contrast revealed no evidence of effect modification by baseline severity, days of fever before therapy, age, or laboratory-confirmed coinfection, with adjusted RRs near unity and interaction p-values >0.05 across strata (**Figure 4**).

Most patients had laboratory confirmation by PCR and/or serology, while a minority were classified as probable cases based on a compatible syndrome with an eschar in the endemic setting when confirmatory testing was unavailable. In sensitivity analyses restricted to strict laboratory-confirmed scrub typhus (PCR positive and/or a four-fold IFA rise), the confirmatory doxycycline vs azithromycin effect estimates for 48-hour defervescence and time-to-defervescence remained close to the null and did not change the study conclusions.

Discussion. In this real-world cohort of scrub typhus patients, the primary confirmatory comparison between initial oral doxycycline and oral azithromycin showed no clinically meaningful difference in early fever control. The sequential doxycycline/azithromycin pathway had poorer crude outcomes and slower fever resolution, and exploratory weighted contrasts favored monotherapy over sequential therapy. Lower crude success in the sequential pathway primarily reflects design-driven

selection of early non-responders; therefore, we avoided pairwise causal contrasts in the main text and provided only associational time-varying/landmark analyses in the Supplement.

We found no significant difference between initial oral doxycycline and oral azithromycin in 48-hour defervescence or time-to-defervescence, while crude outcomes were poorer in the sequential pathway, consistent with clinical escalation. These results align with randomized data in mild scrub typhus showing similar early responses with a single 500 mg azithromycin dose versus a 7-day doxycycline regimen,[12] and with a network meta-analysis and a recent pairwise meta-analysis indicating no overall efficacy or safety advantage of one oral agent over the other.[13,14] By contrast, a multicenter RCT in severe scrub typhus found intravenous doxycycline plus azithromycin superior to either monotherapy, underscoring that disease severity and route of administration modify comparative effects.[15] Heterogeneity across studies likely reflects differences in diagnostic approaches and site-level case mix and may also be influenced by the broad strain diversity of *Orientia tsutsugamushi*.[16,17]

Between-regimen differences often attenuate after controlling confounding factors because outcomes in scrub typhus are driven more by baseline severity and the timeliness of appropriate therapy than by the specific oral agent. Our cohort's sequential group had higher acuity markers, and prior prospective work similarly reports that severity, rather than antibiotic choice, predicts outcome.[18] Severe manifestations typically evolve after the first week of untreated illness, supporting the importance of early, effective coverage and explaining why time-to-antibiotics may overshadow regimen choice in many settings.[19] Apparent discrepancies across studies can also stem from misclassification and dosing schedules that affect adherence and exposure.[12,16] Finally, contemporary reviews argue that the widely cited "doxycycline resistance" in scrub typhus is a misconception; variability in response is more plausibly explained by pathogen, host, and pharmacologic factors, reinforcing our adjusted findings of clinical comparability between oral agents.[20] Our target-trial emulation with IPTW was chosen to mitigate immortal-time and indication biases endemic to observational comparisons of dynamic treatment strategies, improving coherence with randomized evidence.[12,16,18-21]

For empirical management of scrub typhus, current guidance and the weight of the evidence support either oral doxycycline or oral azithromycin for uncomplicated disease, with selection guided by patient factors and availability. Our adjusted estimates and the meta-analyses suggest practical equivalence for early defervescence.[13,14,19] In pregnancy or intolerance to doxycycline, azithromycin is preferred. When early non-response or intolerance occurs, a sequential switch is reasonable in practice, though persistent or severe scrub typhus with organ dysfunction should prompt intravenous therapy rather than prolonged cycling of oral regimens.[15,19] When prescribing azithromycin, clinicians should review QT-prolongation risks and drug interactions, and consider baseline ECGs in higher-risk patients, as recommended by regulators and the pharmacovigilance literature.[22,23] Overall, our findings support agent selection based on clinical context and emphasize early, appropriate therapy, careful monitoring, and timely escalation as severity evolves.[13-15,19,22,23]

Limitations of this study include the possibility of residual confounding despite extensive adjustment, structural non-overlap for pregnancy, which required restricting the confirmatory comparison to the non-pregnant population and limits inference for that subgroup, lingering immortal-time concerns for the sequential pathway despite mitigation, and structural selection bias against the sequential pathway when using a 48-hour endpoint from initial dosing, which we addressed by withholding pairwise causal contrasts vs sequential. Diagnostic heterogeneity and temperature/antipyretic recording imprecision could bias time-to-defervescence estimates. The single-center Chinese hospital setting may limit generalizability across settings, as *Orientia tsutsugamushi* is genetically and antigenically diverse, and circulating strains vary geographically, so the strain distributions in our region may differ from those in South/Southeast Asia. In addition, hospital admission thresholds and referral patterns may differ from civilian settings, affecting case mix and baseline severity. However, scrub typhus represents a distinct disease entity with a proper causative genus. Although some rickettsioses, spotted fever and typhus groups, found in Mediterranean countries,[24,25] are clinically overlapping rickettsial infections with similar antibiotic susceptibility, they should not be considered forms of scrub typhus.

The modest sample size in the sequential arm and the low event rates also constrain power for rare outcomes. Future work should include multi-center validation in diverse epidemiologic contexts, pragmatic randomized or adaptive trials that directly compare commonly used oral regimens and trigger-based escalation versus early intravenous combination therapy, integration of pathogen load, strain typing, and host biomarkers to refine severity phenotyping and heterogeneity-of-treatment-effect analyses, and economic evaluations of diagnostic-therapeutic strategies to inform context-appropriate, value-based care.

In this real-world single-center cohort of scrub typhus, initial oral doxycycline and azithromycin showed comparable effectiveness and safety for early fever control, with no significant difference in 48-hour defervescence or time-to-defervescence after rigorous

adjustment. Observed inferiority of crude outcomes in the sequential doxycycline/azithromycin pathway most likely reflects clinical escalation in sicker or non-responding patients rather than intrinsic regimen differences and should be interpreted cautiously. In practice, either oral agent is reasonable for uncomplicated scrub typhus, with azithromycin preferred in pregnancy or in doxycycline intolerance, and early reassessment/escalation to intravenous therapy is warranted when severity evolves. These findings support individualized, context-aware agent selection while motivating multi-center validation and pragmatic trials to refine escalation strategies and confirm generalizability.

Ethics approval and consent to participate. This study was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by the Ethics Committee of the 970th Hospital of the People's Liberation Army, which waived the requirement for informed consent because the analysis was retrospective and involved de-identified, routinely collected data and posed no more than minimal risk to participants. All data were anonymized prior to analysis.

Data availability statement. Data sets generated during the current study are available from the corresponding author on reasonable request.

Author Contribution Statement. The authors confirm contribution to the paper as follows: study conception and design: H.L.; data collection: W.W., Y.D.; analysis and interpretation of results: W.W., Y.D.; draft manuscript preparation: W.W., Y.D., H.L. All authors reviewed the results and approved the final version of the manuscript.

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