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2026

Neonatal Sepsis: Fighting Infection in the First Days of Life

44TH ANNUAL MEETING OF THE
EUROPEAN SOCIETY FOR
PAEDIATRIC INFECTIOUS DISEASES

Organised jointly by ESPID and the ESPID Foundation

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espidmeeting.org

Conflict of Interest

	No, Nothing to disclose
X	Yes, please specify

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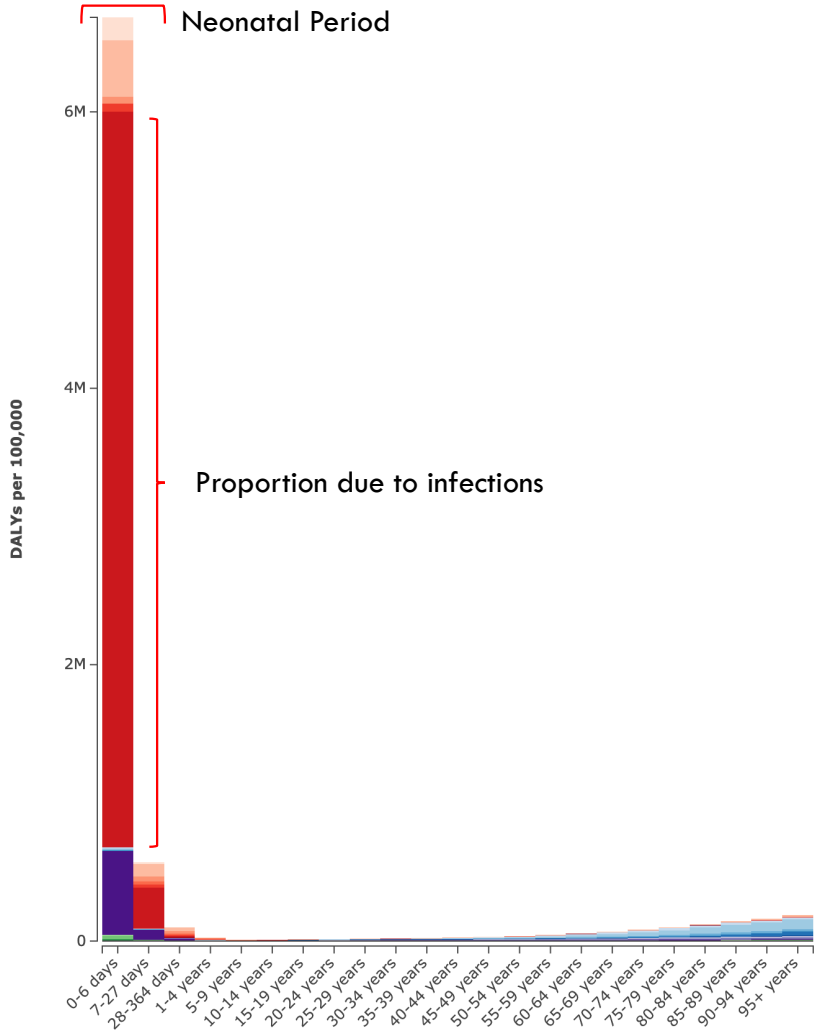
Medical Research Future Fund			X					

Neonatal Sepsis:
Fighting Infection in the First Days of Life

Outline

- Why does it matter?
- Why aren't we making progress?
- What limitations around diagnostics and management are hindering our ability to reduce neonatal sepsis?
- What can we do now, and what can we aim for in the future, to stop babies dying from infections?

The first week of life continues to account for the greatest risk of death and disability – largely due to infections



