Neonatal bacteraemia and antimicrobial resistance surveillance

Bacteraemia & antimicrobial resistance surveillance among vulnerable children session ECCMID 2024

Dr Phoebe Williams

BSc BCom MBBS(Hons.) DCH MSc DPhil FRACP

Paediatrician & Infectious Diseases Physician

NHMRC Fellow, The University of Sydney

THE UNIVERSITY OF SYDNEY

The Significant Global Burden of Neonatal Infections

3m

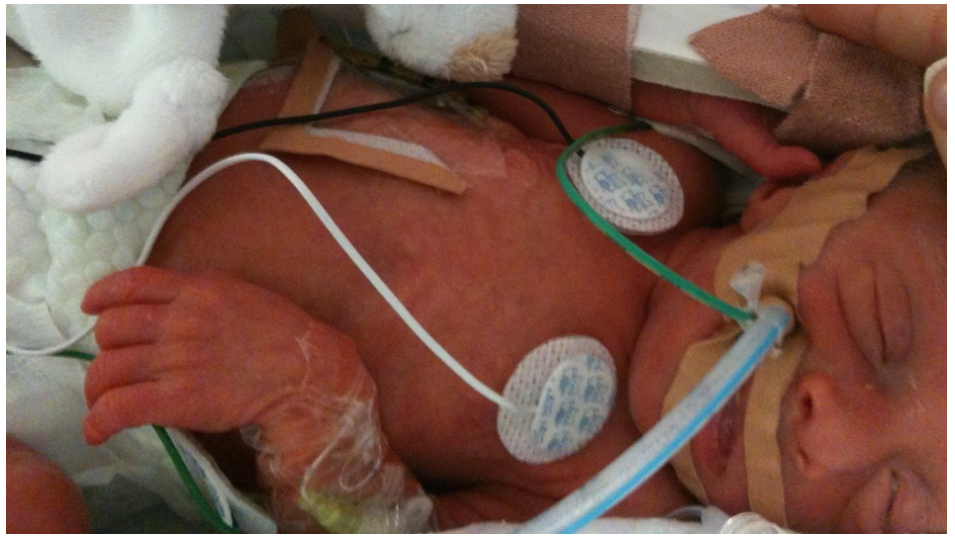
Cases of neonatal sepsis occur each year

~0.5m

Deaths globally in babies due to neonatal sepsis.

~17%

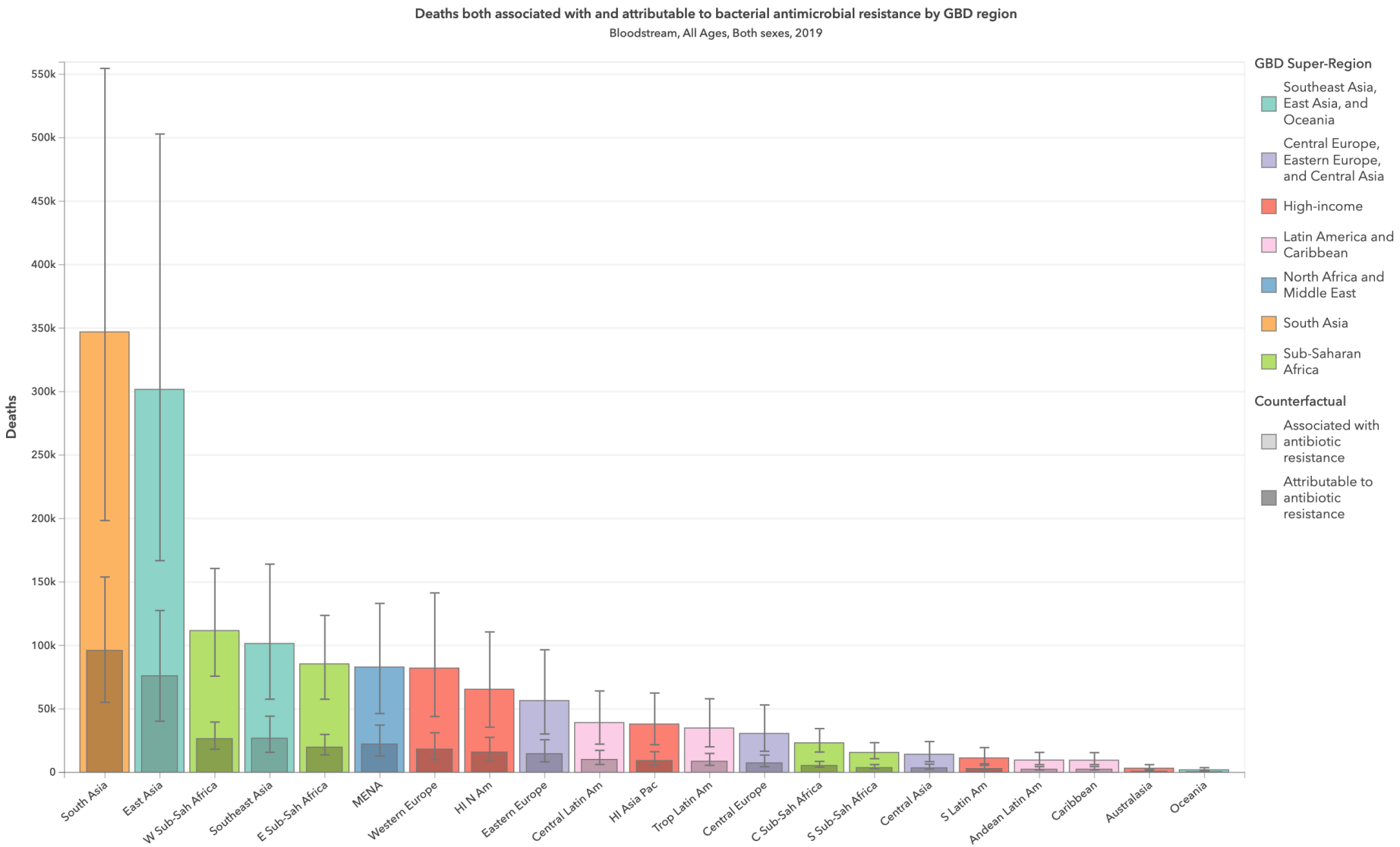
Mortality rate



In the context of growing antimicrobial resistance (AMR),
this burden is gradually rising,
particularly in resource-constrained healthcare settings

Fleischman et al. ADC 2021

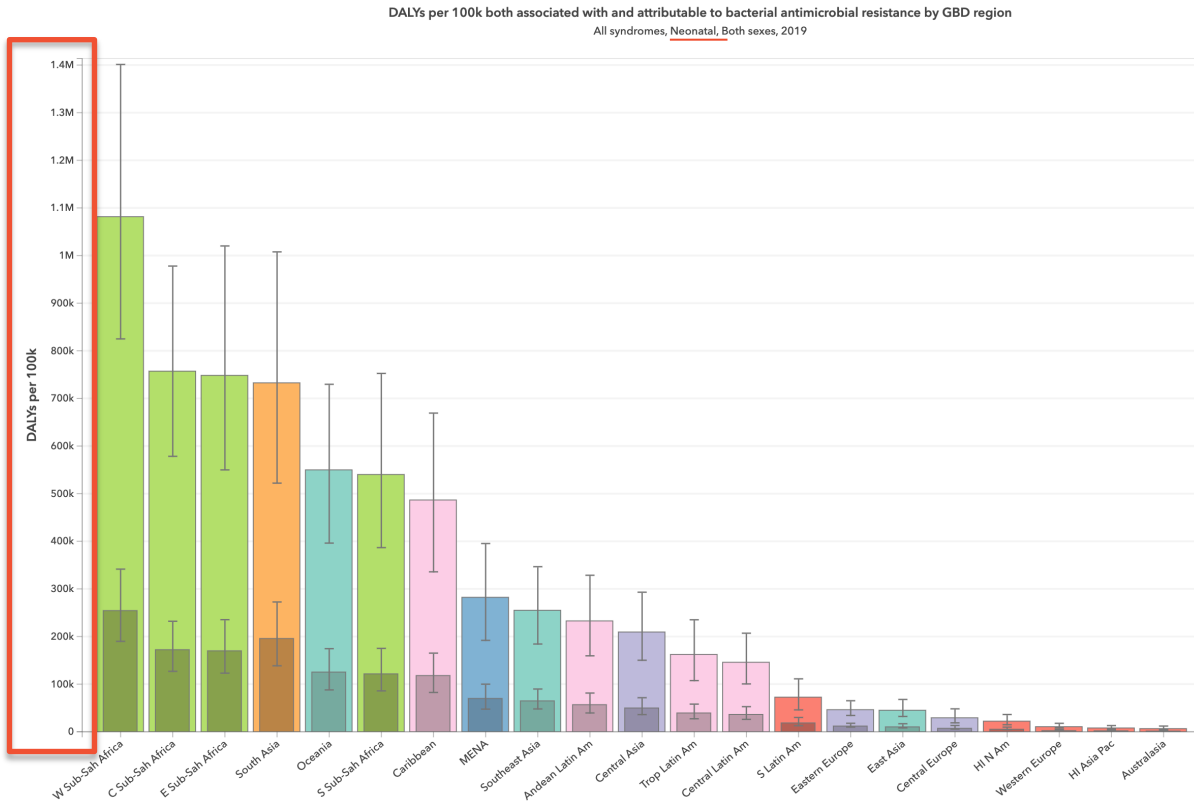
The growing mortality burden of AMR is inequitably globally distributed

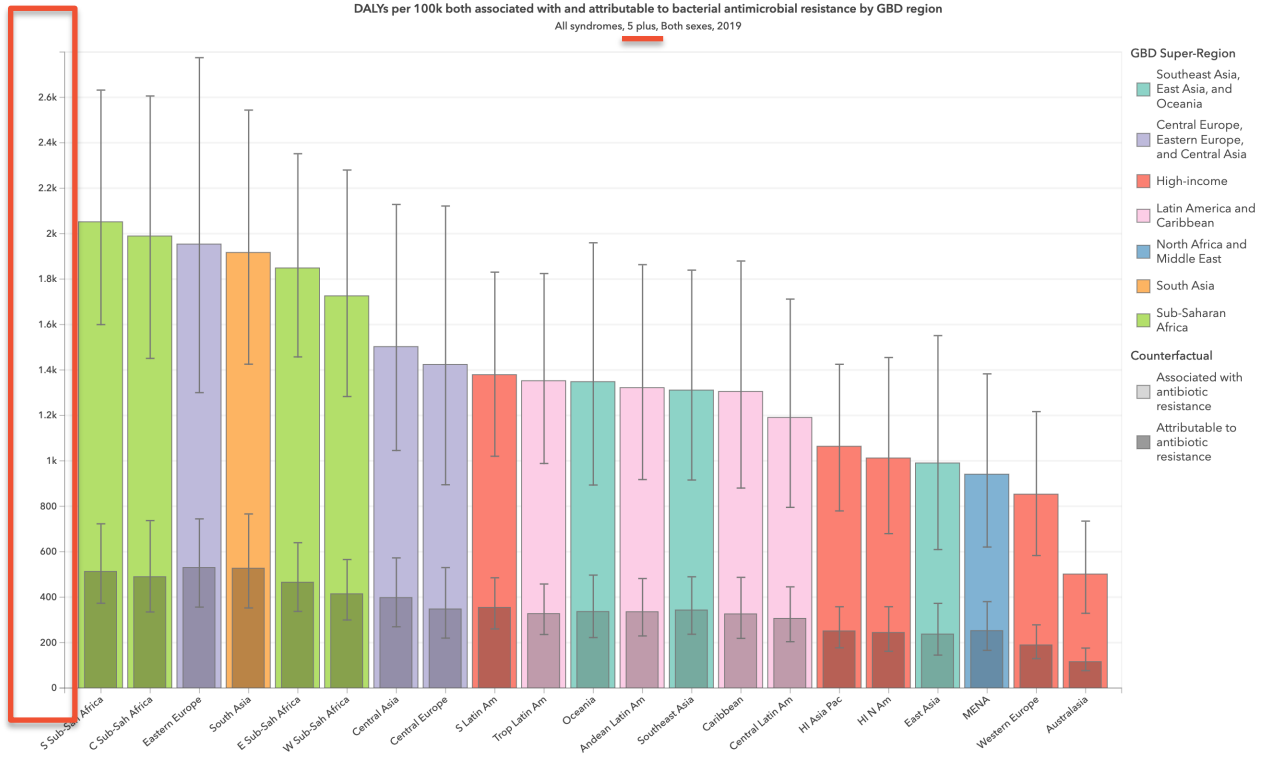


Primarily borne by regions with the least access to surveillance strategies to prevent AMR, and the broad-spectrum antibiotics needed to treat MDR infections

Murray CJL et al. Lancet 2022;399:629e55

The growing mortality burden of AMR is also inequitably distributed across age ranges, with neonates one of the most at risk

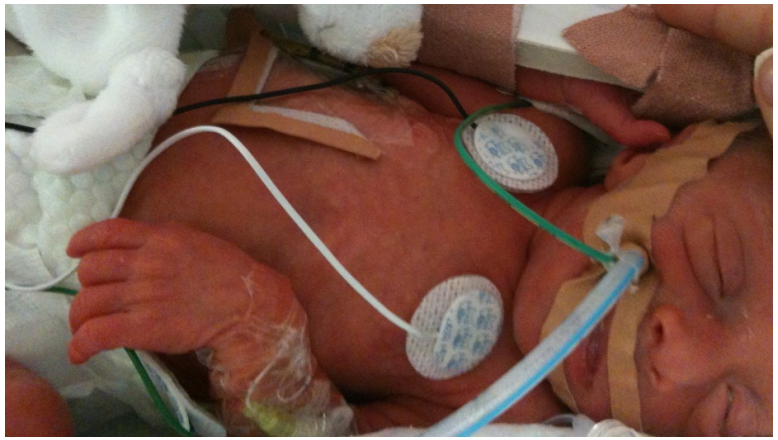




Institute for Health Metrics and Evaluation (IHME), University of Oxford. **MICROBE**. University of Washington, 202

Why are neonates so at risk of infections?

