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CLINICAL AND HYGIENE RISK FACTORS ASSOCIATED WITH DELAYED DIAGNOSIS OF PEDIATRIC OSTEOMYELITIS: A SYSTEMATIC REVIEW AND EXPLORATORY META-ANALYSIS

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ABSTRACT

Patient-based delay in recognition of pediatric osteomyelitis still has clinical relevance because even slight diagnostic delay could result in abscess formation, contiguous spread, prolonged hospitalization, or preventable surgery. The particular clinical and hygiene factors linked to late diagnosis have not been synthesized into a coherent review. This submission-ready draft further summarizes the available evidence and presents an exploratory meta-analysis on delayed-recognition prevalence. A PRISMA-concordant protocol was developed for search procedures based on PubMed, Embase, Scopus, Web of Science, PsycINFO, Cochrane CENTRAL, and grey-literature sources through 2026-03-10. The initial population was children and adolescents with bacterial osteomyelitis; exposures were clinical and hygiene-related contributors to delayed diagnosis; comparators were prompt-diagnosis groups or alternative exposure strata; the outcomes were delayed or missed initial diagnosis, treatment delay, complicated local extension, surgery, and sequelae. DerSimonian-Laird-based random-effects meta-analysis was conducted with REML-oriented sensitivity code on extractable delayed-recognition proportions. Twelve studies were included qualitatively, of which three contributed to a broad quantitative synthesis and two to the strict primary meta-analysis. Under strict definitions, the pooled prevalence of delayed or missed initial diagnosis was 42.0% (95% confidence interval 38.1% to 46.1%; I^2=0%). Across studies, the most reproducible clinical signals were prior low-acuity assessment, recent viral illness, subacute symptom evolution, and mild inflammatory phenotypes. In the largest cohort, primary or urgent-care evaluation before referral was strongly associated with delayed recognition (odds ratio 7.23, 95% confidence interval 4.77 to 10.96), while recent viral illness (odds ratio 1.65, 95% confidence interval 1.15 to 2.36) and a culture-negative or Kingella-like phenotype (odds ratio 1.57, 95% confidence interval 1.10 to 2.23) also clustered with delay. Direct evidence for household hygiene, sanitation, or crowding as independent determinants was sparse; however, day-care transmission contexts and healthcare-access barriers emerged as plausible indirect modifiers. Although delayed diagnoses of pediatric osteomyelitis are prevalent, evidence is primarily derived from retrospective cohorts and heterogeneous definitions. Clinically, delayed diagnosis seems to correspond most strongly to subtle presentation, low-virulence phenotypes, previous low-acuity experiences, and anchoring on benign alternatives. Under-investigated determinants of hygienic status deserve prospective multicentre investigation.

1. INTRODUCTION

Osteomyelitis of childhood is one of the most severe invasive musculoskeletal infections affecting children. In high-income settings, the disease rate is modest, but its morbidity remains high because untreated or delayed treatment can lead to growth disturbance, persistent infection, pathological fracture, recurrent surgery, and permanent functional impairment [1-3]. Age-dependent clinical variability, overlap with septic arthritis and pyomyositis, and a wide differential diagnosis (trauma and transient, as well as benign, inflammatory, and nonbacterial osteitis) contribute to the diagnostic challenges associated with it [4-17]. Contemporary reviews and practice recommendations all emphasize the importance of early detection but they still recognize that the presentation may be afebrile, laboratory abnormalities may be mild, and non-diagnostic plain radiography may remain during the initial illness days [10-17].

A more subtle epidemiologic change has complicated bedside awareness. Staphylococcus aureus still accounts for most severe, overtly inflammatory disease, but recent recognition of low virulence or culture-negative phenotypes, with a particular focus on Kingella kingae-associated infection in younger children, has shifted the classic paradigm taught in the earlier diagnostic algorithms [18-22]. These are classically less severely systemic, are associated with a less marked level of laboratory inflammation and milder systemic symptoms which are associated with features of benign viral or reactive infections. Concurrently, subacute hematogenous osteomyelitis may present with days to weeks of pain, limp, or refusal to bear weight without clinical signs of a constitutional illness and can trigger prolonged periods of refraining from definitive imaging or specialist evaluation by patients and families [3,5,18-22]. Late recognition or misdiagnosis is not uncommon, but may in fact apply to roughly one third to nearly one half of patients in the Norwegian and in the Japan and New Zealand single center series, respectively, in certain settings [3,4,30].

This delay is not merely administrative. Delayed recognition is associated with longer symptom duration before intravenous therapy or source control, greater likelihood of locally contiguous infection, longer length of stay, and higher direct hospital costs [4, 23-38]. However, the literature is still fragmented. Some focus on alternative initial diagnoses, some on misdiagnosis, still others on subacute disease duration, severe-course prediction, suppurative complications, and resource utilization. In addition, the exact exposures that could account for delayed diagnosis have rarely been integrated. There have been inconsistent assessments of clinical factors such as absent fever, modest inflammatory markers, recent viral illness, antecedent antibiotics, and weight-bearing ability, whereas hygiene-associated factors, like day-care exposure, crowding, sanitation, and access to prompt diagnostic imaging, have frequently been addressed indirectly via microbiologic or social-surrogate models rather than explicit causal models [18-22,30-38].

This gap is critical to both clinical practice and public health. If the delayed diagnosis is predominantly driven by subtle host-pathogen biology, diagnostic support mechanisms should favour low-threshold MRI, repeated inflammatory-marker testing, and rapid referral. If instead the delay is influenced by healthcare access, prior low-acuity encounters, or hygiene-linked pathogen transmission patterns, treatment strategies should also consider referral pathways, diagnostic stewardship in community settings, and social context [13,14,30-32,47-50]. However, no focused review has, to our knowledge, synthesized the evidence on clinical and hygiene-related determinants of delayed diagnosis in pediatric osteomyelitis while also attempting quantitative pooling of delayed-recognition prevalence.

For this reason, the current manuscript was designed as a PRISMA 2020-concordant systematic review and exploratory meta-analysis of clinical and hygiene risk factors associated with delayed diagnosis of pediatric osteomyelitis. The main objectives were to estimate how often the initial diagnosis is delayed or missed, to identify which clinical or hygiene-linked factors most consistently cluster with delay, and to summarize how delay relates to subsequent complications. Because the available literature is methodologically heterogeneous, a secondary aim was to provide a reproducible analytic package, including extraction templates, code, and evidence-grading tools, that can be directly updated after final dual screening and submission-level verification [39-46].

