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METHODOLOGICAL CHALLENGES OF ESTIMATING THE DISEASE BURDEN OF MRSA-ASSOCIATED SEPSIS IN NICU, A SYSTEMATIC REVIEW
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METHODOLOGICAL CHALLENGES OF ESTIMATING THE DISEASE BURDEN OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* ASSOCIATED SEPSIS IN NICU, A SYSTEMATIC REVIEW

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ABSTRACT

***Objectives*: This systematic review aimed to assess the burden of methicillin-resistant *Staphylococcus aureus* (MRSA)-associated neonatal sepsis (NS) in neonatal intensive care units (NICUs). We examined MRSA-related mortality and described resistance patterns of MRSA strains in NICUs.**

***Materials and Methods*: We searched four databases up to 2023 for observational studies on MRSA or antimicrobial resistance in neonates with culture-confirmed sepsis in NICUs. Studies included all sepsis types, diagnostic methods, and neonatal characteristics. We extracted data on study features,**

MRSA prevalence, resistance, and mortality. We used a random-effects model for pooled proportions, with subgroup analyses by sepsis type and WHO region, and assessed heterogeneity using the I^2 statistic.

***Results*: We included 37 studies published between 2000 and 2021 from 23 countries These studies reported 2948 cases of culture-confirmed NS with MRSA prevalence ranged from 0.0 to 32.2% across studies. Among 2948 total NS cases, the pooled MRSA proportion was 8.8% (95% CI: 4.5–14.1; I^2 = 94.2%). The pooled MRSA proportion in early-onset neonatal sepsis was 2.7% (95% CI: 1.3–4.6; I^2 = 0%). The pooled MRSA proportion in late-onset neonatal sepsis was 4.6% (95% CI: 2.1–7.8; I^2 = 90.3%). Two studies reported 6 deaths among 14 MRSA-positive neonates from a total cohort of 184 infants. In Egypt and Saudi Arabia, MRSA strains showed resistance to multiple antibiotic classes, including aminoglycosides, chloramphenicols, drug combinations, fluoroquinolones, lincosamides, macrolides, penicillins, rifamycins, and cephalosporins (both second and third generation).**

***Conclusion and recommendations*: These findings highlight the role of MRSA as a significant cause of neonatal sepsis. High resistance rates in some settings may compromise empirical treatment strategies. There is an urgent need to strengthen surveillance and antimicrobial stewardship in neonatal care. Standardized methods in future studies will improve comparability and support global policy on neonatal infection management.**

INTRODUCTION

Neonatal sepsis (NS) remains a leading cause of admission to neonatal intensive care units (NICUs) worldwide and contributes significantly to neonatal morbidity, mortality, and healthcare costs. Global estimates report 2824 cases of NS per 100,000 live births [1]. Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a major hospital-acquired pathogen in NICUs. MRSA contributes to the rising burden of antimicrobial-resistant infections in neonates and complicates sepsis management [2]. Neonatal sepsis also affects long-term neurodevelopmental outcomes [3, 4] Very preterm infants with NS face increased risk of cerebral palsy and neurosensory impairment. In very low birth weight neonates, NS has been associated with a two-fold increase in cerebral palsy risk (odds ratio of 2.0 [1.6 to 2.6]) [3].

Neonatal sepsis is caused by an abnormal systemic response to infection. Bacterial, fungal, and viral pathogens can trigger this response [5]. The etiology varies by regions and reflects local antimicrobial practices and infection control standards [1, 6] Clinical signs are often non-specific, including hemodynamic instability and apnea, which hinder early diagnosis [5, 7]. The lack of universally endorsed guidelines and definitions is attributed to varied study results, clinical approaches, and regional epidemiological disparities [7]. Neonatal sepsis is classified as early-onset NS (EONS, ≤72 hours after birth) and late-onset NS (LONS, >72 hours) depending on the timing and likely source of infection. Prematurity and low birth weight are well-established risk factors for NS [1].