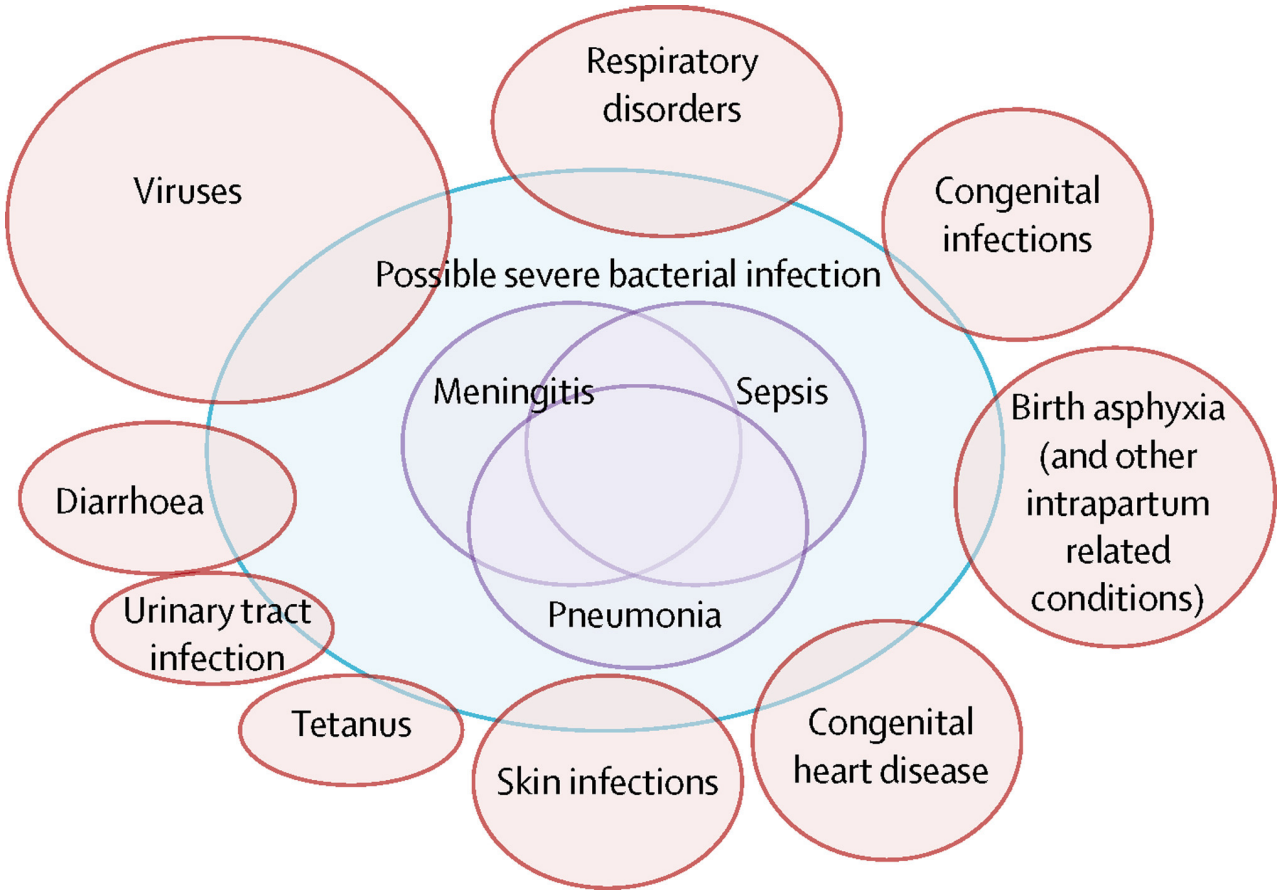
- Immunologically immature:
  - Decreased polymorphonuclear leucocyte and cell-mediate immune function
- Vulnerable microbiome:
  - Particularly following exposure to intrapartum antibiotics
- Preterm infants:
  - Less exposure to breastmilk if unable to tolerate enteral feeds (otherwise protective)
  - Multiple invasive procedures: ventilation, long line access
  - Exposure to multiple caregivers: parents, carers, healthcare workers (colonisation risk)
  - Prolonged hospitalisation → risk of exposure to multiple empirical courses of antibiotics, enhancing selective pressure → risk of MDR infections



Collins et al. 2018 ADC

What are the current challenges in surveillance of neonatal infections?

- Neonatal sepsis is difficult to diagnose:
  - Overlap in signs & symptoms of possible serious bacterial infections (pSBI) and other clinical conditions results in overuse of antibiotics



Seale *et al.* LID 2014

What are the current challenges in the surveillance of neonatal infections?

- Clinical signs of neonatal sepsis are unreliable and difficult to distinguish from other neonatal conditions
- There is subsequently a reliance on microbiological cultures for a definitive diagnosis of sepsis
  - A very insensitive test in neonates due to difficulties in attaining adequate blood volumes and frequent pre-exposure to antibiotics
  - Reliance on blood cultures reduces the inclusion of 'culture negative' infections
    - Responsible for ~half of all cases of neonatal sepsis
  - Even relying on cultures, there is inconsistency in pathogen inclusion (eg, coagulase-negative Staphylococci)
- This is in contrast to adult surveillance, where there is less reliance on microbiological confirmation and multiorgan dysfunction predominates as the key inclusion for sepsis

Lack of consensus for a definition of neonatal sepsis

SYSTEMATIC REVIEW OPEN

Check for updates

Neonatal sepsis definitions from randomised clinical trials

Rían Hayes[1], Jack Hartnett[1], Gergana Semova[1], Cian Murray[1], Katherine Murphy[1], Leah Carroll[1], Helena Plapp[1], Louise Hession[1], Jonathan O'Toole[1], Danielle McCollum[1], Edna Roche[1], Elinor Jenkins[1], David Mockler[2], Tim Hurley[1,3], Matthew McGovern[1,3], John Allen[1,3,4], Judith Meehan[1,4], Frans B. Plötz[5,6], Tobias Strunk[7,8], Willem P. de Boode[9], Richard Polin[10], James L. Wynn[11,12], Marina Degtyareva[13], Helmut Küster[14], Jan Janota[15,16], Eric Giannoni[17], Luregn J. Schlapbach[18,19,20], Fleur M. Keij[21], Irwin K. M. Reiss[21], Joseph Bliss[22], Joyce M. Koenig[23], Mark A. Turner[24], Christopher Gale[25], Eleanor J. Molloy[1,3,4,26,27] ✉ and On behalf of the Infection, Inflammation, Immunology and Immunisation (I4) section of the European Society for Paediatric Research (ESPR)

Table 3. Signs and symptoms present and frequency in the RCT definitions reviewed.

Constitutional		Respiratory		Cardiovascular		Neurological		Gastrointestinal		Miscellaneous	
Symptom	N	Symptom	N	Symptom	N	Symptom	N	Symptom	N	Symptom	N
Lethargy	27	Apnoea	22	Haemodynamic instability	8	Altered consciousness	7	Abdominal distension	11	Disseminated haemorrhage	2
Temperature instability	27	Respiratory distress	12	Hypotension	7	Seizure	6	Vomiting	5	Unexplained bleeding	2
Feeding intolerance	17	Tachypnoea	10	Poor perfusion	7	Hypotonia	4	Hepatomegaly	5	Petechiae	1
Glucose intolerance	9	Ventilatory support	6	Tachycardia	6	Reduced reflexes	2	Splenomegaly	4	Purpura	1
Irritability	5	Supplemental O_2	6	Bradycardia	6	Bulging fontanelle	1	Jaundice/icterus	4	Pyoderma	1
Hypothermia	4	Desaturations	4	Inotropic/fluid support	5			Increased gastric aspirate	1	Sclerema	1
Hyperthermia	3			CRT > 3 s	5					Conjunctivitis	1
Fever	3	Grunting	4	Pallor	3					Organ dysfunction [unspecified]	3
Poor feeding	3	Cyanosis	3	Rate > 2 SD above normal	2					Staff concern	1
Excessive crying	1	Gagging	1	Shock	2						
Poor cry	1	Apnoea	22	Cardiovascular collapse	2						
Colour	1	Respiratory distress	12	BP < 2 SD below normal	2						
		Tachypnoea	10	Rate instability	1						
				Cold extremities	1						

Table 1. Definitions of neonatal sepsis by primary criteria.

Combination of primary criteria	N
Culture alone	35
Culture + signs	29
Signs + laboratory	25
Culture + signs + laboratory	12
Signs alone	7
Culture + labs	6
Signs + radiology	6
Laboratory alone	4
Signs + risk factors	2
Culture + laboratory + radiology	1
Radiology alone	1

(1) Microbiological culture

Microbiological culture was a component of 83 out of 128 definitions of neonatal sepsis (Table 1). These 83 definitions were from 68 different papers.

Culture source: Of the 83 culture-related definitions, 74 specified a site the culture sample was taken from, while 9 mentioned 'culture' without specifying a sample site. Of the 74 that specified culture sites, the frequency of each site mentioned is outlined in Table 2. Three definitions required two positive cultures to diagnose sepsis.

Pathogen: 12 definitions specified a pathogen sought by microbiological culture. Five specified bacteria, 4 specified fungi, and the remainder mentioned 'known virulent pathogens', or 'not *Staphylococcus epidermidis*'.

Incubation time: Only one study mentioned incubation time, which outlined that a microorganism was regarded as infectious if it grew within 48 h incubation.

Hayes *et al*. Neonatal sepsis definitions from randomised clinical trials. Nature, 2021.

Limitations in attempts to define neonatal sepsis:

The nSOFA score

Table 1.

Neonatal sequential organ failure (nSOFA) components and scoring (0–15 point range).

Respiratory score	**0**	**2**	**4**	**6**	**8**
Criteria	Not intubated ***OR*** Intubated, SpO_2/FiO_2 ≥ 300	Intubated, SpO_2/FiO_2 <300	Intubated, SpO_2/FiO_2 <200	Intubated, SpO_2/FiO_2 <150	Intubated, SpO_2/FiO_2 <100
Cardiovascular score	**0**	**1**	**2**	**3**	**4**
Criteria	No inotropes ***AND*** No systemic steroids	No inotropes ***AND*** Systemic steroid treatment	One inotrope ***AND*** No systemic steroids	Two or more inotropes ***OR*** One inotrope AND systemic steroid treatment	Two or more inotropes ***AND*** Systemic steroid treatment
Hematologic score	**0**	**1**	**2**	**3**	
Criteria	Platelet count ≥ 150 × 10^3	Platelet count 100–149 × 10^3	Platelet count <100 × 10^3	Platelet count <50 × 10^3	

Unrealistic in LMIC settings, where the bulk of neonatal infections occur

Published in final edited form as:
Pediatr Res. 2020 July ; 88(1): 85–90. doi:10.1038/s41390-019-0517-2.

A Neonatal Sequential Organ Failure Assessment Score Predicts Mortality to Late-Onset Sepsis in Preterm Very Low Birth Weight Infants

As neonatal sepsis remains so difficult to diagnose, we rely on efficacious empirical antibiotics based on the 'traditional' bacterial causes of neonatal sepsis:

- **"Early onset" sepsis (presumed vertical transmission):**
  - *Streptococcus agalactiae* (GBS)
  - *E coli*
- **"Late onset" sepsis (horizontal transmission):**
  - *E. coli*
  - GBS
  - *S. aureus*
  - *Klebsiella* spp.
  - CoNS

*Classification based on historical surveillance data from HICs

*This classification has significantly influenced surveillance research, and empirical treatment of neonatal sepsis, globally.

