Early versus Late Onset Sepsis in Neonates – Time to shift the paradigm?

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Abstract

Background Neonatal sepsis is traditionally classified as early-onset sepsis (EOS) and late-onset sepsis (LOS) disease categories. This paradigm was based on observed epidemiological data from high income settings. However, increasing availability of microbiology results from diverse settings challenges these assumptions, necessitating re-examination of neonatal sepsis classifications.

Objectives To review the literature describing the aetiology of EOS and LOS in hospitalised neonates with stratification of pathogen spectrum by low- (LIC), middle- (MIC) and high-income (HIC) country settings, to critically re-examine the continued appropriateness of the 'EOS vs LOS' sepsis paradigm in all settings.

Sources PubMed was searched for peer-reviewed English full-text articles published from inception up until August 8th, 2022.

Content Studies often report on either EOS, or LOS, rather than both. We identified only 49 original articles reporting on pathogen distribution of both EOS and LOS in the same hospital setting. Clear differences in sepsis aetiology were shown between LIC-, MIC-, and HIC-settings, with increasing importance of *K. pneumoniae* and decreasing importance of Group B Streptococcus (GBS) in the first 72 hours of life in LIC and MIC.

Implications The concept of 'EOS vs LOS' may be less useful for predicting the pathogen spectrum of neonatal sepsis in LIC and MIC, but the paradigm has shaped reporting of neonatal sepsis, and our understanding. Future neonatal sepsis reporting should utilise STROBE-NI reporting guidelines and clearly describe timing of infection by day, and variation in pathogen spectrum across the neonatal period. Data identified in this review challenge the generalisability of the prevailing EOS/LOS paradigm in LIC and MIC.

Background

The paradigm of early onset sepsis (EOS) vs late onset sepsis (LOS) in neonates is based on epidemiological data from high income country (HIC) settings,[1] but has become ingrained in neonatal practice globally. The dichotomisation likely gained traction with the development of the medical speciality of Neonatology in HIC settings in the 1970s,[2,3] occurring alongside a growing recognition of the importance of Group B Streptococcus (GBS), which together with E. *coli* remains a leading cause of EOS in HIC. In such HIC settings, although increasing medicalisation and survival of extremely

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preterm neonates has influenced the epidemiology of neonatal sepsis, a distinction between EOS and LOS remains justified by important variation in the incidence of different type of pathogens.

Importantly, the exact threshold between 'EOS vs LOS' is disputed, varying from 24-, 48-, 72 hours, up to 7 days of life. Thresholds have also varied by pathogen,[4] and gestational age, since sepsis between day 3 and 7 is uncommon in term and late preterm neonates[5] and more frequent in preterm neonates. The lack of an internationally recognised definition of neonatal sepsis itself is also a challenge.[6]

Recent data from low-income country (LIC) and middle-income country (MIC) settings have challenged the applicability of the EOS/LOS sepsis paradigm globally. [7–9] Here we aimed to review the literature and stimulate reflection on the usefulness of this classification in LIC and MICs.

Why do we talk about early vs late?

The concepts of 'EOS vs LOS' in neonates have practical significance, representing important stages in the life of a newborn. Pathophysiological changes in the fetus can already begin in utero (e.g. changes in cytokines and interleukins due to maternal chorioamnionitis or prolonged rupture of membranes)[10] manifesting with symptoms and signs of infection immediately after birth, or even before. A clinical approach to diagnosis in early onset disease must take into account a unique range of physiological changes and neonatal conditions related to extra-uterine adaptation, and certain infection syndromes may be more or less likely (e.g. urinary tract infections are rare in first 24 hrs) independent from the setting of birth.[11]

Noteably, EOS and LOS categories represent assumed modes of pathogen acquisition. EOS is understood to be associated with vertical transmission from the mother to neonate, either due to haematogenous transmission (in the case of Listeria for example), or more commonly ascending infection via the maternal genital tract (e.g. GBS and *E. coli*). Infection in LOS is understood to be caused primarily by organisms acquired from the environment, either from the community, or from the hospital environment (e.g. surfaces, equipment, hands). This differentiation in the theory of acquisition has largely corresponded with the literature reporting the distribution of neonatal pathogens in HIC settings over the last 5 decades, but has in itself also potentially informed or driven the reporting of pathogens associated with neonatal sepsis globally.[12]