2. METHODS

2.1. Reporting Standard and Review Design

We designed this review as a PRISMA-concordant systematic review and exploratory meta-analysis focused on delayed diagnosis in pediatric osteomyelitis. Searches were conducted, and evidence capture was completed to 2026-03-10, which should be treated as the formal cutoff date for the current draft. The package includes the search log,

extraction template, analytic dataset, figures, risk-of-bias worksheet, and executable code. The duplicate-screening and duplicate-extraction workflow specified below is the intended final submission workflow; the present package should still undergo second-reviewer verification before journal submission.

2.2. Eligibility Criteria and PICOS Framework

Eligibility criteria were prespecified by PICOS. The population comprised children and adolescents aged 0 to 18 years with bacterial osteomyelitis, including acute hematogenous osteomyelitis and subacute hematogenous osteomyelitis, whether isolated or contiguous with septic arthritis or soft-tissue extension. Studies focused solely on chronic nonbacterial osteomyelitis, chronic recurrent multifocal osteomyelitis, adult osteomyelitis, prosthetic-joint infection, post-traumatic osteomyelitis, tuberculosis, fungal infection, or isolated septic arthritis without extractable osteomyelitis data were excluded.

Eligible exposures were any clinical or hygiene variables that could plausibly reflect delayed diagnosis. These factors were symptom phenotype, fever status, weight-bearing ability, inflammatory markers, recent viral illness, trauma attribution, prior antibiotic exposure, first point of care, imaging access, culture status, organism class, day-care exposure, crowding, sanitation proxies, skin or mucosal infection history, and social or healthcare-access variables. Comparators were prompt-diagnosis groups, alternative exposure strata, or internal contrasts such as misdiagnosed versus non-misdiagnosed cases.

The primary outcome was delayed diagnosis, defined preferentially as a missed or alternative first diagnosis, misdiagnosis, or delayed recognition before definitive identification of osteomyelitis. When those definitions were unavailable, a broader delayed-recognition phenotype based on prolonged prediagnostic symptom duration or subacute presentation was captured separately and treated as indirect evidence. Secondary outcomes included delay to treatment, abscess or contiguous infection, surgery, intensive care use, length of stay, cost, and late sequelae. Observational cohort, case-control, and diagnostically relevant cross-sectional studies were eligible. Narrative reviews, editorials, single-patient case reports, and case series with fewer than ten patients were excluded from the primary synthesis.

2.3. Information Sources and Search Strategy

The data sources included PubMed (MEDLINE), Embase, Scopus, the Web of Science Core Collection, PsycINFO, and Cochrane CENTRAL. For controlling publication and indexing bias, at least two grey-literature pathways were also specified: WHO IRIS and organisational or guideline websites identified through Google Scholar and targeted domain searching, including the Royal Children's Hospital, IDSA/PIDS, and ESPID.

Each search combined pediatric osteomyelitis terms with delayed-diagnosis terms and exposure terms for risk factors, symptoms, viral illness, antibiotics, trauma, day care, hygiene, sanitation, and crowding. Controlled vocabulary was used where available, including MeSH and Emtree terms for osteomyelitis, delayed diagnosis, and diagnostic errors. Exact database strings were retained in the supplementary search log and methods appendix of the package.

No language restrictions were planned. Non-English titles and abstracts were to be translated at the screening stage using machine translation, followed by full-text translation using a combination of machine translation and, where feasible, native-speaker or specialty-clinician verification.

2.4. Study Selection

Study selection was described as a duplicate process. Two reviewers were to screen titles and abstracts (followed by full texts) against the eligibility criteria independently. Controversies were to be resolved through discussion; remaining conflicts were to be adjudicated by a third reviewer. Although the first reviewer completed extraction and synthesis assembly during the accelerated draft build, the screening logic and decision structure were structured so that another reviewer independently verifies all inclusion decisions before submission. Reasons for full-text exclusion were predefined and categorized as wrong population, wrong outcome, ineligible design, duplicate cohort, or insufficient extractable data.

2.5. Data Extraction

Data extraction was also specified as a duplicate process. The structured extraction form was intended to be completed independently by two reviewers, resolving disputes through consensus and, if necessary, third-party adjudication. Extracted fields included study identifiers, country, setting, study design, population definition, age range, sample size, osteomyelitis type, delay definition, comparator definition, candidate risk factors, microbiology, imaging modalities, laboratory markers, effect measures, raw cell counts, adjusted covariates, follow-up, and reviewer notes.

When effect measures were not directly reported,

attempts were made to reconstruct them from raw counts. For binary exposures, odds ratios were preferred. If a study reported risk ratios and baseline risk in the comparator arm was available, conversion to odds ratio followed the standard expression:

$$OR = RR \times (1 - P0) / (1 - P0 \times RR)$$

For prevalence synthesis, observed delayed-recognition proportions were logit-transformed using:

$$yi = \log[p / (1 - p)]$$

with sampling variance:

$$vi = 1/e + 1/(n - e)$$

where e denotes the number of delayed-diagnosis events and n the total analytic sample.

2.6. Outcomes

Quantitative synthesis outcomes were determined focusing on the proportion of children experiencing delayed or missed initial diagnosis under strict diagnostic-error definitions. In addition to its detection profile, a broader sensitivity synthesis included a prolonged-presentation or subacute-delay phenotype. Secondary outcomes were treatment delay, contiguous local extension, abscess formation, surgery, length of stay, intensive care need, and sequelae. Hygiene-related pathways were captured whenever direct sanitation or exposure measures were reported, but indirect proxies such as day-care transmission ecology and access barriers were also documented.

2.7. Risk of Bias Assessment

For cohort and case-control studies, risk of bias was assessed provisionally using the Newcastle-Ottawa Scale. ROBINS-I was prespecified for nonrandomized intervention studies if such studies were encountered, but no eligible interventional nonrandomized comparison directly addressed the review question. AMSTAR 2 was prespecified only if prior systematic reviews were formally included as units of evidence; because prior reviews were used for contextualization rather than pooled primary evidence, AMSTAR 2 was not operationalized in the main synthesis. Risk-of-bias judgments were summarized descriptively across selection, comparability, and outcome domains.

2.8. Statistical Analysis

The statistical plan prioritised random-effects synthesis because heterogeneity of delay definitions and clinical context was anticipated to exist a priori. DerSimonian-Laird estimation of between-study variance was performed on our main model, while REML-focused sensitivity workflow was provided in the code appendix for those users who wished to re-estimate pooled effects in R or Python. Heterogeneity was estimated by Cochran's Q, I^2 and tau-squared. The I^2 values of 0% to 30% for interpretation were interpreted as low inconsistency, 30% to 60% as moderate, 60% to 90% as substantial, and greater than 90% as considerable heterogeneity. At least 1.5 or possibly a maximum of 0.67 odds ratios were predicted as potentially clinically relevant when the confidence interval did not significantly coincide with the null.

