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Time From Injury to First Antibiotic Administration and Deep Infection Risk in Open Fractures: A Systematic Review and Meta-Analysis

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Abstract

Deep infection is a serious complication of open fractures, and prompt antibiotic prophylaxis is widely emphasized. However, evidence regarding the association between the timing of initial antibiotic administration and infection risk remains inconsistent, and commonly cited time thresholds are based largely on individual studies. This review makes two contributions. First, it separates studies by the clock used to measure delay, since time from injury and time from arrival begin at different zero points and are different exposures that should not be pooled. Second, it reframes the field's conflicting results as a measurement quality problem, because the disagreement tracks how infection was defined. PubMed, Embase, and Scopus were searched from inception to August 2026 (PRISMA 2020; PROSPERO CRD420261473036) for observational studies reporting time from injury or hospital arrival to the first prophylactic antibiotic and a deep or fracture-related infection outcome. Injury-anchored and arrival-anchored studies formed separate, prespecified strata that were never pooled in the primary analysis; ORs used random-effects models, a post hoc subgroup compared studies by infection-definition validity, and bias and certainty were assessed using Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I), Methodological Index for Non-Randomized Studies (MINORS), and Grading of Recommendations Assessment, Development and Evaluation (GRADE). Twenty-four studies were included, and 16 were poolable (5,283 patients, 508 infections). Delay was not significantly associated with infection in either stratum (injury-anchored OR 1.62, 95% CI 0.87-3.00, k = 11; arrival-anchored OR 1.34, 95% CI 0.86-2.07, k = 5), and no time threshold was estimable. Forcing both anchors into one pool produced a borderline OR 1.53 (95% CI 1.00-2.32), but this is a pooling artifact: a borderline value assembled by adding precision across two individually nonsignificant strata that measure different exposures (anchor moderator p = 0.811). The disagreement instead tracked infection definition: the four studies using a validated definition reported OR 4.34 (95% CI 2.45-7.69, k = 4), roughly four-fold higher odds with delay, while the seven using an operative proxy reported OR 0.86 (95% CI 0.63-1.17, k = 7), with a significant subgroup difference (p = 0.0015). This definition-based signal is post hoc and confounded, since it cannot be separated from whether a study used an adjusted analysis, and overall certainty was very low; it is a hypothesis for prospective testing, not a reliable estimate of the effect of delay. Testing it will require prospective studies that measure timing from injury, define infection by validated criteria, and report adjusted estimates, ideally pooled as individual participant data. Two points follow for practice. A nonsignificant pooled result under very low-certainty evidence is absence of evidence, not license to relax timing. Moreover, the numeric thresholds built into current audit metrics and protocols are not evidence-based, even though giving antibiotics as early as feasible remains sound on biological and guideline grounds.

Categories: Therapeutics, Trauma, Orthopedics
Keywords: antibiotic prophylaxis, fracture-related infection, open fractures, surgical wound infection, time to treatment

Introduction And Background

Deep infection is the most consequential local complication of open fracture care, complicating a substantial minority of injuries and driving reoperation, prolonged antibiotic therapy, nonunion, and, in the most severe cases, amputation [1,2]. Systemic antibiotic prophylaxis is one of the few interventions with a consistent evidence base for reducing that risk [3-6], and it is widely regarded as time-critical. National standards and educational frameworks urge administration "as soon as possible" after injury [7,8]. Several influential cohorts have gone further and proposed specific thresholds, most prominently a 66-minute injury-to-antibiotic window derived from a single institutional series [9,10]. Yet two questions remain unresolved: the interval within which antibiotics must be given, and whether any threshold genuinely reduces deep infection. Reported associations between timing and infection openly conflict [11,12].

Part of that conflict is real disagreement between studies, but part is an artifact of how the exposure is measured. The literature splits into studies that measure time from the moment of injury and studies that measure time from hospital arrival (door-to-antibiotic or admission-to-antibiotic). Many report only a "time

to antibiotics" without naming the zero time, so the anchor often has to be recovered from the full text rather than the abstract, and in one of the 24 studies included here it was reported only as a proxy or left unstated. The two anchors begin at different zero times and therefore estimate different quantities. Prior syntheses have not respected this distinction. The most recent systematic review [11] evaluated time to first antibiotic without separating injury-timed from arrival-timed studies, and earlier reviews did not resolve the timing question or isolate the two anchors [12,13]. Whether such studies are combined statistically or summarized narratively, mixing the anchors leaves no coherent clinical referent: a "three-hour" threshold means something different measured from a roadside than from a triage desk.

To correct both problems, this study examined whether the time from injury, or from hospital arrival, to first systemic antibiotic administration is associated with deep infection or fracture-related infection (FRI) following open fracture, analyzing injury-anchored and arrival-anchored studies as separate, prespecified strata that are never pooled in a primary analysis. The study further examined whether a dose-response relationship and a defensible time threshold could be identified. Open fracture cohorts define infection very heterogeneously, from validated surveillance criteria to operative proxies [14,15]. A post hoc analysis therefore examined whether the way infection is defined explains the field's contradictory results.

Review

Methods

Study Registration and Ethical Considerations

This study was conducted in accordance with the PRISMA 2020 statement [16] and registered with PROSPERO (CRD420261473036). This review analyzed previously published, aggregate data and did not involve human participants or animals; institutional review board or ethics committee approval was therefore not required.

Eligibility Criteria

Eligibility followed a prespecified PICOS framework (Table *1*). Included studies enrolled patients of any age with an open (compound) fracture of a long bone or major limb segment (tibia, femur, humerus, radius, ulna, fibula, or major foot/ankle), of any Gustilo-Anderson type. To be eligible, a study had to report time from injury, or from a defensible injury proxy (emergency medical services dispatch, scene arrival, prehospital administration, or time of wounding), or time from hospital arrival to the first systemic prophylactic antibiotic dose. It also had to analyze that timing against a deep infection, deep surgical site infection, or FRI outcome. Eligible designs were randomized controlled trials, comparative cohorts, registry analyses, case-control studies, and single-arm cohorts of at least 10 patients with an internal timing-infection analysis.

Element	Specification
Population	Open fracture of a long bone or major limb segment; any age; any Gustilo-Anderson type. Excludes isolated hand/phalangeal, axial-skeleton, and non-fracture injuries.
Exposure	Time from injury (or a defensible injury proxy) or time from hospital arrival to the first systemic prophylactic antibiotic dose, analyzed against infection.
Comparator	Longer vs. shorter interval, or continuous dose response.
Outcome	Deep infection, deep surgical site infection, or FRI linkable to the timing exposure.
Study design	Randomized trial, comparative cohort, registry, case-control, or single-arm cohort (≥10 patients) with an internal timing-infection analysis.
Analysis	Injury-anchored and arrival-anchored studies analyzed as separate strata, never pooled in a primary analysis.

