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Procalcitonin-Guided Antibiotic Initiation in Adults Presenting to Emergency Departments With Suspected Infection: An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

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Procalcitonin-Guided Antibiotic Initiation in Adults Presenting to Emergency Departments With Suspected Infection: An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Emergency physicians must balance timely treatment of bacterial infection against unnecessary antibiotic prescribing. We systematically reviewed randomized controlled trials evaluating whether procalcitonin-guided care changes initial antibiotic initiation or prescription in adults presenting to emergency departments with suspected infection. PubMed, Embase, CENTRAL, ClinicalTrials.gov, and WHO ICTRP were searched from inception through August 25, 2026. Trials were pooled when outcome definitions were sufficiently comparable, using random-effects meta-analysis with modified Hartung–Knapp confidence intervals. Ten trials (13,286 participants) were included; four respiratory infection trials (3,602 participants) contributed to the primary synthesis. Procalcitonin-guided care reduced initial antibiotic initiation or prescription (risk ratio, 0.87; 95% confidence interval, 0.82–0.92; I^2=0%; high-certainty evidence), corresponding to approximately 89 fewer patients receiving or being prescribed antibiotics per 1,000. Sensitivity analyses produced similar estimates. For 28- to 30-day mortality, the pooled risk ratio across five trials was 0.92 (95% confidence interval, 0.57–1.49; low-certainty evidence); estimates for intensive care unit admission and antibiotic-related adverse events were imprecise. This updated review provides a decision-specific estimate of reduced initial antibiotic prescribing in emergency department respiratory infections and clarifies how differences in outcome definitions, trial designs, and patient populations affect interpretation of earlier syntheses. Effects on mortality and other clinical outcomes remain uncertain overall, and the respiratory prescribing estimate should not be extrapolated to undifferentiated fever, suspected sepsis, or acute heart failure.

Keywords: Procalcitonin; Emergency department; Antibiotic prescribing; Respiratory tract infection; Systematic review; Meta-analysis.

Introduction

Antibiotics are frequently started in the emergency department (ED) before a definitive diagnosis is established. Clinicians must balance timely treatment of serious bacterial infection against avoiding unnecessary antibiotic exposure. Such exposure can cause adverse drug effects and exert selection pressure favouring drug-resistant organisms [1], contributing to antimicrobial resistance, a major global health threat [2, 3].

Patients presenting to the ED often have nonspecific symptoms, such as fever, cough, or dyspnoea. Microbiological results are rarely available at the initial prescribing decision [1, 4], and this diagnostic uncertainty can lead to antibiotic use when bacterial infection is unlikely, particularly in acute respiratory infections [1]. Procalcitonin (PCT) rises in bacterial infection and usually remains low in viral infection [5, 6]. PCT-guided care uses predefined PCT concentrations or changes over time, alongside clinical assessment, to support decisions to start, withhold, or stop antibiotics [5–7]. In respiratory infection, PCT-guided care reduced antibiotic exposure without evident harm in several settings [5–7], but findings in ED populations have been less consistent [4, 8–10].

Available trials evaluated PCT-guided care in respiratory infection, undifferentiated fever, and acute heart failure [7–9, 11], but their antibiotic outcomes span initiation, continuation, discontinuation, and treatment duration [5–9]. This creates a practical evidence-interpretation problem: a reduction in total antibiotic exposure does not necessarily quantify the effect on the first ED prescription, and evidence from respiratory presentations does not necessarily apply to suspected sepsis or other acute presentations. We therefore performed an updated systematic review and meta-analysis to estimate initial ED or admission antibiotic initiation or prescription using comparable trial-level outcomes, assess the implications of differing trial designs and populations for previous syntheses, and evaluate other antibiotic decisions and patient-important outcomes separately.

Previous systematic reviews and guidelines have evaluated procalcitonin (PCT)-guided antibiotic initiation in emergency care [4, 12, 13]. The 2016 ED systematic review identified evidence of reduced prescribing in adults with respiratory infection but found insufficient evidence to recommend PCT guidance across an undifferentiated ED population [4]. A broader systematic review of PCT testing in ED and intensive-care settings also reported reduced antibiotic prescribing in adults presenting to EDs, while drawing largely on respiratory presentations [14]. The 2024 ESCMID guideline subsequently pooled six respiratory-infection trials reporting prescribing at admission [12], and the 2025 ED guideline translated available evidence into clinical recommendations [13]. Thus, our contribution is not the first identification of a respiratory prescribing benefit, but an updated quantitative synthesis that specifies the initial ED/admission prescribing outcome and separates it from antibiotic exposure over the illness episode and time-sensitive antibiotic administration.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis followed PRISMA 2020 [15], with searches reported according to PRISMA-S [16]. The protocol was registered in PROSPERO (CRD420261490984). Searches and eligibility screening preceded registration; data extraction and risk-of-bias assessment followed registration, as specified in the protocol.

Searches covered PubMed (MEDLINE), Embase (Ovid), CENTRAL, ClinicalTrials.gov, and WHO ICTRP from inception to Aug 25, 2026, without date or language restrictions. Database strategies combined procalcitonin, emergency department, and antibiotic or infection terms; PubMed and Embase additionally included randomised-trial indexing terms and text words. ClinicalTrials.gov was searched using "procalcitonin emergency department antibiotic" and WHO ICTRP using "procalcitonin AND antibiotic" (appendix, Supplementary Table S6). Reference lists of included trials and systematic reviews were hand-searched, and articles citing included trials were screened.

Eligible studies were randomised controlled trials using individual or cluster allocation, comparing PCT-guided care with usual care in adults presenting to a hospital ED or equivalent acute receiving unit with suspected infection. PCT results had to be available to the treating clinician in time to inform the initial antibiotic prescribing decision (panel 1). English-language reports were eligible regardless of publication format. Multiple reports of the same trial were linked to avoid double-counting participants. Two reviewers independently screened records in Rayyan and assessed full texts. Disagreements were resolved through discussion between the reviewers. Each report excluded after full-text assessment received one reason according to a prespecified hierarchy (appendix, Supplementary Table S7).

Two reviewers independently extracted data on study design, setting, population, numbers randomised and analysed, PCT testing methods and thresholds, comparator, outcome definitions and time windows, follow-up, and effect estimates. Discrepancies were resolved through discussion. Outcome definitions were tabulated in a harmonisation matrix before analysis (appendix, Supplementary Tables S4 and S5). We used arm-level analysed denominators and, for repeated measurements, the protocol-defined time point closest to the initial prescribing decision and within 24 h of ED presentation. Arm-level counts not reported in the main article were obtained from published supplementary materials where available; otherwise, the trial was not pooled for that outcome.

