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MAJOR ARTICLE

The burden of Neonatal Invasive Candidiasis in Low- and Middle-Income Countries: a systematic review and meta-analysis.

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Background: Invasive *Candida* infection remains a significant threat to neonates worldwide. Most evidence on neonatal invasive candidiasis (NIC) comes from high-income countries (HICs), leaving the burden and characteristics of NIC in low-and middle-income countries (LMICs) poorly

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described. This study aimed to investigate the incidence, case-fatality rates (CFR), epidemiology and aetiology of NIC in LMICs.

Methods: We conducted a systematic literature review and meta-analyses of all eligible studies in 17 databases published from inception until April 2022 focussing on microbiologically-confirmed NIC in LMICs.

Findings: A total of 257 articles were included, with 10,994 NIC cases from 27 LMICs. The overall incidence rate was 2.6% (95% CI: 2.2%-3.0%). Regional disparities were evident, with South-East Asia reporting the highest incidence rate (6.3%; 95% CI: 3.2%-10.3%). The mean gestational age and birth weight were 31.4 weeks (standard deviation [SD] 3.3) and 1,530 g (SD 644.6) respectively. Among 10,087 included isolates, the predominant species was *C. albicans* (39.0%), followed by *C. parapsilosis* (24.8%) with marked differences in species distribution across World Health Organization regions. Fluconazole was the most commonly-used agent for NIC treatment (55.4%; 1,567/2,826). Overall, 24.8% (1,128/6,613) of isolates with available data were resistant to fluconazole. The pooled estimated CFR was 18.7% (95% CI: 15.5%-22.1%).

Conclusions: A higher NIC incidence rate and CFR in LMICs is noted compared to HICs, although infected babies were less premature with a higher birth weight. The proportion of fluconazole-resistant isolates was high. Prevention and treatment strategies for NIC need to be targeted to LMIC settings.

Keywords: neonatal invasive candidiasis, candidemia, low- and middle-income countries, incidence, case fatality rate.

Article's main point: Our study highlights the higher incidence and case-fatality rates of neonatal invasive candidiasis in low- and middle-income countries compared to high-income countries. Neonates were outside the well-defined high-risk group. Regional disparities in species and fluconazole resistances were observed.

INTRODUCTION

Neonatal invasive candidiasis (NIC) is an important nosocomial infection associated with significant morbidity and mortality.[1] The incidence rate of NIC varies between 0.5% and 2%;[2–5] with higher rates (7%-9%) in high-risk neonates (e.g. gestational age <28 weeks or birth weight <1000 grams).[3,6,7] Most of the current data are derived from high-income countries (HICs). The burden of NIC in low- and middle-income countries (LMICs) remains poorly described.[6] Two recent studies, the Delhi Neonatal Infection Study (DENIS) and Global Neonatal Sepsis Observational Study (NeoOBS), revealed different epidemiological characteristics of NIC in LMICs compared to HICs, with a higher incidence rate outside the high-risk group.[8,9] Mortality rates can reach 40% for high-risk neonates.[2,10–12] Despite the limited data on mortality associated with NIC from LMICs, this may be higher than in HICs.[9,13,14]

The aetiology of NIC in HICs is well described.[15–17] *C. albicans* is the leading pathogen (40-60% of all *Candida* species), followed by *C. parapsilosis* (28%-42%). Fluconazole resistance for *C. albicans* and *C. parapsilosis* remains low (<5%) in HICs.[18] Globally, different epidemiology is observed with higher rates of non-*albicans Candida* isolates causing NIC in LMICs compared to HICs.[19] In addition, fluconazole-resistant NIC cases are increasingly being observed.[20,21,22]

We aimed to address the critical knowledge gaps concerning NIC in LMICs, including burden, case-fatality rate (CFR), clinical and fungal epidemiology, as well as clinical management. Insights into these aspects could inform future policies and targeted research.

METHODS

Search strategy

This systematic review and meta-analysis study was registered with PROSPERO (CRD42022318605). A quality assessment was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for reporting systematic reviews.[23] The databases searched included: Embase, PubMed, CENTRAL (Cochrane Central Register of Controlled Trials), Scopus, Web of Science, LILACS (Latin American and Caribbean Health Sciences Literature), WHOIRIS (WHO Library Dataset), Med-Carib, African Journals Online (AJOL), African Index Medicus (AIM), IMSEAR (Index Medicus for South- East Asia Region), IMEMR (Index Medicus for the Eastern Mediterranean Region), WPRIM (Western Pacific Region Index Medicus), OpenGrey, Google Scholar and WANFAN, and Airity library (for Chinese manuscripts). The search period ranged from each database's inception to the 5th of April 2022. The searches included the following concepts: "candidiasis", "neonates", "antifungal agents", "fatality", and "LMIC" with adjustments made as suitable to each database (detailed searches are listed in the supplementary materials). Five reviewers (DHTT, ICYW, BD, LFC, and MJHL) independently screened titles and abstracts. The full-length articles were retrieved for final review and data extraction. Any disagreements were resolved with senior authors (LFA and YH).