In HIC settings the leading causes of EOS have consistently included GBS and *E. coli*, both of which are well-recognised to colonise the maternal genital tract.[13] LOS conversely, has been more commonly associated with organisms colonising the skin such as CoNS, especially in cases of central line associated blood stream infection (CLABSI), and *S. aureus,* or gram negatives associated with the hospital environment such as *K. pneumoniae.*[14] Some studies in HIC, when reporting day of onset as a continuous variable, have shown 2 distinct peaks of infection, the first on the day of birth, and the second between day 5-15.[1]

As such, observational data from HIC have largely supported differentiated treatment approaches for EOS and LOS, with first-line antibiotics, such as ampicillin and gentamycin, retaining good coverage.[13,15,16] In LIC and MIC it has been less clear whether the aetiology of neonatal sepsis, especially for 'EOS', follows similar patterns to HIC settings,[7,8,17] although treatment approaches have mainly been designed based on the traditional EOS/LOS paradigm.

Global microbiological epidemiology of EOS and LOS

To obtain an overview of neonatal sepsis epidemiology, articles reporting on both EOS and LOS were identified and summarised. Relevant peer-reviewed publications were identified though a Pubmed search (conducted up to 8 August 2022), focusing on English language articles describing neonatal EOS and LOS in hospital settings. Index search terms were early and/or late onset, neonatal sepsis, pathogen, blood borne pathogens, including bacteraemia and blood stream infection, microbiology, and aetiology (see supplementary material). Articles were only included in figures and tables in this review if they reported both EOS and LOS within the same hospital population and differentiated the pathogen profile of each. Studies reporting only on single pathogens, or on community acquired pathogens, were excluded.

Current evidence on the aetiology of neonatal sepsis stratified by country-income status

Of 191 full texts describing EOS and/or LOS, only a minority (n=49) permitted direct comparison of these two categories by defining and reporting on both EOS and LOS in the same population (see Supplementary material). Of the 49 included studies (published between 1976 and 2020), most (n=24; 49.0%) originated in HIC followed by MIC (n=17, 34.7%) and LIC (n=8; 16.3%). Some regions such as North America were over-represented and others such as sub-Saharan Africa were under-represented (see Figure 1). Accordingly, the majority of neonates with confirmed bacterial sepsis were also from HIC (n=24077, 80.9%), followed by MIC (n=4878, 16.4%) and LIC (n=791, 2.7%). We identified relatively few studies reporting on both early and late onset sepsis in the same population from important regions, such as sub-Saharan Africa where a high burden of sepsis related deaths occur.[9] The vast majority of studies reported age of onset as a dichotomous variable, with only 7 articles (HIC=5, MIC=1, LIC=1) reporting postnatal age as a continuous variable throughout the neonatal period (see supplementary table 2).

Heterogeneity in the definition of EOS was apparent, although the majority of EOS episodes were defined as onset of sepsis at ≤ 72 hours or 3 days of postnatal age (n=29; 59.2%). The organism profile of neonatal EOS and LOS differed significantly between HIC-, MIC-, and LIC- settings (Figure 2), with particularly marked disparities between LIC and HIC. Table 1 describes the microbiological profile of these studies in more detail.

Early onset sepsis studies

Studies on EOS from HIC (published between 1976-2019) reported that among 4151 sepsis episodes, GBS (n=1512, 36.4%), *E. coli* (n=1028, 24.8%), and CoNS (n=641, 15.4%) were the dominant pathogens (see Supplementary Table 1 for list of studies). Comparatively, GBS in particular featured less frequently in MIC, accounting for 4.1% of EOS (n=105) in studies reported between 1983 and 2019. The most striking differences in pathogen profile were observed between HIC and LIC settings. Of the 525 episodes of EOS in LIC settings that were reported between 1992-2020, *Klebsiella spp*. (n=170; 32.4%), CoNS (n=77; 14.7%), *E. coli* (n=54; 10.3%), *S. aureus* (n=51; 9.7%), and *Pseudomonas spp*. (n=35; 6.7%) were most frequently reported.