TABLE 1: Eligibility criteria (PICOS).

FRI, fracture-related infection; PICOS, population-intervention-comparator-outcome-study design

Excluded were studies of isolated hand, finger, toe, or distal phalanx fractures (whose baseline infection risk and treatment pathway differ fundamentally); studies reporting only time to surgical debridement, or antibiotic agent, dose, route, duration, or local delivery, with no systemic-timing variable; studies with no infection outcome or with infection not linkable to timing (including process-only quality-improvement reports); ineligible designs (reviews, editorials, conference abstracts, surveys, case reports); and studies

whose full text was unobtainable. Arrival-anchored studies were retained, not excluded. They were assigned at analysis to a separate stratum and never pooled with injury-anchored studies in the primary synthesis. This clock-anchor rule was locked in the protocol before screening.

Information Sources and Search

PubMed, Embase, and Scopus were searched from inception to the search date, without date, language, or study-design restriction, using a sensitivity-first strategy combining population and antibiotic terms without outcome terms (the full search strings are provided in Appendix A). Conference abstracts were excluded at the search stage in Embase and Scopus. Reference lists of included studies and prior reviews were screened for additional records.

Study Selection

Records were managed in Covidence. After duplicate removal, titles and abstracts were screened against the criteria, and the full texts of potentially eligible records were assessed. Because the exposure and clock anchor are frequently not determinable from an abstract, a deliberately sensitive title and abstract stage screening was used, and all uncertain records were carried to full-text screening. Several eligible studies analyze antibiotic timing only within a results table without mentioning it in the abstract, so every full text was assessed against the exposure criterion with the results tables in hand. Where two reports described overlapping patients from the same author group, the less complete report was excluded as a duplicate.

Data Extraction

For each included study, the extracted variables were design, setting, sample size, patient and injury characteristics, the clock anchor and its verbatim source, the timing exposure and any threshold, the infection outcome and its definition, follow-up, and the effect estimate (a 2 × 2 table where derivable, and any adjusted estimate). Every value was source-quoted. Exposure was consistently coded so that an OR above 1 indicates greater infection with delay; studies reporting a paradoxical direction were entered as observed and not normalized.

Risk of Bias and Methodological Quality

Risk of bias was assessed across the seven domains of the 2016 Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [17], applied to every included study because all were non-randomized designs (retrospective and prospective cohorts, registry or administrative-database analyses, and one case-control study), taking deep infection in relation to antibiotic timing as the outcome and pre-specifying the confounders Gustilo grade, wound contamination, time to debridement, diabetes, smoking, and fracture site. Randomized trials were eligible, but, as the protocol anticipated, no trial of antibiotic timing was identified; any such trial would have been appraised with a dedicated randomized-trial tool (Cochrane RoB 2). Methodological quality was assessed with the Methodological Index for Non-Randomized Studies (MINORS) [18], scored 0-2 across 12 items (denominator 24 for comparative studies).

Certainty of Evidence

Certainty was rated with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [19] at the outcome level, separately for the injury- and arrival-anchored strata. Both bodies of evidence started at low certainty (observational), with the five downgrade and three upgrade domains applied to the pooled evidence.

Synthesis Methods

ORs were pooled on the log scale with random-effects models estimated by restricted maximum likelihood, with normal-based (Wald) confidence intervals as the primary inference and Knapp-Hartung, DerSimonian-Laird, and fixed-effect estimators reported alongside. A 95% prediction interval was computed from the fitted model. No continuity correction was required (no study had a zero cell). Heterogeneity was summarized with I^2, τ^2, and the Q statistic. Injury-anchored and arrival-anchored studies were analyzed separately and never pooled in a primary analysis; a single cross-anchor pool is reported, explicitly labeled exploratory, solely to quantify the effect of ignoring the anchor. Dose response was modeled by two-stage generalized least squares (Greenland-Longnecker) among studies reporting three or more exposure categories. Prespecified sensitivity analyses comprised leave-one-out, exclusion of post hoc receiver operating characteristic (ROC)-derived thresholds, restriction to studies with at least 90-day ascertainment, exclusion of critical-risk studies, and fixed-effect re-estimation. Small-study effects were examined by Egger's regression where a stratum reached 10 or more studies. A post hoc subgroup analysis, not prespecified, stratified injury-anchored studies by whether infection was defined by a validated external standard, either the CDC/NHSN surgical site infection criteria, which require a deep or organ/space infection at the operative site within a defined postoperative window, or the 2018 FRI consensus definition, which

requires a confirmatory sign such as a sinus tract communicating with bone or implant, purulent drainage, or phenotypically matching pathogens on two or more deep tissue cultures [14,15], or by an operative proxy. All analyses used R 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria) with the metafor package (4.6.0) [20]; estimates were cross-checked in an independent implementation.

Results

Study Selection

Database searching identified 3,502 records (PubMed 843, Embase 1,210, Scopus 1,449). After duplicate removal, records were screened by title and abstract, and 1,520 were excluded as irrelevant. One hundred fifty-five full texts were assessed, of which 131 were excluded, and 24 met all criteria (Figure *1*). Among the full-text exclusions, the most common reason was the absence of an analyzed antibiotic-timing exposure (chiefly debridement-timing or agent/dose/duration studies), followed by ineligible design, absence of a linkable infection outcome, and unobtainable or conference-only reports. Of the 24 included studies, 16 contributed data suitable for pooling (5,283 patients, 508 infections). The remaining eight were retained for narrative synthesis but were not poolable because they reported infection only as a group mean, a composite that could not be isolated, or a narrative null without extractable numbers.

