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SYSTEMATIC REVIEWS

Epidemiology of carbapenem-resistant *Acinetobacter baumannii* colonization in neonatal intensive care units: A systematic review and meta-analysis

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Abstract

BACKGROUND

The rising prevalence of carbapenem-resistant *Acinetobacter baumannii* (CRAB) in neonatal intensive care units (NICUs) represents an escalating challenge in health-care settings, particularly in managing hospital-acquired infections (HAIs). Studies across various World Health Organization regions have documented a significant incidence of CRAB-related HAIs, with rates as high as 41.7 cases per 1000 patients in ICUs, accounting for 13.6% of all HAIs. These infections pose a doubled mortality risk compared to infections with carbapenem-susceptible *Acinetobacter baumannii*. A particularly concerning aspect of CRAB colonization is its asymptomatic nature, enabling its transmission through healthcare workers (HCWs) or the NICU environment to vulnerable neonates with developing immune systems.

AIM

To explore the prevalence of CRAB colonization in NICUs, focusing on neonates, healthcare workers, and the environmental samples, to enhance epidemiological understanding and inform targeted interventions.

METHODS

We conducted according to PRISMA 2020 checklist guidelines, a comprehensive literature search across multiple databases including MEDLINE (Ovid), EMBASE (Ovid), Global Health (Ovid), Web of Science, and Global Index Me-dicus. Studies were selected based on predetermined criteria, primarily involving neonates, HCWs, and environmental swabs, using culture or molecular methods to detect CRAB colonization. We excluded studies that did not specifically focus on NICUs, were duplicates, or lacked necessary data. The study selection and quality assessment were conducted independently by two reviewers. Data extraction involved collecting comprehensive details about each study. Our statistical analysis used a random-effects model to calculate the pooled prevalence and confidence intervals, stratifying results by regional location. We assessed study heterogeneity using Cochran's Q statistic and I^2 statistic, with regression tests employed to evaluate potential publication bias.

RESULTS

We analyzed 737 records from five databases, ultimately including 13 studies from ten countries. For neonates, the pooled prevalence was 4.8% (95%CI: 1.1% to 10.5%) with the highest rates observed in South-East Asia (10.5%; 95%CI: 2.4% to 23.3%). Among HCWs, a single Indian study reported a 3.3% prevalence. Environmental samples showed a prevalence of 2.3% (95%CI: 0% to 9.3%), with the highest rates in South-East Asia (10%; 95%CI: 4.2% to 17.7%). Significant heterogeneity was found across studies, and no publication bias was detected.

CONCLUSION

This systematic review highlights a significant prevalence of CRAB colonization in neonates across various regions, particularly in South-East Asia, contrasting with lower rates in high-income countries. The study reveals a gap in research on HCWs colonization, with only a single study from India reporting moderate prevalence. Environmental samples indicate moderate levels of CRAB contamination, again higher in South-East Asia. These findings underscore the need for more extensive and focused research on CRAB colonization in NICUs, including exploring the roles of HCWs and the environment in transmission, understanding antimicrobial resistance patterns, and developing effective prevention measures.

Key Words: Colonization; Carbapenem-resistant *Acinetobacter baumannii*; Neonatal intensive-care unit

Core Tip: This study reveals a notable prevalence of carbapenem-resistant *Acinetobacter baumannii* colonization in neonatal intensive care units. The analysis revealed a pooled prevalence of 4.8% in neonates, with a considerable gap in research on healthcare workers colonization and a 2.3% prevalence in environmental samples. The substantial heterogeneity across studies and the observed regional variations underlines the need for more targeted research.

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INTRODUCTION

The escalation of carbapenem-resistant *Acinetobacter baumannii* (CRAB) in neonatal intensive care units (NICUs) is a mounting concern in the healthcare settings. A study has highlighted the significance of CRAB healthcare-acquired infections (HAIs) in various World Health Organization (WHO) regions, revealing an incidence of 21.4 (95%CI: 11.0 to 41.3) cases per 1000 patients in hospital settings, and a higher incidence of 41.7 (95%CI: 21.6 to 78.7) cases per 1000 patients in intensive care units[1]. CRAB accounts for 13.6% (95%CI: 9.7 to 18.7%) of all HAIs in these settings[1]. Another study has highlighted the severe implications of CRAB infections, with patients exhibiting a doubled mortality risk compared to those with carbapenem-susceptible *Acinetobacter baumannii* (CSAB), evidenced by a pooled crude odds ratio of 2.22 (95%CI: 1.66 to 2.98)[2]. A retrospective study from Thailand has highlighted the economic impact of CRAB infections in ventilator-associated pneumonia (VAP), where CRAB VAP patients incurred a median total hospital cost of US$11773, higher than the US$9735 for CSAB VAP patients[3].