Late onset sepsis studies

Of the 28229 LOS episodes reported in HIC, gram positive organisms dominated: CoNS (n=12876, 45%), *S. aureus* (n=3886, 13.8%), and *Enterococcus spp*. (n=1985, 7.0%), while gram negative pathogens including *E. coli* (n=1930, 6.8%) and *Klebsiella spp*. (n=1774, 6.3%) were less common. Similar to HIC, CoNS was the most frequent organism cultured in LOS in MIC. However, the

proportion of gram-negative organisms in MIC and LIC settings was greater, in particular for *Klebsiella spp*., which was more common in both EOS and LOS.

Importantly, the pathogen profiles of EOS and LOS in LIC were strikingly similar, with continuing dominance of gram-negative infections such as *Klebsiella spp.* and *Acinetobacter spp.* throughout the neonatal period, challenging the usefulness of the EOS vs LOS paradigm for directing treatment approaches in LIC. This dominance of gram negatives, and limited EOS vs LOS differentiation in LIC was particularly highlighted in a recent large multi-country study across Africa and Asia (BARNARDS[7]).

Declining relevance of EOS vs LOS Paradigm with lower income levels

When considered collectively, neonatal sepsis data demonstrate 3 important trends with decreasing income level from high to low-income settings; 1) a trend of increasing importance of gram negatives, especially *K. pneumoniae*, 2) a decreasing relative importance of GBS, and 3) a decreasing relevance of CoNS. Ultimately this suggests a declining relevance of the "EOS vs LOS' paradigm in explaining pathogen distributions in settings with lower income level.

Potential factors influencing aetiological variation

The EOS/LOS paradigm was developed during early evolution of neonatal care in HIC settings, and since then a range of evolutions in obstetric and neonatal practice in both high- and low-income settings have led to variations from the patterns initially observed. Evolutions in HIC settings have included increasing complexity of care and survival of extremely preterm neonates, as well as the introduction of intrapartum antibiotic prophylaxis, while in LIC settings there have been increases in facility deliveries and neonatal care, with varying progress in improving infection prevention & control and access to microbiology. The subsequent variations in aetiology of neonatal sepsis suggest that early and late onset disease is a spectrum which is influenced by a number of factors, and in particular, that the degree of overlap between early and late (and vertical and horizontal transmission) is greater in LIC settings due to a number of these factors.

Importantly, GBS accounts for much of the variation described in this review, and a number of factors may influence the reported incidence of early onset GBS such as maternal colonisation prevalence, serotype distribution,[18] difficulty in case detection in very early onset cases in lower resource settings,[20] and the introduction of intrapartum antibiotic prophylaxis in some settings.[19] Interestingly, global estimates of the burden of GBS,[21] and data on GBS incidence[22] do not consistently suggest such dramatic differences in incidence of GBS based on income level, although regional variation exists.[9] The relevance of overall burden of other neonatal pathogens in each setting may be important in determining the relative proportion of GBS. Although global incidence data are limited, overall incidence of neonatal sepsis in general is lower in HIC than LIC, likely in large part due to variation in access to safe delivery and infection prevention & control.[23,24] A large 'excess' burden of neonatal sepsis in LIC settings could potentially be accounted for by pathogens such as *Klebsiella spp,* which may overshadow the organisms more commonly found in HIC settings. Intrapartum antibiotic prophylaxis (IAP) for GBS colonisation may also be changing the aetiology of EOS, with for example *E. coli* overtaking GBS as a leading cause of EOS in some studies.[13] IAP influences the microbiome of the newborn, shifting the balance towards horizontally rather than vertically acquired organisms.[25] However the extent to which IAP influences aetiology of EOS in LIC is less clear, since implementation may be less common.[19]