Case definition

To be more inclusive and capture the full spectrum of late-onset neonatal infections, we defined neonate as any infants aged up to 90 days. NIC was defined as a positive blood and/or cerebrospinal fluid (CSF) culture for *Candida* spp. Although antifungal susceptibility may vary, *C. krusei*, *C. glabrata* and *C. auris* were grouped as *Candida* spp. intrinsically resistant to fluconazole to assist analysis. The 2022 World Bank classification was used to define the country income level as LMICs; among these, further distinction into lower- and upper-middle-income countries was made.[24]

Selection criteria

Original articles reporting NIC incidence, case fatality rate and epidemiologic parameters were included. Eligible studies were retrospective studies, cohort studies, cross-sectional studies, and case series which reported three or more cases of NIC aged 0-90 days in LMICs. We excluded articles on non-neonatal populations, clinical trials, animal studies, case reports, and reviews. Studies were excluded if only aggregated data were presented. There was no language restriction. EndNote reference software (version X9, Philadelphia, PA, Clarivate) was used to manage articles.

Data extraction

Data collected included study design, publication year, study period, geographic location (WHO regions and countries),[25] total admitted neonates, total live births, total high-risk neonates, number of NIC cases, patients' demographics, risk factors for NIC (prolonged hospital admission, known *Candida* colonisation, parenteral nutrition, intravascular catheters and prolonged use of broad-spectrum antibiotics), *Candida* species, susceptibility results, antifungal prophylaxis and treatment, length of hospital stay and clinical outcomes. Preterm neonates were defined as neonates with gestational age of ≤37 weeks. High-risk neonates were defined as neonates with birth weight ≤1,500 grams and/or gestational age ≤28 weeks. Very low (vLBW) or extremely low birth weight (eLBW) were defined as ≤1,500 or ≤1,000 grams at birth, respectively. Prolonged hospital admission was defined as a stay of more than seven days. Prolonged use of broad-spectrum antibiotics was defined as neonates receiving carbapenem, third or fourth-generation cephalosporin, or piperacillin-tazobactam for more than five days. The types of hospital (tertiary care hospital vs. other facilities and public vs. private centres) and the culture samples which were taken (blood vs. cerebrospinal fluid) were also recorded. Data were extracted by one reviewer and verified by a second reviewer (DHTT, ICYW, LFC, and MJHL).

Risk of bias assessment

Risk of bias was assessed with the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) Tool.[26] Two reviewers (DHTT and ICYW) independently completed the assessments for each reported outcome. Any conflicts were resolved by discussion with the senior authors (LFA and YH).

Data analysis

Descriptive analysis was performed to provide an epidemiological overview of NIC. Continuous variables were presented by means with standard deviation (SD), and categorical variables by numbers with percentages. We pooled the continuous variables and weighted them by their patient numbers. For those studies only reporting a median and the interquartile range (IQR), conversion was performed to estimate the sample mean and SD[27]. We used the number of neonates with candidemia or CSF-positive cultures (numerators) from all admitted neonates (denominators) to calculate incidence. We used the number of neonates with candidemia or CSF-positive cultures (denominators) and those cases who died (numerators) to estimate CFR. The meta-analysis with

random-effects models was performed to estimate pooled incidences of NIC and CFR. The Freeman-Tukey double arcsine transformation was used to present regional and overall pooled estimates with 95% Wald confidence intervals, heterogeneity using I^2 and test of significance of the overall pooled estimates.[28–30] All estimates were stratified by World Health Organization (WHO) regions and risk group. We defined all neonates as an overall neonatal population since some articles did not differentiate high-risk neonates from non-high-risk. Two sensitivity analysis were conducted, one included high-risk neonates and the other one excluded Chinese studies, due to the large amount of data from this country. Stata SE software (version 17. College Station, TX: StataCorp LLC.) was used for data management and analyses.