The primary outcome was receipt or prescription of at least one systemic antibiotic as part of the initial ED or admission decision. Secondary outcomes included timely initiation, antibiotic exposure and duration, all-cause mortality (principal window 28–30 days), treatment failure, hospital and ICU admission, length of stay, readmission, serious adverse outcomes, and antibiotic-related adverse events. Antibiotic use after the initial decision was assessed separately. Two reviewers assessed risk of bias using the five-domain RoB 2 form available in Rayyan [17], with final judgements agreed through discussion. For ProRESP, weekly cluster allocation and the potential for participant recruitment after allocation to introduce selection bias were additionally considered in the narrative randomisation assessment.

Data analysis

Analyses were done in R (meta package, version 8.5.0). For the principal analysis, unadjusted risk ratios (RRs; PCT-guided care vs comparator) were calculated from arm-level events and analysed denominators, with Wald-type standard errors. RRs below 1 indicated reduced antibiotic initiation or prescription; for timing outcomes, RRs above 1 indicated more patients receiving antibiotics within the trial-defined window. Trial-reported odds ratios, risk differences, and adjusted estimates were presented separately (appendix, Supplementary Tables S2A and S2B). Absolute effects used the pooled RR and the combined comparator-arm event risk.

As prespecified, trials were combined only when comparable in population, intervention, comparator, outcome, and time point, with respiratory infection as the principal stratum. Pooling decisions were based on reported definitions rather than results (appendix, Supplementary Tables S4 and S5). The principal analysis included CLINPCT (administration after the first PCT result), ProACT (ED prescription, including at discharge), ProCAP (prescription on admission), and ProHOSP (day-zero prescription) [7, 9,

18, 19]. Some participants had received antibiotics before enrolment (ProCAP 27/151 vs 34/151; approximately 27% in ProHOSP), so the outcome represents initial ED or admission prescribing rather than first-ever initiation in antibiotic-naive patients. ProCOLD and ProRESP assessed broader episode-level antibiotic use [20, 21]; HiTEMP and IMPACT-EU involved different populations [8, 11], and IMPACT-EU lacked a clear operational definition of initiation. These findings and the timing outcomes from Dharaniyadewi and PRONTO were presented separately from the principal synthesis.

We used inverse-variance random-effects meta-analysis to allow for variation in treatment effects across trials, with restricted maximum likelihood estimation of τ^2 [22] and Hartung–Knapp (HK) confidence intervals [23] using a t distribution with $k-1$ degrees of freedom. Given the small number of trials, the HK variance multiplier was floored at 1 ($q^*=\max[1, q]$) to prevent intervals narrower than those from the conventional random-effects method [24]. Heterogeneity was assessed using Cochran Q, I^2, and τ^2. Prediction intervals were calculated where estimable [25]; those based on fewer than five trials and syntheses of two trials were exploratory.

Cluster-randomised trials were eligible for pooling only with an estimate accounting for clustering for the relevant outcome, or a design-effect adjustment; otherwise, they were reported separately [26]. ProRESP's cluster-adjusted RR measured antibiotic exposure rather than initial prescribing and was presented separately. ProACT event counts were reconstructed from model-estimated percentages (34·1% and 38·7%) and analysed denominators, yielding 282/826 versus 321/830. The resulting unadjusted RR was approximate; its influence was assessed by excluding ProACT in sensitivity analysis. Continuity corrections of 0·5 for zero-event cells were planned but not required.

Findings were described by clinical presentation. No formal subgroup tests or meta-regression were performed because no synthesis included ten or more trials. Secondary outcomes were pooled when at least two trials reported sufficiently comparable outcomes, assessment windows, and event definitions; safety syntheses other than 28–30-day mortality were exploratory. Sensitivity analyses excluded ProHOSP because of its post-randomisation analysis population, ProACT because of reconstructed counts and its post-randomisation analysis population, and CLINPCT because all comparator participants initiated antibiotics. Alternative analyses used the DerSimonian–Laird estimator and a Mantel–Haenszel fixed-effect model (appendix, Supplementary Figure S2). Funnel plots were not produced because each synthesis included fewer than ten trials.

Two reviewers assessed certainty using GRADE [27, 28], guided by the Cochrane Handbook, with final judgements agreed through discussion. Outcomes assessed were initial antibiotic initiation or prescription, 28–30-day mortality, ICU admission, antibiotic-related adverse events, and serious adverse outcomes. Randomised evidence started at high certainty and was assessed for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Risk-of-bias judgements considered relevant limitations and each trial's contribution to the evidence. Imprecision judgements considered confidence intervals and optimal information size (OIS); intervals spanning appreciable benefit and harm prompted one downgrade when OIS was met and two when it was not. OIS calculations assumed a 20% relative risk reduction, $\alpha=0{\cdot}05$, and 80% power at the observed comparator risk; the 20% reduction was a post hoc planning assumption. Outcome-specific explanations are provided in Supplementary Table S3.

Investigators were not contacted for missing data; available published reports and supplementary materials were used. The HK variance floor of 1 was not explicitly specified in the protocol. Eligibility clarifications during screening (marked † in panel 1) covered pilot or feasibility RCTs with sufficient data, clinician access to PCT results, and exclusion of multifaceted interventions when the effect of PCT could not be separated from other components.

Exploratory comparison with ESCMID: We conducted a post hoc reproduction of the six-trial respiratory antibiotic-prescribing synthesis presented in the 2024 ESCMID guideline, followed by a leave-one-out analysis excluding Long et al. Trial-level event counts and denominators were transcribed from the guideline forest plot. Log risk ratios and sampling variances were calculated from 2 × 2 data, and pooled using inverse-variance random-effects models with restricted maximum likelihood (REML) estimation of between-study variance. Conventional normal-theory (Wald) 95% confidence intervals were used for the reproduction and exclusion comparison; standard Hartung–Knapp intervals were calculated as an additional sensitivity check. Analyses were conducted using metafor version 5.2-1 in R. These exploratory calculations were separate from our prespecified four-trial primary synthesis, which used modified Hartung–Knapp intervals with the variance multiplier floored at one. The guideline did not specify the exact confidence-interval algorithm in the materials examined; matching its reported pooled result does not establish that the original authors used Wald inference. The ProRESP binary counts were analysed as reported in the guideline without an independently derived cluster correction.

Results

Searches identified 626 records from databases (496) and registers (130), plus one report through citation searching. After removing 183 duplicates, 443 records were screened and 415 excluded. Twenty-eight reports from database and register searches and the citation-search report underwent full-text assessment. Three were excluded because of the intervention, setting, or ongoing/awaiting-results status, leaving 26 reports representing ten randomised controlled trials (figure 1).