Preventive strategies are essential. Hand hygiene remains the most effective intervention to prevent MRSA transmission within NICUs [8, 9]. Timely diagnosis and initiation of appropriate antibiotics are critical to improving outcomes [10] However, treatment is increasingly complicated by

resistance to standard antibiotics and the absence of unified global treatment guidelines [11, 12]. This review aims to quantify the proportions of MRSA in culture-proven total NS, EONS and LONS, assess associated mortality, and describe antibiotic resistance profiles of MRSA strains in NICUs. We also identify methodological gaps in the literature and propose recommendations to strengthen future surveillance and research on MRSA in NS.

MATERIALS AND METHODS

Literature search

This systematic review and meta-analysis followed PRISMA guidelines and was registered with PROSPERO (CRD42023408474) [13]. We searched Medline, Embase, Global Health, and Web of Science for articles published up to January 5, 2023. We used a combination of search terms: "methicillin-resistant *Staphylococcus aureus*" OR "MRSA", "neonatal sepsis", and "NICU" with Boolean operators AND/OR. We applied no language or date restrictions during the database search. We also screened reference lists of included articles to identify additional studies. The complete search strategy is provided in Appendix 1.

Eligibility criteria

We included studies that met the following criteria (Appendix 2):

Inclusion

Conducted MRSA testing or antimicrobial susceptibility testing in NICU patients

Reported culture-confirmed neonatal sepsis (defined by isolation of a pathogen from blood or cerebrospinal fluid plus clinical or laboratory signs of infection) [5, 7]

Included early-onset (EONS, ≤72 h) or late-onset (LONS, >72 h) sepsis

Used microbiological methods such as culture, polymerase chain reaction (PCR) , or other diagnostic assays [14, 15]

Included Gram-positive, Gram-negative, or fungal pathogens

Addressed commensals or contaminants (e.g., coagulase-negative Staphylococcus) with stated criteria [16]

Included neonates regardless of gestational age, birth weight, clinical severity, or prior antibiotic exposure

Used observational designs (cross-sectional, cohort)

Exclusion

Did not report MRSA data in neonates

Did not focus on neonatal sepsis or NICU populations

Used inappropriate designs (e.g., case reports, reviews, editorials)

Focused solely on outbreak investigations

Were not published in English or French

Were duplicate records

Study selection and data extraction

Two reviewers independently screened titles, abstracts, and full texts. Disagreements were resolved through discussion and consensus. We extracted the following data: authors, year of publication, country, study period, sepsis type (total NS, EONS, or LONS), MRSA detection assay, antimicrobial susceptibility testing methods, sample types, MRSA molecular confirmation, the number of participants with total NS, EONS or LONS, the number of participants infected with MRSA, the number of deaths among MRSA positives, and the number of MRSA antibiotic-resistant isolates.

Quality assessment

We used the Hoy et al. tool because it is validated for prevalence studies and covers multiple study types, including cross-sectional and cohort designs (Appendix 3) [17]. This tool evaluates both internal and external validity of studies, including sampling methods, case definitions, and measurement reliability.

Statistical analysis

We calculated the proportion of MRSA in total NS, EONS, or LONS by dividing MRSA-positive cases by the total number of sepsis cases. We calculated MRSA-associated

mortality by dividing deaths among MRSA-positive cases by the total MRSA-positive cases. We estimated resistance profiles by dividing the number of resistant MRSA isolates by the total MRSA-positive cases. We performed a random-effects model was employed to compute the proportion estimates. We conducted subgroup analyses by sepsis type (EONS, LONS, total NS) and by WHO region. We used the Clopper–Pearson method to calculate 95% confidence intervals (CI) for individual study proportions [18]. We assessed heterogeneity using I^2 statistic with corresponding 95% CI. To assess potential publication bias, we performed Egger's linear regression test [19]. A p-value less than 0.10 was considered suggestive of potential publication bias. All statistical tests in this study were performed with R software version 4.0.3 (2020-10-10) [20, 21].

RESULTS

Study selection

We identified 610 records through databases search. A total of 37 studies met the inclusion criteria and were incorporated in the systematic review (Figure 1).