RESULTS

We assessed 1,210 articles for eligibility, with 256 from 27 countries meeting the inclusion criteria for full-length review (Figure 1). Of those, 158 studies belonged to the Western Pacific WHO region, 31 from Latin America, 31 from Southeast Asia, 13 from Europe, 13 from the East Mediterranean and 11 from the African region (Supplementary Tables S1 and S2). There were 117 studies reporting NIC incidence and 96 reporting CFR. Most studies reporting NIC incidence (75.2%; 88/117) and over half reporting CFR (56.3%; 54/96) were conducted in China.

Incidence of NIC and CFR

The overall pooled estimated NIC incidence was 2.6% (95% CI, 2.2%-3.0%, I^2, 97.5%). Similar rates were observed across regions except for South-East Asia with the highest reported incidence (6.3% [95% CI, 3.2%-10.3%], I^2, 99.2%) (Figure 2a). The estimated incidence was higher in high-risk neonates (7.7% [95% CI, 5.7-10.0%], I^2, 82.8%) compared to the overall estimated incidence (Figure 2b).

The overall estimated CFR was 18.7% (95% CI, 15.5%-22.1%, I^2, 79.0%) (Figure 3a) with regional differences observed. The Eastern Mediterranean region had the highest reported CFR (39.8% [95% CI, 25.0-55.6%], I^2, 69.7%), followed by Latin America (37.9% [95% CI, 29.3-46.8%], I^2, 54.1%), Africa (33.0% [95% CI, 12.1-58.1%]), South-East Asia (31.4% [95% CI, 21.0-42.7%], I^2, 75.2%), Europe (29.6% [95% CI, 10.0-53.8%], I^2, 85.5%), and the Western Pacific region (9.3% [95% CI, 6.7-12.1%], I^2, 57.2%). For those studies with high-risk neonates data available, the estimated CFR was 7.6% (95% CI, 3.3%-12.9%, I^2, 0%), although eight out of nine studies were conducted in China (Figure 3b). Figure 4 presents the wide variation on NIC incidence and CFR among countries.

The subgroups analyses by low- and lower-middle-income countries versus upper-middle-income countries showed a pooled incidence twice as high in the former group (4.2% [95% CI, 2.5%-6.4%], I^2, 98.9% vs. 2.4% [95% CI, 2.0%-2.8%], I^2, 97.1%). CFR was also higher in low and lower-middle-income countries, 37.5% (95% CI, 28.5%-46.9, I^2, 77.8%), compared to upper-

middle-income countries, 15.0% (95% CI, 11.9%-18.3, I^2, 75.3%]. Detailed data are presented in Supplementary S1, S2, S3a, S3b, S4a and S4b Figures. The sensitivity analysis after excluding studies conducted in China showed a similar incidence of 3.3% (95% CI, 2.4%-4.3%, I^2, 98.3%) (Figure S5a). In contrast, the estimated CFR raised to 34.3% (95% CI, 29.0%-39.9%, I^2, 78.6%) (Figure S5b).

Demographics and clinical characteristics

A total of 10,994 NIC cases were included. The majority were male (57.4%; 3,268/5,692). The mean age at diagnosis of NIC was 15.1 days of life (SD, 9.7); the mean gestational age was 31.4 weeks (SD, 3.3), and the mean birth weight was 1,530.1 grams (SD, 644.6). From those with data available, 66.8% (2,530/3,785) were preterm neonates, and only 12.7% (189/1,488) were neonates with a gestational age of 28 weeks or less. vLBW or eLBW was reported for 44.5% (1,957/4,402) of all the neonates with data available. Excluding the studies from China, the proportion of preterm neonates was 59.0% (1,398/2,369); the proportion of preterm neonates born ≤28 weeks of gestation and those with a birth weight ≤1,500 grams decreased to 7.5% (75/997) and 34.9% (1,078/3,093), respectively. A total of 11.8% (124/1,054) cases had reported positive CSF cultures (with or without candidemia). All neonates with NIC and data available (5,316/5,316; 100%) were treated in tertiary hospitals, with 87.7% (3,915/4,466) admitted in high-dependency units and 79.1% (440/556) in public hospitals. The clinical characteristics and NIC risk factors are summarised in Table 1 (specific data on neonates with NIC from China are presented at Table S3).

***Candida* species isolated**

A total of 10,109 isolates were included. *C. albicans* was the most common species (3,946, 39.0%), followed by *C. parapsilosis* (2,506, 24.8%); *C. tropicalis* (1,162, 11.5%); *C. glabrata* (renamed *Nakaseomyces glabratus*) (635, 6.3%); *C. krusei* (renamed *Pichia kudriavzevii*) (497, 4.9%) and *C. auris* (89, 0.9%). Regional differences in species distribution are illustrated in Figure 5. Other less frequent *Candida* species (1,274, 12.6%) are summarized in Supplementary Table S4.

