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Association Between Antibiotic Timing and Clinical Outcomes in Patients With Cancer-Related Febrile Neutropenia: A Systematic Review and Critical Appraisal of Meta-Analytic Evidence

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Abstract

Febrile neutropenia (FN) is an oncological emergency that should be timely assessed and for which appropriate empirical antibacterial therapy should be initiated. The purpose of this systematic review was to critically assess the correlation between time to antibiotic administration (TTA), all-cause mortality, and specific non-fatal outcomes in children and adults with cancer. Twenty-five primary studies published between 2011 and 2026, including observational cohorts and multicomponent quality improvement interventions, were critically appraised, though the number of unique patients could not be safely added together due to some studies reporting repeated FN episodes. There was a wide range of variations in the timing of the origins, severity of the patient population, appropriateness of treatment, and the definition of endpoints. Hazard ratios (HRs) of individual studies showed discordant associations, with an adult cohort showing a higher HR per additional hour of delay (HR: 1.18, 95% CI: 1.10-1.26) and recent (adjusted) paediatric studies failing to demonstrate a consistent adverse association of delays just beyond the 60-minute threshold with composite outcomes. Previously published pooled estimates from Koenig et al. were considered in interpreting the available evidence; these estimates were not independently recalculated in the present review. Other peer-reviewed studies yielded different results for stable children and those with neutropenic sepsis. Interpretation of the available evidence is constrained by clinical and methodological heterogeneity, residual confounding, variability in outcome definitions, and incomplete documentation of certain review procedures. However, prompt, appropriate antibiotics are still crucial, especially for serious illness, and the data do not support the use of TTA as a causal measure of quality of care.

Categories: Hematology, Oncology
Keywords: antibiotic timing, cancer, empirical antibiotics, febrile neutropenia, mortality, neutropenic sepsis

Introduction And Background

Febrile neutropenia (FN) is defined as fever in the context of profound neutropenia, defined as an absolute neutrophil count <0.5 x 10^9/L or expected to fall below this threshold. In the patient receiving myelosuppressive cancer therapy, fever may be the first symptom of infection in the absence of any focal finding. Therefore, FN should be evaluated clinically at the earliest, risk assessed with microbiological evaluation wherever possible without delay, and suitable empirical antibiotics should be administered [1,2]. For adults, the whole picture of clinical instability, organ dysfunction, and suspected sepsis will remain much more important, although the Multinational Association for Supportive Care in Cancer (MASCC) score could be useful for risk assessment.

Guidance is to start antibiotic therapy promptly, with some interpretation of timeframes. The ASCO/IDSA guidelines for adults suggest that an initial empirical dose should be administered within one hour of triage in patients with FN [1]. The 2023 update focuses on risk-based management, and paediatric guidance includes rapid empirical treatment, particularly for those who are unstable. The Surviving Sepsis Campaign (SSC) 2026 guidelines endorse urgent antimicrobial therapy, within one hour after recognition, for septic shock or suspected/confirmed sepsis and categorise patients with diagnostic uncertainty for a brief and structured evaluation [3]. These recommendations should not be taken as an excuse for withholding therapy in high-risk or deteriorating patients.

Time to antibiotic administration (TTA) can start at the time of fever recognition, arrival at the hospital or emergency department, time of triage, or time of documented treatment decision ("time zero"). These are

not interchangeable exposures. There are also differences in type of cancer, in/emergency department admission, choice of appropriate antibiotic, and all-cause mortality vs clinical deterioration between cohorts. In an adult FN cohort, Rosa and Goldani reported that the hazard of death increased with every hour of delay in the 28-day mortality period, while other observational studies reported null or threshold-dependent associations [4-9]. These differences are not used to define a universal safe delay or a universal causal 60-minute threshold [1].

One of the main threats to interpretation is "confounding by indication": that is, patients with shock or obvious organ dysfunction are treated more rapidly, and they have a higher risk of death. This bias was noted in the earlier systematic review by Koenig et al. [10], and the pooled estimates for mortality and ICU from three studies were reported; those estimates are discussed as previously published findings rather than independently recalculated results. A more recent study of individual patient data (IPD) of 4,006 paediatric FN episodes showed paradoxically fewer composite safety events for longer TTA, which raises concern about the possibility of residual triage confounding, and does not favour delaying antibiotics [11].

The present review critically evaluates 25 primary studies, emphasising differences in antibiotic timing definitions, clinical severity, study design, and outcome assessment, and considers subsequently identified publications as contextual evidence. The contribution is a cross-age, outcome-specific narrative appraisal of later observational studies and pathway initiatives, rather than the Koenig et al. [10] appraisal, which compared the later studies to the original study. These previous pooled estimates are excluded as study-level extraction files, and an independently reproducible quantitative analysis was not provided for verification; this is a systematic review and critical appraisal and not an original meta-analysis.

Review

Study design and reporting

The original review included a systematic search and an initial set of 25 primary studies. This systematic review was reported with reference to the PRISMA 2020 statement [12], with outcome-specific narrative synthesis informed by Synthesis Without Meta-analysis (SWiM) guidance [13]. A prospective protocol registration number was unavailable for verification, limiting assessment of protocol pre-specification. There is no independent quantitative meta-analysis, post hoc registration, or protocol amendment claimed. The Population-Exposure-Comparator-Outcome (PECO) question was: In adult or paediatric patients with cancer-related FN, is a shorter time to first systemic empirical antibacterial administration associated with all-cause mortality and prespecified distinct secondary clinical outcomes compared to a longer time?