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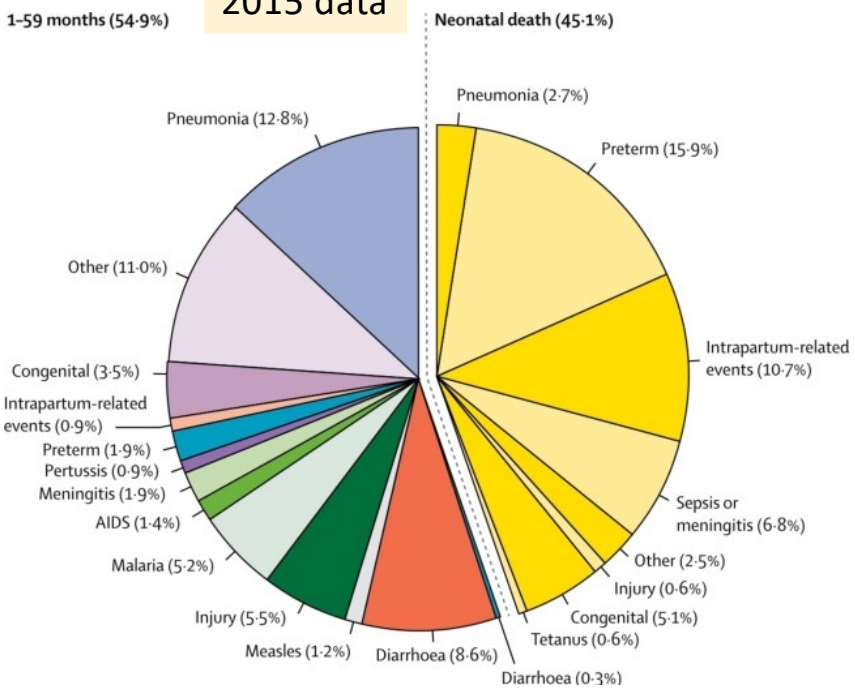
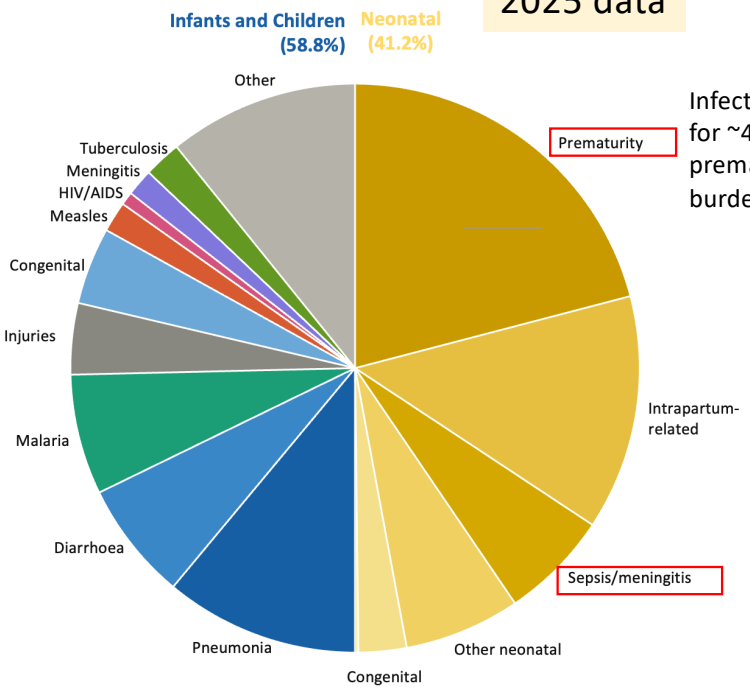
Institute for Health Metrics and Evaluation, 2019
https://vizhub.healthdata.org/gbd-compare/

Progress in Global <5 Mortality

2015 data



2025 data



Infection accounts for ~40% of prematurity burden

What progress have we made since 2015?