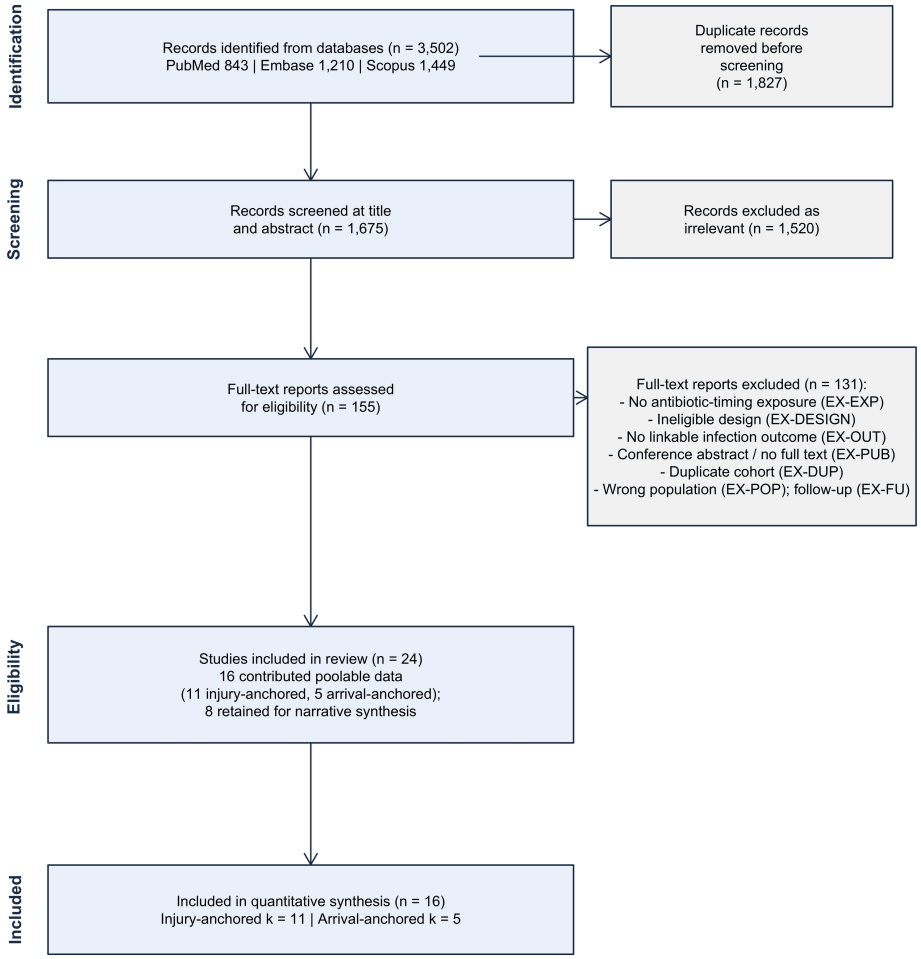

FIGURE 1: PRISMA 2020 flow diagram of study identification, screening, and inclusion.

Study Characteristics

The 24 studies [9,21-43] spanned 1988 to 2026 and five continents and were, without exception, observational: retrospective and prospective cohorts, registry analyses, and one matched case-control study; no randomized trial of antibiotic timing exists. Sixteen were injury-anchored, seven arrival-anchored, and one measured timing from a proxy or an unstated point (Table *2*). Infection outcomes ranged from validated CDC/NHSN surgical site infection criteria and the 2018 FRI consensus definition to operative proxies such as “return to theater for infection.” Follow-up ranged from an index admission of a few days to a minimum of 12 months. Sixteen studies contributed a dichotomous 2 × 2 table (11 injury-anchored, five

arrival-anchored); Weber et al. (2014) [36] contributed only a continuous adjusted estimate and is discussed narratively.

Study	Study design	Study population	Clock anchor	N	Outcome definition	Follow-up	Key findings
Lack et al. (2015) [9]	Retrospective cohort	Type III open tibia; USA	Injury	137	Validated	90 days	Delay associated with higher deep infection (adjusted OR 3.78, 1.26-14.11)
Al-Arabi et al. (2007) [21]	Prospective cohort	Open long bones; UK	Injury	133	Proxy/composite	NR	No significant association; non-monotonic across six timing categories
Zuelzer et al. (2021) [22]	Retrospective cohort	Open tibial shaft (I-IIIA); USA	Injury	127	Validated	42 days	Delay beyond 150 minutes associated with higher deep SSI (adjusted OR 5.6, 1.4-22.2)
Dellinger et al. (1988) [23]	Prospective multicenter cohort	Open extremity (arm and leg) fractures; USA	Injury	230	Proxy/composite	180 days	No association (crude OR about 1.09; multivariable p = 0.90)
Haile et al. (2025) [24]	Matched case-control	Open long bones (femur, tibia, humerus); Ethiopia	Injury	252	Validated	180 days	Delay beyond 12 hours associated with higher FRI (adjusted OR 4.92, 1.63-16.9); three to 12 hours not significant
Leonidou et al. (2014) [25]	Prospective cohort	Open long bones; UK	Injury	161	Validated	NR	No significant association (OR 1.65, 0.31-8.94; seven events)
Padgett et al. (2023) [26]	Retrospective cohort	Pediatric type I open tibia; USA	Injury	26	Proxy/composite	217 days	No significant association (p = 0.215; three infections)
Wilson et al. (2024) [27]	Retrospective analysis of prospective registry	Severe (IIIB/IIIC) open tibia; 23 UK major trauma centers	Injury	1111	Proxy/composite	30 days	No significant association; earlier timing linked to more return to theater (RR 2.04, 0.83-5.04)
Zumsteg et al. (2014) [28]	Retrospective cohort	Open radius and/or ulna; USA	Injury	200	Proxy/composite	180 days	No significant association; infected cases had shorter mean time (OR 2.40, 0.30-19.51)
Sulala et al. (2026) [29]	Retrospective cohort	Open femur (SIGN nailing); Ethiopia	Injury	115	Proxy/composite	14 days	Delay beyond six hours associated with higher FRI (adjusted OR 3.98, 1.04-15.32)
Whiting et al. (2019) [30]	Prospective registry cohort	Open tibial shaft (IM nailing); low- and middle-income countries	Injury	1057	Proxy/composite	140 days	No association between time to antibiotics and infection
Jacobo et al. (2025) [31]	Retrospective registry cohort (ACS-TQIP)	Pediatric open lower-extremity fractures; USA	Arrival	150	Proxy/composite	Three days	No association (adjusted OR 0.62, 0.04-10.24; two events)
Mener et al. (2020) [32]	Retrospective cohort	Open long bones undergoing debridement; USA	Arrival	640	Proxy/composite	NR	No association; infection 8.9% at 60 minutes or less vs. 8.6% beyond 60 minutes (p = 0.90)
Morgan et al. (2026) [33]	Retrospective cohort	Blunt open fractures, multiple long bones; USA	Arrival	477	Proxy/composite	NR	No association (OR 0.88, 0.52-1.51)