Literature search strategy

The original review queried the databases from inception to September 22, 2026, and also used Google Scholar and backward citation searching, including PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library. Its recorded yields were 214, 326, 274, 237, 31, 132, and 17 citations, respectively (total 1,231 before deduplication). The wide concepts that were documented were ("febrile neutropenia" OR "neutropenic fever" OR "neutropenic sepsis") AND ("cancer" OR "malignancy" OR "chemotherapy") AND ("antibiotic" OR "antimicrobial") AND ("time to antibiotic" OR "delayed antibiotic" OR "early antibiotic" OR "one hour" OR "60 minutes" OR "door-to-needle") AND ("mortality" OR "clinical outcomes" OR "ICU"). These are written down key concepts, rather than confirmed platform-specific search strings. The reported literature search identified 1,231 records; incomplete availability of database exports, search history logs, and full-text exclusion records limit independent verification of these yields. The reviewer-identified reports were evaluated individually as contextual evidence and did not retroactively count towards the 25 chosen studies. A supplementary literature search was carried out on electronic databases from inception to September 22, 2026. Electronic databases searched included PubMed/MEDLINE, Embase, Scopus, Web of Science, and the Cochrane Library; back referencing of eligible articles and relevant reviews was performed, and Google Scholar was employed to find additional sources. Boolean operators were used to combine the core search concepts as follows: (“febrile neutropenia” OR “neutropenic fever” OR “neutropenic sepsis”) AND (“cancer” OR “malignancy” OR “oncology” OR “chemotherapy”) AND (“antibiotic” OR “antimicrobial therapy”) AND (“time to antibiotics” OR “time-to-antibiotic” OR “door-to-antibiotic” OR “door-to-needle” OR “early antibiotic administration” OR “delayed antibiotics” OR “one hour” OR “60 minutes”) AND (“mortality” OR “death” OR “intensive care” OR “ICU” OR “clinical outcomes”). The syntax was customised to each database, and both free text and controlled vocabulary terms were used when applicable. The search identified 1,231 records: PubMed/MEDLINE (n=214), Embase (n=326), Scopus (n=274), Web of Science (n=237), Cochrane Library (n=31), Google Scholar (n=132), and reference list/citation searching (n=17). Geographic limitation has not been used. Studies that lacked adequate English language information to assess eligibility and extract data were excluded.

Eligibility criteria

Original comparative or exposure response studies evaluating adults or children with cancer-associated FN with measurable TTA and a clinical outcome were included. Designs ranged from prospective cohort and retrospective cohort to emergency department and inpatient studies and care pathway evaluations. There were three criteria for the synthesis of outcomes: a well-defined time origin, an identifiable exposure

contrast, and an outcome ascertained on a clinically relevant interval. Studies with more than one FN episode per person were kept descriptively but not counted as independent patient level episodes. Antibiotic timing was not considered direct evidence, and such studies of heterogeneous neutropenic sepsis populations or guideline concordant treatment were identified as such [14,15].

The original report excluded designs were reviews/meta-analyses, editorials, case reports (no comparator group), conference-only abstracts (outcomes not extractable), duplicate cohorts, and studies not assessing antibiotic timing or clinically relevant outcomes. The information was all required to be in English, which may have some language bias. The record of excluded full texts was not accessible for external checking; this means that individual exclusion decisions and whether there may be eligible missed reports cannot be independently validated. This limit is not an exhaustive listing, but a limitation.

Definition of FN and antibiotic timing

FN definitions and temperature thresholds were taken as reported by each primary study and not harmonised retrospectively; ANC<0.5 x 10^9/L (or expected decline) was reported as common, but not universal. Major effect modifiers and confounding variables were identified to be clinical severity at presentation, hypotension, respiratory compromise, bacteraemia, organ dysfunction, and shock. A 60-minute threshold was not considered an alternative to the following clinical features.

TTA was the time between the onset of the first empirical systemic antibiotic administration. Studies varied in terms of the starting point, which could be recognition of fever/FN, on arrival to hospital, in triage, in inpatient assessment, or in treatment order. Threshold comparisons (<60 minutes, ⩾60 minutes, ⩽60 minutes, >60 minutes, ⩽4 hours, >4 hours) were not considered equivalent to continuous per hour estimates. The direction of comparison was specified, and whether or not the baseline severity was adjusted in the primary report.

Selection process and record availability

There were 1,231 records, of which 441 were considered duplicates, and 790 unique records were obtained, 679 of which were excluded, 111 full texts were requested, 3 reports were not available, and 108 were evaluated, 83 of which were excluded, and 25 retained. This arithmetic is consistent in-house and shown in Figure *1*, and the individual exclusions and citation library were not available for audit. It cannot be claimed that screening and full-text assessment were performed independently by two reviewers, that conflicts were resolved, or that unavailable full texts were requested from authors. The study selection summary is based on reported screening and eligibility counts; complete screening records and individual exclusion logs were unavailable for independent verification.