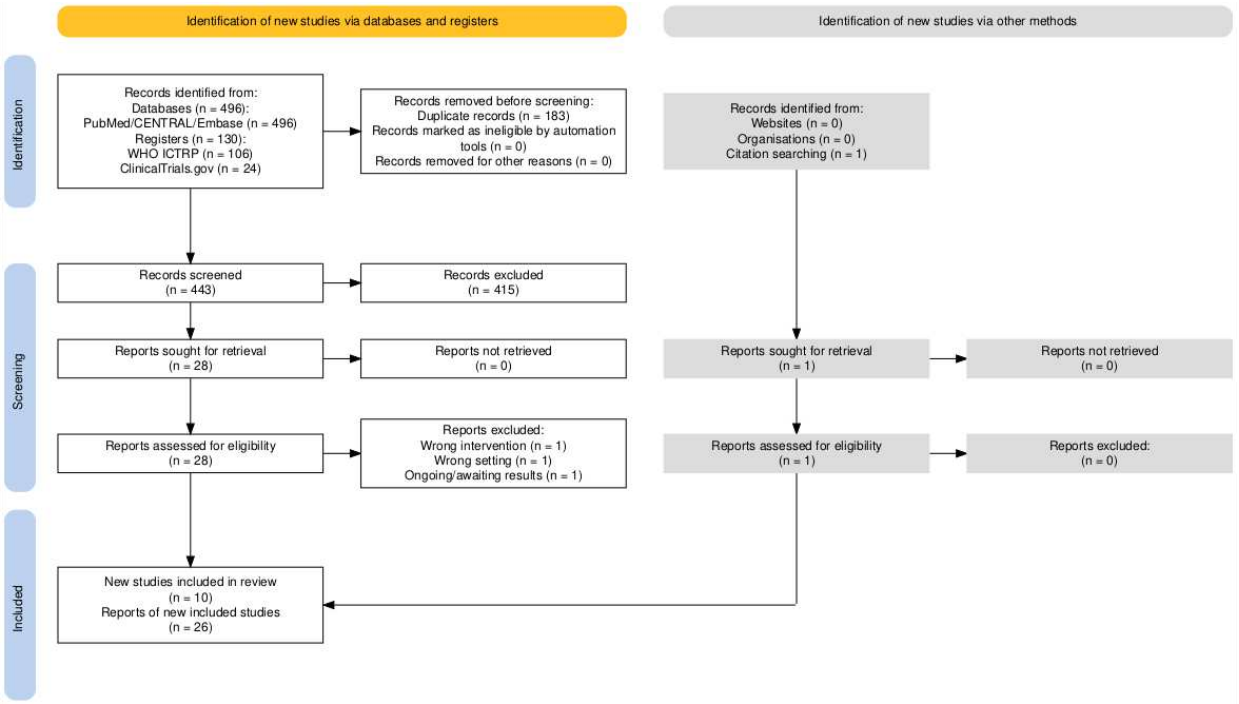


Figure 1: PRISMA 2020 flow diagram

Ten trials involving 13,286 randomised participants were published between 2004 and 2026. Six enrolled patients with respiratory infection, two with sepsis or suspected sepsis, one with undifferentiated fever, and one with acute heart failure. Nine used individual randomisation and one used cluster randomisation. Study characteristics are summarised in Supplementary Table S1.

Four trials were at low risk of bias, five raised some concerns, and PRONTO was at high risk because of missing outcome data (figure 2). Among the four trials in the principal synthesis, ProACT and ProCAP were at low risk, while CLINPCT and ProHOSP raised some concerns.