POCKET BOOK
OF

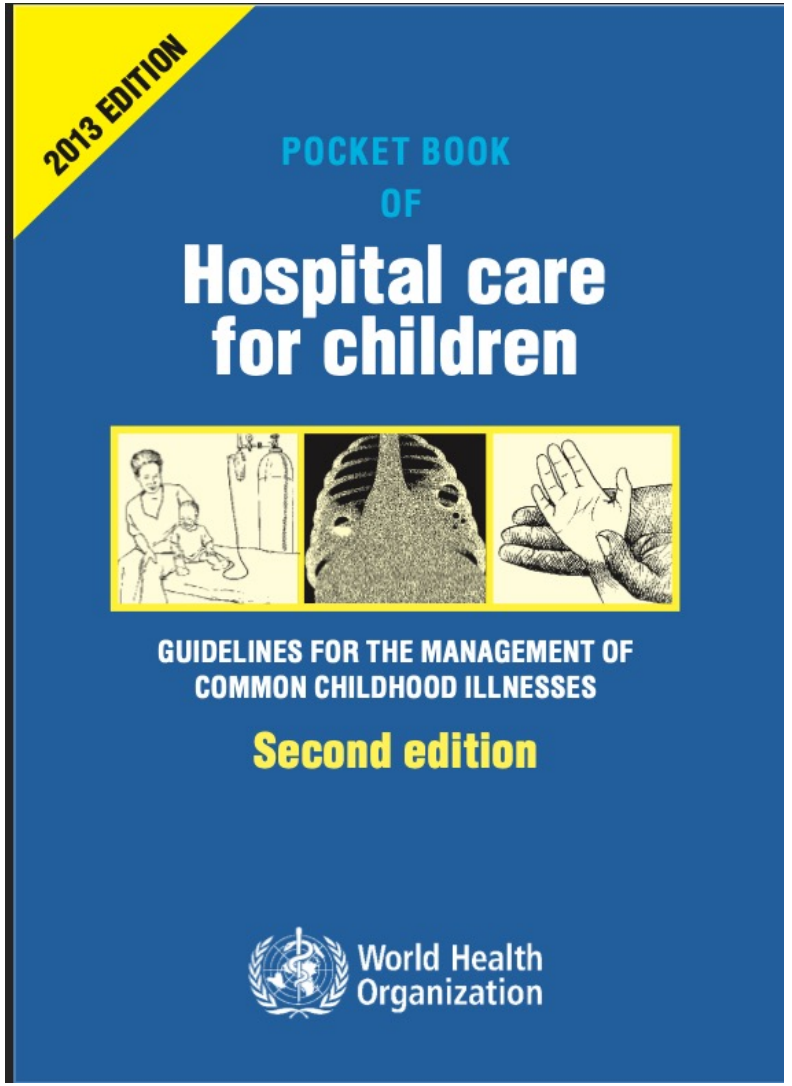
Hospital care for children

GUIDELINES FOR THE MANAGEMENT OF COMMON ILLNESSES WITH LIMITED RESOURCES

- For newborns with any signs of serious bacterial infection or sepsis, give ampicillin (or penicillin) and gentamicin as first-line antibiotic treatment (for dosages see pp. 69–72)
- If at greater risk of staphylococcus infection (extensive skin pustules, abscess or omphalitis in addition to signs of sepsis), give IV cloxacillin and gentamicin.
- The most serious bacterial infections in newborns should be treated with antibiotics for at least 7–10 days.
- If an infant is not improving within 2–3 days, change the antibiotic treatment or refer the infant for further management.

World Health Organization

Global Guidelines reflect (passive) surveillance data from high-income countries, and may be outdated



Questioning the EOS and LOS paradigm

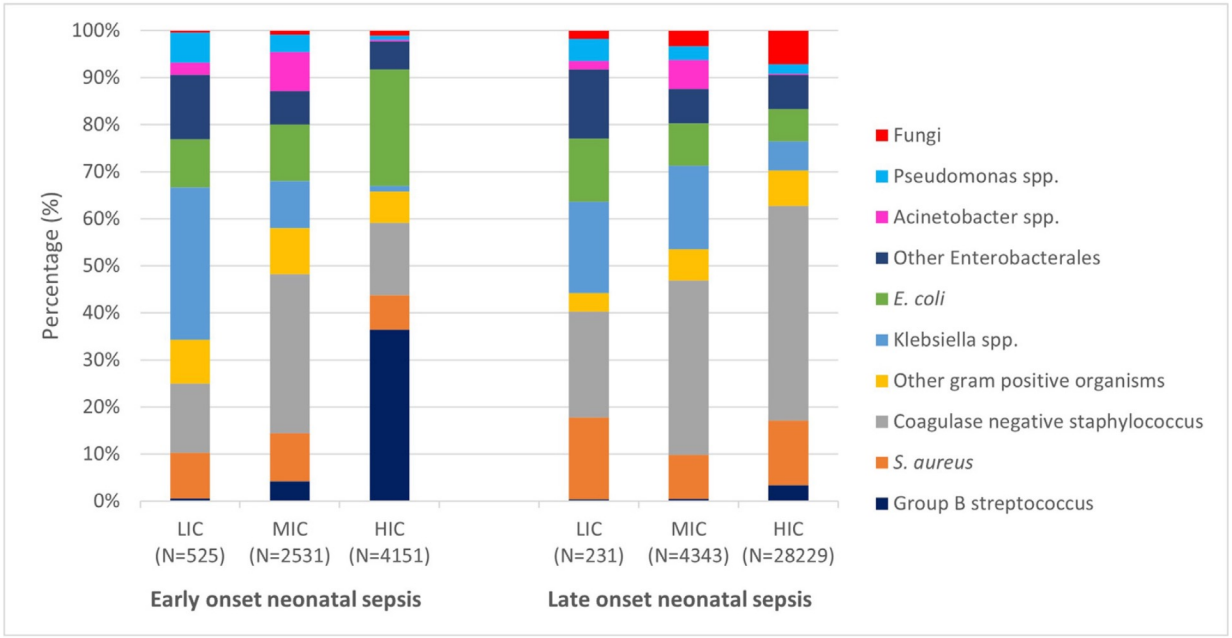


Fig. 1. Published data reporting the number of neonates affected by early- and late-onset sepsis.Total cases of neonatal sepsis: high -income countries (N = 24 077; income counties (N = 4878; 16.4%) and low-income countries (N = 791; 2.7%).Data on numbers of cases not available in 4 studies [41–44] and 1 study excluded as d multiple countries [45].

Clinical Microbiology and Infection 30 (2024) 38–43

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Early-versus late-onset sepsis in neonates – time to shift the paradigm?

Neal Russell [1, *, †], Mikhail Barday [2, †], Uduak Okomo [3], Angela Dramowski [2], Mike Sharland [1], Adrie Bekker [2]

[1] Centre for Neonatal and Paediatric Infection (CNPI), Institute of Infection & Immunity, St George's University of London, London, UK
[2] Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa
[3] Vaccines & Immunity Theme, MRC Unit the Gambia at London School of Hygiene & Tropical Medicine, Fajara, The Gambia

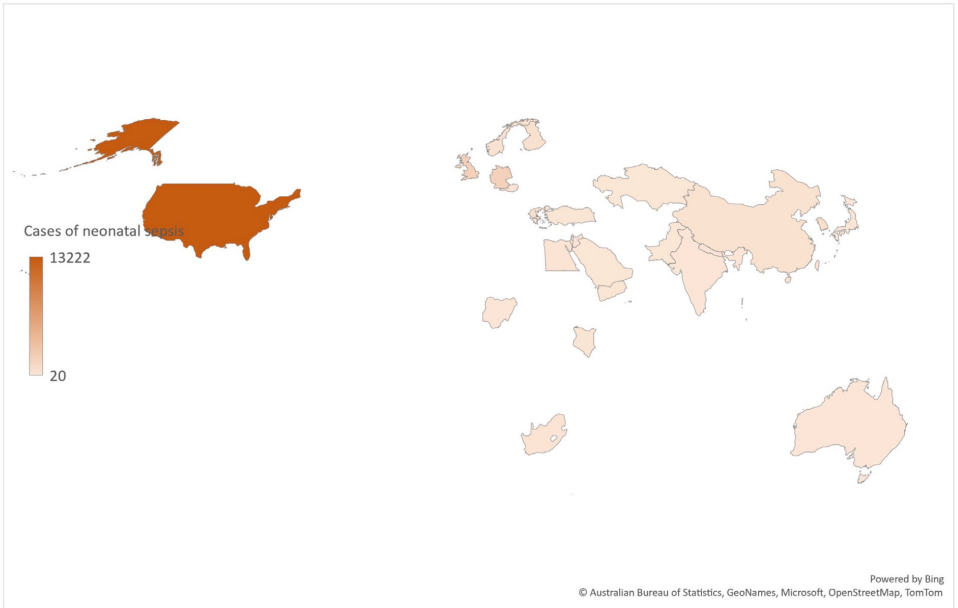


Fig. 2. Pathogen spectrum of early- and late-onset neonatal sepsis stratified by country-income status. HIC, high-income country; LIC, low-income country; MIC, middle-income country.

What surveillance data do we have to clarify the contemporary causes of neonatal sepsis?

What are the contemporary causes of neonatal sepsis?

DeNIS Study: 2016, India

Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study

*Investigators of the Delhi Neonatal Infection Study (DeNIS) collaboration**

"The currently available studies on sepsis are from well-established surveillance networks in high-income countries such as the USA, the UK, and Germany.

Such infection surveillance networks are a rarity in low-income and middle-income countries; the few available ones have used passive surveillance."

-Prospective cohort study of 13,530 neonates across 3 tertiary centres in Delhi (2011-2014)

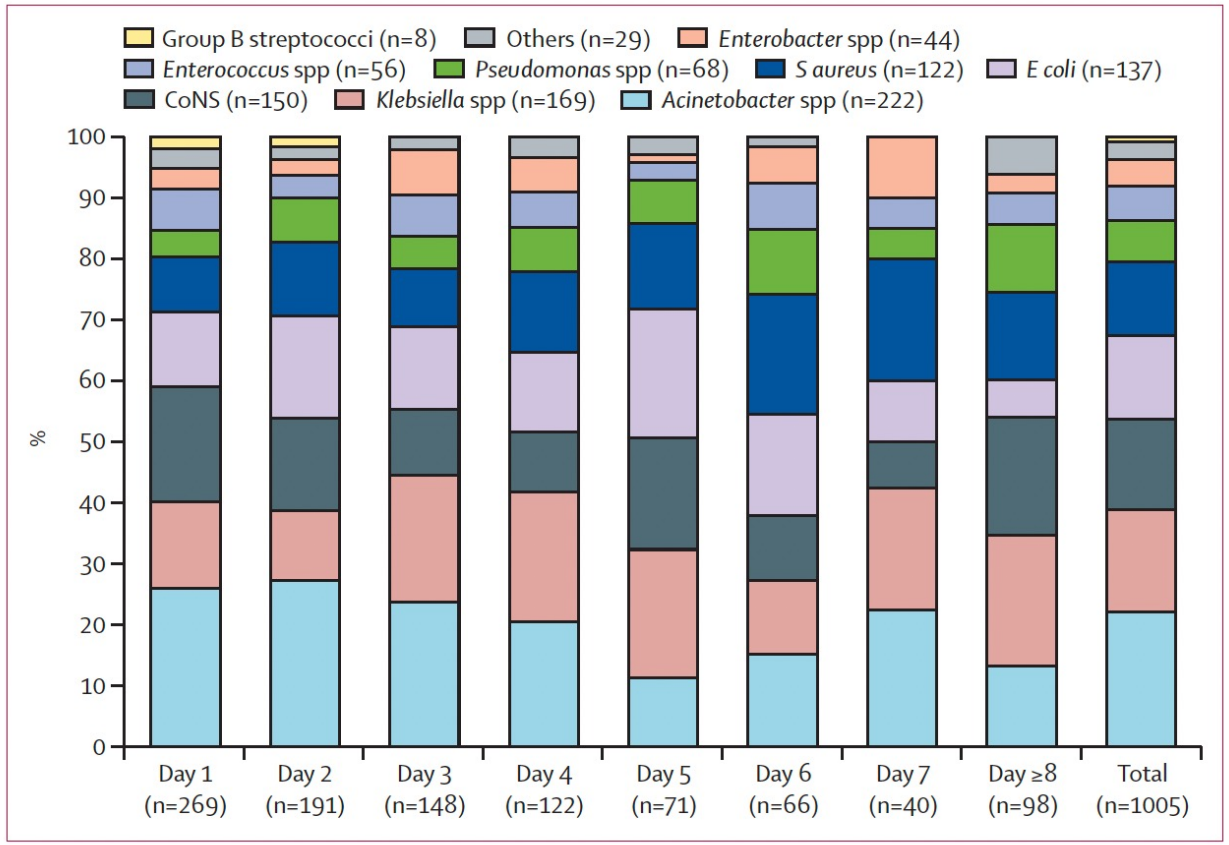


Figure 2: **Profile of pathogens isolated on different days of life**
CoNS=coagulase-negative staphylococci.