-Reduced pneumonia deaths by 18%

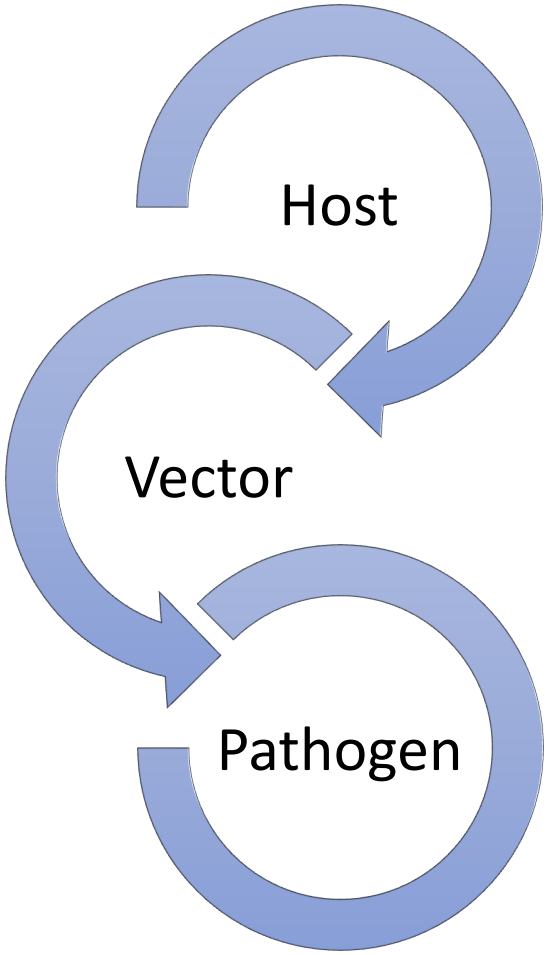
-Reduced diarrhoeal deaths by 28%

-Reduced HIV/AIDS deaths by 26%

-Stagnant progress in malaria and neonatal sepsis/meningitis

Sources: Liu *et al.* Lancet 2016. Global, regional, and national causes of under-5 mortality in 2000–15: WHO Data Platform; Global Under 5 mortality. Platform.who.int

Why are neonates so at risk of infection?



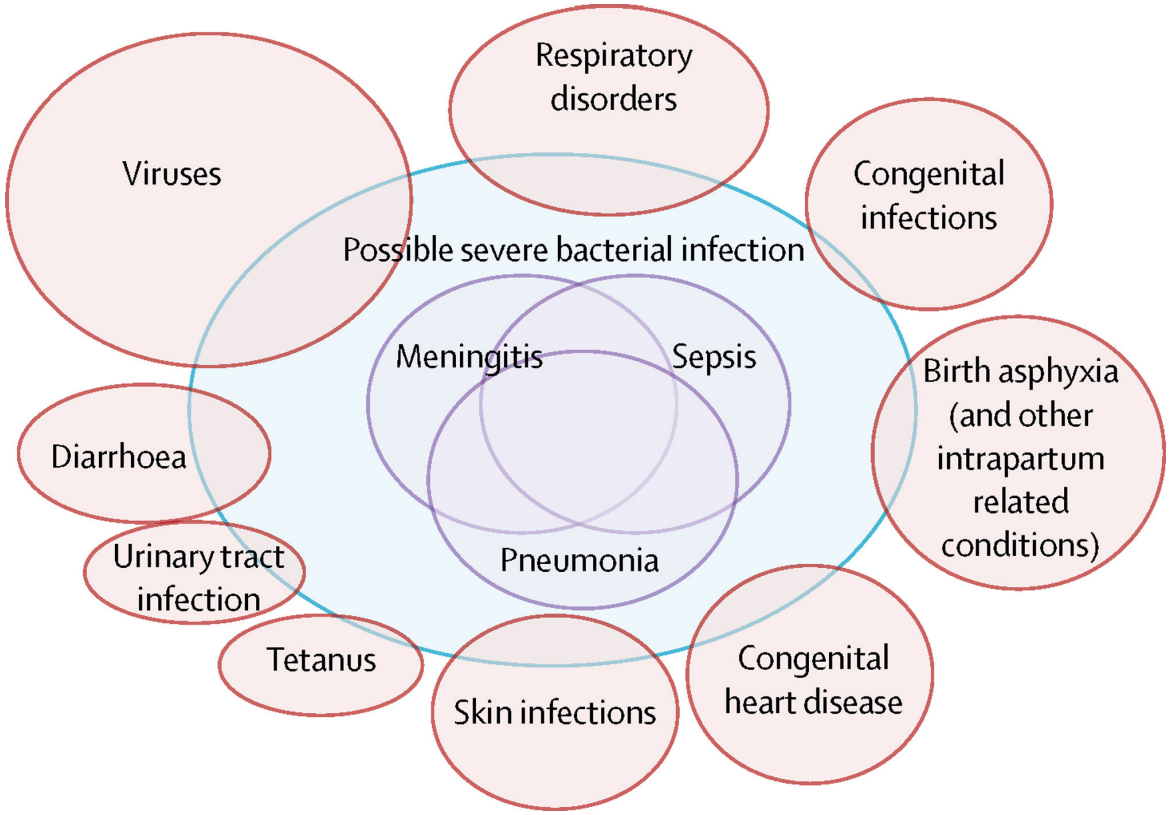
1. **Vulnerable host (esp. preterm):**
   - Immunologically immature: Decreased polymorphonuclear leucocyte and cell-mediate immune function
   - Less diverse microbiome: Particularly following exposure to intrapartum antibiotics