The asymptomatic nature of CRAB colonization and the possibility of its transmission to vulnerable neonates with developing immune systems through healthcare workers (HCWs) or the NICU environment exacerbate this risk[4,5]. This scenario is challenging because the absence of symptoms in colonized individuals makes early detection and isolation difficult, increasing the risk of transmission to vulnerable newborns. The findings from a study investigating nosocomial rectal CRAB colonization in a tertiary-care hospital identified several significant risk factors associated with CRAB colonization, notably the use of permanent devices (OR 10.15, 95%CI: 2.27 to 45.39), mechanical ventilation (OR 40.01, 95%CI: 4.05 to 395.1), urinary catheters (OR 4.9, 95%CI: 1.52 to 16.19), a poorer prognosis (OR 5.45, 95%CI: 1.87 to 15.89), increased length of stay (OR 1.03, 95%CI: 1.01 to 1.05), and carbapenem use (OR 5.39, 95%CI: 1.14 to 25.44)[6]. Effective management in NICUs demands a comprehensive strategy encompassing regular screening of neonates and HCWs, strict hand hygiene, thorough environmental cleaning and disinfection, and adherence to infection control protocols[7]. CRAB, identified by the WHO and the Infectious Diseases Society of America (IDSA) as a high-priority pathogen, poses a significant threat due to its resistance to a wide range of antibiotics[8,9]. CRAB's resistance to a broad range of antibiotics, including cephalosporins, fluoroquinolones, and commonly used hospital antibiotics like piperacillin, ticarcillin, and ampicillin, limits treatment options[10]. Colistin and polymyxin B show the lowest resistance rates, suggesting potential therapeutic alternatives[10]. The prevalence of CRAB colonization in NICUs is subject to significant variation, reflecting disparities in healthcare practices, hospital environments, geographic locations, and patient demographics. Despite the critical impact of CRAB in NICUs, current epidemiological understanding, particularly regarding neonates, HCWs, and the NICU environment, remains limited. The objective of this review is to examine the prevalence of CRAB colonization in NICUs, focusing on neonates, HCWs, and the NICU environment.

MATERIALS AND METHODS

Protocol registration and review design

The protocol was registered on the International Prospective Register of Systematic Reviews, PROSPERO, as CRD-42023463547 and to conduct this systematic review, the study design followed PRISMA 2020 guidelines[11].

Search strategy

The search strategy included looking through five databases, such as MEDLINE (Ovid), EMBASE (Ovid), Global Health (O-vid), Web of Science, and Global Index Medicus (Supplementary Table 1). The databases query was done on September 13, 2023. The reference list of pertinent papers was also hand-searched. The review focused on papers published in Eng-lish or French that were not time limited.

Eligibility criteria

After removing duplicates from the detected papers across bibliographic databases, the titles and abstracts of the re-maining articles were independently examined by two reviewers. The studies were chosen based on preset inclusion criteria, which included studies that recruited neonates, HCW, and swabbed inert surfaces in environment to investigate CRAB colonization or carriage using culture or molecular techniques. Studies focusing on clinical CRAB infections, CRAB outbreaks, research done outside of NICUs, review studies, duplicates, and those without abstracts or complete texts were removed. Publications not in English or French, articles with irrelevant or inadequate data were all excluded from the analysis.

Study selection

The selection was done by two independent reviewers (DSM and SK) based on the predefined inclusion and exclusion criteria. The reviewers individually examined all of the publication titles and abstracts to find potentially qualifying stu-dies. The entire texts of these possibly qualifying papers were then evaluated to decide their inclusion in the review. Any discrepancies or contradictions were reviewed and resolved by consensus. If an agreement could not be reached, a third reviewer was consulted.

Data extraction

SK and DSM independently examined the data retrieved from selected studies. Data was extracted online by google form and summarized in a Microsoft Excel file. From each study we collected first author names, publication year, reason of exclusion if study were excluded, study design, country of study, sampling method, setting, levels of care, number of si-tes, timing of samples collection, countries; Geographic regions; number of participants screened, number of participants colonized with CRAB, isolation method utilized.

Quality assessment

The studies that met the inclusion criteria were rated for methodological quality by two investigators (SK and DSM) independently. Quality assessment of the included studies were done by using the Hoy *et al*[12] tools (Supplementary Table 2). Any disagreements were settled verbally, and consensus was obtained.