Maternal colonisation with other important neonatal pathogens such as *Enterobacterales*, *Acinetobacter spp.* and S. *aureus* may also vary globally, and may be associated with infections in newborns.[26] Nevertheless, whole genome sequencing (WGS) data is also challenging our assumptions about the association between vertical and horizontal transmission and early and late onset sepsis. For example, a recent study in an LIC suggested a large proportion of EOS pathogens may be unrelated to maternal colonisation, even without high coverage of IAP.[27]

Mode of delivery also varies widely between and within countries and may also influence the aetiology of EOS. For example, caesarean section influences vertical transmission and neonatal microbiome, and has been associated with greater neonatal colonisation with antibiotic resistant gram-negative pathogens.[28]

Prematurity exerts an important influence on aetiology of EOS and LOS. Indeed within HIC settings the predominance of gram negative organisms in EOS in very low birth weight (VLBW) infants contrasts with the pattern of GBS dominance in term infants.[29] A higher incidence of preterm birth in some LIC contexts[30] may be a factor underlying some of the variation in aetiology of EOS, and a greater survival of infants <1.5kg in HIC may influence patterns of LOS.

A higher level of care and availability of invasive devices and supportive care such as ventilation and parenteral nutrition in higher income settings is also likely to also play a role. CLABSI is a dominant cause of late onset sepsis in HIC and MIC, and is frequently associated with CoNS. The clinical significance of CoNS as a pathogen in LIC settings with limited use of invasive devices is uncertain.[31] Similar variation may exist with ventilator-associated pneumonia.

Crucially, varying implementation of IPC is a likely modifiable factor driving variation. Resource limited settings may have less capacity to support implementation of extensive IPC interventions. Increasing facility delivery rates and sub-optimal IPC may increase the risk of hospital-acquired colonisation and contribute to the predominance of gram-negative pathogens occurring shortly after birth as neonatal sepsis in LIC and MIC.

Antimicrobial susceptibility and timing of neonatal sepsis onset

Importantly, the literature suggests marked differences between the antimicrobial susceptibility patterns (ASP) of leading pathogens for EOS in HIC versus LIC and MIC. For example, GBS, which is common in HIC settings, is widely sensitive to ampicillin, a typical first-line antibiotic choice.[32] In contrast, in LIC and HIC settings the prominence of pathogens commonly associated with antimicrobial resistance (AMR) in both early and late onset sepsis such as *Klebsiella spp.* And *Acinetobacter spp.* Is cause for concern.[7,8,33,34]

It might be assumed that horizontal transmission drives the majority of AMR, But vertical transmission of extended spectrum beta-lactamase producing *E. coli* and *Klebsiella spp.* also occurs,[35] [36] [37] and regional variation in community prevalence of genital tract colonisation by multi-drug resistant *Enterobacterales* may partly drive variation in ASP of EOS.[26] Studies have also suggested that maternal colonisation by hospital-acquired pathogens may be an important source of vertical transmission of bacteria to the neonate, blurring the distinction between horizontal and vertical transmission.[37] Indeed, some authors argue that any episode of sepsis in a neonate born in hospital is by definition hospital acquired.[38]

Therefore, AMR gram negatives commonly assumed to be associated with LOS acquired from the hospital environment may also be common causes of EOS in LIC and HIC settings,[8,9,34] potentially

increasing the risk of discordant antibiotic therapy when extrapolating EOS vs LOS based treatment protocols from HIC.[39] Studies identified in this review did not consistently report on the difference in ASP of pathogens isolated in EOS vs LOS disease in LIC, and more high-quality pooled microbiology data is needed to interrogate this and inform treatment strategies.