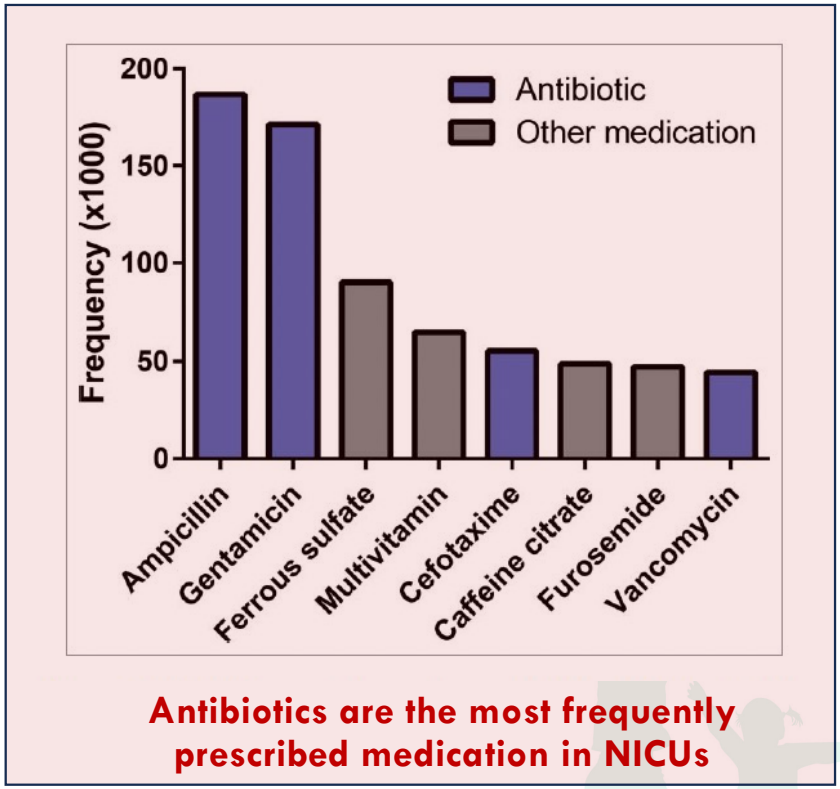
2. **Risk of hospital-acquired infections**
   - Multiple invasive procedures: ventilation, long line access
   - Prolonged hospitalisation → risk of exposure to multiple empirical courses of antibiotics, enhancing selective pressure → risk of MDR infections
   - Exposure to multiple caregivers: parents, carers, healthcare workers (colonisation risk)

3. **Rapidly rising gram-negative bacteria burden**
   - Plasmid-mediated resistance → spread of MDR infections
   - Dry antibiotic pipeline to treat MDR infections, particularly for neonates


What limitations in diagnostics and management are hindering our ability to reduce neonatal sepsis?

Neonatal sepsis is difficult to diagnose – and so we cautiously over-prescribe antibiotics





Antibiotics are the most frequently prescribed medication in NICUs

Neonatal sepsis is a heterogeneous clinical presentation, with symptoms that mimic many other serious conditions in infants

Seale *et al.* LID 2014
Clark *et al. Pediatrics*. 2006;117(6):1979-1987.