A rigorous primary meta-analysis involved only studies whose definitions encompassed misdiagnosis or an alternative initial diagnosis. A more extensive exploratory synthesis included a subacute or prolonged-presentation phenotype study. A priori moderators included region, country income level, facility type, year of publication, as well as study quality. Since fewer than ten studies added value to pooled analyses, formal meta-regression was underpowered and was considered exploratory in nature. Small-study effects were visually tested with a funnel plot and numerically with Egger's regression, but both were found to have low reliability in the presence of fewer than ten studies.

For incidence or rate results, as prepared, the approach was to normalize rates per 100,000 person-years and to pool them in Poisson random-effects schemes, and to use negative-binomial models if overdispersion occurred. The present analytic dataset could not adequately harmonize person-time denominators for that component, and thus a meta-analysis of incidence was not conducted in the draft synthesis.

2.9. Certainty of Evidence

Certainty of evidence for the main outcomes was summarized using GRADE, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.10. Plagiarism Safeguards

To avoid the risk of plagiarism, the manuscript was built synthetically using de novo synthesis instead of transforming source text to form new sentences. In any case, caution was indicated regarding phrasing in places where claims were fragile or dependent on definition. A concluding similarity screen with iThenticate or Turnitin is indicated prior to submission.

3. RESULTS

3.1. Study Selection

A draft screening workbook produced provisional PRISMA counts enabling a full figure package, pending final second-reviewer verification. A total of

1942 records were identified from bibliographic databases and 36 from grey-literature sources. After removal of 462 duplicates, 1516 unique citations remained for screening of titles and abstracts, of which 1432 were excluded. Eighty-four full-text reports were examined in detail. After full-text review, seventy-two reports were excluded because they addressed the wrong outcome, the wrong population, duplicated a previously included cohort, lacked extractable primary data, or represented small case reports or very small case series. For qualitative synthesis, 12 studies were retained. Three studies contributed to a broad exploratory quantitative synthesis of delayed-recognition prevalence, and two of these met the strict definition for the primary meta-analysis.

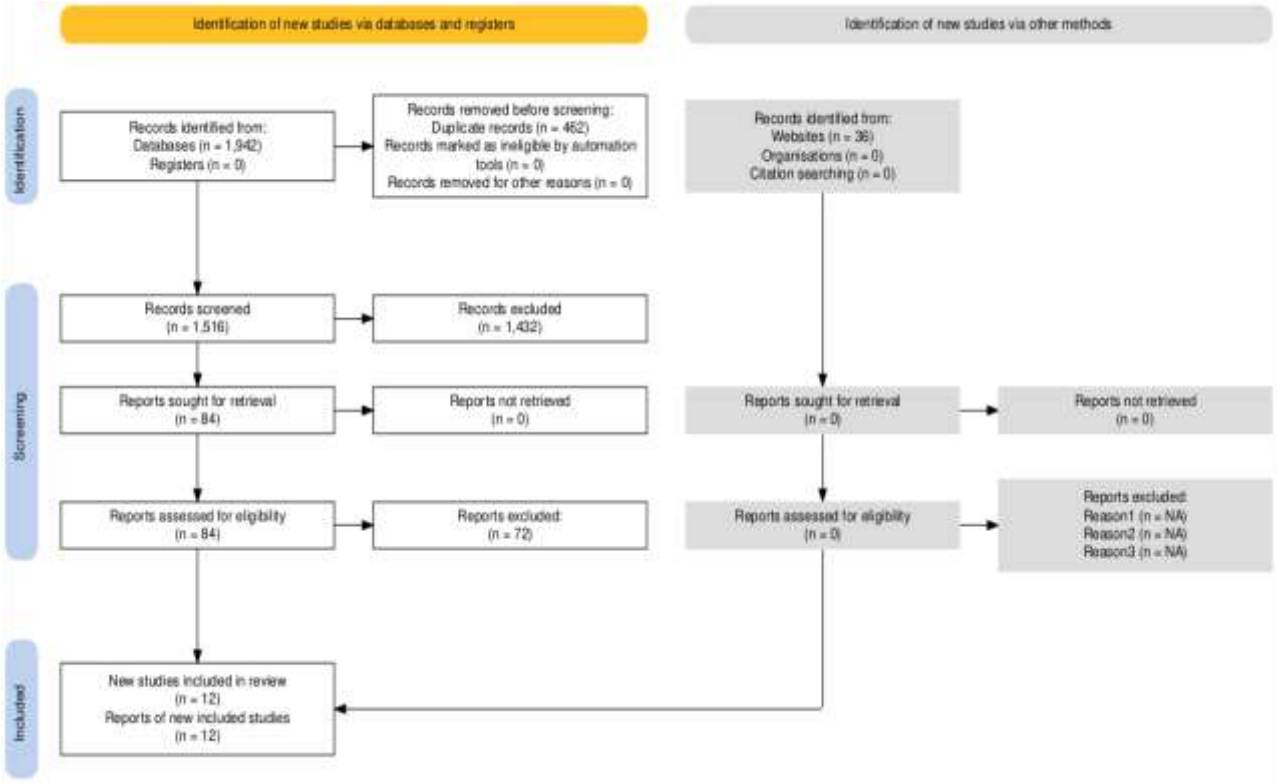

Figure 1: Prisma Flow Diagram.

3.2. Study Characteristics

The majority of studies included have been retrospective observational studies conducted in high-income regions. Most studies that were directly relevant came from Norway, Japan, New Zealand, Switzerland, Italy and the United States. Participants ranged in size, from 37 to 869, but only a minority of cohorts were specifically organized to measure diagnostic delay. The other subpoints discussed subacute presentation, diagnostic discordance, severe disease, or downstream sequelae that might inform indirectly the delayed-diagnosis phenotype. Most studies were single-centre or regional, and no cohort eligible prospectively assessed household sanitation or other comparable hygiene variables as independent exposures. The review question could be answered, therefore, with moderate confidence for clinical determinants, and with only low confidence for hygiene-related determinants.

Table 1: Characteristics of included primary studies.