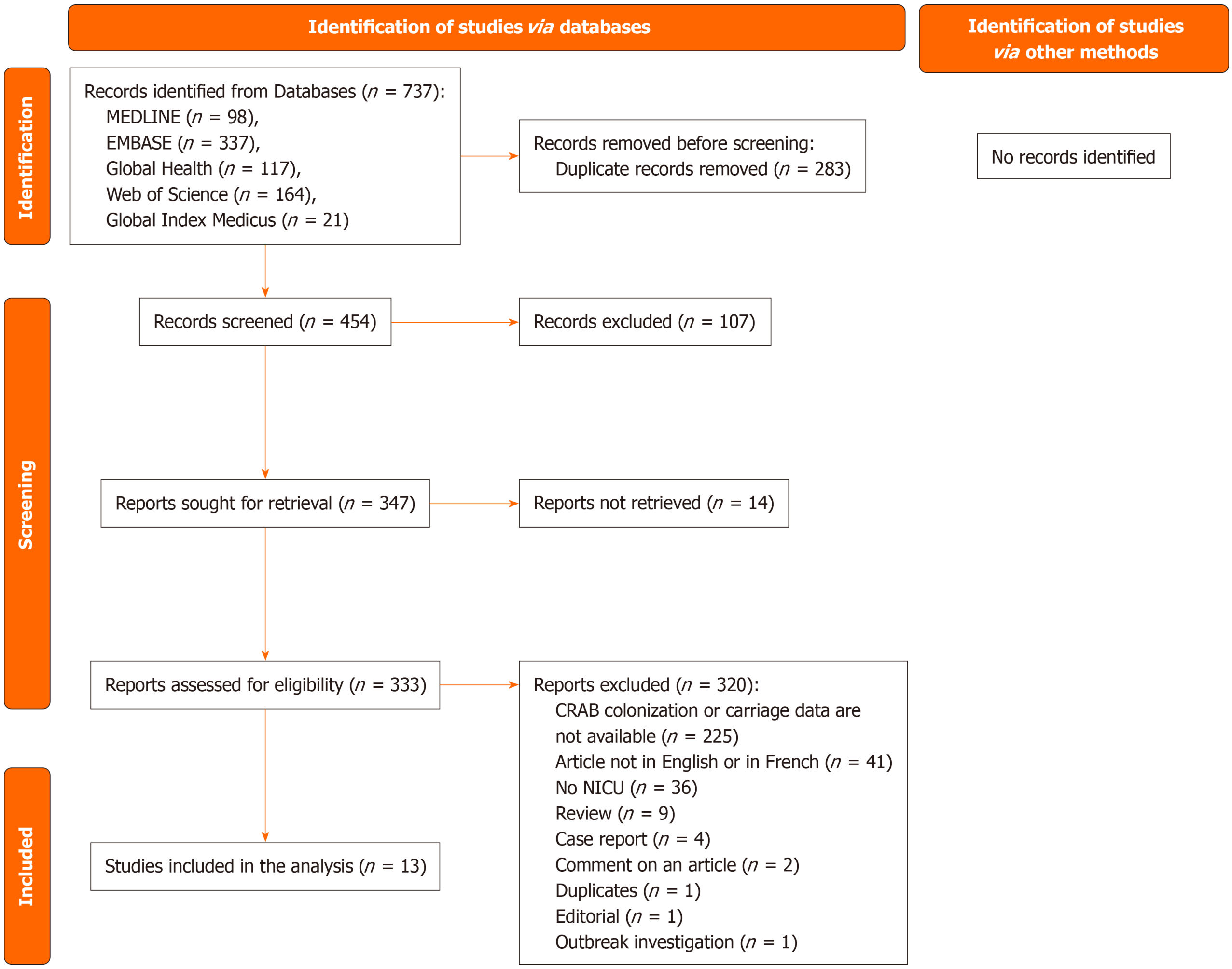

Figure 1 PRISMA diagram showing selection of studies.

Data analysis

The analysis was carried out with R software version 4.0.3 utilising the statistical software packages meta (version 4.18-2) and metafor (version 3.0-2)[13,14]. The pooled percentage and 95% confidence interval (CI) were calculated using a random-effects model[15]. Results in subgroup analysis were stratified by geographical and regional location. Heterogeneity of study effect sizes was evaluated using Cochran's Q statistic and I^2 statistic[16,17]. Significant heterogeneity is defined by a P value < 0.05 for the Cochran Q statistic or by I^2 values > 50%. Regression tests were used to investigate publication bias[18].