A total of 56.5% (5,715/10,109) isolates from 20 countries (20/27, 74.1%) had data on susceptibility to at least one antifungal agent. Overall, 24.8% (1,128/4,544) isolates were resistant to fluconazole, whereas 7.8% (165/2,112), 6.1% (79/1,285), and 2.3% (59/2,566) showed resistance to voriconazole, itraconazole, and amphotericin B respectively. The proportion with fluconazole resistance was highest in *C. krusei* (203/281; 72.2%), followed by *C. auris* (35/49; 71.4%), *C. parapsilosis* (667/1,616; 41.3%), *C. glabrata* (37/279; 13.3%), *C. tropicalis* (94/727; 12.9%) and *C. albicans* (92/1,592; 5.8%). Excluding *C. krusei*, *C. glabrata* and *C. auris*, the fluconazole resistance rate for other species was 21.7% (853/3,935).

Marked regional variations in resistance were observed; South-East Asian region showing the highest proportion of fluconazole-resistant *Candida* spp isolates among those non-intrinsically resistant to fluconazole; 25.7% (48/187) of *C. albicans,* 21.0% (21/100) of *C. parapsilosis* and 26.5% (83/313) of *C. tropicalis* were fluconazole resistant. Notably, *C. parapsilosis* had the

highest fluconazole resistance in the African region, 57.8% (624/1,079). Susceptibility testing results by WHO regions and *Candida* species are presented in Supplementary Table S5.

Prevention and management of NIC

The treatment of NIC was reported in 83 articles (2,826 cases). The most common treatment prescribed was fluconazole (55.4%, 1,567), followed by amphotericin B (27.1%, 767) and a combination of fluconazole-amphotericin B (13.4%, 378). Echinocandins were rarely prescribed (0.7%, 21). Detailed antifungal use by region is presented at table S6.

Antifungal prophylaxis was reported in 25 articles, from 7 countries, of which 404 NIC cases (22.8%; 404/1774) received antifungal prophylaxis. From these 25 studies, 17 were conducted in China. A higher proportion of high-risk neonates received prophylaxis (85/107, 79.4%). Three out of four studies reporting antifungal prophylactic use in high-risk neonates were conducted in China. In most cases (399/404, 98.8%), fluconazole was the agent of choice. Antifungal prophylaxis in NIC cases was reported less frequently in low or lower-middle-income countries (54/1,008, 5.4%) compared to upper-middle-income countries (345/756, 45.6%).

DISCUSSION

This systematic review assessed the disease burden, clinical characteristics and outcomes of NIC in LMICs. Data from 27 countries and 10,994 cases showed that the overall incidence was 2.6%, with marked regional differences. The overall CFR was 18.7%, ranging from 9% to 40% across WHO regions. Where gestational age was reported, the majority of cases occurred in neonates who are not traditionally categorised as high risk for NIC; with only 12.7% of neonates born before 28 weeks and a mean gestational age and birth weight of 31.4 weeks and 1,530.1 grams respectively. Overall, *C. albicans* was the most common isolate, but non-*albicans Candida* species were more prevalent in some WHO regions. Fluconazole-resistant isolates account for a quarter of all the isolates and for more than a fifth of the isolates excluding *C. krusei*, *C. glabrata* and *C. auris*. Whereas fluconazole resistant *C. albicans* was reported in only a small proportion of the cases (5.8%), fluconazole resistance for *C. parapsilosis* was as high as 41.3%. South-East Asian and African regions showed the highest fluconazole resistance rates with variability among the species. The vast majority (95.1%) of the neonates received fluconazole and amphotericin B for treatment, whereas echinocandins were rarely used.

Our results have shown a higher incidence rate of NIC in LMICs (approximately 3%) among admitted neonates compared to published data from HICs (0.5%-2%).[2–4] The South-East Asia region has the highest reported incidence rate, 6%. Several possible reasons could explain the difference in NIC burden between LMICs and HICs. First of all, fewer resources available to implement targeted antifungal prophylaxis and other strategies to prevent healthcare-associated infections (HAI).[2,6,19] These interventions have played a crucial role in the reduction of NIC

incidence in HICs during the past two decades[2,31–33]. Secondly, the colonisation pressure differs; in HICs, *Candida* spp. colonisation occurs in around 26.7% to 62.5% of critically ill neonates within the first two weeks of life. In contrast, data from India or South Africa have shown higher and earlier rates of colonisation.[34,35] Finally, the role of *Candida* vertical transmission; although not fully well-described, some reports suggest its potential contribution to the incidence of NIC, including the transmission of resistant isolates.[36] Previous studies of NIC in HICs have estimated a CFR of approximately 20%.[17] Our sensitivity analysis, once the studies conducted in China were removed, has shown a higher CFR in LMICs, up to 40%. The differences might be multifactorial; gaps in recognition, diagnosis and management of NIC, differences in neonatal care-seeking behaviours or general neonatal health care interventions and weak infrastructures and health systems.[37,38] This emphasises the need to tailor interventions on NIC in resource-limited settings.