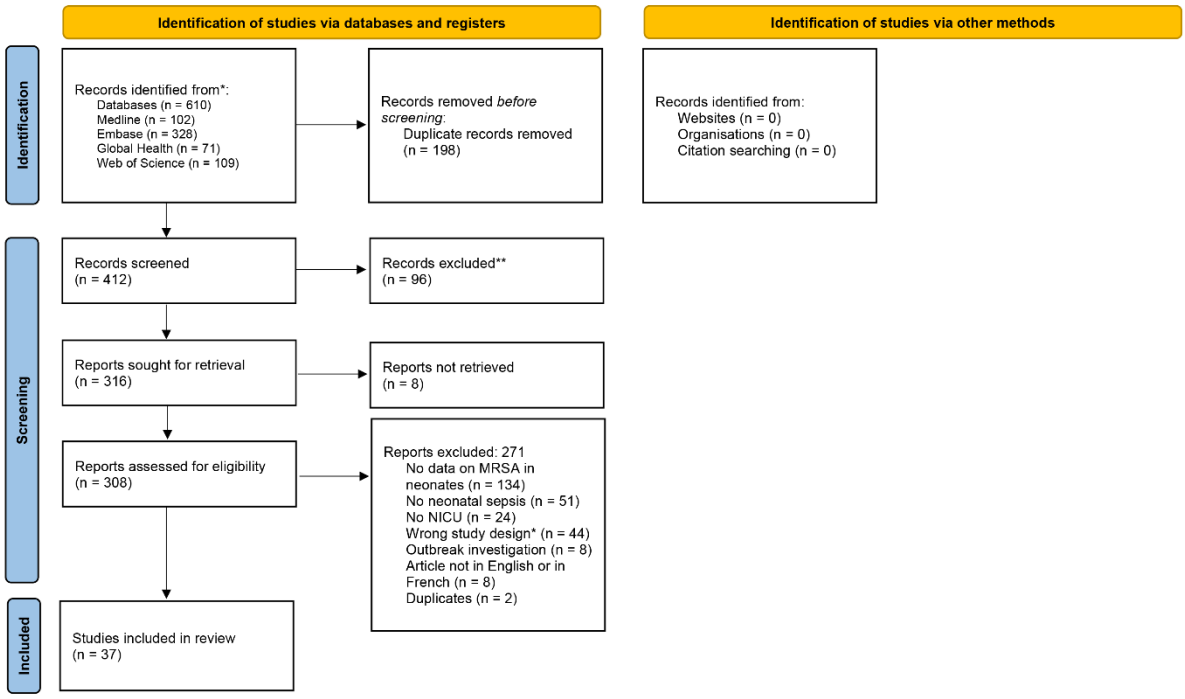

Figure 1: Flowchart of the literature selection process.

Characteristics of included studies

The included studies were conducted in 23 countries. India accounted the largest share (18.9%; 7/37) (Appendix 4). These studies were conducted in the Eastern Mediterranean World Health Organization (WHO) region (27.0%; 10/37), followed by South-East Asia (24.3%; 9/37), the Western Pacific (21.6%; 8/37), and Europe (18.9%; 7/37) (Figure 2). Among all studies, 91.9% had a moderate risk of bias (Appendix 5).