RESULTS

Study selection

A total of 737 records were identified from five databases: MEDLINE (*n* = 98), EMBASE (*n* = 337), Global Health (*n* = 117), Web of Science (*n* = 164), and Global Index Medicus (*n* = 21). Of these, 454 records were screened, leading to the exclusion of 107 reports. Subsequently, 347 reports were sought for retrieval, but 14 could not be retrieved. Upon assessing the 333 retrieved reports for eligibility, 320 were excluded for various reasons, including the absence of CRAB colonization or carriage data (*n* = 225), language barriers (*n* = 41), lack of NICU data (*n* = 36), and other categorizations such as reviews, case reports, article comments, duplicates, editorials, and outbreak investigations. Ultimately, 13 studies were included in the analysis (Figure 1)[19-31].

Study characteristics

We gathered published data from ten countries, with Brazil, Morocco, and Thailand each contributing two studies, and Egypt, Germany, India, Italy, Netherlands, Serbia, and Türkiye each providing one (Supplementary Table 3). Geographically, the majority of the studies hailed from Europe (*n* = 5), followed by the Eastern Mediterranean and South-East Asia each with three studies, and America with two studies (Figure 2). When segmented by income, most of the studies were from upper-middle-income countries (*n* = 6), with lower-middle-income countries providing four and high-income

Table 1 Summary of meta-analysis results for estimates of carbapenem-resistant *Acinetobacter baumannii* colonization in neonatal intensive care units

	Prevalence % (95%CI)	95% prediction interval	N studies	N participants	[1]H (95%CI)	[2]I^2 (95%CI)	P heterogeneity	P egger test
Neonates	4.8 [1.1-10.5]	[0-35.7]	10	6610	8.7 [7.6-9.9]	98.7 [98.3-99]	< 0.001	0.718
HCWs	3.3 [0-13.8]	NA	1	30	NA	NA	1	NA
Environmental samples	2.3 [0-9.3]	[0-51.9]	4	530	2.7 [1.7-4.2]	86.4 [67-94.4]	< 0.001	0.989

[1]H is a measure of the extent of heterogeneity, a value of H = 1 indicates homogeneity of effects and a value of H > 1 indicates a potential heterogeneity of effects.

[2]I^2 describes the proportion of total variation in study estimates that is due to heterogeneity, a value > 50% indicates presence of heterogeneity.

CI: Confidence interval; N: Number; 95%CI: 95% Confidence interval; NA: Not available; HCWs: Healthcare workers.

countries three. The majority of these studies were recent, with various participant recruitment periods ranging from January 1989 to February 2020. Concerning the populations under study, neonates dominated the research (n = 9), compared to environmental samples (n = 4) and HCWs (n = 1). Different methods, such as culture and biochemical (API gallery), were used for CRAB identification, with disk diffusion test being the most common antimicrobial susceptibility testing method and following mainly Clinical and Laboratory Standards Institute guidelines. The antibiotics primarily used for these tests were carbapenem including imipenem and meropenem. Samples varied from endotracheal aspirates and environmental samples to various swabs like rectal and surface. A study in Brazil from September 2013 to September 2015 involving 21 neonates tested CRAB antimicrobial susceptibility and reported 100% resistance to ampicillin/sulbactam, piperacillin/tazobactam, ceftazidime, ceftriaxone, cefepime, gentamicin, and ciprofloxacin, 76.2% to tigecycline, 47.6% to amikacin, and no resistance to colistin[24]. All the studies reviewed had a moderate risk of bias (Supplementary Table 4).

Prevalence of CRAB colonization in neonates in neonatal intensive care units

The prevalence of CRAB colonization in neonatal intensive care units for neonates was 4.8% (95%CI: 1.1 to 10.5%) based on 10 studies with 6610 participants, with a heterogeneity of I^2 = 98.7% (95%CI: 98.3 to 99), indicating significant heterogeneity (Figure 3). A study in Germany during the study period from November 2016 to March 2018 reported a prevalence of 0% among 584 preterm infants and severely ill neonates, including those with very low birth weight[20]. In Serbia, from December 2017 to April 2018, found a colonization prevalence of 13.6% among 103 premature neonates, with 14 neonates testing positive for CRAB[26]. A study in Thailand, during the study period from February 2015 to September 2015, reported a prevalence of 27.9% among 660 outborn neonates, with 184 of these neonates testing positive for CRAB colonization[29]. In a study in Thailand, during the preintervention period from January 2011 to December 2013, which involved pasteurization cleaning of a reused ventilator circuit and daily cleaning of the NICU environment with 0.5% NaOCl, the prevalence was 14.0% among 1437 neonates, with 201 neonates testing positive for CRAB[31]. During the intervention period from January 2014 to December 2014, which implemented the use of disposable HMEs, HME equipment for all ventilated neonates, 0.5% NaOCl for NICU cleaning, 0.05% NaOCl for neonatal environment cleaning, and ongoing education for HCWs about HME and NaOCl use, the prevalence dropped to 5.1% among 455 neonates, with 23 neonates testing positive. In the postintervention period spanning from January 2015 to December 2017, which maintained the use of disposable HMEs and HME equipment for all ventilated neonates, 0.5% NaOCl for NICU cleaning, and 0.05% NaOCl for neonatal environment cleaning without additional training for HCWs, the prevalence further decreased to 2.2% among 1475 neonates, with 33 neonates found to be colonized with CRAB. P values for heterogeneity were significant at less than 0.001, while the Egger test results, indicative of no publication bias was 0.718 (Table 1).