Roddy et al. (2020) [34]	Retrospective cohort	Open fractures, upper and lower limb; USA	Arrival	230	Validated	90 days	Delay beyond two hours associated with higher SSI (adjusted HR 2.4, 1.1-5.7)
Kock et al. (2025) [35]	Retrospective cohort	Open tibial shaft; South Africa	Arrival	237	Validated	90 days	No association (OR 1.2, 0.5-2.9)
Weber et al. (2014)† [36]	Prospective cohort	Open long bones; three Canadian centers	Injury	See text	Proxy/composite	188 days (median)	No association (adjusted OR 1.0 per hour, 0.95-1.05)
Hendrickson et al. (2020) [37]	Retrospective cohort	Severe (IIIB) open tibia; UK	Injury	159	Validated	≥12 months	No association (per-hour coefficient p = 0.431; one hour p = 0.099, three hours p = 0.848)
Fram et al. (2025) [38]	Retrospective series	Low-velocity gunshot femur fractures; USA	Injury	104	Proxy/composite	180 days	No infection-specific timing analysis reported
Gubara et al. (2026) [39]	Retrospective pre/post protocol cohort	Gunshot-related open fractures; USA	Arrival	289	Proxy/composite	NR	No numeric timing estimate; reported as no association narratively
Young et al. (2019) [40]	National prospective registry cohort	Severe open lower-limb (tibia) fractures; UK major trauma centers	Arrival	646	Proxy/composite	30 days	No significant association (p = 0.74); no effect estimate reported
Chan et al. (2021)† [41]	Retrospective cohort	Pediatric open tibia; UK	Injury	See text	Proxy/composite	15 months (mean)	No significant difference in timing between infected and uninfected (4.2 vs. 3.3 hours)
Thomas et al. (2013)† [42]	Prospective comparative cohort	Open extremity fractures (air-medical transport); USA	Injury	See text	Proxy/composite	Six months	No significant difference in infection or nonunion between prehospital and hospital antibiotics
Enninghorst et al. (2011)† [43]	Prospective cohort	Blunt open tibial shaft; Australia	Unclear	See text	Proxy/composite	12 months	No association; all treated promptly (1.2 hours), no difference by infection status

TABLE 2: Characteristics of the 24 included studies.

Sixteen studies (11 injury-anchored, five arrival-anchored) reported infection counts for an early vs. delayed timing contrast and contributed an OR to the pooled analysis. Outcome definition classifies the infection outcome as Validated (an external validated standard, such as CDC/NHSN surgical site infection criteria [15] or the 2018 FRI consensus definition [14]) or Proxy/composite (an operative proxy, such as return to theater for infection, or an unvalidated or composite clinical definition). The dagger symbol (†) indicates a study that reported antibiotic timing only as a continuous or non-dichotomous measure, did not provide an early vs. delayed infection comparison, and was synthesized narratively, with its sample size reported in the text.

ACS-TQIP, American College of Surgeons Trauma Quality Improvement Program; FRI, fracture-related infection; HR, hazard ratio; IM, intramedullary; NR, not reported; RR, risk ratio; SSI, surgical site infection

Timing and Deep Infection: Injury-Anchored Stratum

Delayed antibiotic administration was not significantly associated with deep infection in the injury-anchored stratum (OR 1.62, 95% CI 0.87-3.00; k = 11; I^2 = 72.4%; τ^2 = 0.682; Figure *2*). The Knapp-Hartung and DerSimonian-Laird estimates were concordant (1.62, 0.81-3.24; and 1.61, 0.88-2.96). The 95% prediction interval ran from 0.29 to 9.15. A future injury-anchored study could plausibly find a substantial protective or a large harmful association, and its direction cannot be predicted from these data. Effect directions genuinely conflicted: six studies indicated harm from delay, and the remainder were null or paradoxical (earlier antibiotics associated with more infection). This conflict is the source of the high heterogeneity rather than random scatter.

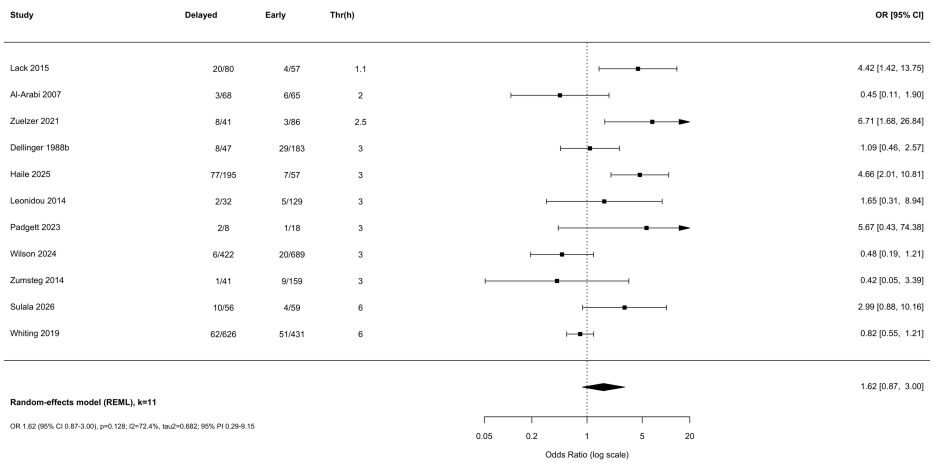

FIGURE 2: Forest plot of the injury-anchored stratum (k = 11).

OR >1 favors early administration (delayed vs. early antibiotics).

[9,21-30]

Timing and Deep Infection: Arrival-Anchored Stratum

The arrival-anchored stratum was likewise nonsignificant (OR 1.34, 95% CI 0.86-2.07; k = 5; I^2 = 36.3%; Figure *3*), with a 95% prediction interval of 0.65-2.75. This stratum's apparent signal rested entirely on a single study [34] whose threshold had been ROC-derived on its own outcome data; removing it returned a null, perfectly homogeneous result (OR 1.09, 95% CI 0.77-1.53; I^2 = 0%).

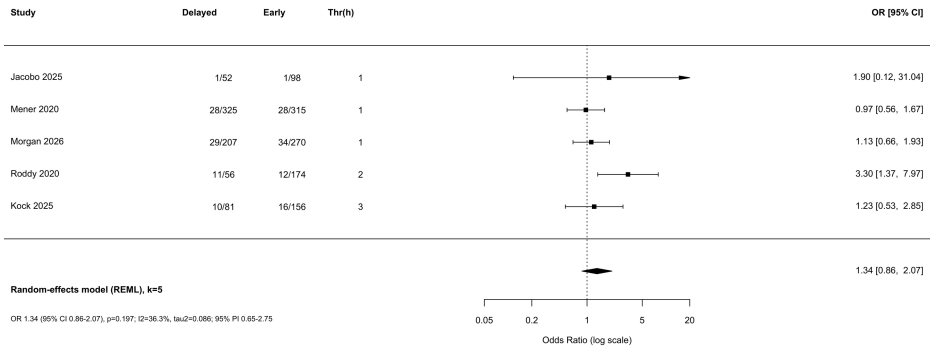

FIGURE 3: Forest plot of the arrival-anchored stratum (k = 5).

OR> 1 favors early administration (delayed vs. early antibiotics).