The low gestational age and birth weight are the main risk determinants of NIC.[2,7] However, the DeNIS study reported high rates of NIC for outborn neonates, of whom most were over 32 weeks' gestation (73.3%) or had a birth weight over 1,500 grams (61.5%).[8] Furthermore, a multi-country study, NeoOBS,[9] showed that in 127 neonates with NIC, the median gestational age at birth was 30 weeks (IQR: 28–34) and the median birth weight was 1,270 grams (IQR: 990– 1,692); only 27.0% of all neonates had a birth weight below 1,000 grams.[9] Our findings have shown similar epidemiological characteristics of NIC in LMICs; with only 12.7% of all NIC cases born less than 28 weeks, the mean gestational age of 31.4 (SD 3.3) weeks and the mean birth weight of 1,524.2 (SD 644.0). This contrasts with other large cohorts from HICs, such as EUROCANDY,[15] where the median age was 27 weeks (IQR, 10). The most plausible explanation might be that more premature and ELBW neonates do not survive long enough to develop NIC.[38] Other factors playing into this are limitations on neonatal infection prevention and care bundles; especially primary prevention interventions, which include the care of central line catheters or other medical devices, as well as the reduction in the use of broad-spectrum antibiotics and adequate handling.[39]

Globally, the majority of the cases of candidemia are now attributed to six main species, *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, C. auris* and *C. krusei*. However, population-based studies have demonstrated that the distribution of these species varies between geographical regions.[40] In children and neonates, whereas *C. albicans* remains the most prevalent species, *C. parapsilosis*, *C. tropicalis*[15,41–43] and, in certain settings, *C. auris* are becoming more common.[9,22] Despite the lack of temporal trends and exhibiting regional variations, our findings have demonstrated that non-*albicans* species were more prevalent than *C. albicans* in LMICs. About 25% of all isolates were resistant to fluconazole. The South-East Asian region had the highest rates of fluconazole-resistant isolates. The emergence of these species and resistant isolates is likely multifactorial; complex healthcare systems, global warming, behavioural factors with extensive use of fluconazole in public health settings or unregulated sale and use of antifungals, different spectrum of comorbidities in certain regions, inadequate infection prevention practices and prolonged use and overuse of antifungals across the One Health spectrum, especially azoles.[22,44–47] These global changes in *Candida* species epidemiology have clear clinical implications,

particularly in LMICs, where the availability of antifungal medicines may be limited and fluconazole remains the principal agent for targeted prophylaxis and treatment of NIC.[44,48–51]

Data from the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC)—Point Prevalence Survey showed that the use of fluconazole was higher in LMICs compared with HICs (66.8% vs. 39.2% of all prescriptions), whereas other triazoles, amphotericin B and echinocandins were more commonly used in HIC.[55] Our findings confirm that fluconazole (55.4%) and amphotericin B (27.1%) are the most used treatment modalities. The use of echinocandins was reported in less than 1% of the cases, despite their extended-spectrum against *Candida* spp. including *C. auris*, efficacy against *Candida* biofilms and a favourable safety profile.[6,58]

There are limitations to our review. First, the robustness of our results relies on the availability and quality of the included studies. There is likely selection and reporting bias. Selection bias, as many countries did not provide data, and most of the studies were from tertiary-level hospitals. Reporting bias, as data are likely affected by a degree of underestimation of the 'true' incidence of disease. We encountered significant heterogeneity. Moreover, there was also variation in the definitions of the neonatal population, in the calculation of gestational age, in the reporting and methodologies employed to identify the species or define isolate susceptibility. A few key clinical variables were incompletely reported in this review. For example, gestational age was available for only 1,789 of 10,994 case (16.3%), birth weight data were available for 1,627 cases (14.8%). Similarly, information on specific risk factors such as *Candida* colonisation, was reported in only a small subset of cases.