Prevalence of CRAB colonization in healthcare workers, and environmental samples in neonatal intensive care units

For HCWs, the prevalence was 3.3% (95%CI: 0 to 13.8) from a singular study conducted in India and involving 30 participants.

In the case of environmental samples, the prevalence was reported at 2.3% (95%CI: 0 to 9.3) from four studies with 530 samples, showcasing a heterogeneity of I^2 = 86.4% (95%CI: 67 to 94.4) (Figure 4). P values for heterogeneity were significant at less than 0.001, while the Egger test results, indicative of no publication bias was 0.989 (Table 1).

Subgroup analysis

In a subgroup analysis of a systematic review aimed at describing the colonization of CRAB in neonatal intensive care units, among neonates, Serbia reported the highest prevalence at 13.6% (95%CI: 7.6% to 21%) followed by Thailand with 10.5% (95%CI: 2.4% to 23.3%) and Türkiye with 7.2% (95%CI: 5.5% to 9.2%) (Supplementary Table 5). When grouped by WHO regions, South-East Asia had the highest prevalence at 10.5% (95%CI: 2.4% to 23.3%), while Europe reported a prevalence of 3.1% (95%CI: 0% to 11.9%). By World Bank Income Groups, upper-middle-income countries showed the highest colonization at 8% (95%CI: 2.5% to 16.1%). For environmental samples, India reported the highest prevalence at