The DeNIS study revealed

(1) A paucity of infections due to traditionally-labelled 'EOS' bacteria

(2) The significant burden of infections due to MDR gram-negative infections in neonatal sepsis

	Number of resistant isolates	CFR in culture-positive sepsis due to resistant pathogens	CFR in culture-positive sepsis due to sensitive pathogens
Gram negative			
Acinetobacter spp (n=222)			
ES cephalosporins	85/222 (38%)	59/85 (69%)	71/137 (52%)
Carbapenems	174/222 (78%)	106/174 (61%)	24/48 (50%)
MDR	181/222 (82%)	112/181 (62%)	18/41 (44%)
Klebsiella spp (n=169)			
ES cephalosporins	105/169 (62%)	57/104 (55%)	38/65 (58%)
Carbapenems	59/169 (35%)	36/59 (61%)	59/110 (54%)
MDR	91/169 (54%)	52/91 (57%)	43/78 (55%)
Escherichia coli (n=137)			
ES cephalosporins	65/137 (47%)	40/64 (63%)	43/73 (59%)
Carbapenems	21/137 (15%)	12/21 (57%)	71/116 (61%)
MDR	52/137 (38%)	30/52 (58%)	53/85 (62%)
Pseudomonas spp (n=68)			
ES cephalosporins	32/68 (47%)	29/32 (91%)	24/36 (67%)
Carbapenems	21/68 (31%)	19/21 (90%)	34/47 (72%)
MDR	13/68 (19%)	11/13 (85%)	42/55 (76%)
Enterobacter spp (n=44)			
ES cephalosporins	20/44 (45%)	6/20 (30%)	10/24 (42%)
Carbapenems	9/ 44 (20%)	4/9 (44%)	12/35 (34%)
MDR	22/44 (50%)	8/22 (36%)	8/22 (36%)
Gram positive			
Coagulase-negative staphylococci (n=150)			
Meticillin	85/140 (61%)	23/85 (27%)	14/55 (25%)
Vancomycin	0/138	..	36/138 (26%)
Staphylococcus aureus (n=122)			
Meticillin	43/114 (38%)	16/43(37%)	22/71 (31%)
Vancomycin	0/114	..	38/114 (33%)
Enterococcus spp (n=56)			
Meticillin	11/14 (79%)	10/11 (91%)	2/3 (67%)
Vancomycin	13/48 (27%)	9/13 (69%)	20/35 (57%)

Data are n/N (%); there are variations in denominators in few cells as antibiotic sensitivity testing for all drugs was not done. CFR=case fatality rate. ES=extended-spectrum. MDR=multidrug resistance (ie, I [intermediate] or R [resistant] to on drug in three of the following classes: ES cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, and piperacillin-tazobactam).

Table 4: **Case fatality rates among common pathogens by their antimicrobial resistance pattern**

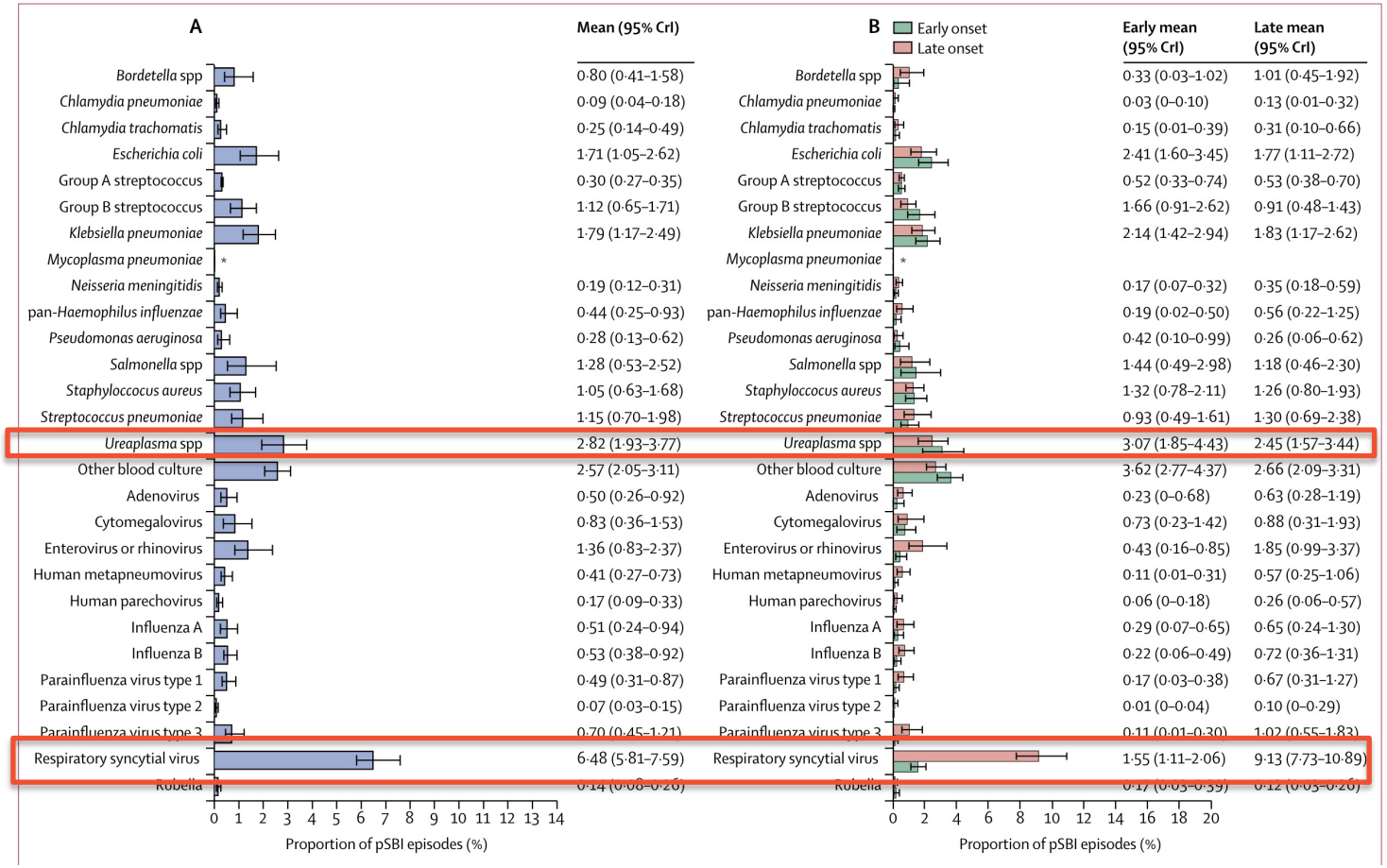
"The dominance of previously considered nosocomial-pathogens in EOS may be due to ultra-early horizontal transmission from delivery rooms and NICUs, or vertical transmission from the maternal genital tract colonised with these pathogens after unhygienic personal and obstetric practices."

What are the contemporary causes of neonatal sepsis?

The ANISA study, 2018

- **Population-based surveillance** of infants 0-59 days in Bangladesh, India, Pakistan from 2011-2014
- Identified proportions of infectious causes of possible serious bacterial infections (pBSI) via blood culture and molecular assay of blood and respiratory samples (TaqMan array).
  - 6,022 pSBI episodes identified among 63,114 babies
- The leading pathogens identified as responsible for pBSI were **respiratory syncytial virus**, followed by ***Ureaplasma* spp.**

Causes and incidence of community-acquired serious infections among young children in south Asia (ANISA): an observational cohort study



Attributed proportions of causal pathogens tested during possible serious bacterial infection episodes, (A) Estimates from overall model. (B) Estimates by age of onset.

What are the contemporary causes of neonatal sepsis?

The ANISA study, 2018

- Molecular methods revealed a substantial proportion of pSBI episodes were not due to infection
  - However, there was a predominance of bacterial causes among babies who died (92% of deaths were attributed to bacterial infections)
  - Gram-negative bacteria (esp *Klebsiella* spp. and *E coli*) were among the top pathogens resulting in death among babies with pSBI

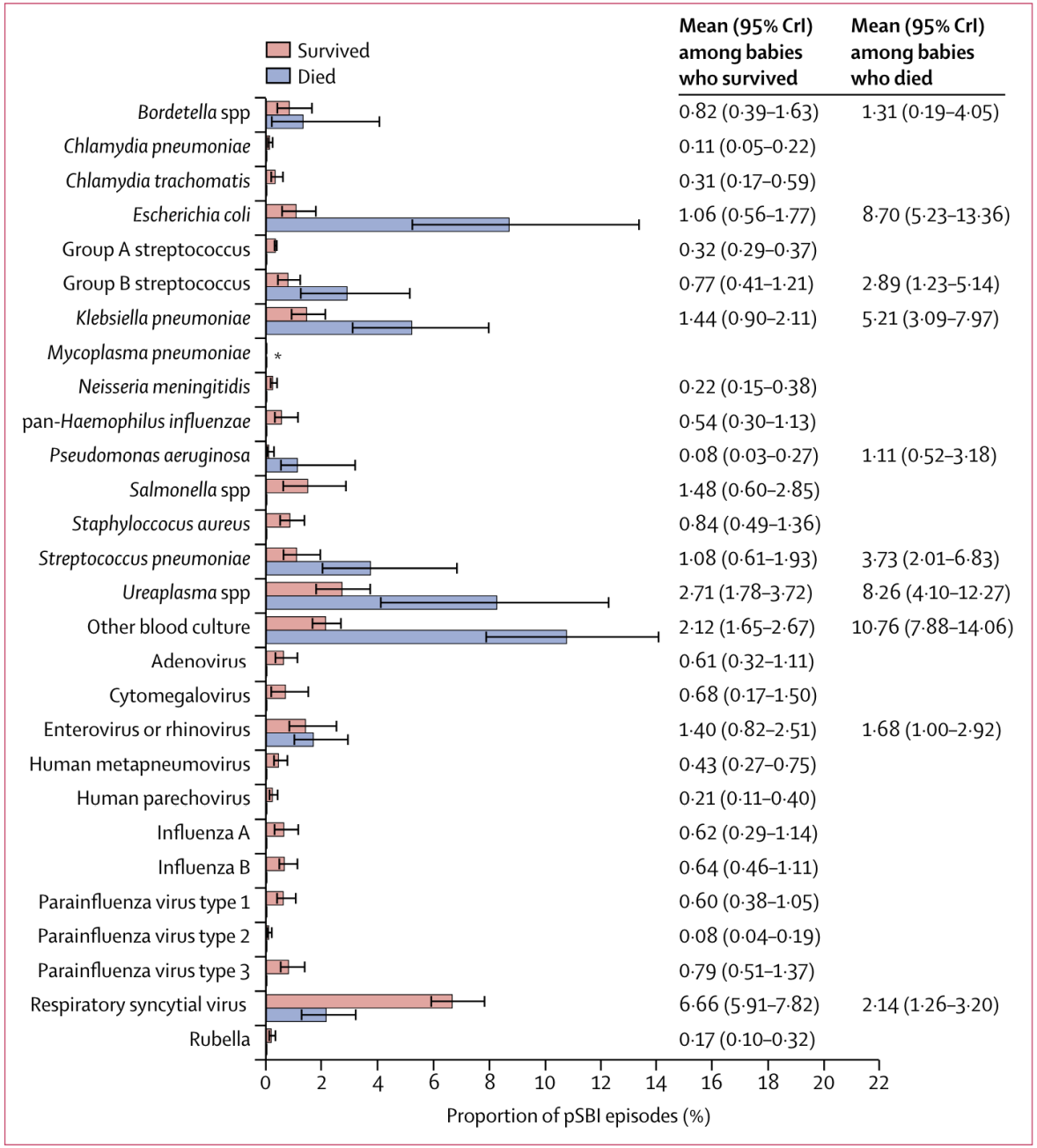


Figure 3: **Attributed proportions of causal pathogens tested during possible serious bacterial infection episodes among babies who died and survived, estimated in a partially latent class model**
CrI=credible interval. *None detected.

What are the contemporary causes of Neonatal Sepsis?

Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) study, 2021

ARTICLES
https://doi.org/10.1038/s41564-021-00870-7
nature microbiology
Check for updates

OPEN

Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries

Kirsty Sands[1,2,25]✉, Maria J. Carvalho[1,3,25]✉, Edward Portal[1], Kathryn Thomson[1], Calie Dyer[1,4], Chinenye Akpulu[1,5,6], Robert Andrews[1], Ana Ferreira[1], David Gillespie[4], Thomas Hender[1], Kerenza Hood[4], Jordan Mathias[1], Rebecca Milton[1,4], Maria Nieto[1], Khadijeh Taiyari[4], Grace J. Chan[7,8,9], Delayehu Bekele[9,10], Semaria Solomon[11], Sulagna Basu[12], Pinaki Chattopadhyay[13], Suchandra Mukherjee[13], Kenneth Iregbu[5], Fatima Modibbo[5,6], Stella Uwaezuoke[14], Rabaab Zahra[15], Haider Shirazi[16], Adil Muhammad[15], Jean-Baptiste Mazarati[17], Aniceth Rucogoza[17], Lucie Gaju[17], Shaheen Mehtar[18,19], Andre N. H. Bulabula[19,20], Andrew Whitelaw[21,22], BARNARDS Group[23,*] and Timothy R. Walsh[1,24]

Antimicrobial resistance in neonatal sepsis is rising, yet mechanisms of resistance that often spread between species via mobile genetic elements, ultimately limiting treatments in low- and middle-income countries (LMICs), are poorly characterized. The Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) network was initiated to characterize the cause and burden of antimicrobial resistance in neonatal sepsis for seven LMICs in Africa and South Asia. A total of 36,285 neonates were enrolled in the BARNARDS study between November 2015 and December 2017, of whom 2,483 were diagnosed with culture-confirmed sepsis. *Klebsiella pneumoniae* ($n = 258$) was the main cause of neonatal sepsis, with *Serratia marcescens* ($n = 151$), *Klebsiella michiganensis* ($n = 117$), *Escherichia coli* ($n = 75$) and *Enterobacter cloacae* complex ($n = 57$) also detected. We present whole-genome sequencing, antimicrobial susceptibility and clinical data for 916 out of 1,038 neonatal sepsis isolates (97 isolates were not recovered from initial isolation at local sites). Enterobacterales (*K. pneumoniae, E. coli* and *E. cloacae*) harboured multiple cephalosporin and carbapenem resistance genes. All isolated pathogens were resistant to multiple antibiotic classes, including those used to treat neonatal sepsis. Intraspecies diversity of *K. pneumoniae* and *E. coli* indicated that multiple antibiotic-resistant lineages cause neonatal sepsis. Our results will underpin research towards better treatments for neonatal sepsis in LMICs.