However, we have conducted several sensitivity analyses to reduce this heterogeneity. Furthermore, we were unable to determine any temporal trends which are of particular significance when assessing the emergence of fluconazole-resistant isolates. Moreover, *Candida* species have the potential to drive infection outbreaks, although we did a sensitivity analysis after identifying the manuscripts where the word "outbreak" was mentioned. Only nine papers included some sort of outbreak data. None of the papers reporting outbreak data had been included in the incidence analysis. A total of 8 papers including outbreak data were excluded for CRF calculation, with a lower CRF of 17.8% (95% CI 14.7% - 21.1%). Finally, a significant number of included studies were conducted in China. A sensitivity analysis was performed to avoid publication bias. After excluding studies conducted in China, there were a similar incidence of 3.3% but a raised CFR of 34.3%. Whereas China is classified as LMIC,[24] there are differences in healthcare services between China and other countries in the Global South.[59]

In 2022, the WHO published the Fungal Priority Pathogens List (FPPL) to systematically prioritize fungal pathogens, considering their unmet needs in research and development and perceived global public health importance.[44,60] Critical and high priority *Candida* species (e.g. *C. albicans*, *C. auris*, *C. parapsilosis*) affect neonatal health globally, but disproportionately in LMICs.[44,51] Nevertheless, there is a paucity of epidemiological data, clinical phase III trials hardly include

neonates, delay in access to newly-developed antifungal medicines, and access to antifungal therapy is severely limited in LMIC.[50,60] From our data and building upon the previous evidence, several specific recommendations are proposed: (1) the integration of NIC research into broader platform studies focused on neonatal sepsis and antimicrobial resistance in neonates, as this will allow a more efficient approach compared to traditional siloed studies. (2) The design of studies to assess the colonization pressure for *Candida* species in neonatal units in resource-limited settings. (3) Prospective epidemiological data collection to define the at-risk population for NIC in LMICs; facilitating a risk-based approach for future interventional studies. (4) The study and subsequent implementation of targeted infection prevention and care bundles for NIC in neonates in LMICs. This should include simple, low-cost, and evidence-based interventions such as breastfeeding, kangaroo mother-child care or the use of probiotics, considering the rising fluconazole resistance rates and limited access to alternative agents. (5) The better understanding on the long-term prognosis of children affected with NIC in LMIC.

In conclusion, we emphasise the importance of NIC as a significant contributor to neonatal morbidity and mortality in LMICs where its true burden is likely underestimated. Collaborative efforts and increased research investment are imperative to identify high-risk neonates in resource-limited settings and implement targeted preventive measures and optimal management strategies.

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Patient consent.

This is a review and meta-analysis piece; it does not include factors necessitating patient consent.

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Conflict of interest

AW has received consultant fees from Gilead and Mundipharma and payment for educational events from Gilead and F2G. All other authors report no potential conflicts.

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ALT TEXT

Figure 1. A PRISMA-style flow diagram illustrating the literature screening and selection process. It begins with the total number of records identified through database searches and other sources, shows the number remaining after duplicate removal, then the number of records screened and excluded at title/abstract review, the number of full-text articles assessed for eligibility (with reasons for exclusion), and finally the number of studies included in the review.

Figure 2a and 2b. Graphs present the incidence of neonatal invasive candidiasis (NIC) grouped by WHO regions (2a) and by publication (2b) for neonates at high risk of NIC.

Figure 3a and 3b. Graphs present the fatality rates as a measure of mortality of neonatal invasive candidiasis (NIC) grouped by WHO regions (3a) and by publication (3b) for neonates at high risk of NIC.

Figure 4. World maps represent the incidence and case fatality rates of neonatal invasive candidiasis in low and middle-income countries. Darker coloured countries correlate with higher incidence or higher fatality rates. Countries in grey colour are high-income countries. Countries in white are those with no data available.

Figure 5. A world map of LMICs (shaded green) overlaid with pie charts showing the relative frequency of different *Candida* species causing NIC in each country. Each pie chart's slices represent species (e.g., *C. albicans*, *C. parapsilosis*, etc.). High-income countries are in grey; countries with no data are white.

Table 1. Demographics and clinical characteristics for neonatal invasive candidiasis