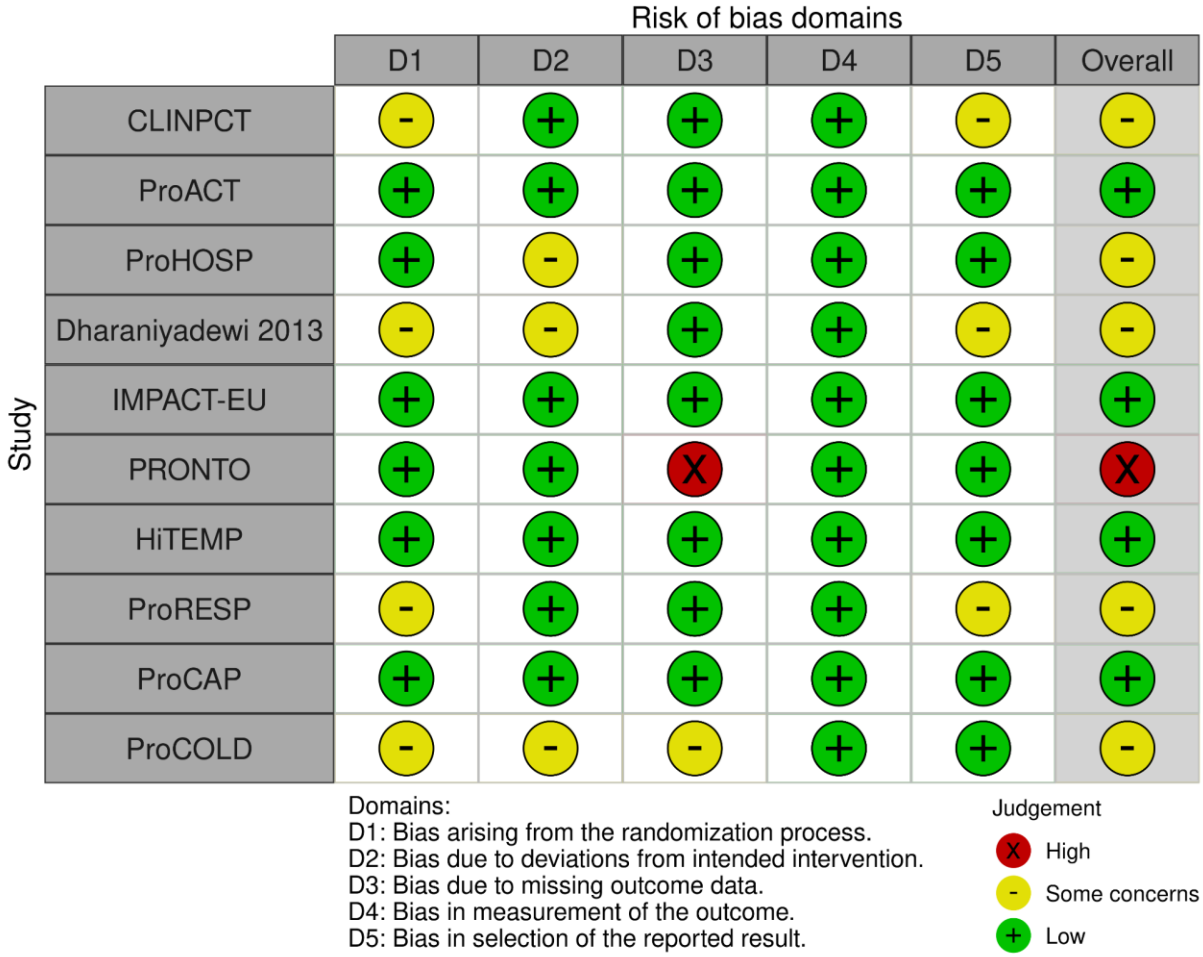


Figure 2: Risk-of-bias assessment

Four respiratory-infection trials involving 3,602 participants contributed to the principal synthesis. PCT-guided care reduced antibiotic initiation or prescription at the initial ED or admission decision (RR 0·87, 95% CI 0·82–0·92; figure 3), equivalent to 89 fewer patients prescribed or receiving antibiotics per 1,000 (95% CI 57–120 fewer), based on a comparator risk of 671 per 1,000. No between-trial heterogeneity was

detected (I^2=0%; τ^2=0). The exploratory 95% prediction interval was 0·82–0·92 (appendix p 2).

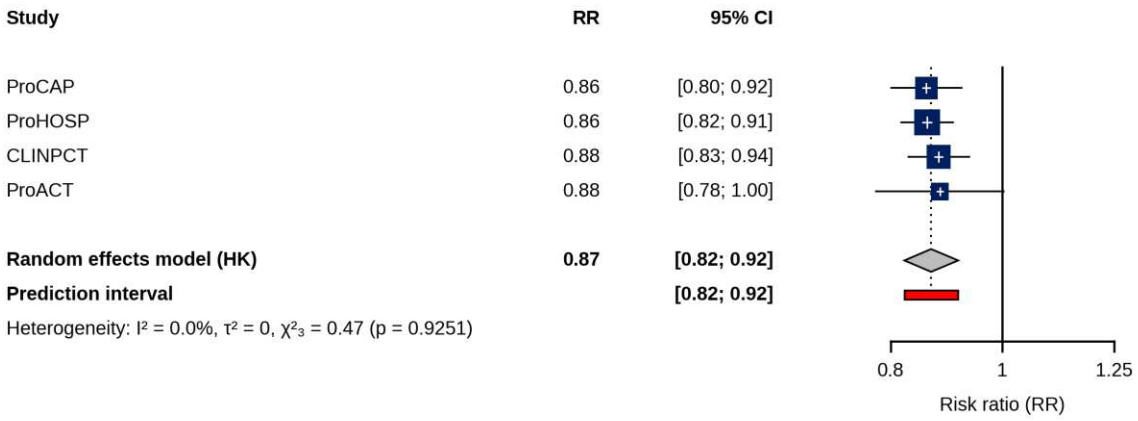


Figure 3: Principal analysis: forest plot of initial ED/admission antibiotic initiation or prescription (four trials: CLINPCT, ProACT, ProCAP, ProHOSP)

Findings outside the principal synthesis were presented separately (figure 4; appendix p 4). Antibiotic use during the broader illness episode was lower with PCT-guided care in ProCOLD (RR 0·56, 95% CI 0·43–0·73), as was cluster-adjusted antibiotic exposure in ProRESP (0·49, 0·44–0·55). HiTEMP showed no clear reduction in ED prescribing among patients with undifferentiated fever (0·95, 0·86–1·04). In acute heart failure, IMPACT-EU's estimate was compatible with either reduced or increased prescribing (1·30, 0·93–1·82).

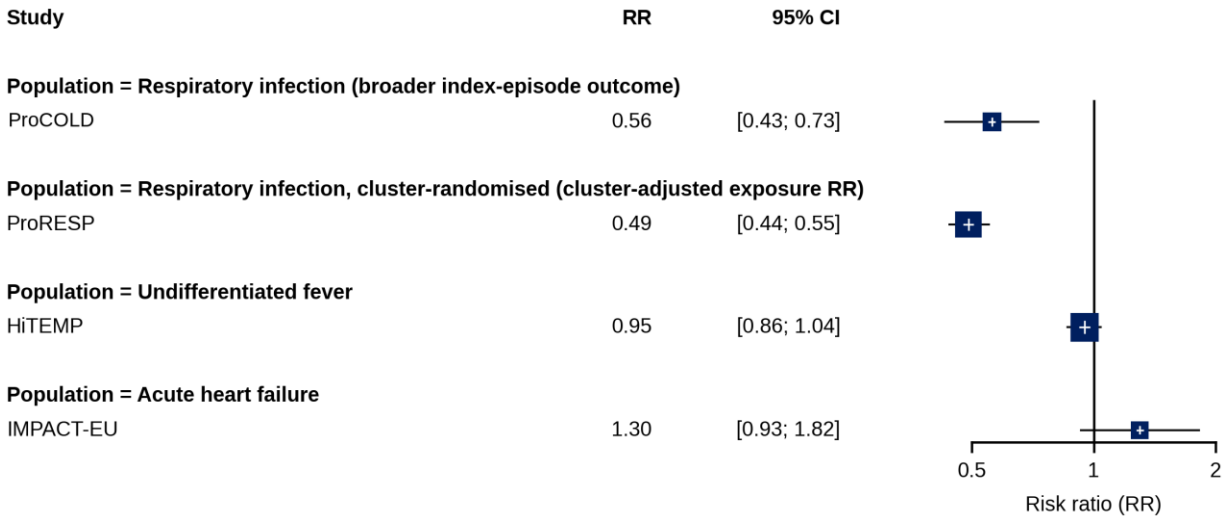


Figure 4: Forest plot of additional (broader index-episode) antibiotic initiation or prescription by clinical population (not pooled)

The primary finding was consistent across all five sensitivity analyses (RRs 0·86–0·87). Excluding ProHOSP, ProACT, or CLINPCT widened the confidence intervals, but all remained below 1. Results were also similar with the DerSimonian–Laird estimator and Mantel–Haenszel fixed-effect model (appendix, Supplementary Figure S2). Timing outcomes were assessed separately because their definitions differed (table 1; appendix p 5). In Dharaniyadewi, antibiotic administration within 6 h was

more frequent with PCT testing (RR 2·48, 95% CI 1·88–3·26), although the starting point was unspecified. PRONTO showed no clear difference in intravenous antibiotic initiation within 3 h of ED triage (1·00, 0·95–1·06). Treatment duration was shorter with PCT-guided care in ProHOSP, ProRESP, and ProCAP, but not in ProACT, PRONTO, CLINPCT, or IMPACT-EU. Duration and exposure outcomes were not pooled because measures and follow-up periods differed (table 1).