Data from Community settings

This hospital-based review did not include neonates admitted from home. Nevertheless, a recent review of community acquired neonatal sepsis in LMIC settings also described a similar pattern of dominance of *Klebsiella spp., E. coli* and *S. aureus*,[40]with limited differentiation between EOS and LOS, a finding which was reinforced by the recent BIRDY multi-country study,[23] and a large community-based study in South Asia, ANISA.[17]

Limitations of the EOS vs LOS Critique

Our critique relies to a large extent on observed differences in pathogen distribution between high- and lower-income settings. This analysis is limited by availability of representative data from low-income contexts. Less than 1 in 5 samples included in the microbiological results in this review were from LIC or MIC, and fewer than 1 in 20 were from LIC. Access to microbiology laboratory services is unevenly distributed and biased in LIC, often towards urban tertiary centres. Comparing this data with more representative data from HIC where microbiology data is more widely available and representative may be problematic. This review is also fundamentally limited by the majority of studies reporting EOS and LOS as a dichotomous variable based on the paradigm itself. More studies reporting on timing of infection as a continuous variable are required for further interrogation of the paradigm.

Conclusion

The EOS and LOS paradigm was inspired by historical data from HIC, and has influenced surveillance, research and treatment of neonatal sepsis globally. While the concept is still useful in HIC, its relevance in lower income settings globally may be limited.

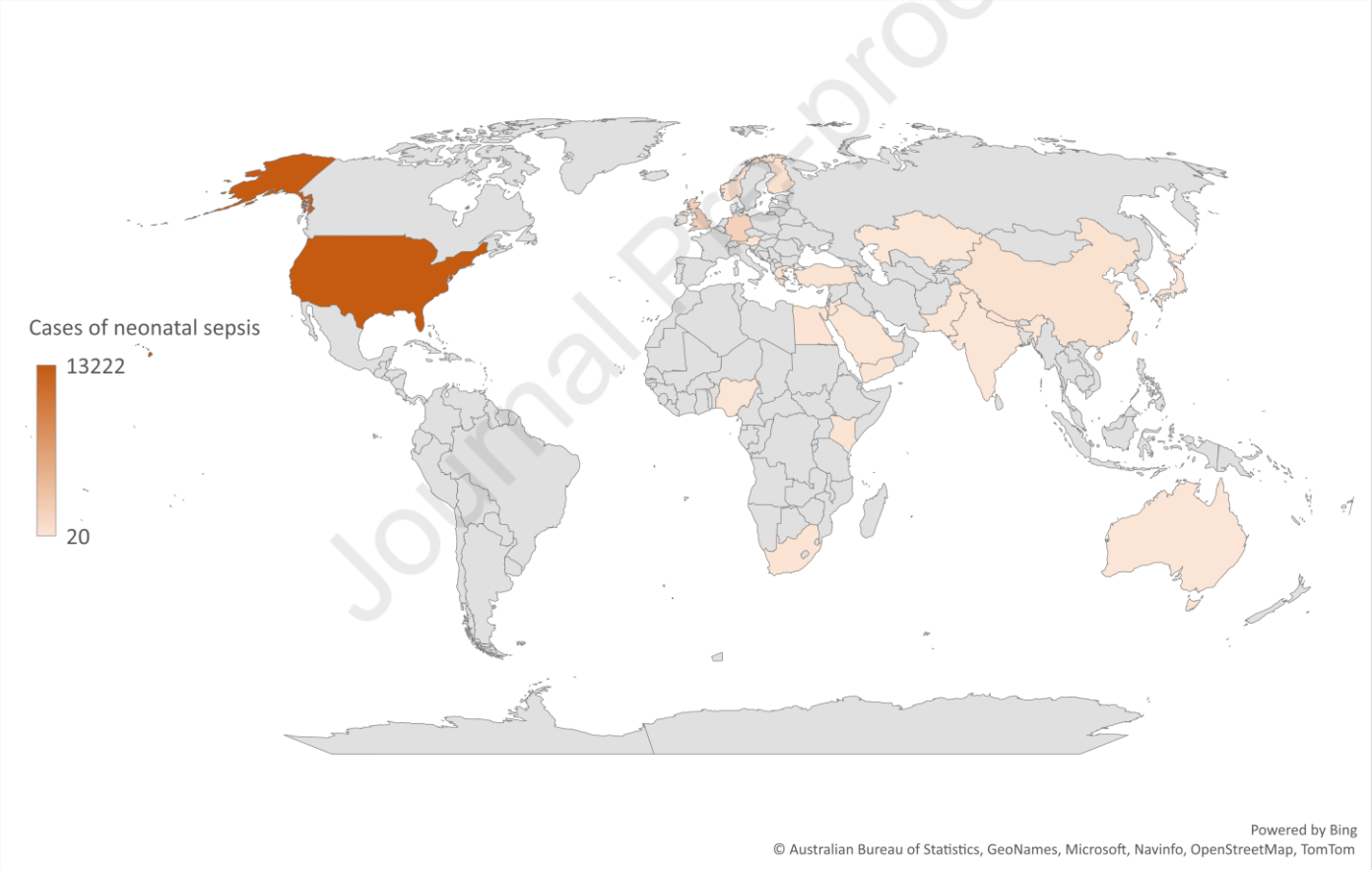
However, while the data presented here challenge the generalisability of the EOS/LOS paradigm, they are insufficient to propose new evidence-based definitions to shift the paradigm, partly due to the influence of the paradigm itself on the reporting of sepsis in the literature.