Patients' characteristics and risk factors	Overall neonatal population (n=10,994)			Low- and lower-middle income countries (n=2,341)			Upper-middle income countries (n=8,653)		
	No. of Countries/ regions*	No. of Neonates	Mean (SD)/ n (%)	No. of Countries/ regions*	No. of Neonates	Mean (SD)/ n (%)	No. of Countries/ region*	No. of Neonates	Mean (SD)/ n (%)
Patient characteristics									
Male sex	20	5,692	3,268 (57.4)	7	1,576	976 (61.9)	13	4,116	2,294 (55.7)
Age, days	10	2,568	15.1 (9.7)	2	177	14.6 (11.1)	8	2,391	15.2 (9.6)
Gestational age (GA), weeks	10	1,789	31.4 (3.3)	2	296	31.5 (2.8)	8	1,493	31.4 (3.4)
Birth weight, grams	11	1,627	1,530.1 (644.6)	4	381	1508.1 (670.4)	7	1,246	1536.9 (636.7)
Length of stay, days	4	2,023	35.0 (21.9)	1	150	23.4 (10.3)	3	1,873	35.9 (22.3)
vLBW or eLBW (<1,500g)	16	4,402	1,957 (44.5)	5	1,146	264 (23.0)	11	3,256	1,693 (52.0)
Preterm neonates (GA< 37 weeks)	20	3,785	2,530 (66.8)	6	1,689	900 (53.3)	14	2,096	1,630 (77.8)
Extremely preterm neonates (GA < 28 weeks)	10	1,488	189 (12.7)	3	779	33 (4.2)	7	709	156 (22.0)
CSF *Candida* infection confirmed	7	1,054	124 (11.8)	2	177	11 (4.2)	5	877	113 (12.9)
High dependency units	15	4,466	3,915 (87.7)	5	786	786 (100)	10	3,660	3,129 (85.5)
Tertiary care hospital	19	5,316	5,316 (100)	7	1,625	1,625 (100)	12	3,691	3,691 (100)
Public hospital	5	556	440 (79.1)	1	305	189 (61.7)	4	251	251 (100)
Risk factors for NIC									
Prolonged (≧7 days) hospital admission	9	717	499 (69.6)	3	127	74 (58.3)	6	590	425 (72.0)
Known *Candida* colonisation	4	58	37 (63.8)	1	35	18 (51.4)	3	23	19 (82.6)
Receiving parenteral nutrition	16	3,817	2,283 (59.8)	4	553	203 (36.7)	12	3,264	2,080 (63.7)
Presence of a central venous catheter	17	4,323	2,457 (56.8)	5	724	313 (43.2)	12	2,144	3,599 (59.6)
Use of antibiotics	16	5,472	3,652 (66.7)	5	1,599	950 (59.4)	11	3,873	2,702 (59.4)
Prolonged use of broad-spectrum antibiotic	10	1,602	980 (61.2)	2	296	272 (91.9)	8	1,306	708 (54.2)

Note: GA; gestational age, vLBW; very low birth weight eLBW; extremely low birth weight, CSF; cerebrospinal fluid, NIC; neonatal invasive candidiasis. For continuous variables such as age, gestational age, birth weight, and length of stay, we reported the mean (SD). For categorical variables, we reported the count and percentage (n [%]).

*A study presented data from Argentina, Brazil, Chile, Colombia, Ecuador, Honduras, Mexico and Venezuela

FIGURES LEGENDS

Figure 1 The PRISMA 2020 flow diagram for new systematic reviews which included searches of databases

Note: Latin American and Caribbean Health Sciences Literature (LILACS); Index Medicus for the Eastern Mediterranean Region (IMSEAR); Index Medicus for the Eastern Mediterranean Region (IMEMR); Western Pacific Region Index Medicus (WPRIM), WHO Library Dataset (WHOIRIS); African Journals Online (AJOL); African Index Medicus (AIM)

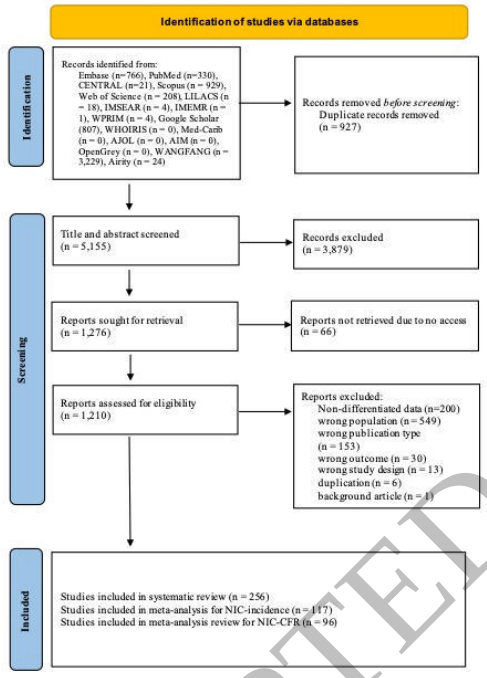

Figure 2a Pooled incidence of NIC in LMICs per WHO region.

Figure 2b Pooled incidence of NIC in high-risk neonates in LMICs.