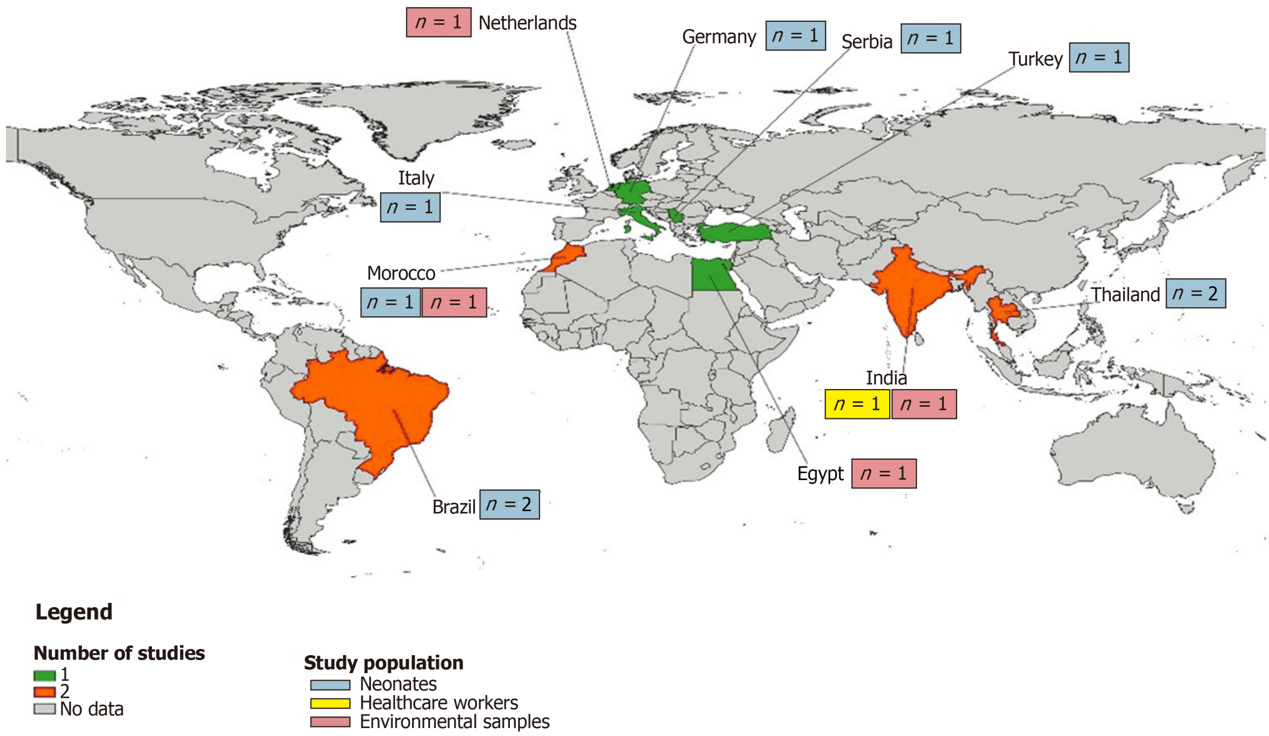

Figure 2 Map of the distribution of carbapenem-resistant *Acinetobacter baumannii* data among neonates, healthcare workers and environmental samples.

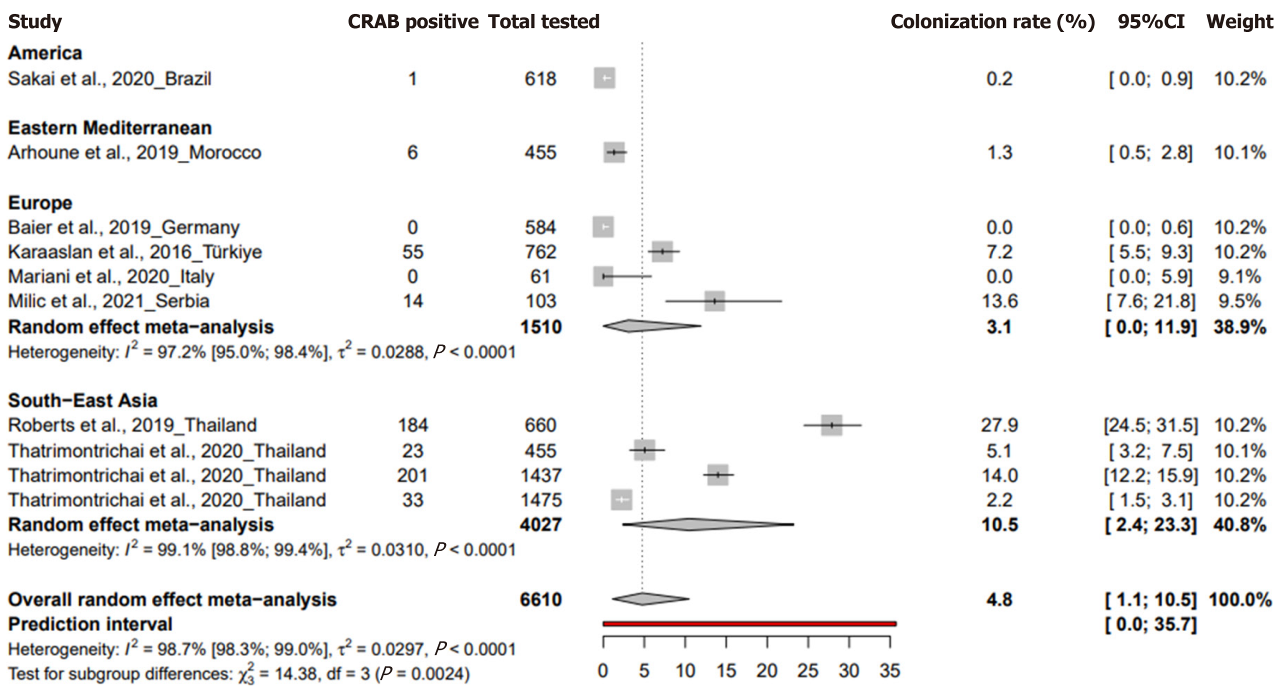

Figure 3 Prevalence of carbapenem-resistant *Acinetobacter baumannii* colonization in neonates in neonatal intensive care units.

10% (95%CI: 4.2% to 17.7%), followed by Morocco at 5.2% (95%CI: 2.9% to 8.1%). In the WHO regional breakdown for environmental samples, South-East Asia had a prevalence of 10% (95%CI: 4.2% to 17.7%). The differences in prevalence among country subtypes for both neonates and environmental samples were significant with P values less than 0.001. In contrast, differences among the WHO regions for environmental samples were not statistically significant with a P value of 0.187.