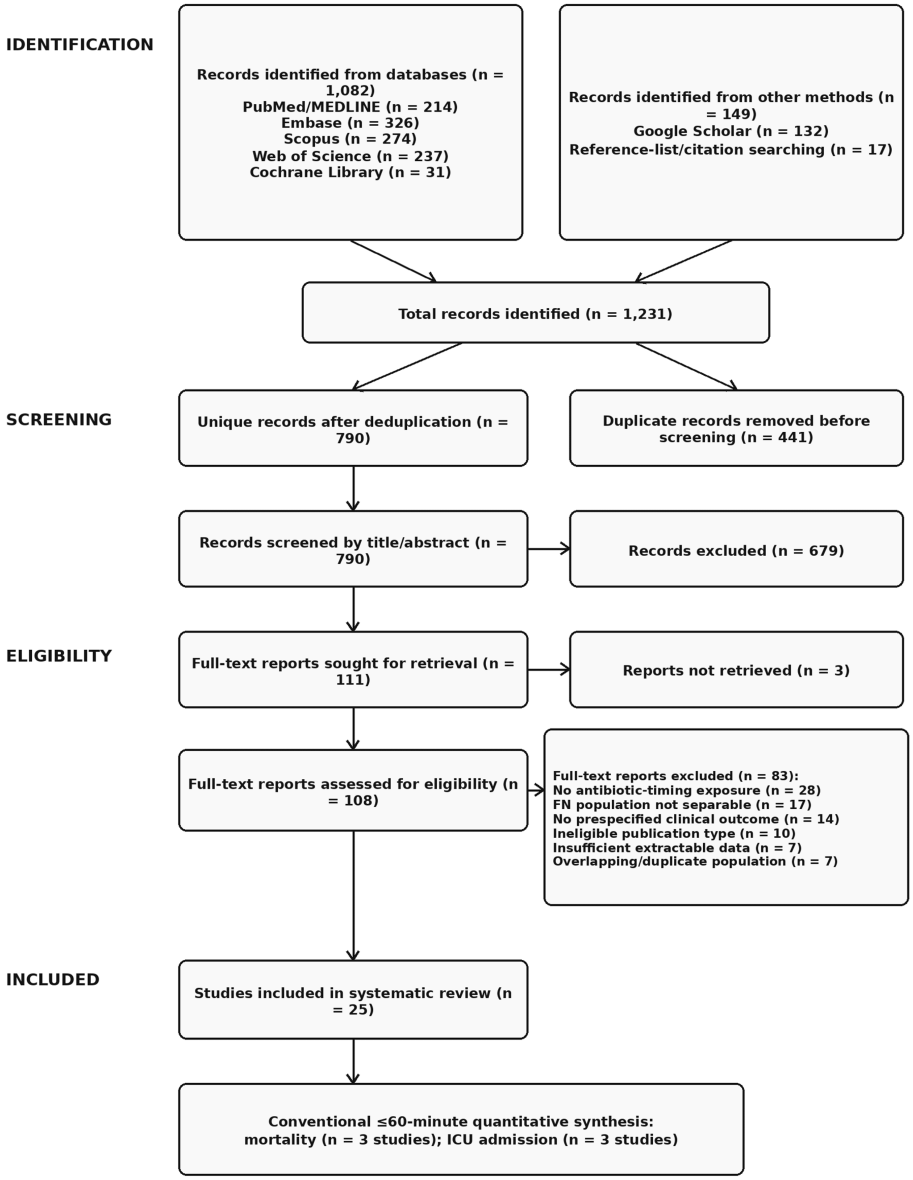


FIGURE 1: PRISMA 2020 flow diagram summarising the reported identification, screening, eligibility assessment, and inclusion of 25 primary studies. Supporting search exports and individual full-text exclusion records were unavailable for independent reconciliation.

Data extraction

The extraction framework provided includes study year and design, adult/paediatric setting, malignancy, numbers of participants and episodes, TTA starting point and thresholds, exposure to first antibacterial, timeframe for all-cause mortality, ICU admission, septic shock, composite adverse outcomes, length of stay, and adjusted and unadjusted estimates with 95% confidence intervals. Unique participants were separated from extraction of repeated episodes. Complete original extraction records and documentation of duplicate extraction, piloting, discrepancy resolution, and investigator contact were unavailable for verification. We have not suggested that those steps did occur.

Study-specific estimates and data reported in the primary articles cited have been retained as effect estimates. When adjusted estimates were available, these were highlighted, but they were not aggregated with crude estimates under a single category. Hazard ratios (HRs), risk ratios, and odds ratios (ORs) were not used interchangeably. The original findings presented in Koenig et al. (2020) [10] are only presented as findings of this previous review and not as a new analysis.

Outcomes

All-cause mortality was the main outcome of interest. They were separated and not combined in-hospital, 28-day, and 30-day mortality. If the primary result measured death or survival for a specific duration of follow-up (e.g., 180 days), then that specific follow-up duration was identified and not reported as a short-term all-cause mortality.

Secondary endpoints included the rates of ICU admission alone, death or ICU admission as a composite, and broader adverse composite endpoints of bacteraemia, septic shock, organ dysfunction, vasopressor use, or mechanical ventilation, and length of stay. Where possible, the makeup of each outcome and the exact denominator was maintained. Within a patient, several FN episodes can give rise to correlated observations, which were assumed to be statistically independent.

Assessment of bias and evidence certainty

There were no completed rating sheets for primary studies (ROBINS-I) or duplicate assessment worksheets with the manuscript. The review therefore does not presume to include a validated formal ROBINS-I assessment or formal GRADE certainty ratings, in retrospect. Rather, each evidence category was descriptively assessed for the potential for confounding by indication/triage, exposure misclassification, outcome ascertainment, loss to follow-up, and selection of the result reported. An independently recorded, duplicated risk of bias, and certainty assessment is therefore recommended to sufficiently meet PRISMA and the reviewer request [10,12], and inference about a 60-minute threshold is considered limited.

Measuring some measured confounding by observational studies with multivariable adjustment, propensity score methods, or target trial emulation cannot eliminate unmeasured acuity or indication bias. Pathway studies are subject to “secular trends” and co-interventions, especially when they involve a “before” and “after” comparison. These design limitations are stated next to the outcomes instead of assuming that statistical significance equates with causal effect.

Narrative synthesis and statistical reporting

The new synthesis is presented for (i) all-cause mortality at conventional or alternate thresholds, (ii) ICU admission and composite safety outcomes, (iii) continuous/hourly TTA, and (iv) before-after quality improvement studies. The study, outcome, direction of the estimate, and whether adjustment was reported are indicated for each comparison, along with the principal interpretive limitation. Direction-of-effect synthesis was used as opposed to vote counting. An outcome-specific narrative synthesis was undertaken because the available study level information did not support an independently reproducible quantitative analysis. Estimates formerly labelled pooled (mortality OR: 0.78, 95% CI: 0.16-3.69; ICU OR: 1.43, 95% CI: 0.57-3.60) are explicitly attributable to Koenig et al. [10], not to this review.

In the previous review, random-effects meta-analysis was performed, and there were 13 primary studies overall, three of which were included in the 60-minute mortality and ICU comparisons [10]. The present manuscript tables of their estimates lack information on arm-specific event counts, comparable endpoints, directions of effect, and variance information. It would be misleading to repeat those sums as pooled over the years and presented under the rubric of a new meta-analysis. Rather, directly verifiable primary study effects are reported here and the results of previous syntheses are cited as external evidence.

Subgroups and sensitivity analyses

Differences between adult and paediatric populations, clinical severity categories, malignancy types, and treatment settings were examined descriptively; formal subgroup meta-analyses and leave-one-out analyses were not undertaken because sufficient study-level data were unavailable. These differences are described and referred to as clinical contrasts rather than statistically tested effect modification. Prospective studies of septic patients and clinically stable children are informative and refer to different baseline-risk populations [16,17].

Reporting bias and small-study effects

Formal Egger testing and funnel-plot assessment were not performed; an independent pool of at least 10 compatible studies was not reconstructed. Publication bias, selective extraction, missing full texts, and selective endpoint reporting are all potential sources of bias. The lack of statistically significant findings should not be interpreted as a formal certainty profile.