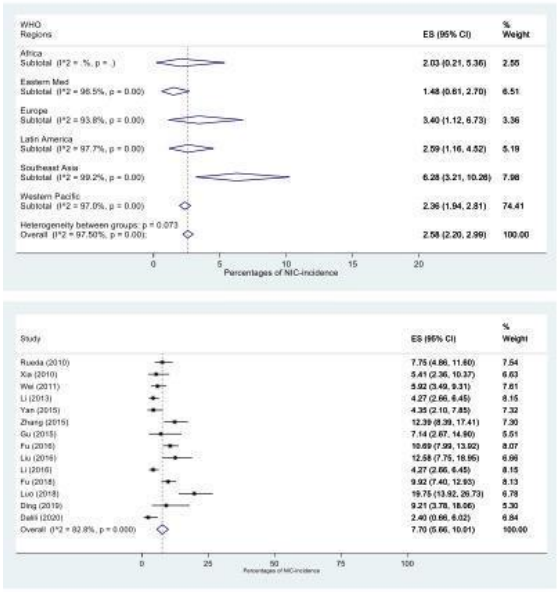

Figure 3a Pooled case-fatality rates (CFR) of NIC in LMICs per WHO region.

Figure 3b Pooled case-fatality rates of NIC in high-risk neonates in LMICs.

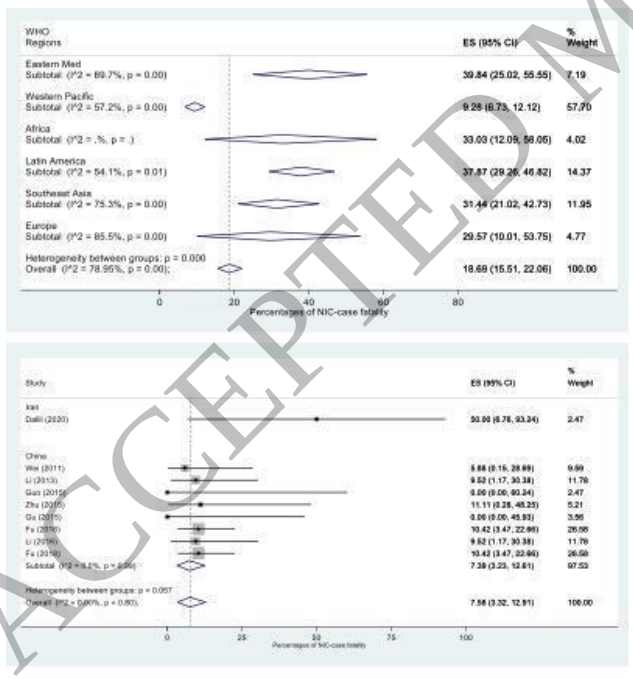

Figure 4 Incidence and CFR of NIC in LMICs by country in LMICs.

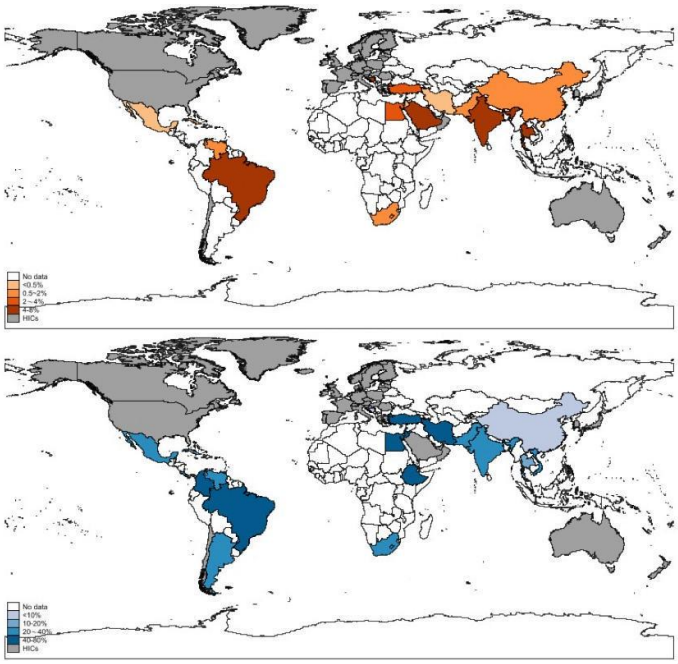

Figure 5. Distribution of the NIC isolates by WHO regions.

Note: Numbers of studies included in each geography: Africa: 11; Latin America: 20; Eastern Mediterranean: 8; Europe: 7, Southeast Asia: 28; Western Pacific: 18.