Therefore, in addition to more data from LIC settings, a paradigm shift that can already be recommended is for future neonatal sepsis studies to move towards reporting of age of onset as a continuous variable, as per the STROBE-NI guidelines, rather than exclusively as either early or late.[41] Such a shift is necessary for further interrogation of the relevance of the EOS versus LOS paradigm itself, and potentially to create an opportunity for more generalisable definitions to be developed, which can better inform treatment and prevention strategies.

NR and AB conceptualised the paper in discussion with the editor. MB, AB and NR designed the methodology. MB conducted the literature review and curated the data, which was reviewed by NR and AB. NR wrote the first draft, which was edited by AB and MB. AD, MS and UO reviewed drafts and provided comments and edits. All authors reviewed the final manuscript.

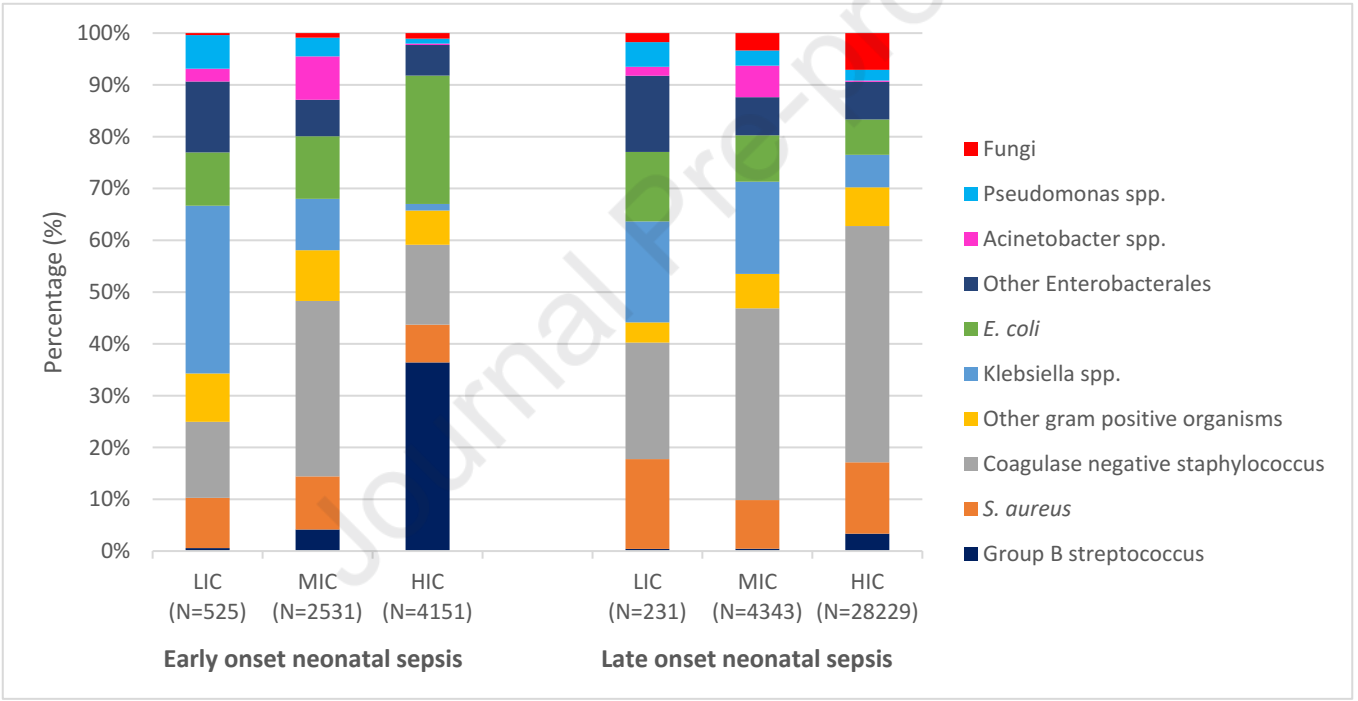
Authors declare no conflicts of interest. No external funding was received for this work.