Synthesis scope and contextual evidence

The systematic data set includes the original 25 primary reports. Following the reviewers' feedback, more relevant published studies and evidence syntheses were identified [3,11-19]. Due to the lack of an authenticated re-run of the original search and/or database-screening export, these publications have been included as a contextual update and were not included as an addition to the denominator (25-study PRISMA diagram). A documented search update is necessary to render the report complete as to the final study count

and revised screening totals.

Eligibility of borderline evidence

The broad neutropenic sepsis audit by Wells et al. [14] and the neutropenic sepsis audit focusing on receipt of guideline-recommended treatment by Gulleen et al. [15] provide only contextual process information. Independent timing exposure cohorts are not combined with Salstrom [20] and other quality improvement interventions. Butts [6] examined both a threshold and continuous TTA and also presents the overall composite, not just mortality. Ko [5] evaluated various cutoffs for composite poor outcomes, not mortality itself.

Results

Study Characteristics

The original search and screening counts are presented in Figure *1* and described in the Methods. The newly identified reports were not added to the historical 25-study flow, as the underlying screening library has not been retrieved. This is not because the newer reports were not eligible but because of transparency.

The original evidence set consists of 25 reports from 2011 to 2026, as shown in Table *1*. The evidence synthesis reflects the originally documented 25-study dataset; subsequently identified publications were considered separately and were not incorporated into the original selection counts. Some studies report multiple episodes, and the episode denominators were not added as if they referred to different individuals. The extraction provided is not complete, or the original study timing start points vary. Two further directly relevant studies identified during review (Kim et al. [16] and Vergara Muñoz et al. [17]) are discussed as a verified contextual update without altering the original search flow.

No.	Study	Population/design	Sample	TTA assessment	Time zero/exposure origin
1	Pakakasama et al., 2011 [21]	Paediatric oncology; retrospective guideline/QI cohort	170 post-guideline febrile episodes plus historical controls	Door-to-antibiotic; principally ≤120 min	ED arrival
2	Gavidia et al., 2012 [22]	Paediatric leukaemia; prospective cohort	251 children; 269 outpatient febrile episodes analysed	Fever-to-assessment and antibiotic delay	Fever recognition/assessment
3	Lynn et al., 2013 [23]	Adult chemotherapy-induced FN; retrospective cohort	81 FN episodes/78 patients	Antibiotic latency as continuous exposure	Not specified in source summary
4	Fletcher et al., 2013 [24]	Paediatric cancer; retrospective cohort	1,628 admissions/653 patients	≤60 min, 61-120 min and longer intervals	Hospital arrival
5	Perron et al., 2014 [25]	Adult cancer FN; retrospective cohort	105 patients	Continuous TTA; median 2.5 h	ED arrival
6	Rosa and Goldani, 2014 [4]	Adult cancer FN; prospective cohort	307 episodes/169 patients	Continuous TTA and ≤30 vs 31-60 min	ED presentation
7	Keng et al., 2015 [26]	Adult oncology; prospective QI pathway	276 pathway FN episodes plus historical/direct admission cohorts	Pathway target ≤90 min	ED arrival
8	De la Maza et al., 2015 [27]	Paediatric cancer; prospective multicentre	388 episodes/226 children	≤60 vs >60 min	Hospital admission
9	Salstrom et al., 2015 [20]	Paediatric oncology; before-after/QI study	Paediatric FN episodes	<60 vs >60 min	ED arrival
10	Ko et al., 2015 [5]	Adult chemotherapy-induced FN; registry cohort	1,001 episodes	1-, 2-, 3-, 4-hour cutoffs; unfavourable outcome composite	Not specified in source summary
11	Wells et al., 2015 [14]	Neutropenic sepsis service audit (indirect FN timing evidence)	Three audit periods	≤1-h door-to-needle target	Door/arrival
12	Butts et al., 2017 [6]	Adult haematological malignancy; retrospective	244 FN events	Continuous TTA and <60 vs ≥60 min for composite outcome	Not specified in source summary

13	Johannesmeyer and Seifert, 2019 [28]	Adult FN; retrospective	93 patients	Time to first antibiotic dose	Not specified in source summary
14	Daniels et al., 2019 [7]	Adult FN; retrospective cohort	3,219 cases	Graded hourly TTA categories	Fever recognition
15	Peyrony et al., 2020 [29]	Adult cancer FN; prospective ED cohort	249 patients	Continuous ED TTA	ED arrival
16	Gulleen et al., 2021 [15]	Acute leukaemia; guideline-concordant antibiotic receipt (indirect TTA evidence)	49 FN events/39 patients	Time to initial and guideline-recommended antibiotics	Initial order vs recommended antibiotic
17	Koenig et al., 2022 [30]	Paediatric cancer; prospective multicentre	266 episodes/140 patients	Continuous/categorical TTA	Fever recognition incl. prehospital
18	Villars et al., 2023 [8]	Adult inpatient haematological malignancy	187 FN cases	<1, 1-2, 2-3, 3-4, and >4 h	Inpatient fever
19	De Castro et al., 2024 [31]	Paediatric oncology; two-centre cohort	2,349 episodes	<60 vs ≥60 min and continuous TTA	Not verified in source summary
20	Haeusler et al., 2024 [32]	Paediatric cancer; multicentre target trial emulation	1,685 episodes/976 patients	<60 vs ≥60 min	Not verified in source summary
21	Iqbal et al., 2024 [33]	Adult oncology; prospective study	79 patients	≤1 vs >1 h	Door/arrival
22	Colunga-Pedraza et al., 2024 [34]	Paediatric haematology-oncology; QI cohort	291 patients	Pre/post Golden Hour intervention	ED/arrival
23	Attas et al., 2025 [35]	Adult oncology ED; retrospective	149 patients	≤60 vs >60 min	ED arrival
24	Malvestiti et al., 2025 [36]	Paediatric cancer; comparative SOP cohort	265 FN episodes	≤30, ≤60 min and longer intervals	Not verified in source summary
25	Van de Louw et al., 2026 [9]	Adult haematological malignancy; propensity score analysis	1,089 patients	Continuous TTA and ≤4 vs >4 h	Not specified in source summary

TABLE 1: Population, design, sample, and timing definition of the 25 studies in the original review dataset

Country and exact time zero require verification against the complete primary reports where not stated; episode counts should not be interpreted as independent patients.