Table 1: Study characteristics, antibiotic initiation and treatment exposure

Study (Year)	PCT initiation, n/N (%)	Comparator initiation, n/N (%)	RR (95% CI)[1]	Antibiotic duration, PCT vs comparator (as reported)
1. CLINPCT (2019)	125/142 (88·0%)	143/143 (100%)	0·88 (0·83–0·94)	10 vs 9 days (median); p=0·21
2. ProACT (2018)	282/826 (34·1%)[2]	321/830 (38·7%)[2]	0·88 (0·78–1·00)[2]	4·2 vs 4·3 days (mean); p=0·87
3. ProHOSP (2009)	506/671 (75·4%)	603/688 (87·6%)	0·86 (0·82–0·91)	5·7 vs 8·7 days (mean)
4. Dharaniyadewi (2013)	83/95 (87·4%), first dose <6 h	36/102 (35·3%), first dose <6 h	2·48 (1·88–3·26)[3]	Not reported
5. IMPACT-EU (2020)	66/370 (17·8%)	51/372 (13·7%)	1·30 (0·93–1·82)	8 vs 8 days (median); p=0·659
6. PRONTO (2026)	1,325/2,738 (48·4%), IV antibiotics ≤3 h	1,308/2,715 (48·2%), IV antibiotics ≤3 h	1·00 (0·95–1·06)[3]	5 vs 5 days (median); IRR 1·00
7. HiTEMP (2018)	200/275 (72·7%)	212/276 (76·8%)	0·95 (0·86–1·04)	Not reported
8. ProRESP (2004)	55/124 (44·4%)	99/119 (83·2%)	0·49 (0·44–0·55)[4]	10·9 vs 12·8 days (mean); p=0·03
9. ProCAP (2006)	128/151 (84·8%)	149/151 (98·7%)	0·86 (0·80–0·92)	5 vs 12 days (median); p<0·001; total antibiotic exposure RR 0·52 (95% CI 0·48–0·55)[5]
10. ProCOLD (2007)	41/102 (40·2%)	76/106 (71·7%)	0·56 (0·43–0·73)	Not reported

Abbreviations: CI, confidence interval; ED, emergency department; IRR, incidence rate ratio; IV, intravenous; PCT, procalcitonin; RR, risk ratio.

[1] Risk ratio (PCT-guided vs comparator) for the initiation outcome shown, calculated from arm-level counts with a Wald-type 95% CI; these are the study estimates entered in the meta-analyses (Figure 3). Trial-reported effect measures (risk differences, odds ratios, P values) are given in Supplementary Table S2A.

[2] ProACT reported model-estimated percentages (34·1% and 38·7%); event counts were reconstructed by multiplying these by the analysed denominators (826 and 830). The trial-reported adjusted risk difference was −4·6 percentage points (99·86% CI −12·2 to 3·0).

[3] Timing outcomes, not included in the pooled initiation analysis: first empirical antibiotic dose within 6 hours (Dharaniyadewi) and intravenous antibiotics within 3 hours of triage (PRONTO; RR calculated from counts; trial-reported adjusted risk difference −0·08 percentage points, 95% CI −2·58 to 2·42).

[4] ProRESP was cluster-randomised. The estimate shown is the cluster-adjusted RR reported by the trial, which relates to antibiotic exposure; the participant-level RR from the initiation counts, which does not account for clustering, is 0·53 (95% CI 0·43–0·66).

[5] ProCAP reported a relative risk of 0·52 (95% CI 0·48–0·55) for total antibiotic exposure. This is not an initiation estimate and was not used in the initiation analyses; the initiation RR in the RR column was calculated from the counts. Full definitions, page/table citations, and additional context are provided in Supplementary Table S2A.

Five trials involving 8,365 participants contributed to the 28–30-day mortality synthesis (RR 0·92, 95% CI 0·57–1·49; I^2=44·6%; 95% prediction interval 0·44–1·94), with estimates compatible with benefit or harm (table 2; appendix p 6). At other follow-up periods, Dharaniyadewi reported lower 14-day mortality with PCT testing (RR 0·53, 95% CI 0·36–0·77). At 90 days, PRONTO reported lower mortality (OR 0·78, 95% CI 0·68–0·88), whereas IMPACT-EU reported 10·3% versus 8·2% with usual care (log-rank p=0·32). These outcomes were not pooled across follow-up periods.

Table 2: Mortality and other clinical outcomes

Study (Year)	Mortality, PCT vs comparator, n/N (%) [follow-up]	Mortality RR (95% CI)[2]	Hospital LOS, PCT vs comparator (median or mean, as stated)	Serious/antibiotic-related AE, PCT vs comparator, n/N (%) [type][3]
1. CLINPCT (2019)	2/142 (1·4%) vs 3/143 (2·1%) [30 d]	0·67 (0·11–3·96)	6 vs 5 days (median)	22/142 (15·5%) vs 29/143 (20·3%) [serious adverse outcomes, composite]
2. ProACT (2018)	Not reported by arm[1]	Not estimable	5·0 vs 4·7 days (mean)	96/826 (11·7%) vs 109/830 (13·1%) [30-day composite safety outcome; RD −1·5 pp, 95% CI −4·6 to 1·7; non-inferior]; no significant difference in serious AEs
3. ProHOSP (2009)	34/671 (5·1%) vs 33/688 (4·8%) [30 d]	1·06 (0·66–1·69)	9·4 vs 9·2 days (mean)	133/671 (19·8%) vs 193/688 (28·1%) [antibiotic-associated AEs]
4. Dharaniyadewi (2013)	26/95 (27·4%) vs 53/102 (52·0%) [14 d]	0·53 (0·36–0·77)	Not reported	Not reported
5. IMPACT-EU (2020)	25/370 (6·8%) vs 16/372 (4·3%) [30 d]	1·57 (0·85–2·89)	7 vs 8 days (median)	Not reported
6. PRONTO (2026)	372/2,738 (13·6%) vs 450/2,715 (16·6%) [28 d]	0·82 (0·72–0·93)	6 vs 6 days (median)	56/2,798 (2·0%) vs 53/2,764 (1·9%) [antibiotic-related AEs]
7. HiTEMP (2018)	4/262 (1·5%) vs 11/264 (4·2%) [30 d]	0·37 (0·12–1·14)	4·0 vs 4·0 days (median)	Not reported separately
8. ProRESP (2004)	4/124 (3·2%) vs 4/119 (3·4%) [mean 13 d]	0·96 (0·25–3·75)	10·7 vs 11·2 days (mean)	Not reported
9. ProCAP (2006)	18/151 (11·9%) vs 20/151 (13·2%) [4–6 wk]	0·90 (0·50–1·63)	12·0 vs 13·0 days (mean)	Not reported separately
10. ProCOLD (2007)	5/102 (4·9%) vs 9/106 (8·5%) [6 mo]	0·58 (0·20–1·66)	9 vs 10 days (median)	Not reported separately