Supplementary Figure. 1. BARNARDS' centres including clinical sites.

- Seven LMICs across Africa and South Asia
- 36,285 neonates enrolled across 2015-2017
  - -Of whom 2,483 were diagnosed with culture-positive sepsis
- WGS conducted on 916 isolates

What are the contemporary causes of Neonatal Sepsis?

Findings from the BARNARDS study, 2021

Class B metallo-β-lactamases predominate

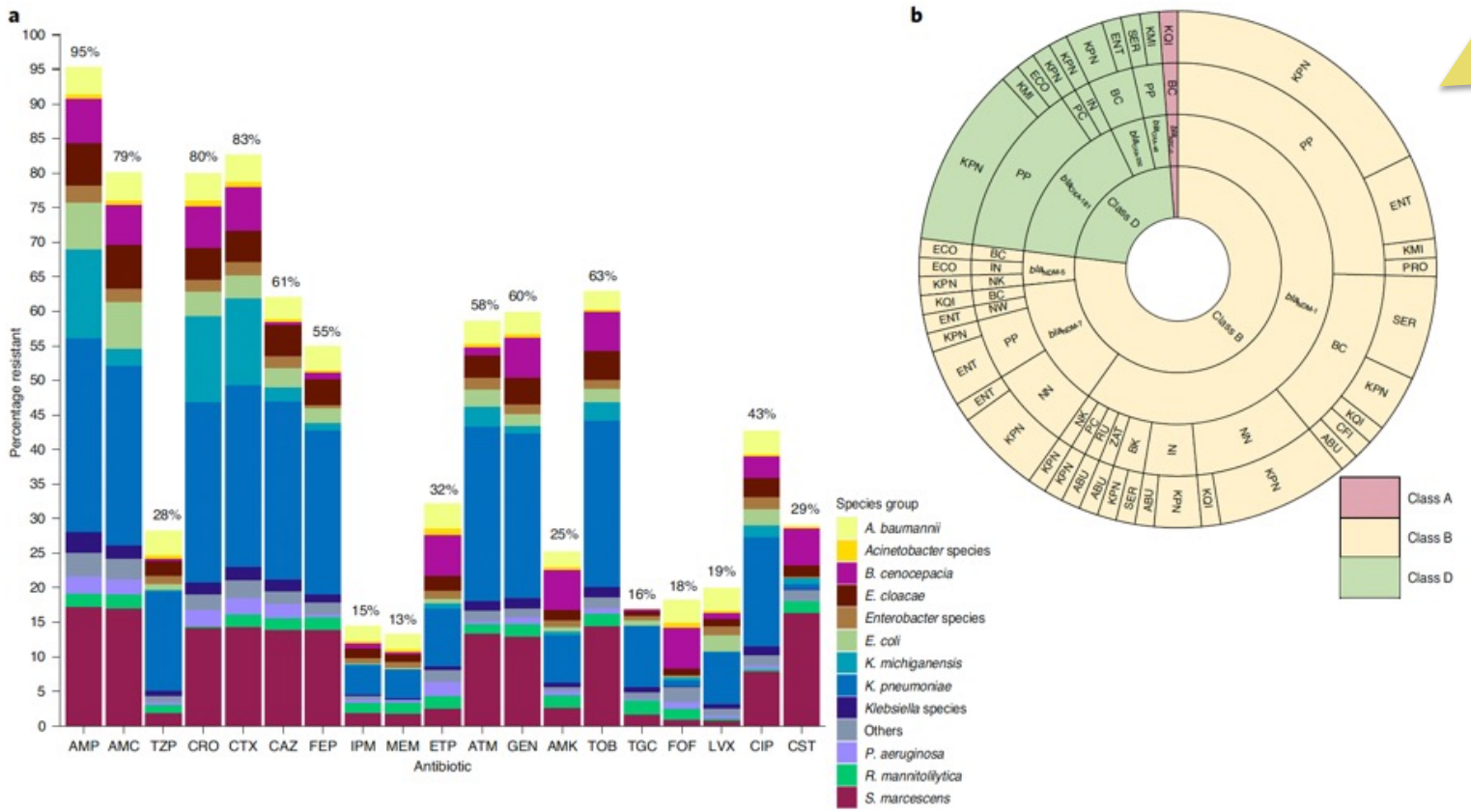


Fig. 3 | AMR of neonatal sepsis-causing pathogens. a, Percentages of antimicrobial-resistant aetiological agents of neonatal sepsis, coloured according to bacterial species/group ($n = 885$ isolates of GNB). The MICs of the antibiotics were determined by agar dilution and the results were interpreted according to EUCAST guidelines and documents[20,21]. AMC, amoxicillin/clavulanate; AMK, amikacin; AMP, ampicillin; ATM, aztreonam; CAZ, ceftazidime; CIP, ciprofloxacin; CRO, ceftriaxone; CST, colistin; CTX, cefotaxime; ETP, ertapenem; FEP, cefepime; FOF, fosfomycin; GEN, gentamicin; IPM, imipenem; LVX, levofloxacin; MEM, meropenem; TGC, tigecycline; TOB, tobramycin; TZP, piperacillin/tazobactam. **b**, Sunburst diagram detailing the class A (red), B (yellow) and D (green) carbapenemase resistance genes detected. The second ring from the centre shows the carbapenemase genes identified. The distributions across species and clinical sites are shown in the outer rings. ABU, *Acinetobacter baumannii*; CFI, *Citrobacter freundii*; ECO, *Escherichia coli*; ENT, *Enterobacter cloacae* complex; KMI, *Klebsiella michiganensis*; KPN, *Klebsiella pneumoniae*; KQI, *Klebsiella quasipneumoniae*; PRO, *Providencia rettgeri*; SER, *Serratia marcescens*.

- *Klebsiella pneumoniae* (n = 258) was the predominant cause of neonatal sepsis
- 67% (597/885) of gram-negative isolates were resistant to at least one β-lactam and one aminoglycoside, suggesting WHO guidelines are unlikely to be efficacious
- All isolated pathogens were resistant to multiple antibiotic classes, including those used to treat neonatal sepsis.

What are the contemporary causes of Neonatal Sepsis?

Findings from the NeoObs study, 2023

PLOS MEDICINE

RESEARCH ARTICLE

Patterns of antibiotic use, pathogens, and prediction of mortality in hospitalized neonates and young infants with sepsis: A global neonatal sepsis observational cohort study (NeoOBS)

The neonatal sepsis observational study, which has looked at **over 3200 newborns** at **19 sites** in **11 countries** on **4 continents**, is providing evidence to fill knowledge gaps, help transform treatment and save lives.

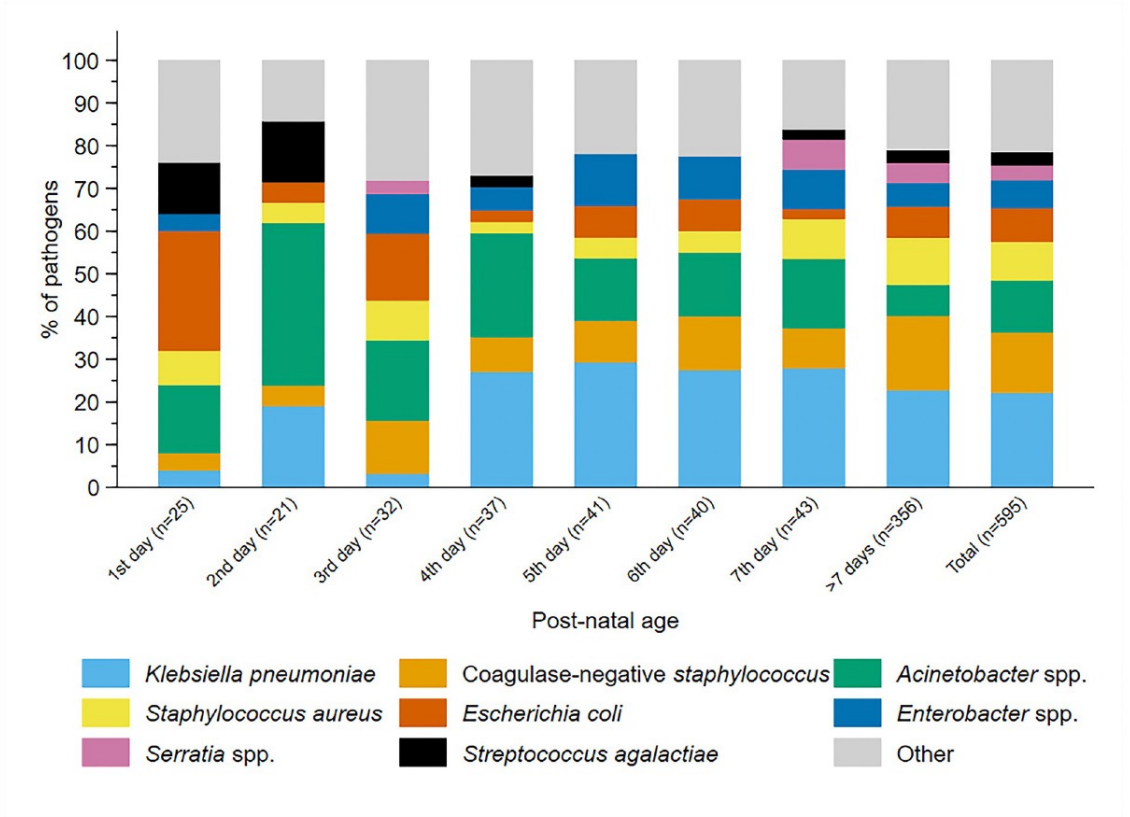


Fig 2. Pathogens isolated in baseline blood culture, overall and by infants' day of life.

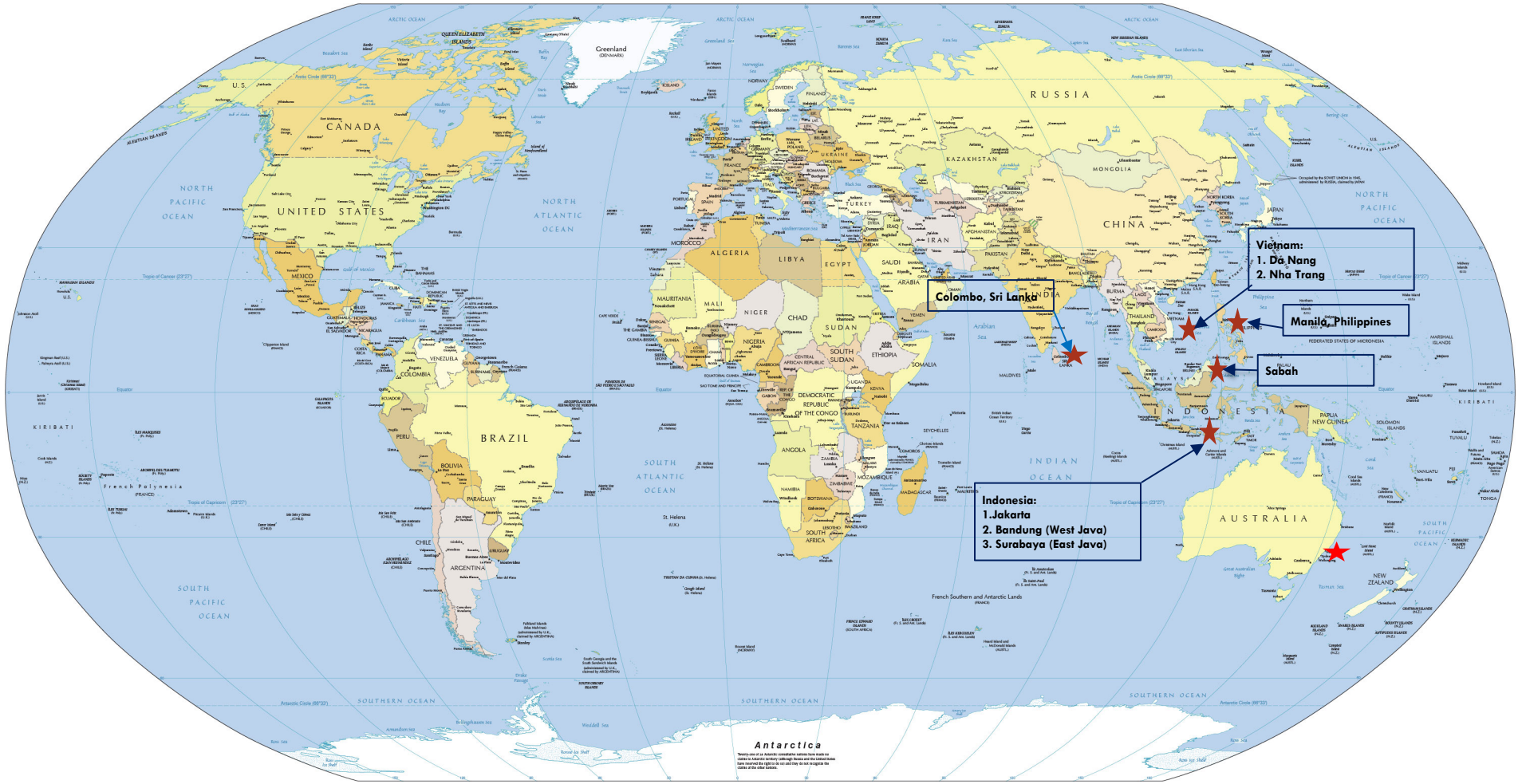
https://doi.org/10.1371/journal.pmed.1004179.g002

17.7% of infants were (blood) culture-positive (564/3,195), of which 63% (355) had gram-negative bacterial infections (predominantly *Klebsiella pneumoniae* (n=132) or *Acinetobacter* spp (n=72), which were frequently resistant to WHO-recommended regimens (n=43, 33%) and carbapenems (n=50, 71%)

What are the contemporary causes of Neonatal Sepsis? Findings from the NeoSEAP study, 2024

Neonatal Sepsis in South East Asia and the Pacific

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific



Analysis of 14,804 blood cultures collected over 2019-2020, of which 2,131 were positive (1,483 with significant pathogens)

The University of Sydney

What are the contemporary causes of Neonatal Sepsis?