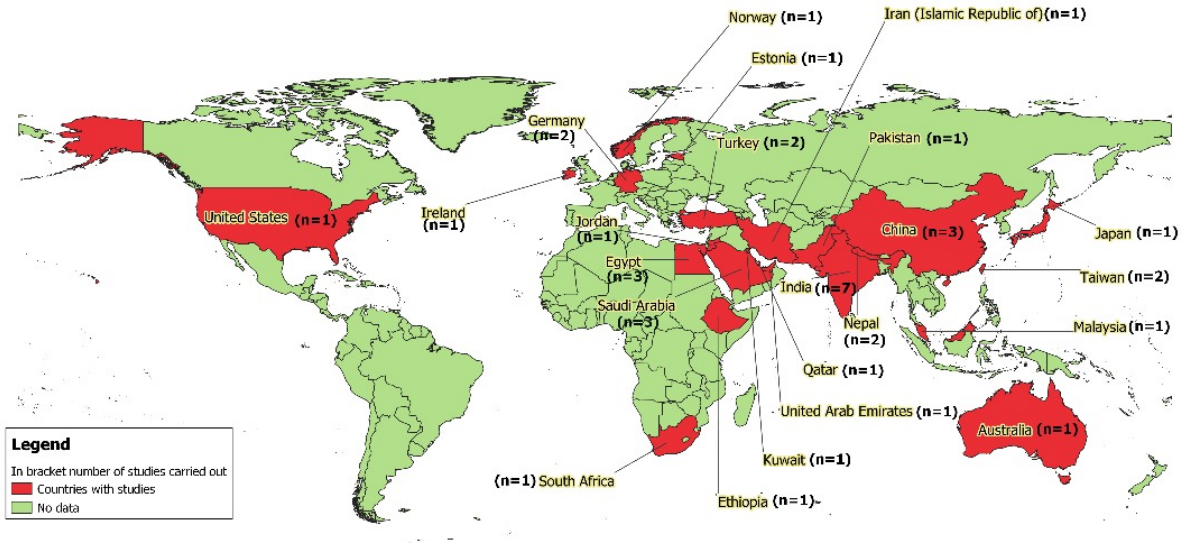

Figure 2: Geographical distribution of included studies on MRSA-Associated Neonatal Sepsis in NICUs

Proportion of MRSA-associated total neonatal sepsis in NICU

We analyzed 2948 culture-confirmed total NS cases. Among them, 207 were MRSA positive. MRSA proportion ranged from 0.0 to 32.2% across studies. The pooled MRSA proportion was 8.8% (95% CI: 4.5; 14.1), with substantial heterogeneity (I2= 94.2%). Egger's test for funnel plot asymmetry yielded a p-value of 0.088, indicating marginal evidence of potential publication bias. Proportion varied by region, with highest values in the Eastern Mediterranean and South-East Asia for total NS (Table 1).