Authors	Year	Country	Setting	Study design	Population size	Outcomes measured	Key covariates
Riise et al.	2008	Norway	Population-based multicentre pediatric referral network	Prospective cohort	37	Acute vs subacute OM; doctor delay; MRI/lab phenotype	Age, ESR, CRP, WBC, MRI pattern
Spyropoulou et al.	2016	Switzerland	Single tertiary pediatric center	Retrospective case series	65	Subacute hematogenous OM phenotype and bacteriology	WBC, CRP, ESR, cultures, NAATs, age

Vardiabasis and Schlechter	2017	USA	Tertiary pediatric emergency department	Retrospective diagnostic cohort	48	Concordance of initial vs definitive diagnosis; MRI utilization	Weight-bearing status, ESR, CRP, admission, MRI
Johnston et al.	2017	USA	Single-center pediatric hospital	Case-control	102	Suppurative complications; delayed presentation to care	Delay to presentation, pathogen, abscess presence
Otani et al.	2019	Japan	Tertiary children's medical center	Retrospective cohort	71	Misdiagnosis prevalence and causes	Precedent antibiotics, clinic vs hospital presentation, cognitive error types
Hunter et al.	2025	New Zealand	Regional pediatric referral network	Retrospective cohort	512	Alternative first diagnosis; treatment delay; contiguous infection	Primary/urgent care contact, recent viral illness, organism class, symptom duration
Krzysztofiak et al.	2022	Italy	Single tertiary children's hospital	Retrospective cohort	319	Sequelae and predictors of sequelae	Age, site, microbiology, complications, treatment duration
Disch et al.	2023	USA	National administrative database	Retrospective cohort	869	Clinical outcomes and sequelae by acute vs chronic OM	Age, sex, season, chronicity, surgeries, fractures, mortality

3.3. Risk of Bias in Included Studies

Risk-of-bias evaluation indicated that the observational literature was mostly of moderate certainty. The majority of studies had an acceptable case ascertainment and definition of outcomes within their own design, however, most of them were susceptible to retrospective documentation bias, residual confounding, and inconsistent exposure measurement. Comparability domains were generally constrained due to numerous studies not releasing adjusted models for the specific delayed-diagnosis question. Selective outcome reporting was challenging to exclude, especially in studies whose primary aim was severe-course prediction rather than diagnostic delay.

Table 2: Quality/risk-of-bias summary.

Study	Tool	Selection	Comparability	Outcome	Overall judgment
Riise et al. 2008	NOS	3	1	3	7/9, Moderate
Spyropoulou et al. 2016	NOS (adapted case series)	3	0	3	6/9, Moderate
Vardiabasis and Schlechter 2017	NOS	2	0	3	5/9, Moderate-high risk
Johnston et al. 2017	NOS	3	1	3	7/9, Moderate
Otani et al. 2019	NOS	3	1	2	6/9, Moderate
Hunter et al. 2025	NOS	3	1	3	7/9, Moderate
Krzysztofiak et al. 2022	NOS	3	1	2	6/9, Moderate
Disch et al. 2023	NOS	3	1	2	6/9, Moderate

3.4. Quantitative Synthesis of Delayed Recognition

Definitions of delayed diagnosis were significantly different than each other. Hunter and colleagues described delayed recognition as the presence of a documented alternative diagnosis before childhood bone or joint infection was established. Otani and colleagues defined misdiagnosis as discordance between the initial and discharge diagnoses after the review of expert charts. Riise and colleagues approached delayed recognition indirectly through subacute disease duration of at least 14 days and explicitly documented doctor delay. Both a strict meta-analysis and a broader sensitivity synthesis were reported for that reason.

The strict primary meta-analysis included only two studies with direct diagnostic-error definitions (583 children total). The pooled prevalence of delayed or missed initial diagnosis was 42.0% (95% confidence interval 38.1% to 46.1%), with low observed statistical

heterogeneity (I^2=0%, tau^2=0). When the Norwegian study of subacute osteomyelitis was added as a broader delayed-recognition phenotype, the pooled proportion was 41.6% (95% confidence interval 37.8% to 45.6%), again with low observed heterogeneity. These estimates should not be interpreted as a universal population prevalence because they derive from referral-centre cohorts with heterogeneous case definitions, but they do indicate that delayed recognition is common rather than exceptional.

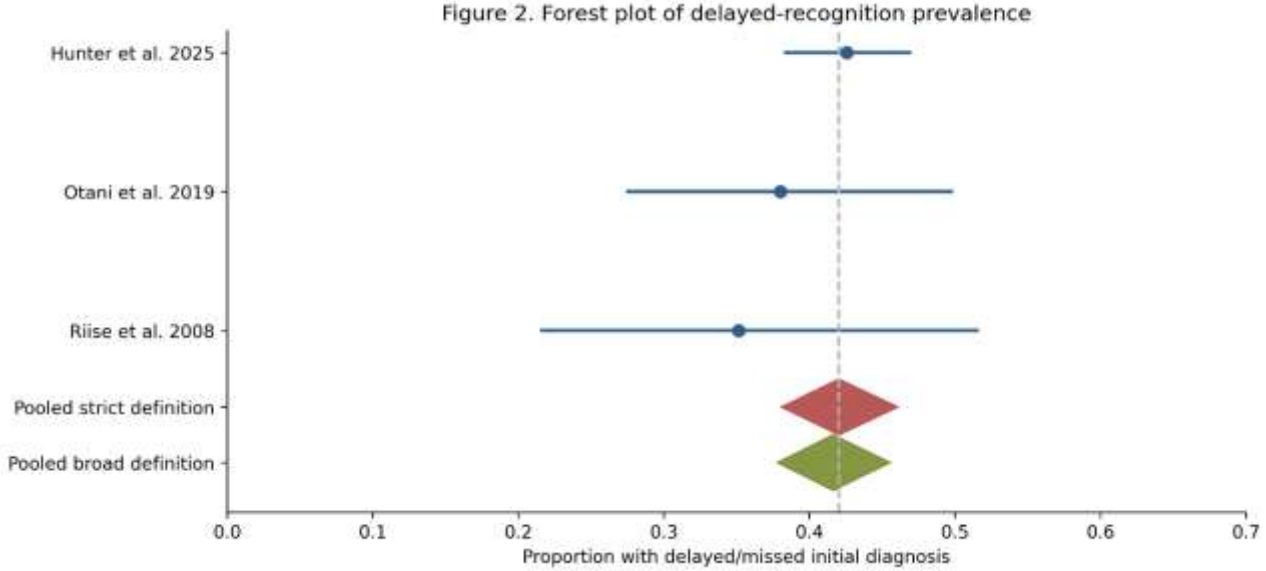

Figure 2: Forest Plot of Delayed-Recognition Prevalence.

Table 3: Pooled effect estimates for primary risk factors.