Findings from the NeoSEAP study, 2024

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific

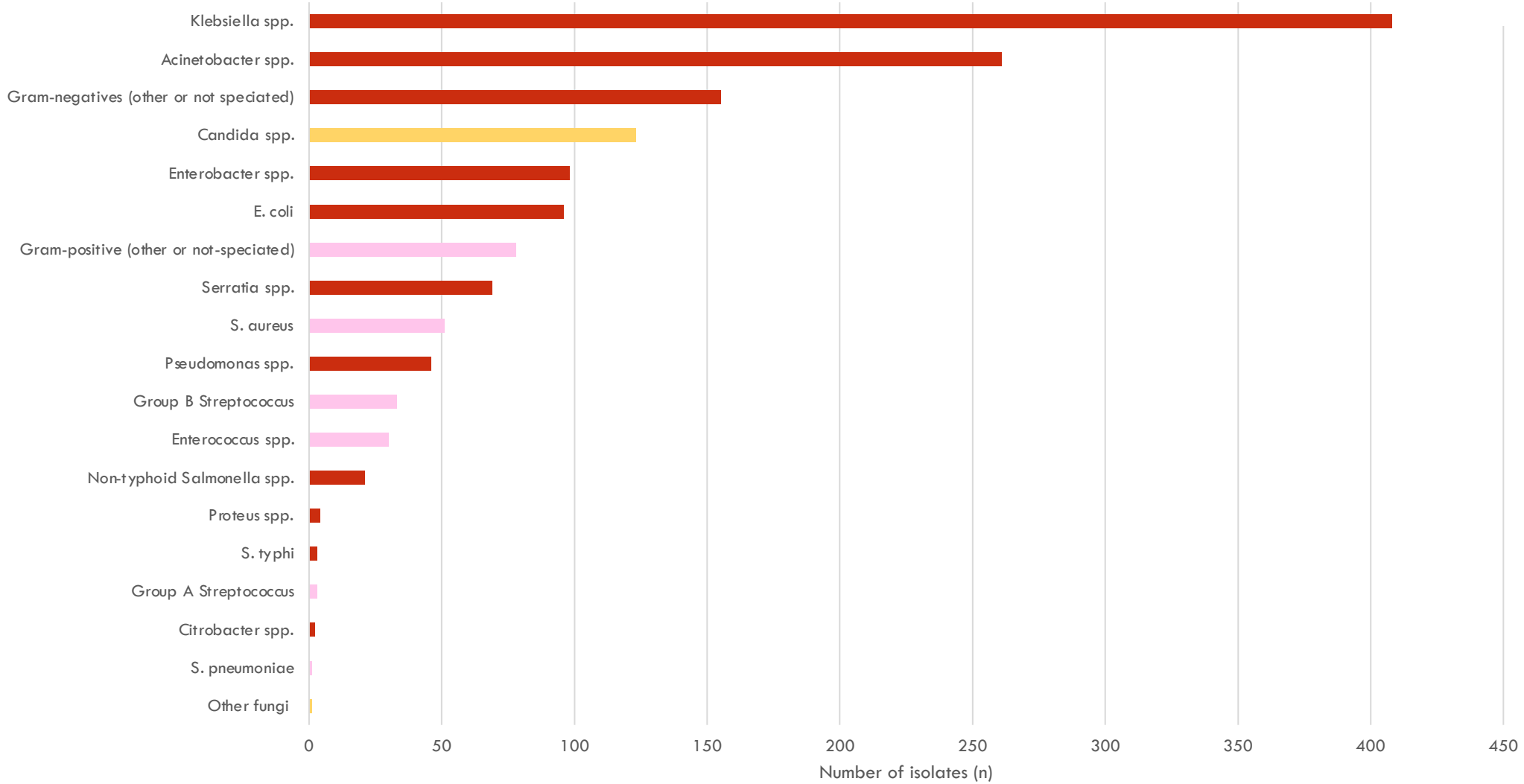


Figure 3. Pooled frequency of positive species isolated across all-sites (n=1,483). Pink = gram-negative bacteria, blue = gram-positive bacteria, green= fungi.

Dickson, B. *et al.* 2024, in submission

What are the contemporary causes of Neonatal Sepsis?

Findings from the NeoSEAP study, 2024

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific

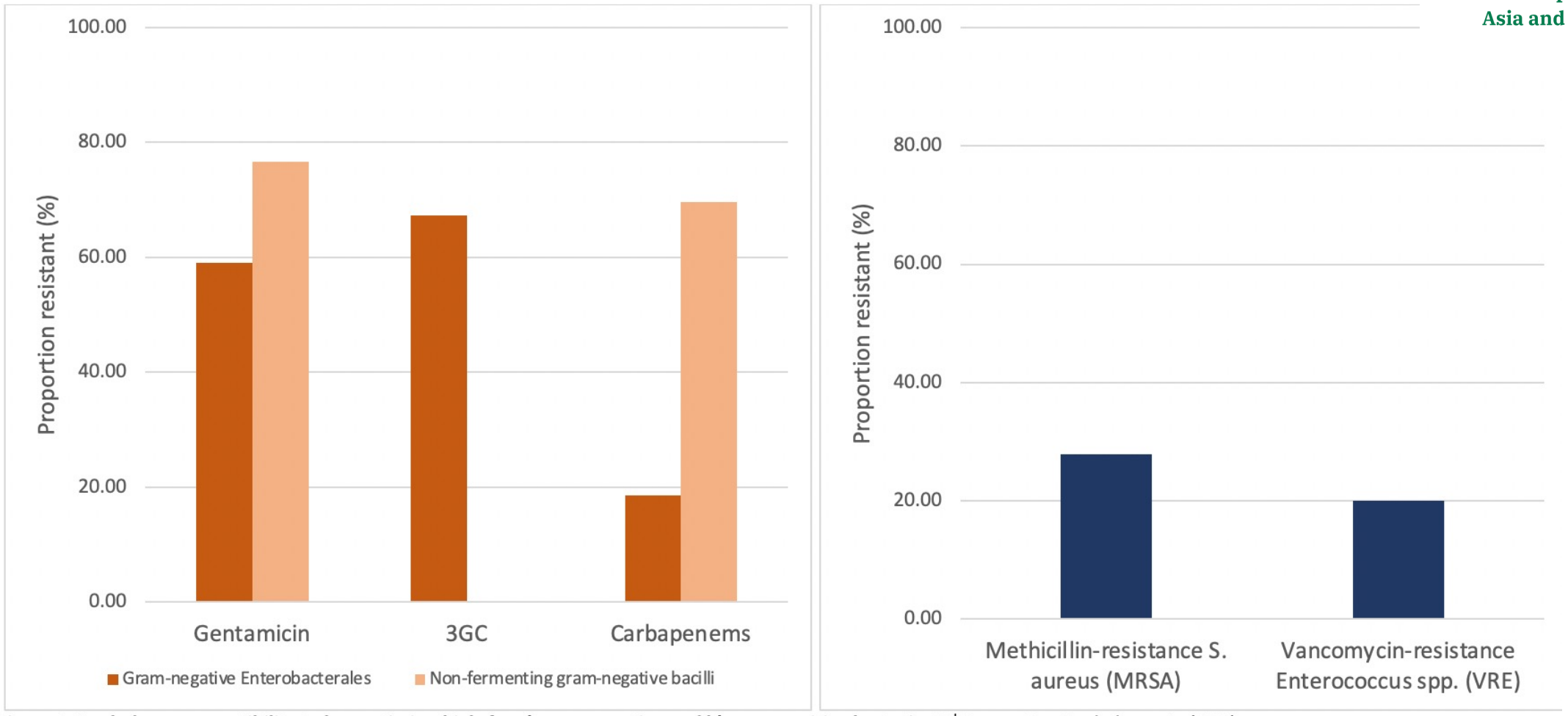


Figure 4. Pooled non-susceptibility to key antimicrobials for a) gram-negative and b) gram-positive bacteria. 3rd Generation Cephalosporin (3GC).

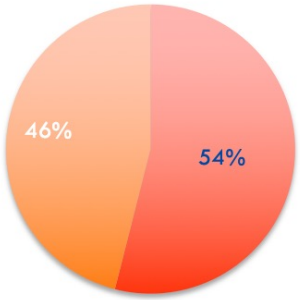
Dickson, B. *et al.* 2024, in submission