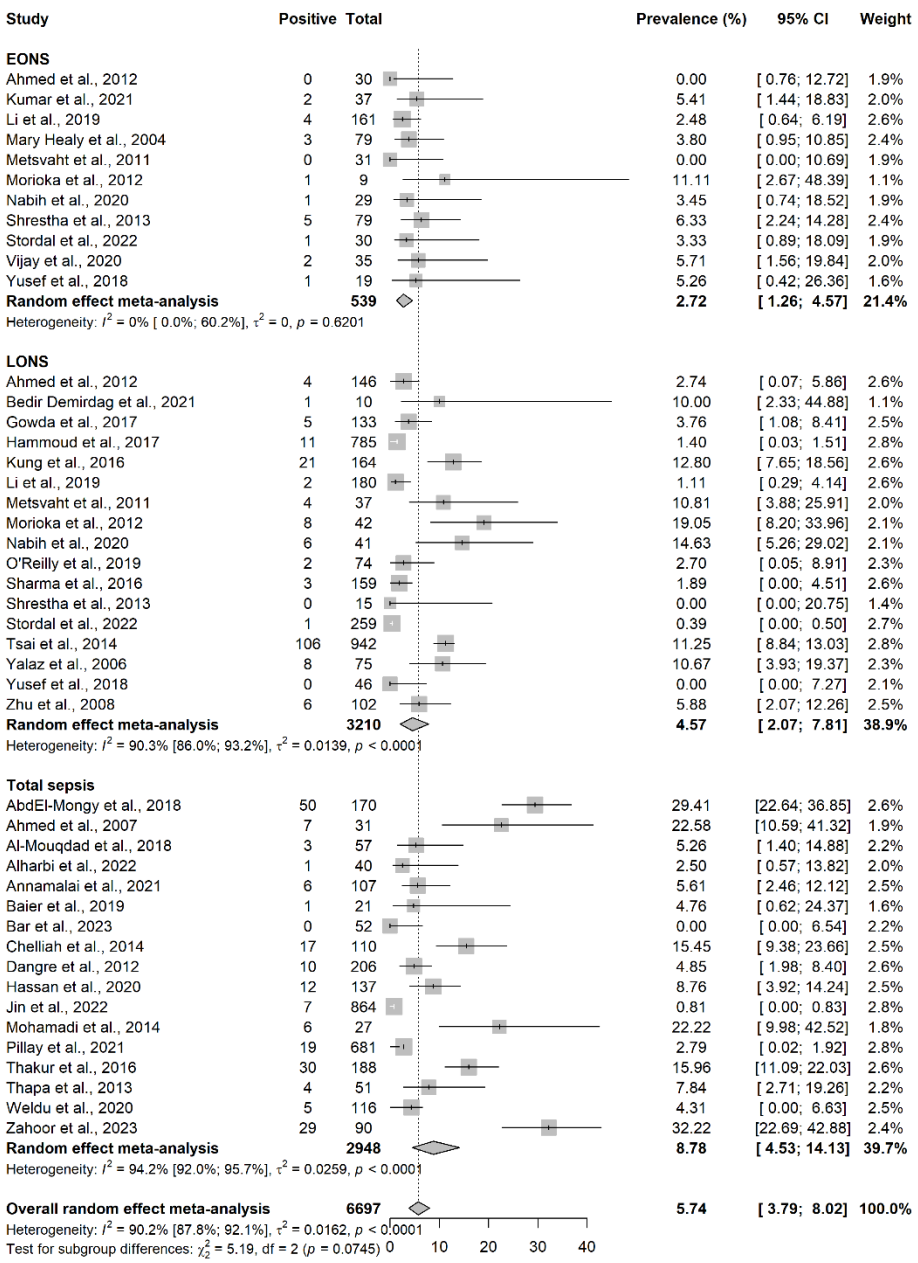

Figure 3: Pooled prevalence of MRSA among neonates with early-onset, late-onset, and total culture-confirmed sepsis in NICUs

Table 1

Proportion of MRSA among culture-confirmed neonatal sepsis cases in NICU patients, by WHO region and sepsis onset type

	WHO Region					
	Africa	**Eastern Mediterranean**	**Europe**	**South-East Asia**	**Western Pacific**	**America**
Neonatal sepsis						
Prevalence (95% CI)	2.9[1.8-4.2]	15.1[6-27.1]	0.9[0-9.3]	9.5[4.9-15.3]	7.5[0-40.7]	/
N Studies	2	6	2	5	2	/
N Cases	797	521	73	662	895	/
I^2 [95% CI]	0	0.9[0.8-0.9]	0.6[0-0.9]	0.8[0.5-0.9]	1[0.9-1]	/
EONS						
Prevalence (95% CI)	/	1.8[0-6.8]	1[0-6.3]	5.8[2.4-10.4]	2.7[0-14.6]	3.8[0.5-9.4]
N Studies	/	3	2	3	2	1
N Cases	/	78	61	151	170	79
I^2 [95% CI]	/	0[0-0.9]	0	0[0-0.9]	0.5	NA
LONS						
Prevalence (95% CI)	/	2.6[0.2-7]	4.6[0.1-12.8]	0.7[0-3.3]	7.5[3.4-13]	/
N Studies	/	4	5	2	6	/
N Cases	/	1018	455	174	1563	/
I^2 [95% CI]	/	0.8[0.4-0.9]	0.8[0.6-0.9]	0	0.9[0.8-0.9]	/

95% CI: 95% confidence interval; EONS: Early-onset neonatal sepsis; LONS: Late-onset neonatal sepsis; WHO: World Health Organization

Proportion of MRSA-associated early-onset neonatal sepsis in NICU

A total of 539 EONS were analyzed with MRSA detected in 20 cases. The highest observed proportion was 11.1% (Figure 3). The pooled MRSA proportion in EONS was 2.7% (95% CI: 1.3; 4.6), with low heterogeneity (I2= 0%). MRSA proportion in EONS was generally lower across all regions (Table 1)

Proportion of MRSA-associated late-onset neonatal sepsis in NICU

We included 3210 LONS cases, among which 188 were MRSA-positive. The pooled proportion of MRSA in LONS was 4.6% (95% CI: 2.1; 7.8), with high heterogeneity (I2= 90.3%) (Figure 3). MRSA proportion in LONS showed greater variability (Table 1).