FN, febrile neutropenia; QI, quality improvement; TTA, time to antibiotic administration.

In multiple studies, recurrent FN episodes in the same patient were counted. In pooled data, it was not possible to determine the number of unique patients from the data provided; associations should be read with the understanding that there may be correlation within patients. Figure *2* shows the distribution of the original 25 studies over time, rather than the contextual reports being discovered through peer review.

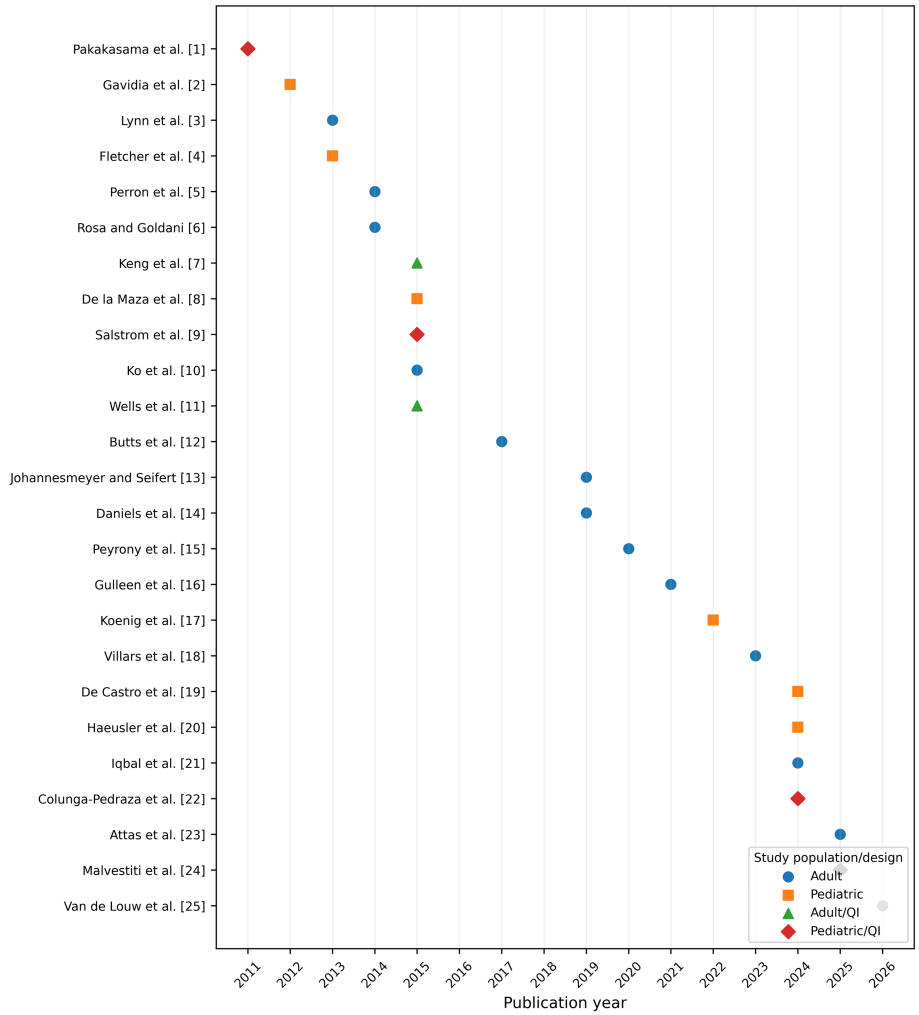


FIGURE 2: Chronological distribution of the 25 primary studies in the original evidence synthesis, categorised according to study population and research design

QI, quality improvement.

Outcomes in the Original Study Dataset

The all-cause mortality signal with the shortest duration (28 days) had the clearest report from Rosa and Goldani [4]: 29 deaths occurred over 307 FN episodes, with a modelled per-hour HR of 1.18 (95% CI: 1.10-1.26). The model is based on a per-hour functional relationship, not on the notion that risk rises linearly for each individual patient or that there is a cut-off at 60 minutes. There were 169 individuals in their cohort who experienced repeated episodes and whose independence assumptions were limited. An alternative question was evaluated by Fletcher et al. [24], who reported worse composite adverse outcomes at 61-120 vs ≤60 minutes (OR: 1.81, 95% CI: 1.01-3.26), where the endpoint was not just death, and where hypotensive/severe presentations were not excluded.

Several studies did not find a negative association for death at short cutoffs. Ko et al. [5] assessed 1,001 FN episodes with a composite of adverse outcomes with 1-, 2-, 3-, and 4-hour thresholds; such a result cannot be termed a pure assessment of all-cause mortality. Butts et al. [6] found an inpatient FN event rate of 244 and no significant correlation to a death/ICU/vasopressor composite. Daniels et al. [7] identified a non-monotonic relationship between adjusted 30-day mortality and treatment time within 2 hours: ORs were 0.87 at 2-3 hours, 1.57 at 3-6 hours, 1.37 at 6-24 hours, and 2.08 at >24 hours (the latter group being the least favourable) (Table *2*). Different cutoffs, illness severity, and outcomes preclude direct numerical comparison.