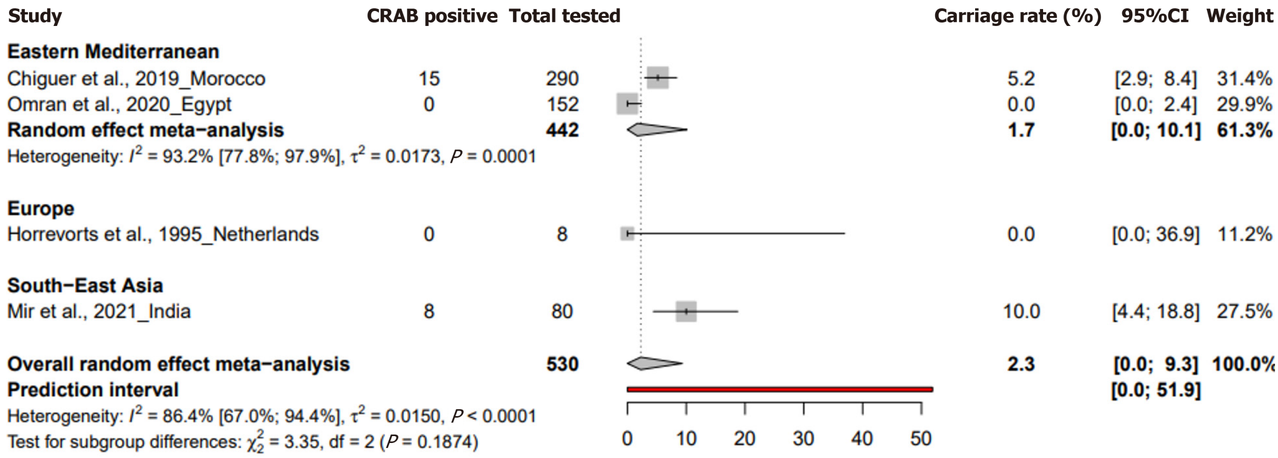

Figure 4 Prevalence of carbapenem-resistant Acinetobacter baumannii environmental contamination in neonatal intensive care units.

DISCUSSION

The present systematic review is the first to examine CRAB colonization in neonates, HCWs, and environmental samples in NICUs in ten countries, encompassing 13 included studies. The review found a substantial variability in CRAB colonization rates among neonates, with a pooled prevalence of 4.8% (95%CI: 1.1% to 10.5%). For HCWs, a single study from India reported a 3.3% prevalence, while environmental samples showed a pooled prevalence at 2.3% (95%CI: 0% to 9.3%). South-East Asia recorded the highest prevalence of CRAB colonization for both neonates (10.5%; 95%CI: 2.4% to 23.3%) and environmental samples (10%; 95%CI: 4.2% to 17.7%). High-income countries exhibited minimal prevalence of CRAB colonization in these categories. A Brazilian study involving neonates found 100% resistance to several antibiotics, but no resistance to colistin. In Thailand, interventions like the use of disposable ventilation equipment and improved cleaning protocols significantly reduced CRAB prevalence in NICUs.

The review identifies a pooled prevalence of 4.8% (95%CI: 1.1% to 10.5%) among neonates, with notable geographical variability, highlighting the influence of regional socioeconomic factors and healthcare practices. South-East Asia showed the highest prevalence at 10.5% (95%CI: 2.4% to 23.3%), contrasting with minimal rates in high-income countries. This disparity in CRAB colonization rates may be attributed to infection control standards, healthcare infrastructures, distinct local healthcare protocols, environmental conditions, and variations in antibiotic usage, which warrant further detailed investigation to understand their contributions to these regional differences[7,32,33]. However, a significant limitation is the absence of data on neonatal length of stay in NICUs in included studies, a critical factor in assessing colonization risk [34]. Another limitation of this study is the absence of data from low-income countries, which potentially limits the generalizability of the findings. There is a clear need for further research on CRAB in NICUs from low- and middle-income countries.

The review also points to a significant knowledge gap regarding HCW colonization, with only one study from India indicating a 3.3% prevalence. Given the potential of HCWs as vectors for asymptomatic transmission of CRAB to highly susceptible neonates, this lack of data hampers the development of comprehensive infection control strategies in non-outbreak settings in NICUs[35]. Environmental samples revealed a pooled prevalence of 2.3% (95%CI: 0% to 9.3%), with a peak prevalence of 10% in South-East Asia (95%CI: 4.2% to 17.7%), suggesting that hospital environments, particularly in resource-limited settings, can act as reservoirs for CRAB, facilitating its spread within NICUs[5,36].

Antimicrobial resistance patterns in neonates are poorly represented in the literature, with only one Brazilian study included, reporting a 100% resistance rate to several antibiotics except for colistin. This finding aligns with Lima's 2019 study, which documented high resistance rates to various antibiotics in CRAB isolates from burn injury patients[10]. The emerging challenge in treating CRAB infections is evident, highlighting the urgent need for judicious antibiotic use and alternative therapeutic strategies[5,37].