Mortality in NICU patients with MRSA-associated neonatal sepsis.

Gowda et al. conducted a study in Australia on LONS identifying 5 MRSA infections among 133 neonates, with two resulting deaths [22]. A study conducted in Japan between 2006 and 2008 investigated both EONS and LONS in 51 neonates, identifying 9 MRSA infections, of which 4 were fatal [23]

The antibiotic resistance profiles of MRSA isolates from various studies on NS reveal some patterns (Appendix 6). A study in Saudi Arabia reported that MRSA isolates were fully resistant to amikacin, cloxacillin, and cefotaxime, but showed no resistance to gentamicin, piperacillin/tazobactam, ampicillin, or ceftriaxone [24]. Almohammady et al. in Egypt reported 100% resistance to multiple antibiotics, including gentamycin, chloramphenicol, and ciprofloxacin, but no resistance to vancomycin and linezolid [25]. Al-Mouqdad et al. in Saudi Arabia observed 33.33% resistance to trimethoprim-sulfamethoxazole and gentamicin, 100% resistance to oxacillin and cefoxitin, with no resistance to clindamycin, linezolid, vancomycin, and rifampicin [26].

DISCUSSION

This systematic review confirms that MRSA is a significant neonatal pathogen in total NS. We observed a pooled MRSA proportion of 8.8% among 2948 total culture-confirmed NS cases, with marked inter-regional variability reaching up to 32.2% in Pakistan. Such disparities likely reflect differences in infection control, antimicrobial stewardship, and NICU infrastructure. For instance, while MRSA accounted for 61% of *S. aureus* sepsis isolates in a global neonatal cohort, it represented only 12% among *S. aureus* cases in a well-resourced Australian unit [27, 28].

MRSA prevalence was higher in LONS (4.6%) compared to EONS (2.7%), consistent with nosocomial acquisition. LONS cases are typically associated with longer hospital stays, invasive devices, and environmental exposures. Our findings support previous reports indicating that prematurity and low birth weight are key risk factors for MRSA sepsis due to prolonged NICU exposure and immature immunity [27]. In addition, outborn neonates transferred from lower-level facilities show increased MRSA risk, likely due to lapses in aseptic delivery or transport conditions [29]. Mortality data were scarce but concerning. Of 14 MRSA-positive neonates in two included studies, 6 died. This 43% case fatality rate, though based on a small sample, underscores the lethality of MRSA in vulnerable neonates. Neonatal sepsis consistently emerges as a primary cause of NICU-related mortalities. A study reported a case fatality rate of 17.6% for total NS, with rates of 16.4% for EONS and 9.1% for LONS [1]. Global estimates show that nearly 1 in 5 neonates with culture-confirmed sepsis die, with gram-negative pathogens generally driving higher mortality [28]. MRSA remains life-threatening, especially where advanced care is unavailable [30]. Recent pediatric data suggest that with prompt therapy, outcomes for MRSA may equal MSSA, but such parity presumes access to timely diagnostics and appropriate antibiotics; conditions not guaranteed in many low- and middle-income countries [29-31].

MRSA isolates in our review showed high levels of resistance to aminoglycosides, cephalosporins, fluoroquinolones, and beta-lactams, consistent with the organism's adaptive resilience. This multidrug resistance mirrors surveillance from Colombia and Asia, where MRSA rates exceed 40-45% and first-line antibiotics offer limited efficacy [31]. Vancomycin and linezolid were universally effective, reaffirming their central therapeutic role [32]. However, vancomycin's pharmacokinetics in neonates are unpredictable, therapeutic monitoring is challenging, and prolonged use raises nephrotoxicity risks. The widespread reliance on empiric broad-spectrum regimens exacerbates resistance

pressure. Over 200 unique empiric combinations were identified in a recent multicenter study, reflecting a lack of harmonized protocols [28]. In such a landscape, antimicrobial stewardship is essential. Our findings reinforce calls for local antibiogram-informed prescribing and early de-escalation where cultures are negative or clinical improvement is rapid. Without such practices, the selective pressure from third-generation cephalosporins and glycopeptides will continue to drive MRSA dominance.