A closer look - Indonesia

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific

Indonesia

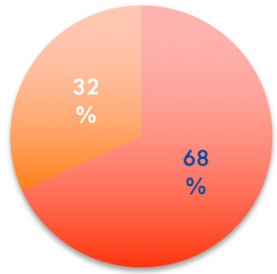
Surabaya



Total Gram negative
Total Gram positive

Denominator:
- 1,731 BC collected;
- 138 (8%) culture positive

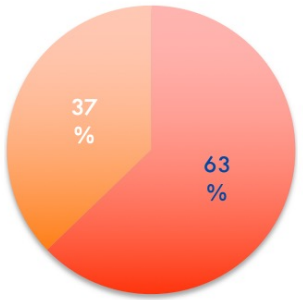
Jakarta



Total Gram negative
Total Gram positive

Denominator:
- 2,059 BC collected;
- 601 (29%) culture positive

Bandung

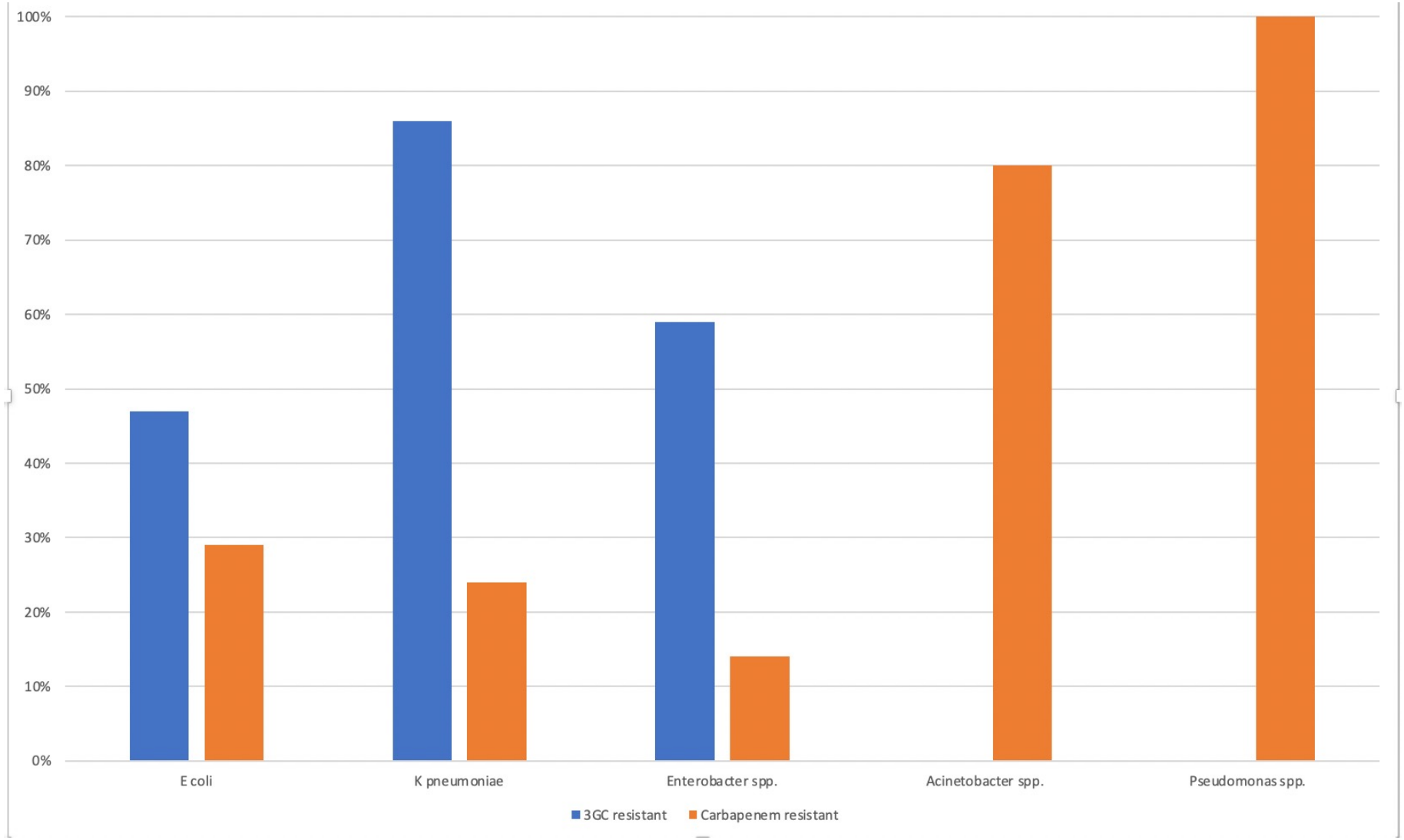


Total Gram negative
Total Gram positive

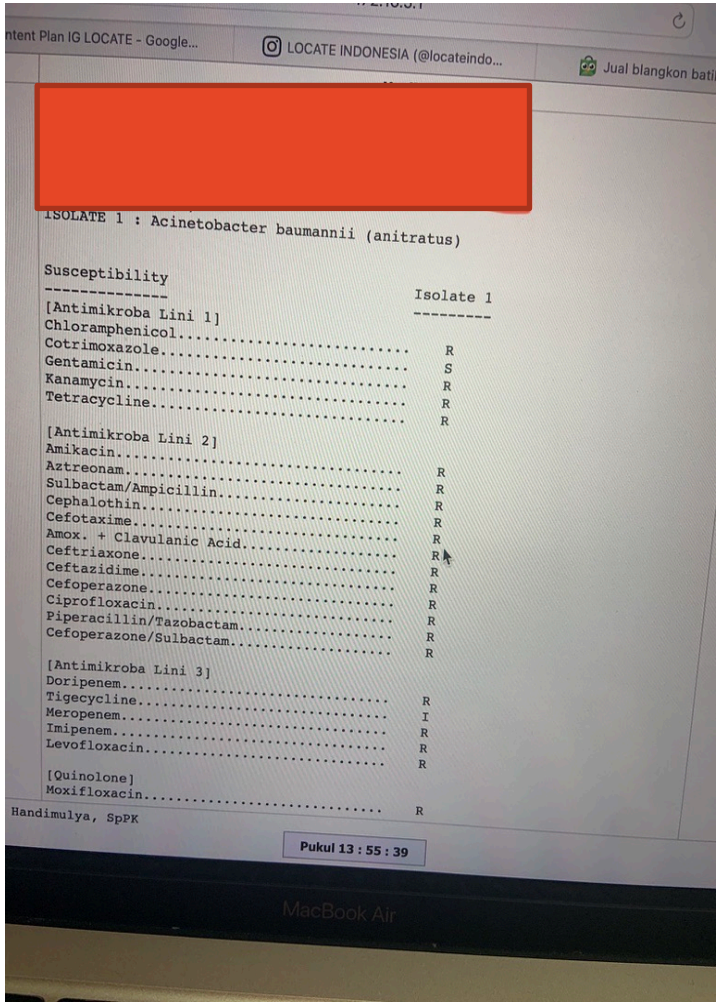
Denominator:
- 1,649 BC collected;
- 374 (23%) culture-positive

Klebsiella spp., *Acinetobacter* spp., and *Enterobacter* spp. responsible for ~60% of culture-positive neonatal sepsis cases

Gram-negative resistance: NeoSEAP sites, Indonesia



MDR neonatal sepsis in Indonesia



Treatment regimens for neonatal infections: Indonesia

	1st line	2nd line
Neonatal sepsis		
EOS (community-acquired)	Ampicillin + gentamicin	Ampicillin-sulbactam + gentamicin
LOS (community-acquired)	Ampicillin + gentamicin	Ampicillin-sulbactam + gentamicin
Neonatal meningitis	Cefotaxime	
Late-onset, hospital-acquired sepsis Or HAP/VAP	Cefoperazone-sulbactam + amikacin	Piperacillin-tazobactam + amikacin; or Meropenem
ESBL-producing pathogen identified	Meropenem	
CRE pathogen identified	-Polymixin + meropenem +/- fosfomycin -Ceftazidime-avibactam, if available -Tigecycline + fosfomycin -Tigecycline + levofloxacin *microbiologically-guided where possible; all consulted with Paed ID	With no culture results: Levofloxacin+tigecycline

GAD05-05

High rates of watch and reserve antibiotic prescribing in the treatment of neonatal infections among resource-constrained settings in Southeast Asia

Benjamin F.R. Dickson[1], M. Harrison [1], M.E. Villanueva-Uy [2], N. Putri [3], R. Adrizain [4], L. Kartina [5], G. Gunaratna [6], C. Le [7], H. Tran [7], N. Huong [8], S. M. Fong [9] , Phoebe CM Williams

[1]The University of Sydney - Sydney (Australia), [2]Institute of Child Health and Human Development, National Institutes of Health - Manila (Philippines), [3]Universitas Indonesia - Jakarta (Indonesia), [4]University of Padjaran - Bandung (Indonesia), [5]University of Airlangga - Surabaya (Indonesia), [6]Faculty of Medicine, University of Kelaniya - Colombo (Sri Lanka), [7]Da Nang Hospital for Women and Children - Da Nang (Vietnam), [8]Pham Chau Trinh University - Da Nang (Vietnam), [9]Sabah Women's and Children's Hospital, Sabah (Malaysia)

BACKGROUND

- The rise of antimicrobial resistance (AMR) poses a major challenge to global health.[1]
- Neonates are highly vulnerable to this threat (214,000 AMR-attributable deaths/year).[2]
- Understanding antimicrobial prescribing patterns is crucial to address the rising burden of AMR globally.
- There remains sparse data on antibiotic usage in resource-constrained healthcare settings, where the burden of AMR is the greatest and access to newer agents is limited.[3]

METHODS

- We conducted a comprehensive prospective antibiotic Point Prevalence Survey (PPS) as part of the NeoSEAP project (Neonatal Sepsis in Southeast Asia and the Pacific).
- 10 clinical sites across Indonesia, Vietnam, The Philippines, Sri Lanka & Malaysia participated in the PPS, undertaken on one day between December 2022-December 2023 (Figure 1).
- Inclusion criteria: All admitted Infants ≤ 180 days old.

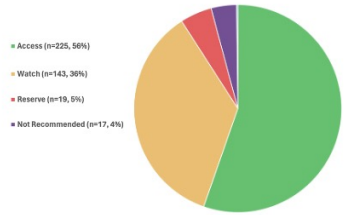


Figure 2. Proportion of antimicrobials prescribed (by WHO AWaRe Category) across ten clinical sites in South and Southeast Asia

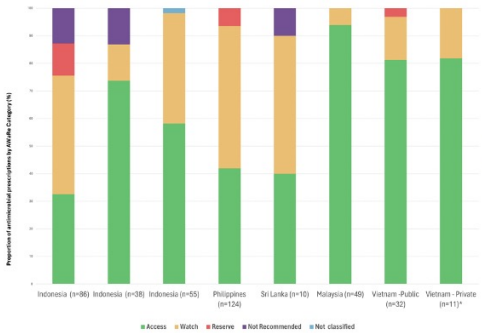


Figure 3. Proportion of antimicrobial prescriptions by Access, Watch & Reserve classification by clinical site

**Three private hospital sites in Vietnam are represented together*

Figure 1: Location of participating point prevalence survey sites

RESULTS

- 667 hospitalised infants were included in the study, who were prescribed a total of 405 antibiotics (Figures 2-4).
- 42 different antibiotics were prescribed across the ten clinical sites.
- 218 infants (33%, 218/667) were prescribed ≥1 antibiotic.
- 85% of infants (191/218) had blood cultures collected, but only 19% (42/218) were prescribed antibiotics targeted to a causative bacteria.
- *Klebsiella pneumoniae* (n=23) and *Acinetobacter* spp. (n=11) were the most frequently isolated bacteria on blood culture.

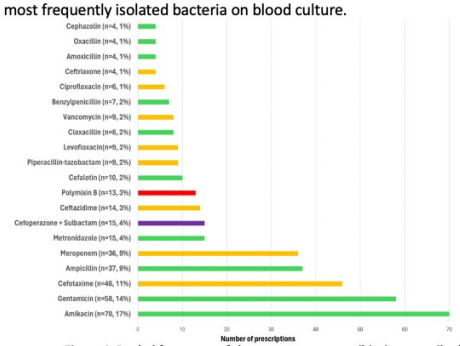


Figure 4. Pooled frequency of the most common antibiotics prescribed across all 10 clinical sites in South and Southeast Asia

**Frequencies of <1% of the total prescriptions have been omitted from this figure.*
Colors depict WHO Access, Watch, Reserve classification for each antibiotic (see Figure 2 legend)

CONCLUSION

- WHO categorized 'Watch', 'Reserve' and 'Not recommended' antibiotics are commonly prescribed to treat hospitalized neonates in South and Southeast Asia.
- Empirical antibiotics frequently include broad-spectrum agents in these settings, as infections are rarely confirmed with positive cultures.
- Where (blood or cerebrospinal fluid) cultures are positive, multidrug-resistant gram-negative infections are common, driving the use of broad-spectrum empiric therapy and further propagating antimicrobial selection pressure in clinical settings.
- There is an urgent need for improved diagnostics and treatment options to improve the management of neonatal sepsis globally.

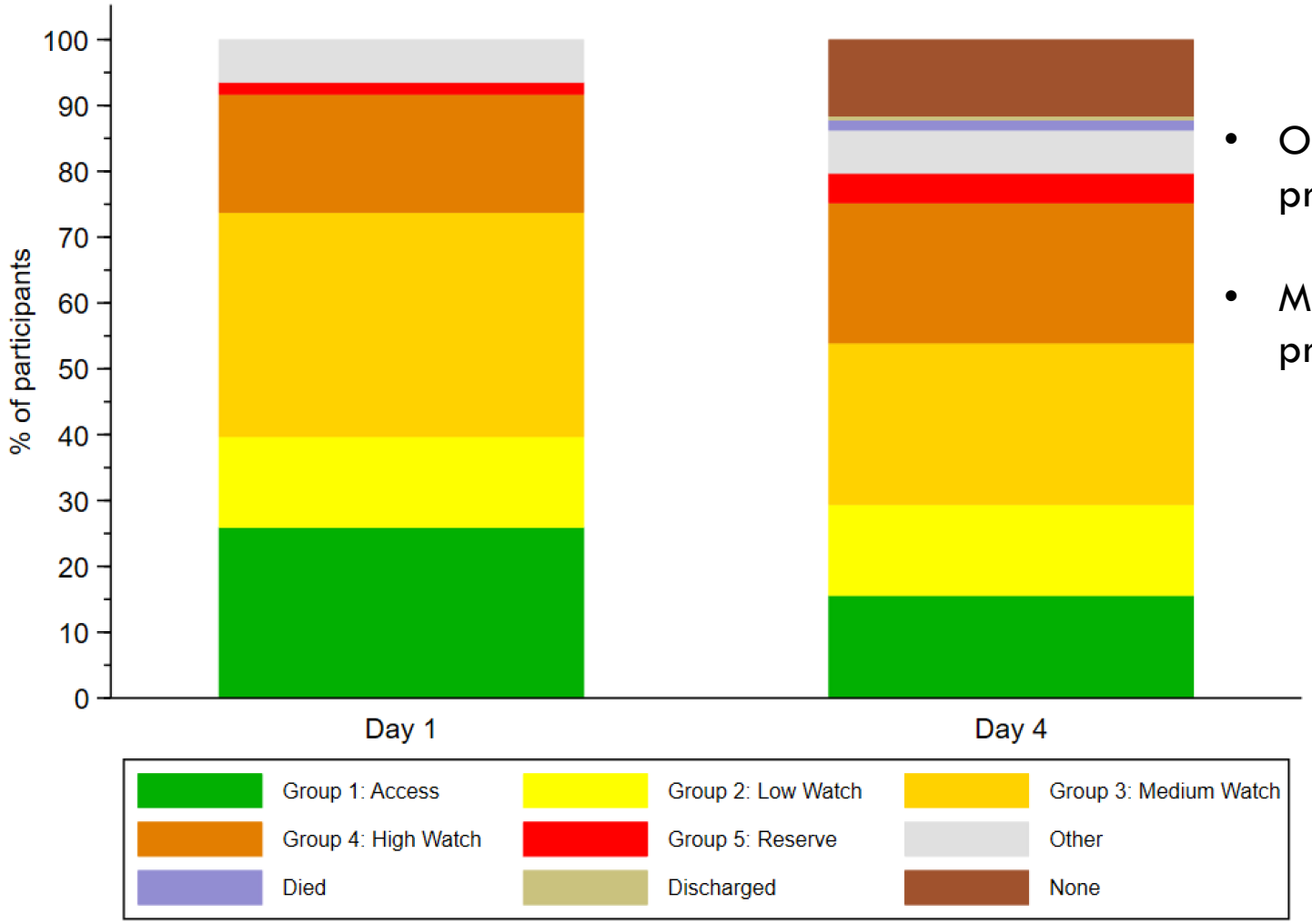
References:

1. Laxminarayan R et al. Access to effective antimicrobials: a worldwide challenge. Lancet. 2016.
2. Antimicrobial resistance collaborators. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis.
3. Williams PCM., et al. Antibiotics needed to treat multidrug-resistant infections in neonates. Bulletin of the World Health Organization. 2022

34th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Barcelona, Spain
27 – 30 April 2024

Without adequate surveillance, there is broad-spectrum empirical prescribing, driving selection pressure and increasing hospital-acquired MDR infections

Findings from the NeoObs study



- Over 200 different empiric antibiotic combinations prescribed
- Most common empirical therapy combinations prescribed:
  1. Meropenem+vancomycin (n=438, 13.9%)
  2. Ceftazidime+amikacin (n=435, 13.8%)
  3. Piperacillin/tazobactam+amikacin (n=410, 13%)

What is needed for active, prospective, surveillance-based programs?