Study	Main outcome	Key result

Pakakasama 2011 [21]	Septic shock, ICU, infection-related death	Septic shock and ICU admission decreased after guideline implementation; no infection-related deaths occurred in the post-guideline cohort.
Gavidia 2012 [22]	Sepsis/infectious death	Delayed assessment and treatment were associated with adverse infectious outcomes; socioeconomic and access factors were important determinants of delay.
Lynn 2013 [23]	Serious complications/death	25/81 episodes developed serious complications; antibiotic latency was an independent predictor of complications.
Fletcher 2013 [24]	Composite: mortality/PICU/fluid resuscitation (not mortality alone)	61-120 vs ≤60 min: OR: 1.81 (95% CI: 1.01-3.26) for a composite outcome; patients with systolic hypotension at presentation were excluded.
Perron 2014 [25]	ICU/death and LOS	Five patients died or required ICU monitoring; TTA did not independently predict mortality/ICU use, but each additional hour was associated with longer hospitalisation.
Rosa 2014 [4]	28-day mortality	HR: 1.18 (95% CI: 1.10-1.26) for each additional hour of TTA.
Keng 2015 [26]	TTA, LOS, ICU	FN pathway markedly reduced TTA and hospital stay; pathway intervention involved several simultaneous care process changes.
De la Maza 2015 [27]	Hypotension, ICU, sepsis, mortality	Median TTA was 132 min; administration after 60 min was not associated with worse outcomes.
Salstrom 2015 [20]	ICU use; before-after quality improvement	Quality improvement intervention; association of earlier delivery and fewer ICU admissions does not isolate a mortality effect of TTA.
Ko 2015 [5]	Composite unfavourable outcome (including serious complications/death)	Across 1-, 2-, 3-, and 4-hour cutoffs, adjusted analyses found no consistent effect on the unfavourable outcome composite; these were not separate mortality-only analyses.
Wells 2015 [14]	Neutropenic sepsis outcomes	Before-after mortality 14/36 (39%) vs 0/79 (0%) across audited service periods; multiple care changes and a broadly defined neutropenic sepsis population.
Butts 2017 [6]	Death/ICU/vasopressor composite	35/244 events had an unfavourable composite outcome. <60 vs ≥60 min: OR: 0.98 (95% CI: 0.44-2.12) for the composite (as summarised in Koenig et al. [10]); not an all-cause mortality OR.
Johannesmeyer 2019 [28]	Hospital length of stay; death/ICU (secondary)	TTA did not independently predict hospitalisation length and was not shown to predict mortality or ICU admission.
Daniels 2019 [7]	ICU/30-day mortality	Adjusted 30-day mortality ORs relative to ≤2 h: 0.87 (2-3 h), 1.57 (3-6 h), 1.37 (6-24 h) and 2.08 (>24 h); non-monotonic pattern, rather than a uniform increase per hour.
Peyrony 2020 [29]	Composite ICU admission or death	TTA was not independently associated with the ICU/death composite; non-guideline concordant initial therapy was associated with the composite (OR: 3.50, 95% CI: 1.49-8.28).
Gulleen 2021 [15]	Guideline-recommended treatment receipt and in-hospital mortality	Process of receiving appropriate antibiotics, not an isolated door-to-first dose time comparison; interpret as indirect evidence.
Koenig 2022 [30]	Death/ICU/severe sepsis/bacteraemia	Fever recognition to antibiotic interval included prehospital time (median about 120 min); propensity methods only partially addressed triage bias.
Villars 2023 [8]	180-day survival	TTA categories were not significantly associated with overall survival (p=0.420).
De Castro 2024 [31]	Major complications	<60 vs ≥60 min was not associated with major complications: adjusted OR: 0.99 (95% CI: 0.62-1.59).
Haeusler 2024 [32]	ICU admission/death	≥60 vs <60 min adjusted RR: 0.62 (95% CI: 0.32-1.21) for ICU/death, based on 43 composite events; direction favoured later therapy, illustrating likely confounding, not benefit from delay.
Iqbal 2024 [33]	Mortality, ICU, LOS	Only two deaths among 79 patients; mortality comparisons are underpowered even if ICU admission or LOS differed.
Colunga-Pedraza 2024 [34]	Clinical deterioration/PICU	Median TTA declined from 269.4 to 50.54 min; clinical deterioration/PICU admission declined from 6.6% to 2.3% (p=0.03).
		No statistically significant association with mortality (p=0.611), ICU admission (p=0.682),

Attas 2025 [35]	Mortality/ICU/LOS	or LOS (p=0.959) in 149 adult patients.
Malvestiti 2025 [36]	Adverse events/TTA	Median TTA declined from 93 to 44 min, but adverse event rates did not significantly change.
Van de Louw 2026 [9]	Hospital mortality	Retrospective single-centre propensity-matched study: hospital mortality 8.0% (≤4 h) vs 11.9% (>4 h); matched OR: 0.55 (95% CI: 0.31-0.96). Hourly and sepsis/bacteraemia subgroup analyses were not independently significant.

TABLE 2: Outcome-specific results and limitations in the original 25-report evidence set

CI, confidence interval; FN, febrile neutropenia; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; PICU, paediatric intensive care unit; QI, quality improvement; RR, risk ratio; TTA, time to antibiotic administration.

Previously Published 60-Minute Meta-Analysis

Koenig et al. published a systematic review in 2020 with three studies contributing to their 60-minute all-cause mortality synthesis and three to ICU admission [10]. They reported pooled effects of OR: 0.78 (95% CI: 0.16-3.69) for mortality and OR: 1.43 (95% CI: 0.57-3.60) for ICU admission, with large uncertainty and considerable susceptibility to triage bias. The submitted manuscript mistakenly included these numbers as new pooled analyses, and they are presented here with the investigators explicitly named as 2020. They do not demonstrate equivalence, no harm, or the safety of delaying antibiotic treatment (Table *3*).

Evidence group	Representative original studies	Outcome type	Interpretive limitation
All-cause mortality, ≤60 vs >60 min	Original primary literature with suitable counts only; original pooled counts unavailable	Mortality by stated time frame	Cannot independently calculate a new pooled OR; earlier review results belong to [10]
Composite events at ≤60 min	Fletcher [24], Butts [6], De Castro [31], Haeusler [32]	Unfavourable outcome/ICU or death/major complications	Not interchangeable with all-cause mortality; adjustment and reference direction differ
Mortality at longer thresholds	Daniels [7], Villars [8], Van de Louw [9]	30-day mortality, 180-day survival, hospital mortality	Different time zero and endpoints; no common meta-analytic effect
Continuous/hourly timing exposure	Rosa [4]; selected other cohort analyses	28-day mortality hazard or non-fatal outcomes	Assumed per-hour functional form; episode clustering and residual confounding
Multicomponent quality initiatives	Pakakasama [21], Keng [26], Salstrom [20], Wells [14], Colunga-Pedraza [34], Malvestiti [36]	Treatment interval, ICU use, and other process/outcome metrics	Before-after secular trends and co-interventions prevent attributing benefits to TTA alone
Indirect or borderline eligibility	Gavidia [22], Gulleen [15]	Treatment access, guideline concordance, and infection outcomes	May not measure the same first-dose TTA; keep as contextual evidence

TABLE 3: Evidence categories, eligible outcomes, and limitations for interpretation

As there were no original per-arm event counts, study weights, model specification, statistical code, or forest plots for a potential independent pooled analysis from the source manuscript, no new meta-analytic estimate is asserted. Substantive conclusions below depend on the direction and design of individual original studies, the previous published synthesis, and separately labelled contextual evidence.