Neonatal Sepsis is Difficult to Diagnose and Difficult to Define

Blood cultures remain the gold standard of diagnosis, yet high rates of culture-negative sepsis abound, due to:

1. Challenges in obtaining adequate blood culture volumes in small, sick neonates
2. High rates of pre-exposure to intrapartum and postnatal antibiotics
3. Limited microbiological capacity in many health-care settings

Poor diagnostic tests + Overlap in signs & symptoms with other clinical conditions
→ Overuse of empiric antibiotics
→ Challenges in targeting treatment to microbiologically-confirmed diagnoses
→ Prolonged broad-spectrum therapy
→ Drives selection pressure & propagates AMR

Reliance on blood cultures reduces the inclusion of 'culture negative' infections in research

- Risks selection bias, as culture-negative infections are responsible for ~50% of all cases

As neonatal sepsis remains so difficult to diagnose, we rely on empirical antibiotics being efficacious

But are our EOS/LOS assumptions still accurate & appropriate?

The rules we inherited vs the evolving reality

1970s
EOS/LOS dichotomy established in US NICUs

1990s
GBS + *E. coli* entrenched as primary EOS pathogens (HIC data)

2005 2013
WHO Pocketbook: Amp + Gent as first-line globally

2015-2025
DeNIS, ANISA, BARNARDS, NeoObs & NeoSEAP studies identify high rates of MDR gram-negative infections as early as day one of life

Today
Global Guidelines remain
Local hospitals increasingly use broad-spectrum (carbapenem-based) therapy without clearer recommendations to treat MDR infections → propagates AMR

The founding assumption:

Classification*	Assumed pathogen(s)	Assumed acquisition	First-line empiric regimen
Early-onset sepsis (≤72h)	GBS, *E. coli*	Vertical (maternal)	Ampicillin + gentamicin
Late-onset sepsis (>72h)	*E. coli*, GBS, *S. aureus*, CoNS	Horizontal (environmental)	Amp/gent (or cloxacillin/vancomycin if MSSA/MRSA/CoNS suspected; amikacin if hospital-acquired)

*Classification based on historical surveillance data from HICs

Questioning the paradigm of 'EOS' and 'LOS'

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**

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

'What is increasingly obvious is that the historic delineation of early- and late-onset sepsis in an era of increasing antimicrobial resistance is perhaps out-dated."