[31-35]

Cross-Anchor Pooling (Exploratory)

Pooling all 16 studies irrespective of anchor produced OR 1.53 (95% CI 1.00-2.32; p = 0.049). This nominally significant association appeared only when the two individually nonsignificant strata were combined, and a pooled estimate can cross the significance threshold even when neither stratum does. The more fundamental objection, however, is clinical and methodological rather than statistical: injury-anchored and arrival-anchored intervals are measured from different zero times and are therefore different exposures, so an estimate pooled across them lacks a coherent clinical referent regardless of its statistical significance. The formal test for a difference between anchors was itself nonsignificant (p = 0.811), so the data do not empirically demonstrate that the anchors differ in magnitude. The justification for separating them is conceptual. This exploratory pool is reported only to quantify what cross-anchor combination yields, not as an endorsed estimate. Its interpretation is taken up in the Discussion.

Dose Response

A dose-response curve and threshold estimate could not be estimated. Only three studies reported three or more exposure categories, and they disagreed on the shape of the relationship rather than merely its magnitude. One was monotonic over a narrow early range, one was a step function, and one was non-monotonic in the opposite direction, with three zero-event categories that rendered it non-estimable without an arbitrary continuity correction (Figure *4*). The one study with a signal at longer delays reported it only as an open-ended category (a step above 12 hours, with no upper bound), so the interval containing any threshold could not be localized. The dose-response objective is therefore reported as not estimable.

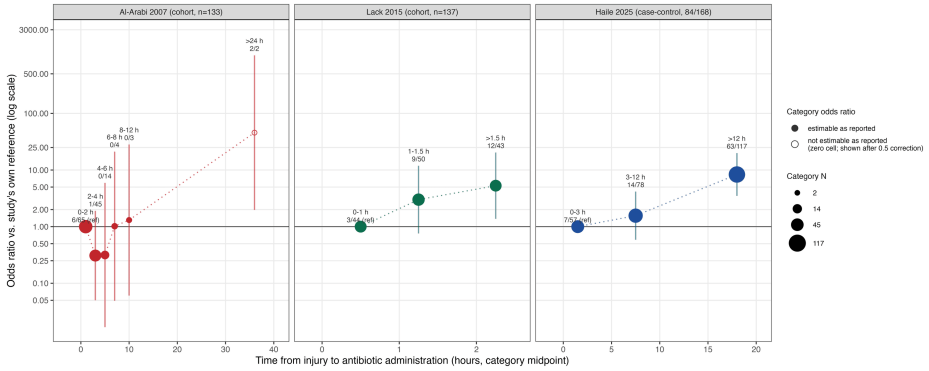

FIGURE 4: Infection rate by antibiotic-timing category in the three included studies that reported three or more timing categories.

The three studies are Lack et al. (2015) [9], Al-Arabi et al. (2007) [21], and Haile et al. (2025) [24]. Each point is the category-specific OR (log scale) vs. that study's own earliest (reference) category, plotted at the category midpoint; note that the x-axis scale differs between studies. The fraction beside each point is the number of infections divided by the number of patients in that timing category (for example, Lack et al. recorded three infections among 44 patients treated within one hour and nine among 50 treated at one to 1.5 hours, and Al-Arabi et al. recorded zero among four patients treated at six to eight hours). Point size is proportional to category size, and open circles mark categories that are not estimable as reported because of a zero cell (shown after a 0.5 continuity correction). Al-Arabi et al. is non-monotonic, Lack et al. shows a monotonic gradient over a narrow 0.5- to 2.25-hour range, and Haile et al. shows a step above 12 hours; no bounded category between 12 and 24 hours is reported, so no threshold is estimable.

Outcome-Definition Validity (Post Hoc Subgroup)

The between-study conflict was not random. In a post hoc subgroup analysis, injury-anchored studies that defined infection by a validated external standard reported OR 4.34 (95% CI 2.45-7.69; k = 4; I^2 = 0.0%). Those using an operative proxy or clinical impression reported an OR of 0.86 (95% CI 0.63-1.17; k = 7; I^2 = 0.0%; Figure *5*). The subgroup difference was significant and accounted for essentially all between-study heterogeneity (p = 0.0015; R^2 = 100%). Four studies from three countries, with three different thresholds, agreed completely once outcome validity was accounted for. Both subgroups were internally homogeneous (I^2 = 0.0%): the validated subgroup around the four-fold estimate, the proxy subgroup around the null.

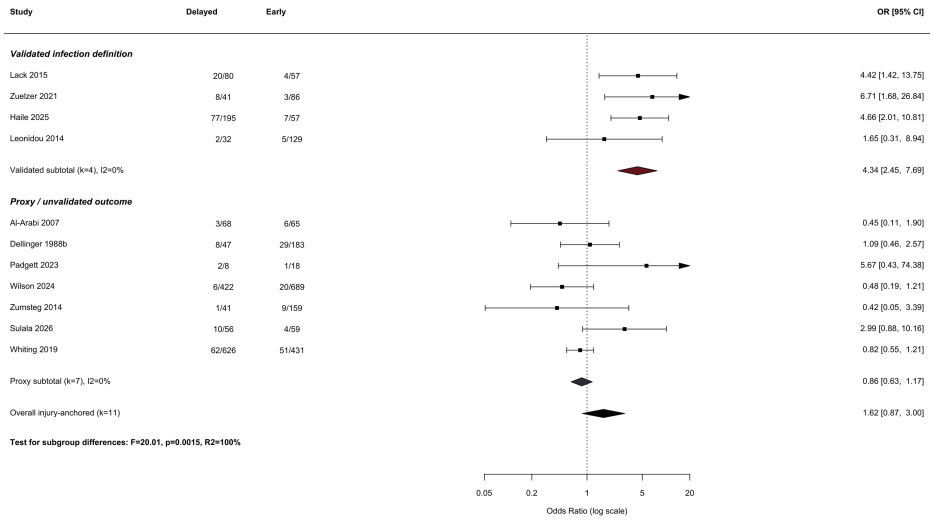

FIGURE 5: Post hoc subgroup: injury-anchored studies stratified by outcome-definition validity.

OR >1 favors early administration (delayed vs. early antibiotics).

[9,21-30]

This finding must be interpreted cautiously for two reasons stated here and not repeated. First, an alternative classification fitted the heterogeneity equally well: whether a study reported any multivariable-adjusted estimate. It could not be separated from outcome validity, as the two classifications agreed on nine of 11 injury-anchored studies. The pattern is therefore equally consistent with a real effect visible only to well-conducted studies and with selective analysis and outcome reporting. Second, the most methodologically rigorous included study, Weber et al. (2014) [36] (MINORS 21/24, an adjudicated deep-infection outcome, a fully adjusted analysis), found no association (adjusted OR 1.0 per hour, 95% CI 0.95-1.05). A single well-conducted study with a validated outcome that is null is a genuine counterweight to the subgroup signal.