Adult Evidence: Mortality and Alternative Thresholds

Rosa and Goldani [4] found a hazard for mortality within 28 days that was significant per hour but did not specifically test for linearity in the association. A different endpoint was short-term mortality; likewise, Villars et al. [8] observed 180-day survival and found no relationship among the different categories of TTA inpatient grading (p=0.420). However, if length of stay is assessed, Johannesmeyer and Seifert [28] did not demonstrate a reliable independent association of TTA with mortality or admission to the intensive care unit. Neither should be considered to be a positive or negative 60-minute mortality study.

Antibiotic within two hours of fever (in predominantly an inpatient population) was the reference in Daniels et al. [7]. There was no monotonic association between the 30-day mortality odds for the various timing categories, and this suggests that a simple linear delay model is not supported. By contrast, Van de Louw et al. [9] found a mortality of 8.0% in TTA ⩽4 hours vs 11.9% in TTA >4 hours (propensity-matched OR: 0.55 (0.31-0.96) for earlier vs later TTA). Causal generalisation is limited by its single-centre retrospective design, 2005-2020 timeframe, median TTA of approximately 132 min, and limited evidence of a subgroup effect in sepsis/bacteraemia.

Paediatric Evidence: Composite Outcomes and Severity

Fletcher et al. [24] found an increased risk of a composite endpoint among children treated with antibiotics within 61-120 minutes of presentation but did not exclude those with systolic hypotension. Salstrom et al. [20] conducted a before-after quality improvement study and should not be treated as a separate conventional mortality cohort. De la Maza et al. [27] reported 388 FN episodes in 226 children and a median arrival-to-antibiotic interval of 132 minutes; administration after 60 minutes was not associated with worse reported outcomes. The differing start points and exclusions affect comparisons.

De Castro et al. [31] assessed 2,349 episodes and found no association of <60 vs ⩾60 minutes with major complications (adjusted OR: 0.99, 95% CI: 0.62-1.59). Haeusler et al. [32], in 1,685 episodes, reported an adjusted risk ratio of 0.62 (95% CI: 0.32-1.21) for ⩾60 vs <60 minutes on an ICU-admission/death composite, with 43 outcome events (39 ICU admissions and five deaths, with overlap possible). Its direction does not support a causal claim of safety from waiting: sicker children were often treated earlier. Koenig et al. [30] measured time from fever recognition, including prehospital time; their analyses could only partially address triage bias.

Quality Improvement and Before-After Designs

Multicomponent FN pathways reduced measured delays but cannot isolate the treatment-timing effect from changes in recognition, triage, prescribing, staffing, monitoring, or supportive care. In Pakakasama et al. [21], reported ICU admission decreased from 9.4% to 2.9% and septic shock from 10.9% to 3.5%, while infection-related mortality changed from 6.5% (9/138) to 0% (0/170). These are pre/post comparisons and do not establish that TTA reduction alone produced the outcome changes.

Wells et al. [14] reported mortality of 39% (14/36) before versus 0% (0/79) after service development, but the audited population and accompanying care changes limit attribution to the one-hour target. Colunga-Pedraza et al. [34] reported median TTA declining from 269.4 to 50.54 minutes and deterioration/paediatric intensive care unit admission from 6.6% to 2.3% (p=0.03); the pathway changed several processes simultaneously. Malvestiti et al. [36] shortened median TTA from 93 to 44 minutes without statistically significant improvement in adverse event rates (Table *4*).

Study and comparison	Denominator	Published effect (95% CI if reported)	Specific outcome/limitation
Rosa and Goldani 2014 [4]	307 FN episodes/169 patients	HR: 1.18 (95% CI: 1.10-1.26) per additional hour	28-day all-cause mortality; per-hour modelled association, observational
Fletcher 2013 [24]	1,628 admissions	OR: 1.81 (95% CI: 1.01-3.26), 61-120 vs ≤60 min	Composite adverse events; hypotensive children excluded
Butts 2017 [6]	244 FN events	OR: 0.98 (95% CI: 0.44-2.12), <60 vs ≥60 min	Broad composite; historical estimate described by prior review [10]
Daniels 2019 [7]	3,219 cases	30-day mortality OR: 2.08 (>24 h vs ≤2 h)	Adjusted; other intermediate timing categories were non-monotonic
De Castro 2024 [31]	2,349 FN episodes	aOR: 0.99 (95% CI: 0.62-1.59), <60 vs ≥60 min	Major complications, not all-cause mortality
Haeusler 2024 [32]	1,685 episodes/976 children	Adjusted RR: 0.62 (95% CI: 0.32-1.21), ≥60 vs <60 min	ICU admission/death composite; 43 events
Attas 2025 [35]	149 patients	Mortality comparison (p=0.611)	No significant reported difference; two-group mortality counts require source extraction
Van de Louw 2026 [9]	1,089 haematology patients	Propensity-matched OR: 0.55 (95% CI: 0.31-0.96), ≤4 vs >4 h	Hospital mortality; longer threshold, single centre
Kim 2026 [16] -- contextual update	942 patients, 20 hospitals	IPTW OR: 1.26 (1-3 h vs <1 h); OR: 1.50 (≥3 h vs <1 h)	In-hospital mortality in neutropenic sepsis; not original 25 study cohort
Vergara Muñoz 2025 [17] -- contextual update	192 episodes/163 stable children	No independent TTA association with poor outcome composite	12 composite events and no deaths; not original 25 study cohort

TABLE 4: Individual published effect estimates

aOR, adjusted odds ratio; CI, confidence interval; FN, febrile neutropenia; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; RR, risk ratio; TTA, time to antibiotic administration.