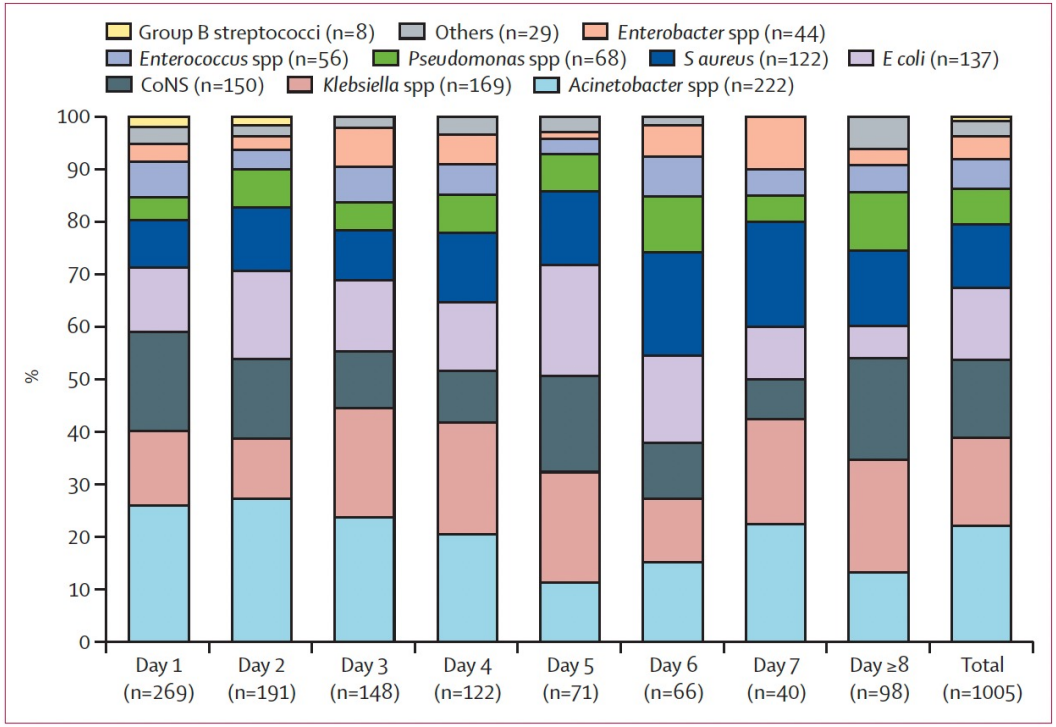
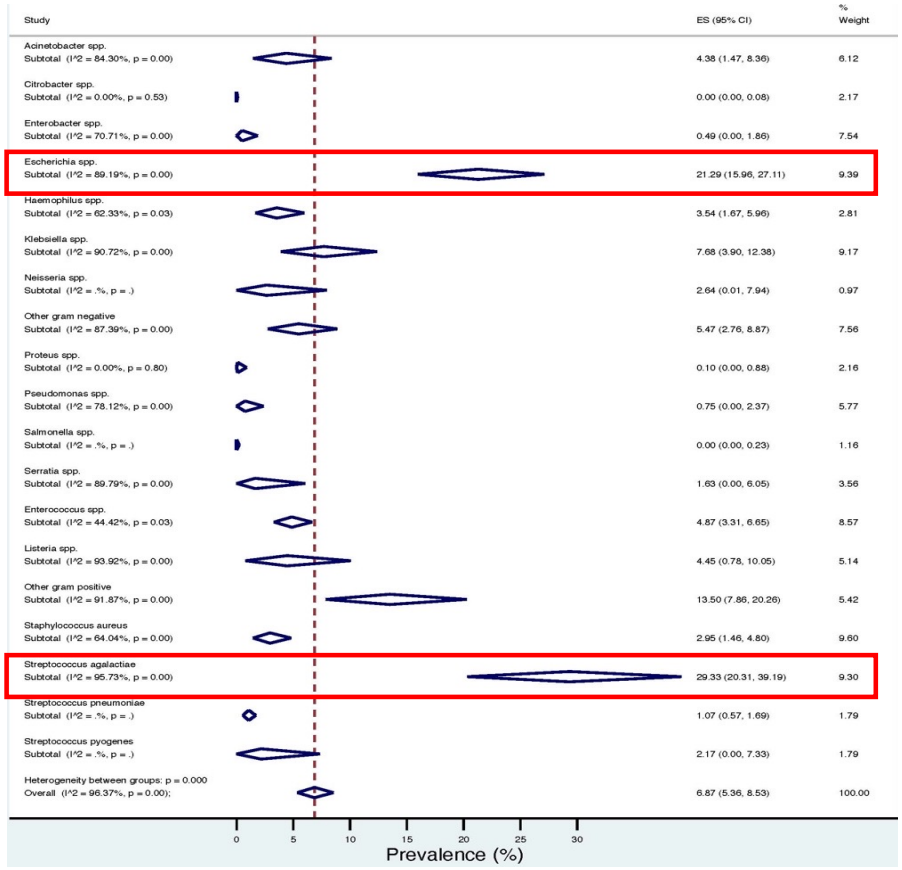