Figure 1. Published data reporting the number of neonates affected by early and late onset sepsis



Total cases of neonatal sepsis: high income countries (N=24077; 80.9%), middle income counties (N=4878; 16.4%) and low income countrie (N=791; 2.7%)
Data on numbers of cases not available in 4 studies (Pillay et al. BMC Infect Dis (2021); Labi et al. BMC Infect Dis (2016); Muller-Pebody et al. Arch Dis Child Fetal Neonatal Ed (2011); van den Hoogen et al. Neonatology (2010)) and 1 study excluded as data pooled from multiple countries (Tiskumara et al. Arch Dis Child Fetal Neonatal Ed (2009))

Figure 2. Pathogen spectrum of early and late onset neonatal sepsis stratified by country-income status



LIC: low income countries, MIC: middle income countries, HIC: high income countries

Table 1. Microbiological profile of early and late neonatal sepsis stratified by country-income status

	LIC		MIC		HIC	
	EOS N=525 (69.4 %)	LOS N=231 (30.6 %)	EOS N=2531 (36.8 %)	LOS N=4353 (63.2 %)	EOS N=4151 (12.8 %)	LOS N=28229 (87.2 %)
Gram positive organisms						
Group B Streptococcus	3 (0.6)	1 (0.4)	105 (4.1)	20 (0.5)	1512 (36.4)	950 (3.4)
S. aureus	51 (9.7)	40 (17.3)	260 (10.3)	407 (9.4)	302 (7.3)	3886 (13.8)
Coagulase negative staphylococcus	77 (14.7)	52 (22.5)	857 (33.9)	1608 (37.0)	641 (15.4)	12876 (45.6)
Enterococcus spp.	27 (5.1)	7 (3.0)	144 (5.7)	212 (4.9)	120 (2.9)	1985 (7.0)
Other streptococci	21 (4.0)	2 (0.9)	54 (2.1)	59 (1.4)	50 (1.2)	37 (0.1)
Other gram-positives[a]	1 (0.2)	0 (0)	50 (2.0)	18 (0.4)	104 (2.5)	89 (0.3)
Gram negative organisms						
Enterobacterales						
Klebsiella spp.	170 (32.4)	45 (19.5)	251 (9.9)	773 (17.8)	53 (1.3)	1774 (6.3)
E. coli	54 (10.3)	31 (13.4)	306 (12.1)	389 (9.0)	1028 (24.8)	1930 (6.8)
E. cloacae	0 (0)	1 (0.4)	0 (0)	10 (0.2)	4 (0.1)	41 (0.1)
Other Enterobacterales	32 (6.1)	13 (5.6)	150 (5.9)	307 (7.1)	64 (1.5)	1980 (7.0)
Non-fermenting gram negative bacilli						
Acinetobacter spp.	13 (2.5)	4 (1.7)	212 (8.4)	264 (6.1)	11 (0.3)	74 (0.3)
Pseudomonas spp.	34 (6.5)	11 (4.8)	92 (3.6)	127 (2.9)	40 (1.0)	583 (2.1)
Other non-fermenters	39 (7.4)	20 (8.7)	27 (1.1)	3 (0.1)	7 (0.2)	6 (0.0)
Other gram-negatives[b]	1 (0.2)	0(0)	1 (0.0)	0 (0)	171 (4.1)	16 (0.1)
Fungi						
Candida spp.	2 (0.4)	4 (1.7)	22 (0.9)	146 (3.4)	44 (1.1)	1997 (7.1)
Other fungi[c]	0	0	0	0	0	5 (0.0)