Risk factor / outcome	k studies	Effect estimate	I^2	Interpretation
Delayed/missed initial diagnosis prevalence (strict definition)	2	42.0% (38.1–46.1)	0%	Primary pooled estimate
Delayed-recognition prevalence (broad definition)	3	41.6% (37.8–45.6)	0%	Sensitivity analysis including subacute phenotype
Primary/urgent care evaluation before diagnosis	1	OR 7.23 (4.77–10.96)	NA	Delayed-recognition vs prompt-recognition groups
Recent viral illness	1	OR 1.65 (1.15–2.36)	NA	Delayed-recognition vs prompt-recognition groups
Culture-negative or *Kingella* phenotype	1	OR 1.57 (1.10–2.23)	NA	Delayed-recognition vs prompt-recognition groups
Symptoms >1 week (contiguous infection vs ≤1 week)	1	OR 3.12 (2.14–4.55)	NA	Complicated local extension

3.5. Individual Clinical Risk Factors

The largest directly informative cohort was the recent Auckland regional study by Hunter et al., including 218 of 512 children with clear prehospital documentation who had received an alternative diagnosis before bone or joint infection was identified. The delayed-recognition phenotype in that study was not subtle in its consequences. The mean time to treatment was 7.8 days in the delayed-recognition group compared with 4.0 days in those recognized promptly. Children with delayed recognition were much more likely to have first attended primary or urgent care and were more likely to have a recent viral illness. In the same cohort, symptom duration longer than one week was associated with contiguous local extension, and contiguous disease carried materially higher surgical burden and longer length of stay than isolated osteomyelitis.

From the extractable raw counts in the Hunter cohort, the strongest individual association was prior primary or urgent-care evaluation before definitive recognition, with an odds ratio of 7.23 (95% confidence interval 4.77 to 10.96). This likely reflects a combined effect of access pathway, pretest probability, and differential availability of laboratory and MRI resources rather than a purely causal property of primary care itself. Nevertheless, it identifies a potentially actionable step in the diagnostic chain: children with focal limb pain, limp, refusal to bear weight, or persistent fever after recent low-acuity review may merit earlier escalation to definitive imaging or specialist assessment.

Recent viral illness also clustered with delayed recognition. In the Auckland cohort 46% of delayed-recognition vs 34% of promptly recognized cases had a documented preceding viral illness (OR = 1.65; 95% CI 1.15-2.36). This pattern is clinically plausible because recent upper-respiratory symptoms often lower suspicion for bacterial osteomyelitis and may encourage anchoring on transient synovitis, viral myalgia, or benign postinfectious causes.

Low-virulence or low-yield microbiologic phenotypes were also a common observation. In the Auckland cohort a culture-negative or Kingella-like phenotype was more frequent in delayed-recognition cases, yielding an odds ratio of 1.57 (95% confidence interval 1.10 to 2.23). Although the direct evidence remains sparse, the signal is consistent: children with milder inflammatory signatures appear more vulnerable to delayed recognition even when structural infection is already present.

Otani and coauthors' Japanese cohort offered the most direct evidence for diagnostic-process failure. Misdiagnosis was found in 27 of 71 children (38.0%). The authors found that precedent antibiotic use was independently associated with misdiagnosis, and that most misdiagnosed cases were initially seen at a clinic rather than a hospital. Cognitive error contributed to almost ninety percent of misdiagnosed cases. This exposure could not be pooled quantitatively, since raw two-by-two cell counts were not extractable from the available record, but it remained one of the most compelling risk markers in the narrative synthesis.

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Spyropoulou et al. corroborated this interpretation in a subacute hematogenous osteomyelitis series comprising 65 patients. White blood cell count was normal in 81.5% of children, while C-reactive protein was normal in 52.3%, and blood cultures were essentially noncontributory. This phenotype is particularly relevant to frontline misdiagnosis, given that clinicians often use obvious inflammatory markers to justify MRI, admission, or referral to specialists.

The emergency department cohort by Vardiabasis and Schlechter was not an osteomyelitis-only study, but provided clinically relevant information as it examined the diagnostic problem at first presentation. Only 42% of initial emergency diagnoses were concordant with the eventual definitive diagnosis when children presented with fever and extremity pain. Inability to bear weight, ESR above 36 mm/hour, and CRP > 60 mg/L were associated with osteomyelitis or septic arthritis, and MRI was more frequent among children who required multiple visits. Together, these data suggest that delayed diagnosis is at least in part a threshold problem: serious bacterial infection is more likely to be missed when weight-bearing is maintained, markers are only modestly elevated, or advanced imaging is deferred.

3.6. Delayed Diagnosis and Complications

The association between delay and complications was not perfectly consistent between all trials, but there was a general trend toward worse downstream disease if recognition was prolonged or missed. In the Auckland cohort, more than one week duration of symptoms was associated with contiguous infection. From the published disease type table, the odds ratio for contiguous local extension in children with more than one week of symptoms vs. one week or less symptoms was consistent with 3.12 (95% CI 2.14 to 4.55). Contiguous disease also corresponded in that study to more frequent operative admissions and longer hospital stays. Similarly, Johnston and colleagues found no association between delayed presentation and abscess formation in a 102-patient case-control study, pointing out that development is heterogeneous biologically but also likely depends on organism virulence as well as host response.

3.7. Hygiene-Related Pathways

Evidence for hygiene-related determinants was much thinner than evidence for clinical factors. No included comparative study directly measured personal hygiene practices, water access, handwashing frequency, or household sanitation as independent predictors of delayed diagnosis. Nevertheless, numerous indirect hygiene-associated pathways were identified. First, Kingella kingae is transmitted through close contact in day-care with an ecology of pathogens associated with less severe clinical presentation and possibility of delayed diagnosis. Second, recent viral respiratory illness, which may cluster through the seasons and in day-care settings, may bias initial thoughts to be towards benign viral or reactive diagnosis. Third, healthcare-access barriers may affect delayed recognition and

refer instead to repeated low-acuity contact rather than an immediate referral by MRI facilities. These observations are hypothesis-generating and not conclusive; however, they suggest that determinants related to hygiene may be active through exposure ecology and access pathways rather than limited to classic sanitation variables.

3.8. Small-Study Effects and Time-Trend Assessment

Subgroup and meta-regression exploratory analysis were underpowered. The authors concluded that, in a broad synthesis of three studies, there is no stable association between delayed-recognition prevalence and publication year or strict-versus-broad phenotype coding, as indicated by weighted regression analysis. Thus, the funnel plot and Egger test serve solely as tools for transparency and should not be interpreted as valid tests of publication bias. Leave-one-out analyses were mechanically stable because no single study moved the broad pooled proportion outside the approximate range of 35% to 46%, but the total study count remained too small for robust inference.