Sensitivity Analyses and Small-Study Effects

No sensitivity analysis rendered either stratum robust (Table *3*). In the injury-anchored stratum, excluding the two post hoc ROC-derived thresholds moved the estimate to OR 1.23 (0.66-2.30), and even the fixed-effect estimate was nonsignificant (1.23, 0.94-1.62). Restriction to at least 90-day ascertainment raised the estimate in only six studies (1.79, 0.80-4.03). A funnel plot was not presented. With only 11 injury-anchored studies and substantial heterogeneity (I^2 = 72.4%), a funnel plot is uninformative and prone to misinterpretation. The arrival-anchored stratum (k = 5) fell below the minimum of 10 studies at which such displays carry any information. As an exploratory check, Egger's regression in the injury-anchored stratum was nonsignificant (p = 0.231). This provides no strong evidence of small-study effects, but it is underpowered at this number of studies and should not be read as excluding reporting bias.

Analysis	k	OR	95% CI	I² (%)
Injury reference (REML)	11	1.62	0.87-3.00	72.4
Injury: exclude ROC thresholds (Lack et al. (2015) [9]; Zuelzer et al. (2021) [22])	9	1.23	0.66-2.29	67.5
Injury: ≥90-day ascertainment	6	1.79	0.80-4.03	74.6
Injury: exclude ROBINS Critical (Sulala et al. (2026) [29])	10	1.52	0.78-2.98	74.6
Injury: exclude Haile et al. (2025) [24] (case-control)	10	1.4	0.75-2.61	67.6
Injury: exclude all three new studies (original k = 8)	8	1.81	0.81-4.05	70
Injury: fixed-effect	11	1.23	0.94-1.62	71.3
Arrival reference (REML)	5	1.33	0.86-2.07	36.3
Arrival: exclude Roddy et al. (2020) [34] (only ROC)	4	1.09	0.77-1.53	0
Arrival: exclude Mener et al. (2020) [32] (new)	4	1.57	0.87-2.83	41.1

TABLE 3: Pooled estimates and sensitivity analyses (random-effects, REML).

REML, restricted maximum likelihood

Risk of Bias, Methodological Quality, and Certainty

Methodological quality was modest (mean MINORS 55.0%, range 33.3-87.5%; Table *4*), with unbiased endpoint assessment and prospective sample-size calculation the most frequently unmet items. All 24 studies were at serious or critical overall risk of bias on ROBINS-I (21 serious, three critical; none low or moderate; Table *5*). This was driven chiefly by uncontrolled confounding: antibiotic timing was unadjusted in nearly all studies, and wound contamination was unmeasured in the large majority. GRADE certainty was very low for both strata (Table *6*), downgraded for risk of bias, inconsistency, indirectness, and imprecision. No domain supported an upgrade, and the exploratory small-study check (Egger's regression, p = 0.231) gave no reason to downgrade further for publication bias.

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total	%
Lack et al. (2015) [9]	2	2	0	2	1	1	1	1	2	2	1	1	16	67%
Al-Arabi et al. (2007) [21]	2	2	2	1	0	2	0	0	1	2	0	1	13	54%
Zuelzer et al. (2021) [22]	2	1	0	2	0	1	0	0	2	2	0	1	11	46%
Dellinger et al. (1988) [23]	2	2	2	2	1	2	1	0	1	2	1	2	18	75%
Haile et al. (2025) [24]	2	1	0	2	0	1	0	2	2	2	1	1	14	58%
Leonidou et al. (2014) [25]	2	2	1	2	0	1	0	0	1	2	0	1	12	50%
Padgett et al. (2023) [26]	2	2	0	2	0	2	2	0	2	2	0	1	15	62%
Wilson et al. (2024) [27]	2	1	1	1	0	0	0	0	1	2	0	1	9	38%
Zumsteg et al. (2014) [28]	2	1	0	2	0	1	0	0	2	2	0	1	11	46%
Sulala et al. (2026) [29]	2	1	0	1	0	0	0	0	1	2	0	1	8	33%
Whiting et al. (2019) [30]	2	2	2	1	0	1	0	0	1	2	0	1	12	50%
Jacobo et al. (2025) [31]	2	1	1	2	1	0	0	0	2	2	1	1	13	54%
Mener et al. (2020) [32]	2	2	0	1	1	0	0	0	2	2	0	1	11	46%
Morgan et al. (2026) [33]	2	1	0	1	0	0	0	0	2	2	1	1	10	42%
Roddy et al. (2020) [34]	2	2	1	2	0	1	0	0	2	2	1	1	14	58%
Kock et al. (2025) [35]	2	1	0	2	0	1	0	0	2	2	0	1	11	46%
Weber et al. (2014) [36]	2	2	2	2	1	2	1	2	2	2	1	2	21	88%
Hendrickson et al. (2020) [37]	2	1	0	2	1	2	2	0	1	2	0	1	14	58%
Fram et al. (2025) [38]	2	1	0	2	1	2	0	0	2	2	1	0	13	54%
Gubara et al. (2026) [39]	2	2	0	2	0	1	1	0	2	0	1	2	13	54%
Young et al. (2019) [40]	2	2	2	1	0	0	1	0	1	2	0	0	11	46%
Chan et al. (2021) [41]	2	2	0	2	0	2	0	0	1	2	0	1	12	50%
Thomas et al. (2013) [42]	2	2	2	2	0	2	0	2	2	2	0	1	17	71%
Enninghorst et al. (2011) [43]	2	2	2	2	1	2	2	0	1	2	1	1	18	75%

TABLE 4: MINORS methodological quality (0-2 per item; maximum 24).

The 12 MINORS items (each scored 0-2) are as follows: Item 1, clearly stated aim; Item 2, inclusion of consecutive patients; Item 3, prospective collection of data; Item 4, endpoint appropriate to the aim of the study; Item 5, unbiased assessment of the study endpoint; Item 6, follow-up period appropriate to the aim of the study; Item 7, loss to follow-up less than 5%; Item 8, prospective calculation of the study size; Item 9, an adequate control group; Item 10, contemporary groups; Item 11, baseline equivalence of groups; Item 12, adequate statistical analyses. Total is the sum across the 12 items (maximum 24); % is total divided by 24. Mean 55.0%.