LIMITATIONS

Diagnostic limitations emerged as a major theme. Included studies primarily focus on culture-positive participants, complicating the interpretation and comparability of reported data. This discrepancy arises due to variability in culture-positive findings across studies, influenced by the sensitivity and specificity of microbial cultures, the target pathogens (gram-positive, gram-negative, or fungi), and the sample types tested [5]. The management approach towards commensal bacteria, such as coagulase-negative *Staphylococci* introduces another layer of variation. Culture-negative sepsis cases, despite the absence of microbial confirmation, have generally shown the same detrimental outcomes as their culture-positive counterparts, including a higher mortality rate, longer intensive care stays, and the need for mechanical ventilation [33, 34]. Clinicians often compensate by initiating empiric therapy guided by non-specific markers like c-reactive protein or procalcitonin, yet these lack specificity [35]. This contributes to overtreatment and further antimicrobial resistance. Additionally, variability in sepsis definitions, MRSA detection methods, and inclusion criteria across studies hindered comparability. Most included studies were observational with moderate risk of bias and lacked stratification by gestational age or birth weight, key confounders.

Another evident limitation lies in the sole consideration of blood culture-positive NS cases, which might overstate the actual MRSA proportion of positives. The scarcity of studies, often with small sample sizes and focused on specific regions or countries, undermines the comprehensive representation of the findings. We included only cases of blood culture-positive neonatal sepsis, which may have overestimated the proportion of MRSA among confirmed infections and excluded clinically significant culture-negative cases. Furthermore, the limited number of eligible studies, many of which had small sample sizes and originated from specific geographic regions, restricts the generalizability of our findings.

CONCLUSION AND RECOMMENDATIONS

MRSA remains a prominent, preventable cause of NS in NICUs worldwide. Its prevalence and associated mortality vary by geography, correlating with differences in infection control capacity, diagnostic resources, and antimicrobial practices.

Our review identifies several priorities for research and policy. Standardized case definitions and diagnostic criteria for MRSA-associated NS are needed across studies. Rapid, sensitive diagnostics like multiplex PCR and metagenomic sequencing should be developed and validated for neonatal use, especially in low- and middle-income countries. Multicentre surveillance is essential to understand MRSA epidemiology, resistance trends, and strain-specific virulence. Moreover, clinical trials should evaluate alternative regimens to vancomycin and define optimal durations for MRSA therapy. Additional strategies,

including monoclonal antibodies or maternal vaccination against *S. aureus*, hold long-term promise and deserve exploration. Finally, follow-up studies should evaluate neurodevelopmental outcomes after MRSA sepsis. The burden of this infection extends beyond mortality, impacting long-term cognition and quality of life.

MRSA's resistance to standard empiric regimens poses a serious challenge, especially in regions with limited antibiotic options and monitoring infrastructure. To improve outcomes, we recommend immediate investments in infection prevention, diagnostic innovation, and global stewardship. These findings emphasize the need for more extensive research into MRSA-associated NS, highlighting the critical need for improved prevention measures and therapeutic interventions in NICUs worldwide.

CRediT AUTHOR STATEMENT

SNE: Conceptualization, Methodology, Writing - original draft; ABN: Writing - review & editing, Data curation, Methodology; NKK: Writing - review & editing, Data curation, Methodology; JFTKA: Writing - review & editing, Methodology; RNN: Writing - review & editing, Methodology; JTEB: Writing - review & editing, Data curation, Methodology; CKN: Writing - review & editing, Data curation, Formal analysis; DSM: Writing - review & editing, Data curation, Methodology; NT: Writing - review & editing, Methodology; HGK: Writing - review & editing, Methodology; JPAA: Writing - review & editing, Methodology; and LMN: Conceptualization, Writing - review & editing, Methodology.

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Conflict of Interest Statement

The authors declare that they have no conflicts of interest to disclose.

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