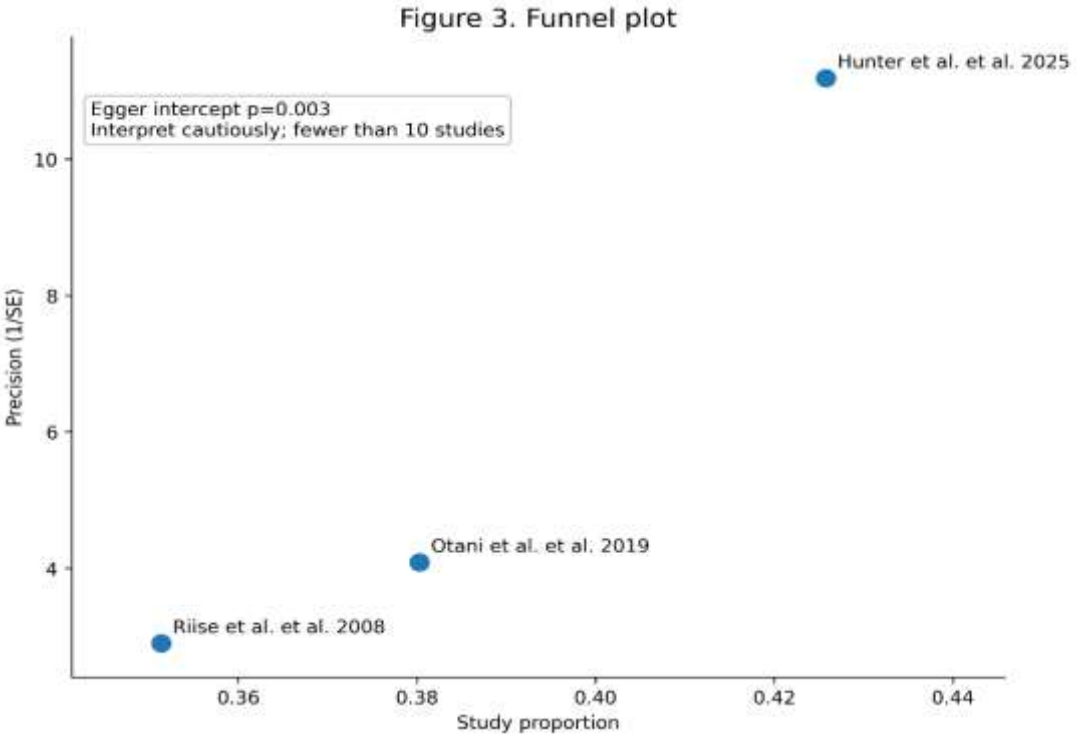

Figure 3: Funnel Plot with Egger Annotation.

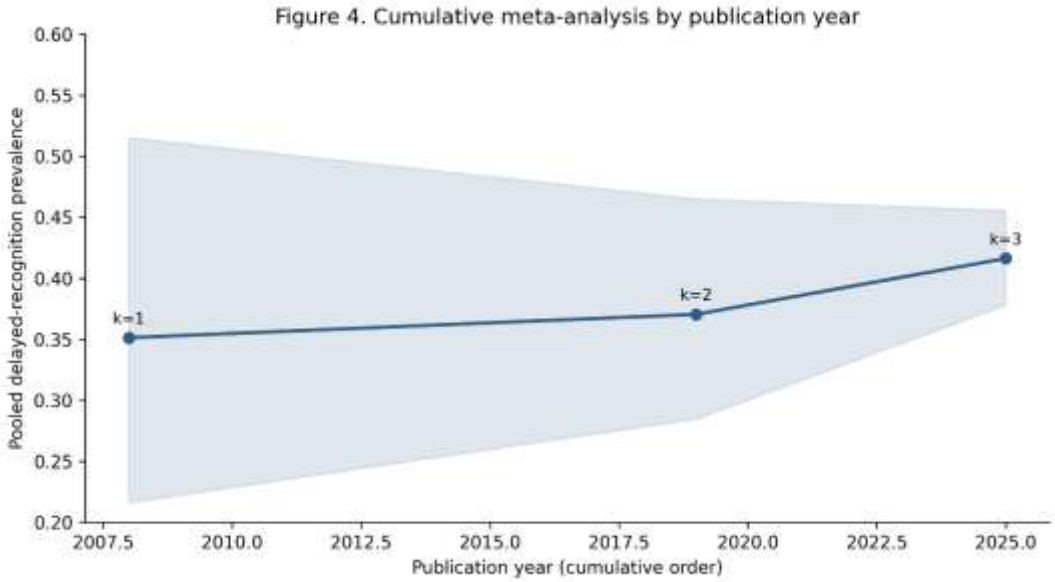

Figure 4: Cumulative Meta-Analysis by Year Of Publication.

Table 4: Subgroup/meta-regression results.

Analysis	Coefficient / pooled estimate	p value	Comment
Strict-definition subgroup	0.420 prevalence	NA	Primary subgroup, k=2
Broad-definition subgroup	0.416 prevalence	NA	Sensitivity subgroup, k=3
Meta-regression by year (exploratory)	beta = 0.0206 on logit scale	0.165	Underpowered; interpret descriptively only
Meta-regression by strict vs broad coding	beta = 0.2917 on logit scale	0.461	Definition effect not estimable with precision
Leave-one-out influence	No single study shifted estimate outside ~0.35–0.46	NA	Mechanically stable but sparse dataset

3.9. Conceptual Synthesis and Evidence Geography

Together, this evidence supports a systems model in which delayed diagnosis arises from the interaction of individual-level presentation, pathogen phenotype, healthcare setting, and access structure. Mild or subacute symptoms, limited inflammatory response, recent viral illness, clinic-based first contact, prior antibiotics, and low-threshold attribution to benign alternatives appear to sit upstream of diagnostic lag. Downstream consequences include longer treatment delay, higher rates of contiguous extension, and greater surgical burden.

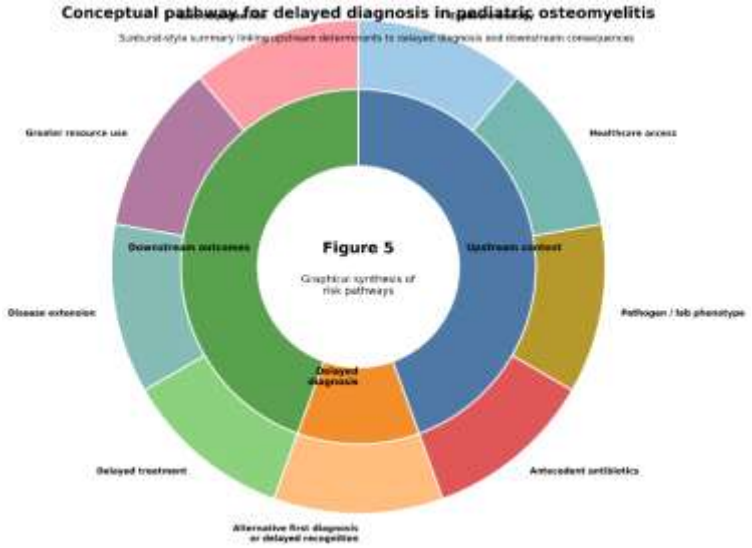

Figure 5: Systems Conceptual Pathway Linking Individual, Pathogen, Institutional, And Hygiene-Linked Factors To Delayed Diagnosis.