Abbreviations: AE, adverse event(s); CI, confidence interval; LOS, length of stay; PCT, procalcitonin; pp, percentage points; RD, risk difference; RR, risk ratio; SAE, serious adverse event(s).

[1] A total of 26 deaths by day 30 were reported across both arms combined; arm-specific counts were deferred to supplementary material not available in the source document, so no mortality effect estimate could be calculated for ProACT. Treatment-failure, additional adverse-event, and other secondary outcomes are provided in full in Supplementary Table S2B.

[2] Risk ratio (PCT-guided vs comparator) calculated from arm-level counts with a Wald-type 95% CI at the follow-up shown; trial-reported effect measures (risk differences, odds ratios, P values) are given in Supplementary Table S2B. RRs at different follow-up windows are not interchangeable; the pooled 28–30-day analysis comprises CLINPCT, ProHOSP, IMPACT-EU, HiTEMP, and PRONTO.

[3] Adverse-event definitions differ across trials and are not interchangeable: composite serious adverse outcomes (CLINPCT), a composite safety outcome potentially attributable to withholding antibiotics (ProACT), antibiotic-associated adverse effects (ProHOSP), and antibiotic-related adverse outcomes (PRONTO) are shown as defined by each trial.

Treatment failure and hospital admission were not pooled because definitions or assessment windows differed. Neither ProCAP nor ProCOLD showed a clear difference in treatment failure; CLINPCT reported more hospital admissions with PCT-guided care (RR 1·11, 95% CI 1·01–1·23). The pooled ICU-admission estimate was imprecise (RR 1·00, 95% CI 0·33–3·05; I^2=49·2%). Antibiotic-related adverse-event estimates differed between ProHOSP and PRONTO, and the exploratory pooled estimate was highly imprecise (0·83, 0·07–9·54; I^2=69·9%; appendix p 8). CLINPCT alone reported the serious-adverse-outcome composite (0·76, 0·46–1·26; table 2).

Certainty was high for initial antibiotic initiation or prescription. The remaining risk-of-bias concerns were not judged serious enough to warrant downgrading, and sensitivity analyses supported the primary finding. Certainty was low for 28–30-day mortality because of risk of bias and imprecision, and low for ICU admission and the CLINPCT serious-adverse-outcome composite because of very serious imprecision. Certainty was very low for antibiotic-related adverse events because of risk of bias, inconsistency, and very serious imprecision (table 3; appendix, Supplementary Table S3).

Table 3: GRADE summary of findings

Certainty assessment							No. of patients		Effect			
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**PCT-guided care**	**Usual care**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
28–30-day mortality												
5	RCTs	serious[a]	not serious[b]	not serious	serious[c]	none	437/4,183 (10·4%)	513/4,182 (12·3%)	RR 0·92 (0·57 to 1·49)	10 fewer per 1,000 (53 fewer to 60 more)	●●○○ Low[a,b,c]	Critical
Any antibiotic initiation/prescription (initial ED/admission decision)												
4	RCTs	not serious[d]	not serious[e]	not serious[f]	not serious[g]	none[h]	1,041/1,790 (58·2%)	1,216/1,812 (67·1%)	RR 0·87 (0·82 to 0·92)	89 fewer per 1,000 (120 fewer to 57 fewer)	●●●● High[d,e,f,g,h]	Critical
ICU admission												
3	RCTs	not serious[i]	not serious	not serious	very serious[j]	none	71/1,075 (6·6%)	81/1,095 (7·4%)	RR 1·00 (0·33 to 3·05)	No difference per 1,000 (50 fewer to 151 more)	●●○○ Low[i,j]	Critical
Antibiotic-related adverse events												
2	RCTs	serious[k]	serious[l]	not serious	very serious[m]	none	189/3,469 (5·4%)	246/3,452 (7·1%)	RR 0·83 (0·07 to 9·54)	12 fewer per 1,000 (66 fewer to 609 more)	●○○○ Very low[k,l,m]	Important
Serious adverse outcomes (composite; single trial)												
1	RCTs	not serious[n]	not serious	not serious	very serious[o]	none	22/142 (15·5%)	29/143 (20·3%)	RR 0·76 (0·46 to 1·26)	49 fewer per 1,000 (110 fewer to 53 more)	●●○○ Low[n,o]	Important

Abbreviations: CI, confidence interval; PCT, procalcitonin; RCT, randomised controlled trial; RR, risk ratio. Relative effects are random-effects (Hartung–Knapp) pooled risk ratios from Supplementary Figures S1 (initiation or prescription), S5 (mortality), S7 (ICU admission) and S8 (antibiotic-related adverse events); serious adverse outcomes are from a single trial (CLINPCT, composite outcome). Importance: outcomes were rated as critical or important for decision-making. Certainty of evidence: ●●●● high, ●●●○ moderate, ●●○○ low, ●○○○ very low. Imprecision was rated very serious (two levels) when the confidence interval included both appreciable benefit and appreciable harm and the optimal information size was not met. Absolute effects are events per 1,000 patients, calculated from the pooled RR and the observed risk in the usual-care group (upper limits capped at 100%). Superscript letters refer to the downgrading explanations in Supplementary Table S3. Post hoc OIS checks assumed a 20% relative risk reduction, two-sided α=0·05, 80% power, equal allocation and observed comparator risks (two-proportion normal approximation). Required/available participants: initiation 416/3,602; mortality 5,122/8,365; ICU admission 8,912/2,170; antibiotic-related adverse events 9,276/6,921; serious composite 2,846/285. The 20% assumption is for sample-size planning, not a prespecified clinical threshold. See Supplementary Table S3 for the outcome-specific certainty rationale and calculation details.