”Most people from LMICs know their own problem but there is a lack of time, high clinical burden of our job, low opportunity of funding for surveillance research.

Local funding opportunities are small and scattered – we need capacity to be part of bigger and better funding for research.”

Dr Nina Dwi Putri
Paediatric Infectious Diseases Specialist & PhD Candidate
Cipto Mangunkusumo Hospital, Jakarta, Indonesia

What are the limitations of our currently available surveillance data that guides empirical treatment for neonatal infections?

- Data from HICs
- Biased towards sampling of hospital-acquired infections in preterm babies

- Data from LMICs
- Community-acquired infections
  - Particularly early-onset infections

Practical solutions: The ACORN project

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific

Active surveillance to develop a comprehensive data capture system for **patient-focussed AMR surveillance** in LMIC settings

ACORN

- About ACORN
- ACORN Roadmap
- Dashboard Access
- Dashboard Use Cases
- Data Elements
- Data Management
- Dashboard Customisation
- Acknowledgments and Credits

A Clinically Oriented antimicrobial Resistance Network (ACORN)

ACORN is a Wellcome funded human health clinical AMR surveillance project led by the Mahidol-Oxford Tropical Medicine Research Unit (MORU) and the Oxford University of Oxford Clinical Research Unit (OUCRU).

Why is ACORN needed?

Existing AMR surveillance systems are based mostly on diagnostic microbiology laboratory antimicrobial susceptibility testing results alone, which limits interpretability of resistant proportions. Resulting data fail to give relevant feedback for treatment decisions for local clinicians and do not allow for direct assessment and subsequent modelling of the clinically relevant impacts and burden of drug resistant infections (DRI). Tools to capture and analyse AMR data in low- and middle-income countries (LMIC) are scarce, which hinders engagement with and use of available data.

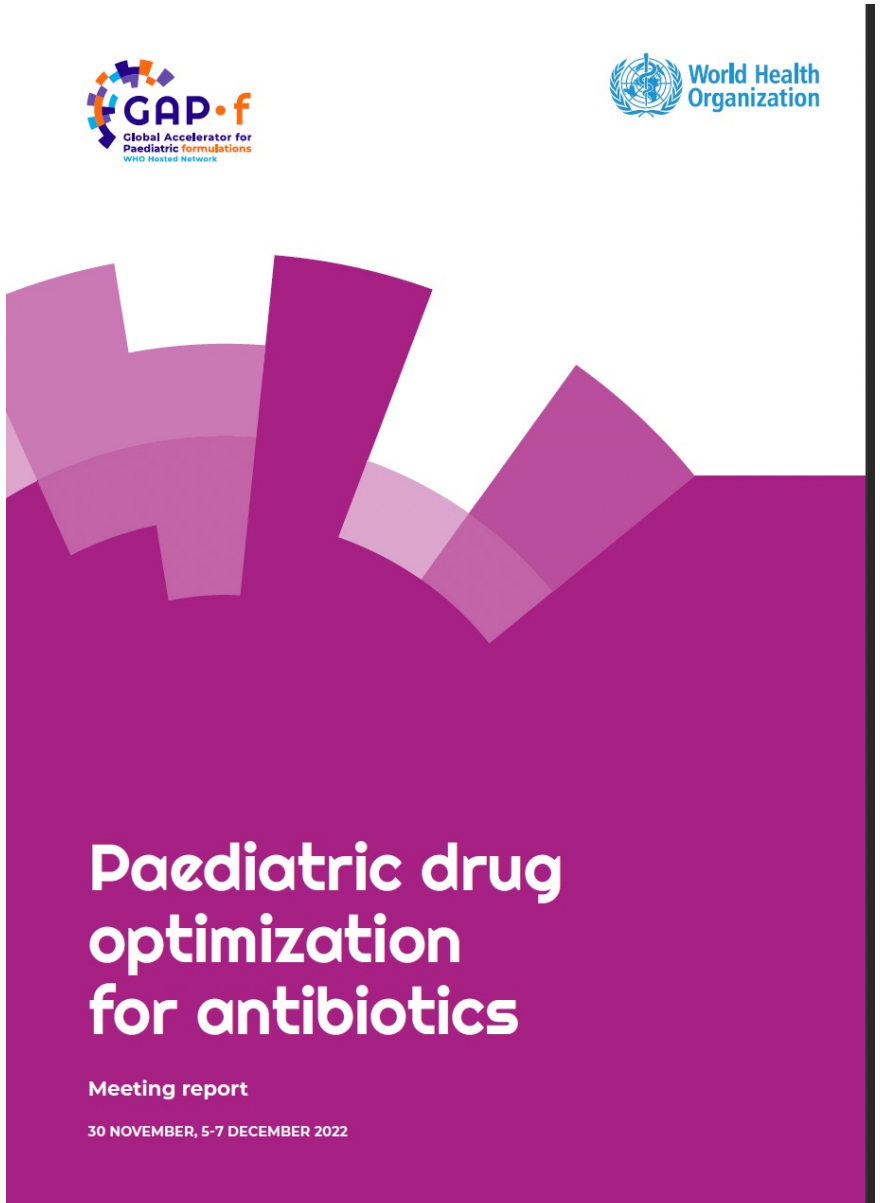
To fill these gaps, the major aim of ACORN is to develop and test a comprehensive data capture system for patient-focussed AMR surveillance in LMIC settings. Surveillance will include diagnostic stewardship activities. Data collected will harmonise with and expand on the pathogen-focussed WHO Global Antimicrobial Resistance Surveillance System to enable accurate classification of infection syndromes and patient outcomes. These data will be of critical importance to estimate syndromic and/or pathogen outcomes and associated costs: i.e. how many people die from DRIs and how much does AMR cost?

Where is ACORN surveillance being done?

A pilot project was done at Angkor Hospital for Children (Siem Reap, Cambodia), Mahosot Hospital (Vientiane, Lao PDR), and the National Hospital for Tropical Diseases (Hanoi, Vietnam). In the second phase, surveillance is being rolled out at 15 hospitals across 9 Asian and African countries.

Phase 1: Cambodia, Laos, Vietnam.
Phase 2: Ghana, Indonesia, Kenya, Malawi, Nepal, Nigeria.

Improved surveillance data can enable the development of efficacious empirical antibiotic regimens to treat neonatal infections



Review

Tackling the threat of antimicrobial resistance in neonates and children: outcomes from the first WHO-convened Paediatric Drug Optimisation exercise for antibiotics

Alasdair Bamford, Tiziana Masini, Phoebe Williams, Mike Sharland, Valeria Gigante, Devika Dixit, Hatim Sati, Benedikt Huttner, Yasir Bin Nisar, Bernadette Cappello, Wilson Were, Jennifer Cohn*, Martina Penazzato*, on behalf of the PADO-antibiotics participants†

Panel 2: Main results of the Paediatric Drug Optimisation (PADO) exercise adapted from the PADO report[32]

PADO priority list

Short-term (3–5 years) time horizon for development of paediatric formulations or approval of paediatric indications

- Amoxicillin–clavulanic acid
- Nitrofurantoin
- Azithromycin
- Cefiderocol

PADO watch list

Medium-term and long-term (5–10 years) time horizon for development of paediatric indications and formulations

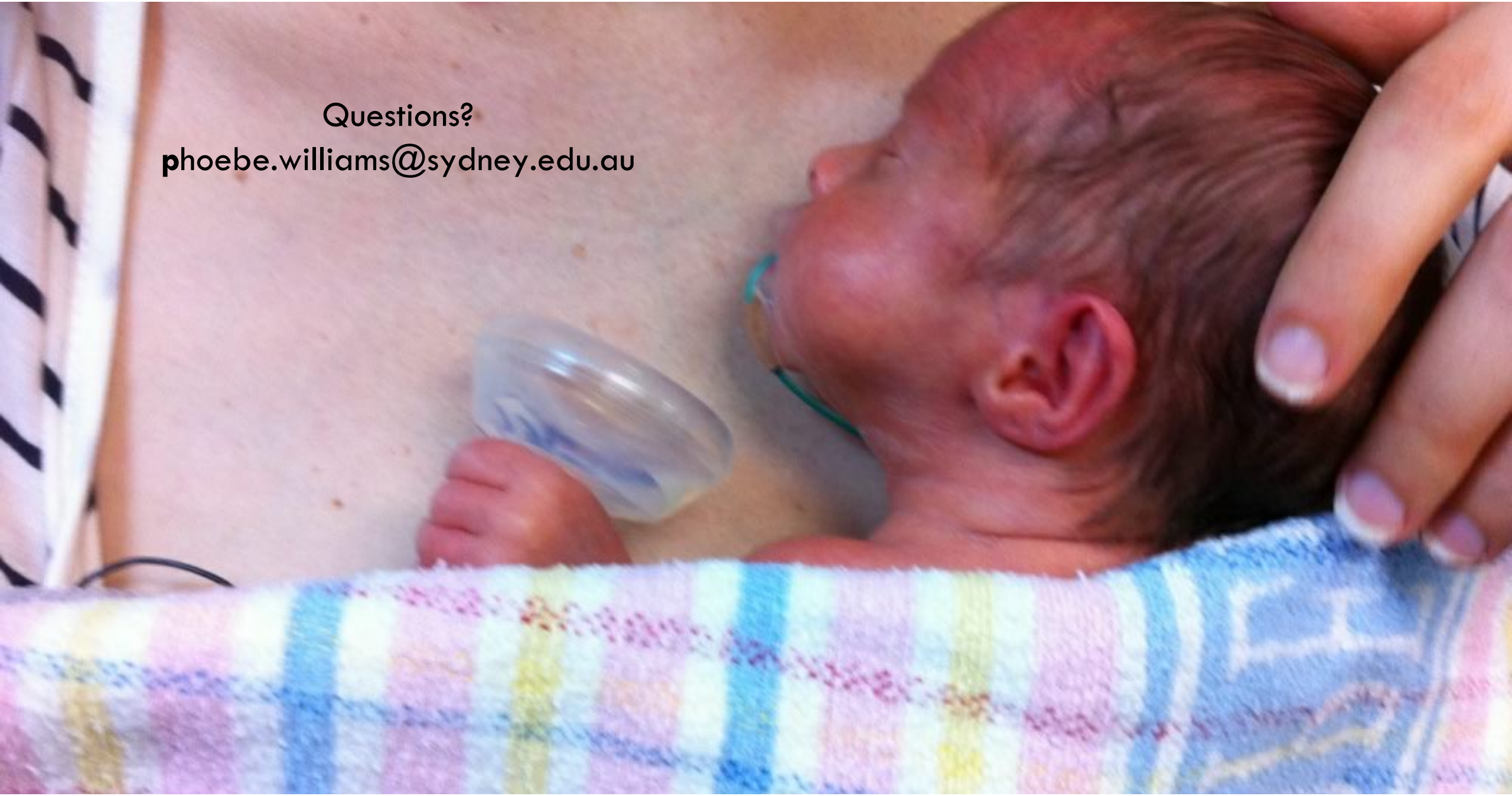
- Cefepime–taniborbactam
- Sulbactam–durlobactam

Noteworthy compounds

- Cefepime–zidebactam
- Aztreonam–avibactam

In summary:
What do we need for improved surveillance of neonatal infections?

- More data from low-income countries and community-based settings
- Consensus on a validated neonatal sepsis definition
- Improved diagnostics to remove the reliance on culture-based methods
  - Molecular methods, metagenomics
- Reporting of age of onset of neonatal infections as a continuous variable
  - To remove the paradigm of ‘EOS’ vs ‘LOS’



Questions?

phoebe.williams@sydney.edu.au