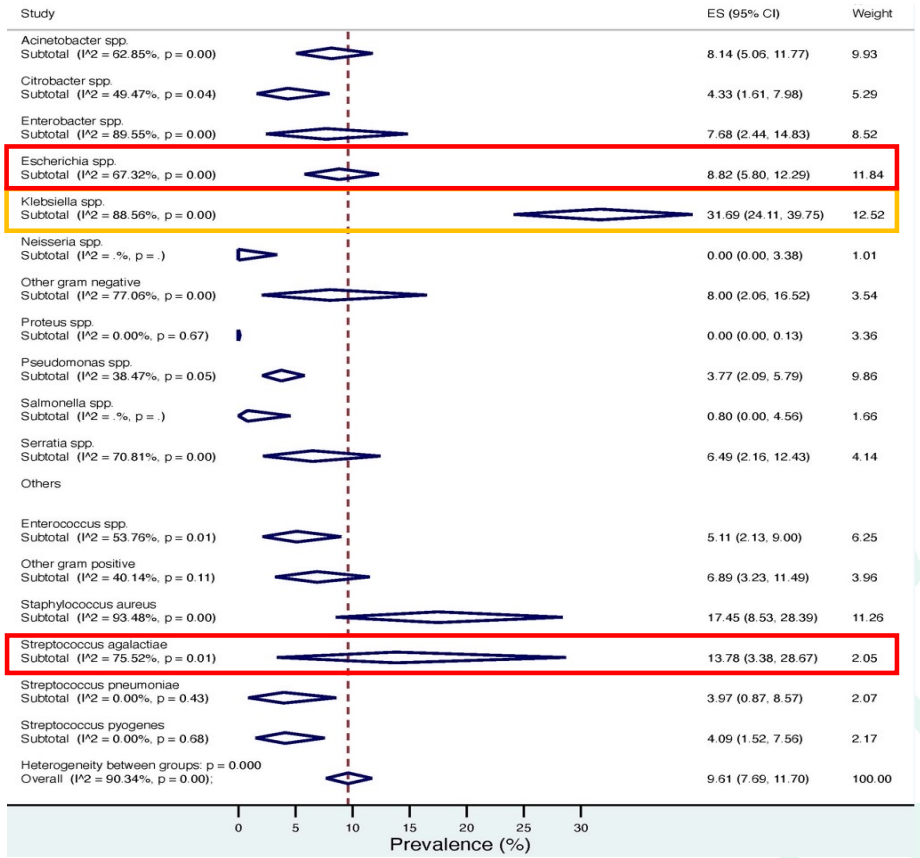
Figure 2: **Profile of pathogens isolated on different days of life**
CoNS=coagulase-negative staphylococci.

There are significant differences in the bacteria causing neonatal sepsis in lower vs upper-middle income countries