MINORS, Methodological Index for Non-Randomized Studies

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Lack et al. (2015) [9]	Serious	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	SERIOUS
Al-Arabi et al. (2007) [21]	Serious	Serious	Moderate	Moderate	Serious	Moderate	Serious	SERIOUS
Zuelzer et al. (2021) [22]	Serious	Serious	Moderate	Moderate	Serious	Moderate	Serious	SERIOUS
Dellinger et al. (1988) [23]	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate	SERIOUS
Haile et al. (2025) [24]	Serious	Serious	Serious	Moderate	Moderate	Moderate	Moderate	SERIOUS
Leonidou et al. (2014) [25]	Serious	Serious	Moderate	Moderate	Serious	Moderate	Moderate	SERIOUS
Padgett et al. (2023) [26]	Serious	Moderate	Serious	Moderate	Serious	Moderate	Moderate	SERIOUS
Wilson et al. (2024) [27]	Serious	Moderate	Serious	Moderate	Serious	Serious	Moderate	SERIOUS
Zumsteg et al. (2014) [28]	Serious	Serious	Moderate	Moderate	Serious	Serious	Moderate	SERIOUS
Sulala et al. (2026) [29]	CRITICAL	Moderate	Serious	Serious	Moderate	Serious	Serious	CRITICAL
Whiting et al. (2019) [30]	Serious	Serious	Moderate	Moderate	Serious	Serious	Moderate	SERIOUS
Jacobo et al. (2025) [31]	Serious	Moderate	Low	Moderate	Moderate	Serious	Moderate	SERIOUS
Mener et al. (2020) [32]	Serious	Low	Moderate	Low	Moderate	Moderate	Moderate	SERIOUS
Morgan et al. (2026) [33]	Serious	Moderate	Low	Serious	Moderate	Serious	Moderate	SERIOUS
Roddy et al. (2020) [34]	Serious	Serious	Moderate	Serious	Serious	Moderate	Serious	SERIOUS
Kock et al. (2025) [35]	Serious	Serious	Serious	Moderate	Serious	Moderate	Moderate	SERIOUS
Weber et al. (2014) [36]	Serious	Low	Moderate	Low	Moderate	Moderate	Low	SERIOUS
Hendrickson et al. (2020) [37]	Serious	Moderate	Moderate	Moderate	Moderate	Low	Moderate	SERIOUS
Fram et al. (2025) [38]	Serious	Serious	Moderate	Moderate	Moderate	Moderate	Serious	SERIOUS
Gubara et al. (2026) [39]	Serious	Moderate	Moderate	Serious	Serious	Moderate	CRITICAL	CRITICAL
Young et al. (2019) [40]	CRITICAL	Serious	Moderate	Moderate	CRITICAL	Serious	Serious	CRITICAL
Chan et al. (2021) [41]	Serious	Low	Moderate	Low	Moderate	Moderate	Moderate	SERIOUS
Thomas et al. (2013) [42]	Serious	Moderate	Low	Low	Serious	Serious	Low	SERIOUS
Enninghorst et al. (2011) [43]	Serious	Low	Moderate	Low	Low	Moderate	Serious	SERIOUS

TABLE 5: ROBINS-I risk of bias (deep infection vs. antibiotic timing).

D1 confounding, D2 selection, D3 classification of exposure, D4 deviations, D5 missing data, D6 outcome measurement, D7 reported result. Overall equals worst domain. 21 serious, three critical.

ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions

Outcome	k	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
Deep infection/FRI (injury-anchored)	11	-1	-1	-1	-1	Not lowered (Egger p = 0.231)	Very low
Deep infection/FRI (arrival-anchored)	5	-1	-1	-1	-1	Not assessable (k<10)	Very low

TABLE 6: GRADE certainty of evidence (per outcome, by stratum).

A value of -1 in a GRADE domain denotes a downgrade of one level of certainty for that domain (the GRADE domains shown are risk of bias, inconsistency, indirectness, imprecision, and publication bias). Both bodies of evidence start at low (observational).

FRI, fracture-related infection; GRADE, Grading of Recommendations Assessment, Development and Evaluation

Discussion

The clinically important message of this study is that the reassuring null findings in this literature should not be read as evidence that delaying antibiotics is safe. Across the 16 poolable studies, delay was not significantly associated with deep infection in either the injury-anchored or the arrival-anchored stratum; both estimates sat close to the null, heterogeneity was high, and certainty was very low. Under evidence of this quality, a nonsignificant pooled association is absence of evidence, not evidence that timing does not matter [4]. The early thresholds that are widely cited [9] are similarly unsupported by the pooled data. They trace to individual studies that selected their own cut points on the same data used to test them, and that dependence between ROC-derived thresholds and larger reported effects was itself detectable in the sensitivity analyses.

The more informative finding is that the field's contradictions are not random noise. Almost all the disagreement between studies is explained by a single characteristic: whether infection was measured with a validated definition and analyzed with adjustment. Studies that did both reported a consistent, homogeneous four-fold association with delay; studies that did neither reported nothing or the opposite. This is a specific, quantified diagnosis of why two decades of open fracture cohorts have failed to converge. It reframes the literature's "conflicting evidence" as a predictable consequence of measurement and analytic quality rather than a genuine biological disagreement. It comes, however, with a caution that is central rather than peripheral. Because "used a validated outcome" and "reported an adjusted analysis" identify almost the same studies, the two explanations cannot be told apart. The pattern is equally consistent with a true effect that only rigorous studies can detect and with selective analysis and reporting in the studies that found one. These data cannot distinguish the two. The most rigorous single included study (prospective, multicenter, with an adjudicated deep-infection endpoint and a fully adjusted model) found no association at all [36]. The four-fold figure should therefore be read as a hypothesis about study quality, not as an effect estimate for delay.

The second contribution is methodological. In the present data, merging injury-anchored and arrival-anchored studies into a single, explicitly exploratory pool manufactured a nominally significant association (OR 1.53) that neither stratum supported on its own. The only prior review to synthesize antibiotic-timing studies was narrative and did not analyze the two anchors separately [11]; no synthesis has quantified the effect of pooling across them. The pre-hospital interval is unmeasured in arrival-anchored studies, and several of their authors acknowledge that their "early" groups very likely exceed the nominal threshold once measured from injury. An arrival-anchored estimate therefore answers a different question, and averaging it with injury-anchored estimates produces a number with no clinical referent. The separation enforced here is what makes the present headline appropriately cautious, and arguably more defensible than a synthesis that leaves the two anchors mixed [11].

Clinically, none of this justifies relaxing early antibiotic administration. Prompt prophylaxis is supported by strong biological rationale and by guideline consensus [7,8], and non-significance under very low-certainty evidence is absence of evidence, not evidence of safety [4]. What these results do not support is any specific numerical target: the data are compatible with a threshold anywhere, or nowhere, within the ranges studied. Institutional protocols that audit performance against a fixed cut point should recognize that the cut point itself is not evidence-based, even though the underlying principle of "give antibiotics promptly" is sound. Future studies should measure and report time from injury rather than from arrival, apply consensus FRI criteria with at least 90-day ascertainment, provide bounded exposure categories with cell counts, and report adjusted estimates regardless of statistical significance. Individual participant-data synthesis, with timing modeled continuously, would resolve both the threshold question and the reporting-quality confound that aggregate synthesis cannot.