In terms of preventive measures, the review includes a study from Thailand, demonstrating a significant reduction in CRAB prevalence in NICUs following specific interventions. This contrasts with Tomczyk's 2019 review, which provides a broader view of effective infection prevention and control measures across various healthcare settings[38]. The specific challenges and needs of neonatal populations in NICUs, however, remain under-researched, underscoring the necessity for more focused interventional studies on effective preventive strategies for this vulnerable group.

CONCLUSION

This systematic review finds a notable prevalence of CRAB colonization in neonates, with significant regional differences, being higher in South-East Asia and lower in high-income countries. The research on HCWs colonization is limited, with only one study from India indicating a moderate prevalence. Environmental samples also show a moderate CRAB contamination, with higher rates again observed in South-East Asia. This study highlights the need for more comprehensive research focused on CRAB on neonatal populations in NICUs, including studies on HCW colonization, environmental contamination, antimicrobial resistance patterns, and effective prevention measures. The development of tailored strategies that address the unique vulnerabilities of neonates in NICUs is essential to combat the threat of CRAB colonization and ensure the safety and health of these patients.

ARTICLE HIGHLIGHTS

Research background

The surge of carbapenem-resistant *Acinetobacter baumannii* (CRAB) in neonatal intensive care units (NICUs) has emerged as a significant healthcare concern, particularly due to its role in healthcare-acquired infections (HAIs). CRAB doubles the mortality risk compared to patients with carbapenem-susceptible Acinetobacter baumannii.

Research motivation

The asymptomatic nature of CRAB colonization, especially in NICU settings, and its potential transmission through healthcare workers (HCWs) or the environment, intensify the risks to vulnerable neonates with developing immune systems.

Research objectives

This review aims to examine the prevalence of CRAB colonization in NICUs, focusing on neonates, HCWs, and the NICU environment.

Research methods

Our systematic review was conducted following the PRISMA 2020 guidelines. We initiated our search across MEDLINE (Ovid), EMBASE (Ovid), Global Health (Ovid), Web of Science, and Global Index Medicus. We also conducted a manual search through the references of relevant papers. Our inclusion criteria focused on studies in English or French that investigated CRAB colonization in neonates, HCWs, and environmental samples using culture or molecular techniques. Studies that did not focus on NICUs, were duplicates, or lacked adequate data were excluded. A random-effects model was applied to calculate the pooled prevalence and 95% confidence intervals, with subgroup analysis stratified by regional location.

Research results

Our systematic review collated data from 13 studies across ten countries. We found that neonates had a pooled CRAB colonization prevalence of 4.8%, though this varied widely by region, with South-East Asia reporting the highest rates. The prevalence in HCWs was only documented in a single study from India, suggesting a significant research gap in understanding the role of HCWs as potential vectors in CRAB transmission. Environmental samples exhibited CRAB presence, with a pooled prevalence of 2.3%, again with the highest rates in South-East Asia.

Research conclusions

The study revealed significant geographical variability in CRAB colonization rates, with a pooled prevalence of 4.8% among neonates and notable higher rates in South-East Asia and lower in high-income countries. A critical gap in research was identified regarding HCW colonization, with only a single study from India reporting a prevalence of 3.3%. Environmental samples showed a 2.3% pooled prevalence, with the highest rates again in South-East Asia.

Research perspectives

This study underscores the necessity of tailored research and intervention strategies in NICUs to address the unique challenges of neonatal populations and combat the threat of CRAB colonization effectively.

FOOTNOTES

Author contributions: Mbaga DS, Kenmoe S, Njiki Bikoï J and Riwom Essama SH were responsible for conception and design of the study as well as project administration; Mbaga DS, Kenmoe S, Nkie Esemu S, Kaah Keneh N, Tatah Kihla Akoachere JF, Gonsu Kamga H, Ndip Ndip R, Ebogo-Belobo JT, Kengne-Ndé C, Mbaga DS, Tendongfor N, Mande Ndip L, Assam Assam JP, Njiki Bikoï J and Riwom Essama SH were responsible for the data curation and interpretation of results; Kengne-Nde C and Kenmoe S were responsible for statistical analysis; Kenmoe S Njiki Bikoï J and Riwom Essama SH were responsible for the project supervision; Mbaga DS and Kenmoe S wrote the original draft; All authors critically reviewed the first draft and approved the final version of the paper for submission, and have read and approve the final manuscript.

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