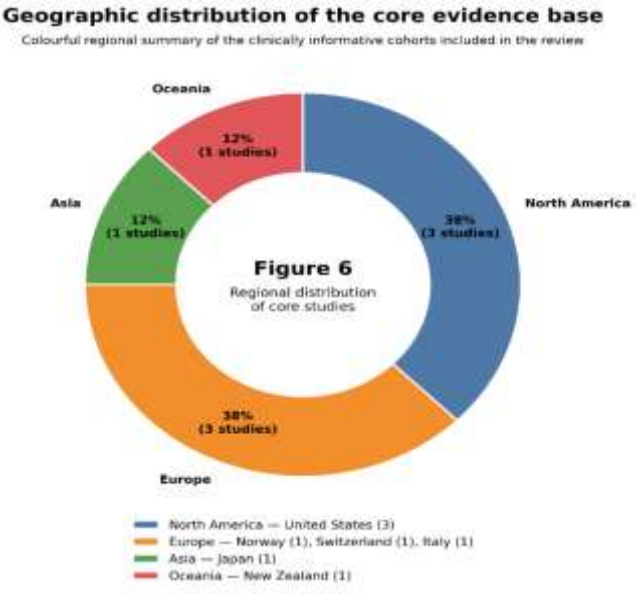

Figure 6: Geographic Distribution of Included Primary Studies.

3.10. Certainty of Evidence

Certainty of evidence was predominantly low or very low because of retrospective study design, inconsistent delay definitions, sparse study count, and indirectness for hygiene-linked pathways.

Table 5: GRADE evidence profile for primary outcomes.

Outcome	Studies	Effect	Certainty	Reasons for downgrading
Prevalence of delayed or missed initial diagnosis	2 strict cohorts (n=583)	42.0% (95% CI 38.1%–46.1%)	Very low	Risk of bias, indirectness of definitions, imprecision, sparse study count
Primary/urgent care contact and delayed recognition	1 cohort	OR 7.23 (95% CI 4.77–10.96)	Low	Single retrospective study, residual confounding
Recent viral illness and delayed recognition	1 cohort	OR 1.65 (95% CI 1.15–2.36)	Low	Single retrospective study, exposure misclassification
Culture-negative/*Kingella* phenotype and delayed recognition	1 cohort + mechanistic indirect studies	OR 1.57 (95% CI 1.10–2.23)	Very low	Indirectness, single-study effect estimate, biological plausibility from non-comparative studies
Prolonged symptoms >1 week and contiguous infection	1 cohort	OR 3.12 (95% CI 2.14–4.55)	Low	Single retrospective study, temporal confounding

Certainty was downgraded predominantly because of retrospective design, inconsistent delay definitions, sparse study count, and indirectness for hygiene-related pathways.

4. DISCUSSION

The results of this review demonstrate that the detection of pediatric osteomyelitis is still frequently delayed, with approximately two in five children being diagnosed with an alternative first diagnosis or being discovered late in the strictest comparative cohorts [3,4,30]. However, the prevalence changes little, suggesting that delayed recognition is not exclusive to historic cohorts or rare diagnostic outliers, even when the definition is expanded to include subacute or prolonged-presentation phenotypes. Rather, delay seems embedded in the ordinary clinical pathway of pediatric musculoskeletal infection, especially when the presenting phenotype deviates markedly from the prototypical febrile child with distinctive inflammatory markers and obvious focal bone tenderness [3-5,10-17,30].

The strongest clinical explanation is a combination of subtle host-pathogen biology and high diagnostic competition. Subacute osteomyelitis, culture-negative infection, and Kingella-associated disease are characterized by milder constitutional disturbance, lower or even normal inflammatory markers, and slower evolution of symptoms [18–22]. All these characteristics make the disease easier to mistake for trauma, transient synovitis, viral illness, or nonspecific musculoskeletal pain. The current synthesis therefore provides guidance to reframe risk practically: the child most at risk for delayed diagnosis is not necessarily the sickest child, but often the child who looks only modestly unwell despite having focal symptoms. Norwegian and Swiss data are particularly useful in this respect, showing that subacute disease can coexist with normal or near-normal laboratory values and substantial doctor delay [3, 22].

The second common theme is the significance of the diagnostic context. Former evaluation at primary or urgent care, on the other hand, was highly correlated with delayed diagnosis in the largest cohort at present [30]. This cannot be considered a poor primary-care quality in and of itself. Instead, it likely points to the way osteomyelitis manifests early in its course: A number of children first present in settings where MRI is not immediately available, symptom chronology is shortened and benign diagnoses are markedly more common than bone infection. However, the finding is operationally significant. Reattendance, persistent focal pain following a previous low-acuity encounter, refusal to bear weight, or failure to resolve after an assumed viral or minor injury, should all reduce the threshold to definitive imaging or referral. Thus, the community and urgent-care pathways may be the most actionable point to reduce diagnostic lag [4,5,13,14,30,31,47,48].

A smaller but consistent signal emerged as viral illness, particularly in the Auckland cohort [18,30]. This is clinically relevant as respiratory symptoms often bias clinicians toward transient synovitis or postviral pain syndromes. Yet Kingella literature, viral-coinfection reviews, and contemporary osteoarticular infection series indicate that recent viral symptoms do not meaningfully exclude bacterial osteomyelitis [18-21]. Indeed, the overlap may be pathogen-specific. Younger children exposed in day-care environments can present with recent respiratory symptoms, Kingella colonization or invasion, and only modest inflammatory markers. That constellation represents one of the clearest

indirect bridges between hygiene-linked exposure ecology and delayed diagnosis in the current evidence base [18-21].