Interpretation of the 60-Minute Target

The original study reports and the existing quantitative synthesis [10] do not establish that the 60-minute threshold is a universal causal boundary for mortality. This does not mean that it is safe to wait longer than one hour. These are still vital to consider when interpreting the quality of care, treatment appropriateness, presentation severity, and standardised measurement of time zero.

Discussion

The present synthesis provides an outcome-specific clinical and methodological appraisal of heterogeneous observational and quality improvement evidence rather than an independently reproduced meta-analysis. This review extends the clinical interpretation of previously published evidence by considering subsequent studies and differences in patient severity, treatment timing, and outcomes; no independent pooled effect estimates were calculated [10]. The 2026 IPD meta-analysis of paediatric data [11] further underlines the importance of residual triage bias: a total of 4,006 episodes of FN in 2,073 children resulted in paradoxical inverse associations between longer TTA and adverse composites, with no evidence that treatment delay should be selected for therapeutic benefit.

Kim et al. [16] importantly conducted a prospective study on 942 neutropenic sepsis patients in 20 South Korean hospitals using inverse probability of treatment weighting. Relative to treatment within one hour, adjusted in-hospital mortality odds were higher with treatment at 1-3 hours (OR: 1.26, 95% CI: 1.04-1.53) and at ⩾3 hours (OR: 1.50, 95% CI: 1.22-1.85). This severity-selected adult population directly calls into question an unqualified statement that delays of less than an hour are of no importance. Vergara Muñoz et al. [17], however, did not identify any independent association of TTA >60 minutes with an adverse composite in 192 episodes in clinically stable children, as no deaths occurred and only 12 (6.3%) episodes experienced the composite. The results pertain to various severity strata and not necessarily to each other;

that is, they are not mutually contradictory.

Careful interpretation of null associations in the paediatric population also needs to be applied in the context of time zero and repeated episodes and study overlap. The studies of Koenig et al. [30], De Castro et al. [31], Haeusler et al. [32] applied different endpoints, which may have included a significant prehospital interval after fever recognition. Some of the participants in earlier paediatric cohorts may be included in the later IPD meta-analysis [11], and the total number of participants should not be counted as evidence for the earlier studies. The observed "protective" relationship of longer TTA is consistent with confounders of severity and differential triage.

Observational associations may be weakened, or even lost or reversed, due to triage bias. Antibiotics tend to be administered earlier to patients who have shock, hypotension, or altered mental status and are at higher risk for death at the time of presentation. Multivariable and propensity score analyses might not account for how bad or when the initial evaluation is. Thus, the SSC 2026 [3] distinguishes between septic shock (and higher confidence sepsis) and diagnostically uncertain presentations. Similarly, Gupta et al. [18] (in a more general suspected sepsis cohort, not a cancer-FN-only cohort) identified that short delays were correlated with higher mortality mainly in septic shock. These results validate the importance of severity-based urgency and do not replace the standard of care for antimicrobials.

The quality of antibiotic treatment and the choice of antibiotic should not be confused with timing. Peyrony et al. [29] classified inadequate empirical antibiotic treatment as the lack of adherence to the guideline-recommended treatment, and its primary adverse endpoint was the composite of death or admission to the ICU. Non-guideline concordant treatment was reported to have an independent association with the composite (OR: 3.50, 95% CI: 1.49-8.28), but TTA was not associated with the composite after adjustment. This highlights the need for immediate appropriate empirical selection based on local susceptibility patterns and previous colonisation and patient's clinical status.

Before-after quality improvement studies, which are the most convincing, report reduced treatment intervals, although other changes such as triage protocols, antimicrobial use, and teams and follow-up were frequently implemented at the same time as TTA. Thus, the previous companion systematic review on TTA reduction interventions [37] is a valuable comparison to the purely exposure response cohorts. In case of process achievement and causal mortality benefit, these benefits must be reported separately.

An absolute threshold of exactly 60 minutes cannot be used to describe all clinically relevant delay. In longer delays, van de Louw et al. [9] reported that the mortality rates were still higher at 36-48 hours and did not reach a levelling-off effect at more than 48 hours, whereas Kim et al. [16] reported excess mortality at 1-3 hours in clinically significant neutropenic sepsis and Daniels et al. [7] reported a non-monotonic pattern. Thus, the results in stable, low-risk patients cannot be extrapolated to unstable or septic patients. It also needs to be considered in the context of the broader review of sepsis and neutropenic fever timing by Gretland et al. [19].

Limitations in this review must be separated from limitations of the original studies. Timing of origin, baseline severity and FN definitions, appropriateness of antibiotic regimen, repeated episodes, and timeframes for the outcomes were variable across the primary studies, and some were small or used composites with few deaths. Important methodological limitations include incomplete availability of protocol documentation, detailed electronic search histories, study-level risk-of-bias assessments, original full-text exclusion records, and data needed to independently reproduce previous pooled estimates. Comprehensiveness is further restricted by language and abstract exclusions and incompletely assessed overlap with IPD cohorts of children. Before strong comparative certainty claims can be made, a reproducible updated search and a prospectively documented ROBINS-I/GRADE assessment is needed.

Conclusions

Good empirical broad-spectrum antibacterial therapy continues to be a mainstay of FN care. There is no universal causal mortality cutoff at 60 minutes, as originally assembled observational literature suggests. But that lack of proof should not be taken as proof of safety for antibiotic delay: there are now new multicentre data showing increased adjusted mortality for delays of 1-3 hours and more of antibiotic therapy in neutropenic sepsis. These severity-specific findings support the paradigm of prioritising rapid treatment in clinically unstable/high-risk patients, in accordance with existing guidelines.

Future studies should use prospective multicentre cohorts, target trial emulation, or IPD studies; standardise time zero (when fever is recognised, when triage occurs, or when patients arrive at hospital); report only all-cause mortality; and report antibiotic appropriateness and illness severity. An updated systematic search replicating the outcomes and a formal, reproducible risk-of-bias assessment are required to assess whether timing thresholds differ by treatment setting, age, and/or severity.

Additional Information

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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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