Discussion

PCT-guided care reduced initial antibiotic prescribing in adults with respiratory infection, with consistent findings across sensitivity analyses. This supports its consideration alongside clinical assessment at the ED or admission prescribing decision. Whether fewer prescriptions translate into more appropriate antibiotic use or improved patient outcomes remains uncertain.

At the comparator prescribing risk observed across the included trials (671 per 1,000), the pooled effect corresponds to approximately 89 fewer patients receiving or being prescribed antibiotics per 1,000. This absolute estimate is specific to the observed baseline risk; the reduction in prescribing should not be interpreted as proof that every avoided prescription was inappropriate.

PCT should support, not replace, clinical assessment in selected respiratory presentations. Clinical severity, haemodynamic stability, examination findings, and the likelihood of bacterial infection remain central; a low PCT result should not delay indicated treatment for suspected sepsis or serious bacterial infection. For implementation, turnaround time, interpretation of discordant results, and reassessment pathways are important considerations.

Earlier meta-analyses also reported reduced antibiotic initiation with PCT-guided care. The Cochrane individual-patient-data meta-analysis reported an adjusted OR of 0·27 (95% CI 0·24–0·32), and 0·49 (0·41–0·58) in its ED subgroup [6]. Our synthesis reports RRs, which directly express proportional changes in prescribing probability. Because prescribing was common, the earlier ORs cannot be interpreted as equivalent RRs or compared numerically with our estimate to establish a larger treatment effect. Differences in populations and outcome definitions further limit direct comparison.

Our four-trial primary synthesis differs from the six-trial respiratory prescribing synthesis reported by ESCMID: CLINPCT, ProACT and ProHOSP appear in both; ProCAP contributes to ours, whereas ESCMID also included ProRESP, Long and Kristoffersen [7, 9, 12, 18, 20, 29]. This is a difference in study selection and outcome handling, not evidence that the previous review was necessarily incorrect. ESCMID reported a pooled RR of 0·84 (95% CI 0·71–0·99) with high heterogeneity, compared with 0·87 (0·82–0·92; I^2=0%) in our four-trial synthesis [12]. The estimates agree in direction; the difference in precision or heterogeneity cannot be attributed solely to any single eligibility decision because the study sets and statistical analyses differ.

Three specific considerations inform interpretation of the ESCMID synthesis. First, Long and colleagues reported antibiotic prescribing at admission in 65/77 versus 77/79 participants in the per-protocol population, whereas ESCMID's supplementary evidence table lists 68/81 versus 79/81 [12, 29]. The latter counts can be reproduced by applying the trial's reported prescribing percentages (84·4% and 97·5%) to the larger 81-per-arm analysis denominators; however, the source of initiation-specific events for those denominators is not explained in the published materials examined. This is an unresolved data-provenance question, not proof of incorrect extraction. The resulting crude risk ratios are similar (approximately 0·87 and 0·86, respectively), so the discrepancy should not be portrayed as reversing the effect.

Second, ProRESP allocated treatment by week and analysed possible cluster effects using generalised estimating equations [20]. ESCMID reported crude initiation counts (55/124 vs 99/119), but the published guideline and supplement do not clearly document a cluster-specific variance adjustment for this trial in the pooled initiation analysis [12, 20]. We therefore retained the trial's cluster-adjusted estimate for its

reported antibiotic-exposure outcome separately; that estimate is not interchangeable with the binary initiation outcome. Third, Long enrolled low-risk community-acquired pneumonia patients treated as outpatients, including ED or observation-unit discharge within 24 h, whereas ESCMID's PCT recommendation targets lower respiratory infection in patients likely to be admitted [12, 29]. This is a question of applicability to the recommendation population, not automatic ineligibility for an ED initiation review.

In an exploratory, post hoc reanalysis of the six trial-level counts displayed by ESCMID, inverse-variance REML pooling with conventional Wald inference yielded RR 0·842 (95% CI 0·714–0·993; p=0·0410; τ^2=0·0388; I^2=94·89%). Excluding Long et al. yielded RR 0·835 (95% CI 0·678–1·030; p=0·0917; τ^2=0·0528; I^2=96·25%). The pooled point estimate changed little, although the five-trial Wald confidence interval included unity. Standard Hartung–Knapp inference using the same data gave RR 0·842 (95% CI 0·669–1·060; p=0·1127) for six trials and RR 0·835 (95% CI 0·613–1·138; p=0·1816) after excluding Long. Thus, the nominal statistical significance of the six-trial result was sensitive to the interval method, while the estimated effect direction was stable. The ESCMID forest plot reported I^2 of approximately 84%, rather than the 94·89% obtained here; the published methods and appendix did not specify enough analytical detail to reconcile this discrepancy. These are independent exploratory calculations, not additional results reported by ESCMID, and they retain the limitation of using unadjusted ProRESP binary counts despite cluster randomisation. The findings do not demonstrate that Long was ineligible or that PCT has no effect.

Earlier evidence syntheses are compared in Table 4. The 2016 ED review evaluated antibiotic initiation, the 2015 health-technology assessment quantified antibiotic receipt in ED populations, and the Cochrane individual-patient-data review evaluated respiratory-infection antibiotic decisions across settings [4, 6, 14]. Ji and colleagues subsequently evaluated point-of-care testing in community-acquired pneumonia, including all four trial families in our principal synthesis, but extracted CAP-specific subsets from some broader respiratory trials.[30] Our analysis instead focuses on the initial ED/admission prescribing outcome in eligible respiratory populations and examines other acute presentations and antibiotic-management decisions separately.

For clinical application, the four-trial estimate corresponds to approximately 89 fewer patients receiving or being prescribed antibiotics per 1,000 at the observed comparator risk of 671 per 1,000. It can inform PCT-supported prescribing pathways for selected respiratory presentations when results are available before the decision, with clinical assessment and reassessment remaining essential. In suspected sepsis, evidence concerning timely antibiotic administration addresses a different decision and must be interpreted separately. These distinctions also help guideline panels specify the population, endpoint, and strength of evidence underlying a recommendation [12, 13].