LIC: low income countries, MIC: middle income countries, HIC: high income countries, EOS: early onset sepsis, LOS: late onset sepsis

[a] Group A Streptococcus, *Listeria spp*., *S. pneumoniae*, *S. viridans*, *Micrococcus spp*., *Bacillus spp*., and *K. kristinae*

[b] *H. Influenzae*

[c] *Malassezia spp.*

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	LIC		MIC		HIC	
	EOS N=525 (69.4 %)	LOS N=231 (30.6 %)	**EOS N=2531 (36.8 %)**	**LOS N=4353 (63.2 %)**	EOS N=4151 (12.8 %)	LOS N=28229 (87.2 %)
Gram positive organisms						
Group B streptococcus	3 (0.6)	1 (0.4)	**105 (4.1)**	**20 (0.5)**	1512 (36.4)	950 (3.4)
S. aureus	51 (9.7)	40 (17.3)	**260 (10.3)**	**407 (9.4)**	302 (7.3)	3886 (13.8)
Coagulase negative staphylococcus	77 (14.7)	52 (22.5)	**857 (33.9)**	**1608 (37.0)**	641 (15.4)	12876 (45.6)
Enterococcus spp	27 (5.1)	7 (3.0)	**144 (5.7)**	**212 (4.9)**	120 (2.9)	1985 (7.0)
Other streptococci	21 (4.0)	2 (0.9)	**54 (2.1)**	**59 (1.4)**	50 (1.2)	37 (0.1)
Other gram-positives[a]	1 (0.2)	0 (0)	**50 (2.0)**	**18 (0.4)**	104 (2.5)	89 (0.3)
Gram negative organisms						
Enterobacterales						
Klebsiella spp.	170 (32.4)	45 (19.5)	**251 (9.9)**	**773 (17.8)**	53 (1.3)	1774 (6.3)
E. coli	54 (10.3)	31 (13.4)	**306 (12.1)**	**389 (9.0)**	1028 (24.8)	1930 (6.8)
E. cloacae	0 (0)	1 (0.4)	**0 (0)**	**10 (0.2)**	4 (0.1)	41 (0.1)
Other Enterobacterales	32 (6.1)	13 (5.6)	**150 (5.9)**	**307 (7.1)**	64 (1.5)	1980 (7.0)
Non-fermenting gram negative bacilli						
Acinetobacter spp.	13 (2.5)	4 (1.7)	**212 (8.4)**	**264 (6.1)**	11 (0.3)	74 (0.3)
Pseudomonas spp.	34 (6.5)	11 (4.8)	**92 (3.6)**	**127 (2.9)**	40 (1.0)	583 (2.1)
Other non-fermenters	39 (7.4)	20 (8.7)	**27 (1.1)**	**3 (0.1)**	7 (0.2)	6 (0.0)
Other gram-negatives[b]	1 (0.2)	0(0)	**1 (0.0)**	**0 (0)**	171 (4.1)	16 (0.1)
Fungi						
Candida spp.	2 (0.4)	4 (1.7)	**22 (0.9)**	**146 (3.4)**	44 (1.1)	1997 (7.1)
Other fungi[c]	0	0	**0**	**0**	0	5 (0.0)