Limitations

The evidence base is entirely observational and uniformly at serious or critical risk of bias. Residual confounding therefore cannot be excluded, and it plausibly explains the paradoxical directions in several studies. The dominant threat is confounding by indication, whereby the most severe and contaminated injuries are triaged to the fastest antibiotics. Infection was defined heterogeneously, and several studies used composite outcomes from which deep infection could not be isolated, contributing to the indirectness that drove certainty to very low. Per-stratum study counts remained small, so the subgroup and moderator analyses are exploratory and underpowered. The outcome-validity finding in particular is post hoc and confounded with analytic thoroughness, as described above. The antibiotic agent was not standardized across studies: reported regimens ranged from a first-generation cephalosporin (usually cefazolin, often with an aminoglycoside for higher grades) to a second-generation cephalosporin or co-amoxiclav, and several studies did not state the agent. This regimen variation, unrelated to the timing exposure, adds clinical heterogeneity that could not be addressed.

Conclusions

This study's principal contribution is to explain why open fracture cohorts have long failed to agree. The disagreement is systematic. It tracks study quality: the association between delay and infection is concentrated in studies with a validated infection definition and adjusted analyses, and disappears in those without. Separately, the two clock anchors measure different intervals and must not be combined. Taken together, these findings mean the reassuring null studies should not be read as evidence that delaying antibiotics is safe. Pooled observational evidence still does not establish whether injury-to-antibiotic time affects deep infection risk, and it identifies no defensible threshold; early antibiotic administration therefore remains appropriate on biological and guideline grounds. What is unresolved is the precise numerical target, and resolving it will require studies that measure timing from injury, define infection rigorously, and report their estimates whatever the result.

Appendices

Appendix A

Database	Component	Search terms	Results
PubMed (NCBI E-utilities; searched August 1, 2026)	Population	"Fractures, Open"[Mesh] OR "open fracture"[tiab] OR "open fractures"[tiab] OR "compound fracture"[tiab] OR "compound fractures"[tiab] OR Gustilo[tiab] OR "open tibia"[tiab] OR "open tibial"[tiab] OR "open limb fracture"[tiab] OR "open limb fractures"[tiab] OR "open extremity fracture"[tiab] OR "open extremity fractures"[tiab] OR "open long bone"[tiab] OR "open long-bone"[tiab] OR "open lower extremity fracture"[tiab]	11,390
	Antibiotic	"Antibiotic Prophylaxis"[Mesh] OR "Anti-Bacterial Agents"[Mesh] OR antibiotic[tiab] OR antibiotics[tiab] OR antibiotic*[tiab] OR antimicrobial*[tiab] OR prophylaxis[tiab] OR prophylactic[tiab] OR cefazolin[tiab] OR cephalosporin*[tiab] OR gentamicin[tiab] OR "co-amoxiclav"[tiab] OR amoxicillin[tiab] OR clindamycin[tiab] OR ceftriaxone[tiab] OR "piperacillin"[tiab]	1,166,463
	Timing	"Time-to-Treatment"[Mesh] OR timing[tiab] OR "time to"[tiab] OR "time from"[tiab] OR delay[tiab] OR delays[tiab] OR delayed[tiab] OR early[tiab] OR earlier[tiab] OR immediate[tiab] OR immediately[tiab] OR interval[tiab] OR "golden hour"[tiab] OR prehospital[tiab] OR "pre-hospital"[tiab] OR "door to"[tiab] OR "door-to"[tiab] OR minutes[tiab] OR hours[tiab] OR "time from injury"[tiab] OR duration[tiab]	5,761,389
	Combined	Population AND Antibiotic AND Timing NOT "Congress"[pt]	843
Embase (searched August 1, 2026)	Combined	('open fracture'/exp OR 'open fracture':ti,ab,kw OR 'compound fracture':ti,ab,kw OR gustilo:ti,ab,kw OR 'open tibia':ti,ab,kw OR 'open tibial':ti,ab,kw OR 'open limb fracture':ti,ab,kw OR 'open long bone':ti,ab,kw OR 'open extremity fracture':ti,ab,kw) AND ('antibiotic prophylaxis'/exp OR 'antibiotic agent'/exp OR antibiotic*:ti,ab,kw OR antimicrobial*:ti,ab,kw OR prophyla*:ti,ab,kw OR cefazolin:ti,ab,kw OR cephalosporin*:ti,ab,kw OR gentamicin:ti,ab,kw OR ceftriaxone:ti,ab,kw) AND ('time to treatment'/exp OR timing:ti,ab,kw OR 'time to':ti,ab,kw OR 'time from':ti,ab,kw OR delay*:ti,ab,kw OR early:ti,ab,kw OR immediate*:ti,ab,kw OR interval:ti,ab,kw OR 'golden hour':ti,ab,kw OR prehospital:ti,ab,kw OR 'pre-hospital':ti,ab,kw OR minutes:ti,ab,kw OR hours:ti,ab,kw) NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	1,210
Scopus (searched August 1, 2026)	Combined	TITLE-ABS-KEY(("open fracture*" OR "compound fracture*" OR gustilo OR "open tibia*" OR "open limb fracture*" OR "open long bone*" OR "open extremity fracture*") AND (antibiotic* OR antimicrobial* OR prophyla* OR cefazolin OR cephalosporin* OR gentamicin OR ceftriaxone) AND (timing OR "time to" OR "time from" OR delay* OR early OR immediate* OR interval OR "golden hour" OR prehospital OR "pre-hospital" OR minutes OR hours)) AND NOT DOCTYPE(cp)	1,449

TABLE 7: Electronic search strategies for PubMed, Embase, and Scopus.

Databases were searched on August 1, 2026, from inception, with no date, language, or study-design restriction. A sensitivity-first strategy combined a population block, an antibiotic block, and a timing block (population AND antibiotic AND timing); outcome and infection terms were deliberately omitted from the primary search to maximize sensitivity, because requiring an infection term risks excluding cohorts that report infection only within their results tables. Conference records were excluded at the search stage. The Results column gives the number of records returned by each line; the three databases returned 3,502 records in total before deduplication.

cp, conference paper; exp, exploded Emtree term; MeSH, Medical Subject Headings; pt, publication type; ti,ab,kw, title, abstract, or keyword field; tiab, title or abstract field

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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