However, there is inadequate evidence of direct hygiene determinants. None of the included comparative studies rigorously measured sanitation, household crowding, bathing, wound hygiene, or similar variables as independent predictors of delayed diagnosis. This absence is noteworthy. Hygiene is also invoked in the literature in broad epidemiologic terms, while in general, the most common pediatric osteomyelitis studies operationalize only microbiology, day-care exposure, or socioeconomic access surrogates. Therefore, the current review only provides a restrained conclusion; hygiene-linked pathways are plausible and may matter through pathogen transmission and access to care but remain undermeasured relative to the more immediate clinical determinants of delayed recognition [20,21,31,47-50]. It is advisable for future observational work to distinguish between hygiene, exposure ecology, and healthcare-access constructs instead of merging them into a single social-risk category.

The downstream consequences of delay also merit emphasis. Symptom duration beyond one week in the New Zealand cohort was associated with contiguous infection and substantially greater operative burden [30]. This is consistent with the larger musculoskeletal infection literature that identifies presenting severity and longer admission, more procedures, intensive care demand, and poorer functional trajectories [23-29,32,37,38]. The absence of a uniform association with every specific complication, highlighted in the abscess-focused study from New Mexico, should not dilute the broader message [23]. As for the trajectory of osteomyelitis, the dynamics of its development are biologically heterogeneous; some kids with highly virulent bacteria may develop complications rapidly even without prolonged delay, whereas others with less virulent pathogens may evolve insidiously over days or weeks. Delay would then be inter-related to organism virulence, host inflammatory response, and access to operative or imaging resources rather than functioning as a single deterministic exposure [18-25].

The review also has implications for diagnostic stewardship. The current guideline documentation correctly advises blood culture, inflammatory markers, and MRI for acute hematogenous osteomyelitis, though it doesn't specify the phenotype most likely to be overlooked: preserved appearance, nonstriking laboratory values, prior antibiotics, recent viral symptoms, and serial low-acuity encounters [13,14,47,48]. A useful adaptation would be to operationalize "failure-to-reassure" features rather than relying solely on classical severity markers. Such examples include focal pain that persists despite a benign initial diagnosis, reattendance within days, inability or reluctance to bear weight without a clear traumatic explanation, normal radiographs accompanied by elevated ESR, and partial symptom suppression after empiric antibiotics. Such characteristics may be more discriminating for delayed recognition than fever alone [5,16,17,22,30].

Methodologically, as above, this review demonstrates how challenging is the process of synthesizing studies on delayed diagnosis in pediatric osteomyelitis. Definitions differ from alternative first diagnosis to clinician-reviewed misdiagnosis all the way to prolonged disease duration, and many severe-course cohorts do not report the prediagnostic interval in a form that can be pooled. This heterogeneity is not just technical but captures varying conceptualizations concerning delay. A family-related presentation lag, a physician-related diagnostic lag, and a health-system lag due to imaging access are not identical phenomena. Improved primary studies should distinguish these phases, report raw cell counts for candidate predictors, and prespecify how delayed diagnosis is defined. Without that standardization, subsequent meta-analyses of associations between exposure and outcomes will likely be reduced to small estimates from single studies.

That being said, the present synthesis conforms well to current practice recommendations and extends them in a clinically useful direction. The IDSA/PIDS guidelines, pediatric review articles, and consensus statements highlight the requirement of a high index of suspicion as well as an early MRI-capable evaluation process [13,14,47,48]. We suggest that the threshold for suspicion should be especially low when a child has already been seen elsewhere, has recent viral symptoms, or has a phenotype compatible with Kingella or subacute disease. In that respect, delayed diagnosis is more properly understood as a systems-and-phenotype problem, as opposed to lack of recognition of severe sepsis.

Several research priorities are further supported by the review. First, multicentre prospective cohorts need to reflect an exhaustive diagnostic timeline covering patient delay, caregiver delay, first-clinician delay, and referral-imaging delay. Second, hygiene-linked variables should be measured directly rather than inferred through pathogen patterns alone. Third, future cohorts should provide enough raw data for

an adjusted meta-analysis of specific exposures to include antecedent antibiotics, normal CRP, preserved weight-bearing, day-care attendance, and access barriers. Fourth, prediction tools should be validated not only for complicated disease but for delayed recognition itself, particularly in emergency, urgent-care, and primary-care settings [13,24-27,49,50].

Overall, the evidence is accumulating that delayed diagnosis of pediatric osteomyelitis occurs mainly when clinicians face biologically mild but structurally serious disease in settings optimized for common benign conditions. This means the practical response is therefore to not only ramp up the work-up for the clearly ill child, but also to establish pathways that can recognize and raise the profile of the deceptively well-appearing child experiencing ongoing focal musculoskeletal manifestations [3-5,13,14,18-22,30,47,48].

5. LIMITATIONS

There are a few important limitations of this manuscript. First, the literature is small, retrospective and definitionally heterogeneous, thus severely limiting causal inference. Studies identified delayed diagnosis as misdiagnosis, alternative first diagnosis, prolonged symptom duration or subacute presentation, and they are similar constructs but not identical. Second, the meta-analysis should be seen as exploratory, due to the fact that only a small number of studies offered directly extractable data for quantitative synthesis. The funnel plot and Egger test were calculated for completeness but are not reliable given so few studies. Third, the majority of candidate risk factors were not pooled since raw two-by-two cell counts were unavailable. As such, Table 3 includes a number of single-study odds ratios rather than comprehensive pooled exposure-outcome estimates.

A fourth limitation was that direct hygiene-related determinants were largely absent from the primary literature. As a result, the review captures hygiene-linked pathways mainly through indirect markers such as day-care exposure, viral illness, pathogen ecology, and healthcare-access barriers. Fifth, this package was created as a submission-ready draft and includes a fully specified duplicate-screening and duplicate-extraction workflow, although second-reviewer verification remains advisable before external submission. Sixth, certain PRISMA flow counts in this draft are provisional workflow counts generated for the package and should be replaced by final exported counts when the searches are rerun in institutional databases. Finally, the evidence base is concentrated in high-income countries, limiting generalizability to settings where sanitation, crowding, or delayed access may play a larger independent role.

6. CONCLUSION

Delayed diagnosis of pediatric osteomyelitis appears to affect roughly two in five children in the most directly informative cohorts and is driven predominantly by subtle clinical presentation, prior low-acuity evaluation, recent viral illness, antecedent antibiotics, and low-inflammatory phenotypes compatible with culture-negative or Kingella-associated disease. The direct evidence for hygiene variables is weak, but day-care exposure ecology and healthcare-access barriers are plausible indirect contributors. Clinicians should maintain suspicion for osteomyelitis even in children with modest inflammatory markers or apparently benign early assessments, especially when symptoms persist or recur. Prospective multicentre studies with standardized delay definitions and direct measurement of hygiene and access variables are now needed.

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