Table 4. Comparison with previous systematic reviews and guidelines

Previous synthesis	Scope / key findings	Verified overlap	Present review: added analysis or clarification
2015 health technology assessment [14]	Seven ED studies; antibiotic receipt RR 0·77 (95% CI 0·68–0·87).	ED antibiotic receipt and respiratory presentations.	Defines initial ED/admission prescribing separately from episode exposure and antibiotic timing; updates the search.
van der Does et al., 2016 [4]	Systematic review of PCT-guided antibiotic initiation in ED patients.	Direct overlap in the initiation question, particularly respiratory infection.	Harmonises the initial-prescribing endpoint in an updated trial-level synthesis and evaluates other ED presentations separately.
Cochrane IPD review, 2017 [6]	PCT-guided antibiotic initiation and discontinuation in acute respiratory infections across settings.	Respiratory infection, ED patients, and initiation outcomes; adjusted ORs are not directly comparable with RRs.	Reports an initial ED/admission prescribing RR and distinguishes other antibiotic decisions and clinical populations.
ESCMID guideline, 2024 [12]	Six-trial respiratory prescribing synthesis; RR 0·84 (95% CI 0·71–0·99).	Three trial families shared with our primary synthesis: CLINPCT, ProACT, and ProHOSP.	Examines Long event-count provenance, ProRESP cluster adjustment, and Long population applicability; reports a four-trial RR of 0·87 (0·82–0·92).
Ji et al., 2026 [30]	Nine CAP-focused POCT trials (seven PCT, two molecular); PCT subgroup prescribing RD −0·12 (95% CI −0·17 to −0·08).	All four primary trial families shared: CLINPCT, ProACT, ProCAP, and ProHOSP; CAP subsets used for some trials.	Restricts intervention to PCT, harmonises initial ED/admission prescribing, and separately evaluates sepsis timing. The inclusion of cluster-randomised ProRESP merits clarification against Ji et al.'s stated eligibility criteria.

Note: A shared trial family does not imply identical participants or endpoint extraction. Ji et al. trial identities and CAP-subgroup sample sizes were checked against Supplementary Appendices 2–3 and Figure 2. CAP, community-acquired pneumonia; ED, emergency department; IPD, individual participant data; PCT, procalcitonin; POCT, point-of-care testing; RD, risk difference; RR, risk ratio.

The sepsis trials addressed a different clinical context: Dharaniyadewi and colleagues [31] reported more empirical antibiotic administration within 6 h, whereas PRONTO [10] found unchanged intravenous antibiotic initiation within 3 h but lower 28-day mortality, the mechanism of which remains unexplained. PRONTO's mortality finding informed NICE's September 2026 recommendation to consider PCT testing alongside standard assessment in adults with suspected sepsis at moderate or high risk of severe illness or death [32]. PCT concentrations may reflect both bacterial infection and the severity of the inflammatory response, and elevations can occur in severe viral illness without bacterial coinfection [33]. This biological context reinforces the need to interpret PCT alongside clinical findings, although neither trial established that these mechanisms explained its results. These findings distinguish a potential survival benefit from an effect on antibiotic initiation. Testing should not delay urgently indicated antibiotics [32].

Individual trials provided reassuring safety findings. ProACT and HiTEMP met their prespecified non-inferiority criteria for composite safety outcomes, ProHOSP reported fewer antibiotic-associated adverse effects, and PRONTO reported lower mortality [7–10]. Our pooled mortality and antibiotic-related adverse-event estimates nevertheless remained imprecise, limiting conclusions about their overall effects across the populations studied.

The absolute prescribing benefit may vary with baseline antibiotic use and the applicability of the trial populations to local ED practice. The observed comparator prescribing risk of 67·1% provides the reference for the absolute effect reported here.

Strengths include restriction to randomised trials and separation of the initial prescribing decision from subsequent antibiotic management. The principal synthesis comprised four respiratory-infection trials with modest differences in outcome definitions and assessment windows. ProHOSP contributed approximately 42% of the weight, ProACT required reconstructed counts, and CLINPCT had universal comparator-arm initiation; excluding each trial produced similar estimates. With four trials, between-study heterogeneity was difficult to estimate and small-study effects could not be assessed reliably. The prescribing outcome did not establish whether individual prescriptions were appropriate, and pretreatment in some participants means it does not represent first-ever antibiotic initiation. Clinical outcomes were less precisely estimated, and differences in definitions limited some syntheses. English-language eligibility and the predominance of high-income settings also constrain applicability.

Procalcitonin-guided care was associated with reduced initial antibiotic prescribing, primarily among adults presenting with respiratory infections. These findings support its potential role as an adjunct to clinical assessment; however, evidence remains insufficient to establish improvements in prescribing appropriateness or patient outcomes or to support its use across all suspected-infection presentations.

Declarations

Funding

There was no funding source for this study.

Competing Interests

All authors declare no competing interests.

Author Contributions

Muhammad Ifrahim Tariq conceived and designed the study and performed the statistical analyses using R in Posit Cloud. Niraj S. Kukreja reviewed the statistical outputs and forest plots and confirmed their accuracy. Muhammad Ifrahim Tariq and Niraj S. Kukreja independently screened records and assessed full texts and extracted data. They assessed risk of bias and certainty of evidence, resolving differences through discussion. They accessed and verified the underlying extracted trial-level data. Muhammad Hassan Javaid drafted the Methods, Sanya drafted the Results, and Areeba Samad drafted the Introduction and Discussion. Muhammad Ifrahim Tariq subsequently substantially revised all manuscript sections. All authors interpreted the results, critically revised the manuscript, had full access to all the data, and accepted responsibility to submit for publication.

Data Availability

The protocol is available in PROSPERO (CRD420261490984; https://www.crd.york.ac.uk/PROSPERO/view/CRD420261490984). Full search strategies, extracted data, risk-of-bias assessments, excluded full-text reports with reasons, and results of all analyses are provided in the appendix. No individual participant data were collected. The R analysis code will be available to researchers on reasonable request to the corresponding author (ifrahim311@gmail.com), from the date of publication, for verification or secondary analysis; no data access agreement is required.

Ethics approval

Ethics approval was not required for this systematic review and meta-analysis because it involved only secondary analysis of aggregate data reported in previously published studies. No participants were recruited, no new interventions were performed, and no identifiable individual participant data were accessed. Consequently, no institutional review board or ethics approval committee was involved, and no committee name or approval number is applicable.

Ethical standards and reporting guidelines

No human-participant research ethics standard requiring prospective ethics committee review (such as the Declaration of Helsinki) was applicable to this secondary analysis of publicly reported aggregate study data. The systematic review and meta-analysis was reported in accordance with the PRISMA 2020 reporting guidelines, with searches reported according to PRISMA-S. PRISMA and PRISMA-S are reporting guidelines, not substitutes for ethics committee approval.

Human Ethics and Consent to Participate declarations

Not applicable.

Consent for publication

Not applicable.

Declaration of AI use

During preparation of this manuscript, the authors used Claude (Anthropic; version [sonnet 5.5 medium]) to format and design forest plots so they look similar and check formatting and consistency between the manuscript and appendix. The authors then revised and verified all content and take full responsibility for the manuscript. Original forest plots will be provided with manuscript for journal use

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