Upper-middle and high-income countries



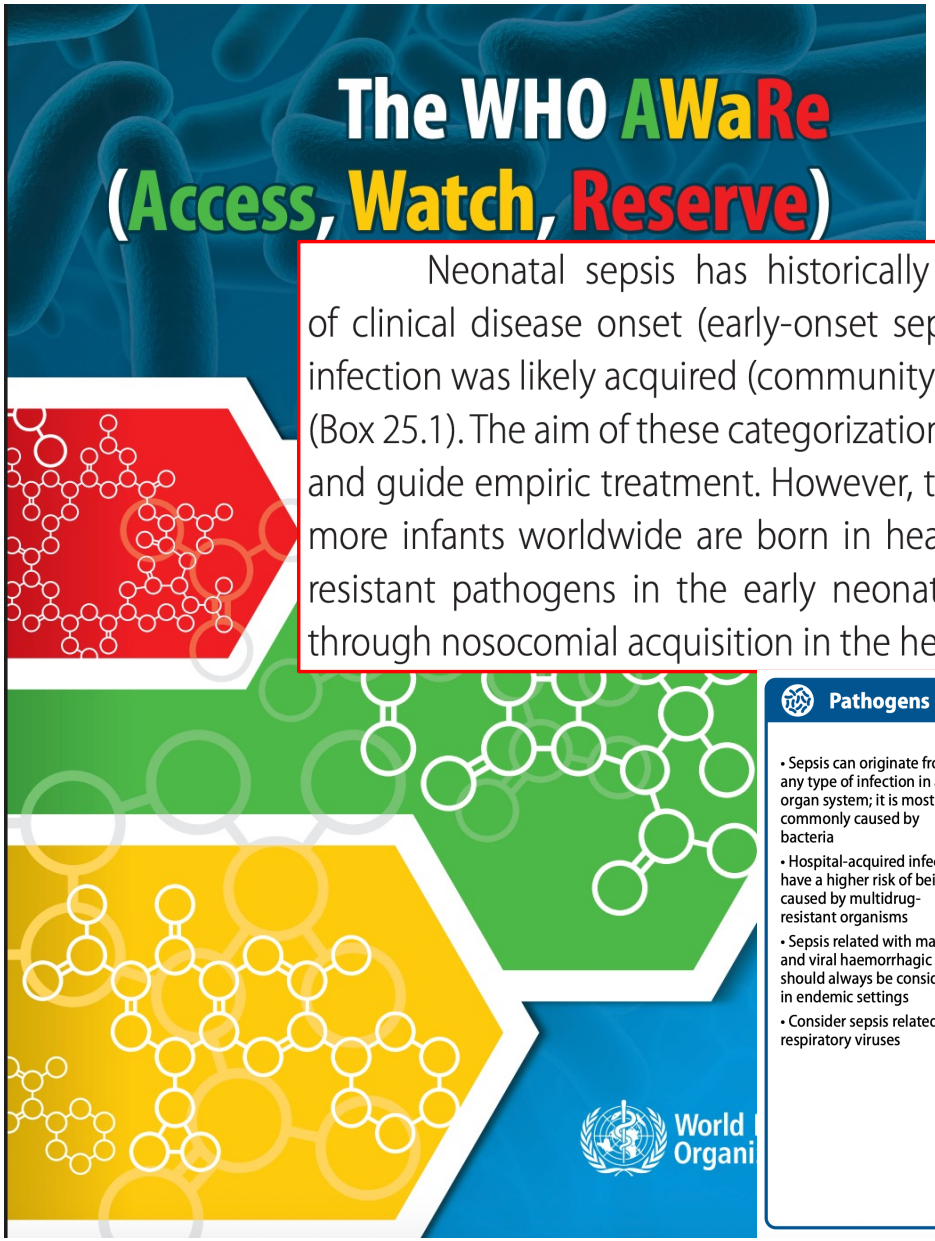
Low and lower-middle income countries



#E

Meta-analysis of species prevalence causative of EOS (%) in upper vs low- and lower-middle income countries

Harrison *et al.* PIDJ 2024



Neonatal sepsis has historically been categorized based on either the timing of clinical disease onset (early-onset sepsis or late-onset sepsis) or based on where the infection was likely acquired (community-acquired infection or hospital-acquired infection) (Box 25.1). The aim of these categorizations is to predict the most likely causative pathogens and guide empiric treatment. However, these categorizations have become less helpful as more infants worldwide are born in health care facilities and are exposed to multidrug-resistant pathogens in the early neonatal period, either acquired from their mother or through nosocomial acquisition in the health facility or hospital.

Pathogens Most Frequently Identified in Blood Cultures in Neonates with Sepsis

- Sepsis can originate from any type of infection in any organ system; it is most commonly caused by bacteria
- Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms
- Sepsis related with malaria and viral haemorrhagic fevers should always be considered in endemic settings
- Consider sepsis related with respiratory viruses

	Low and Middle Income Setting	High Income Setting
Community Acquired	• *Escherichia coli** • *Staphylococcus aureus* (including MRSA) • *Klebsiella* spp.* More rare • *Acinetobacter* spp.* • *Streptococcus agalactiae* • *Streptococcus pyogenes* • *Streptococcus pneumoniae*	• *Escherichia coli** • *Staphylococcus aureus* (including MRSA) • *Streptococcus agalactiae*
Hospital Acquired	• *Klebsiella* spp.* • *Escherichia coli** • *Acinetobacter* spp.* • *Staphylococcus aureus* (including MRSA) • Other Gram-negative bacteria* • *Enterococcus* spp.	• *Escherichia coli** • *Klebsiella* spp.* • *Staphylococcus aureus* (including MRSA) • Other Gram-negative bacteria* • *Enterococcus* spp.

**Including multidrug-resistant strains such as those producing ESBL and carbapenemases*

First Choice

ACCESS Ampicillin 50 mg/kg/dose **IV**
- ≤1wk of life: q12h
- >1wk of life: q8h

OR

ACCESS Benzylpenicillin 30 mg/kg/dose (50 000 IU/kg/dose) q8h **IV**

COMBINED WITH

ACCESS Gentamicin 5 mg/kg/dose q24h **IV**

Second Choice

WATCH Cefotaxime 50 mg/kg/dose q8h **IV**

OR

WATCH Ceftriaxone 80 mg/kg/dose q24h **IV**

OR

ACCESS Cloxacillin 25-50 mg/kg/dose q12h **IV**

Cloxacillin is a useful second-choice option when an infection caused by S. aureus is suspected (in community settings with high MRSA prevalence, consider vancomycin instead). If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used

COMBINED WITH

ACCESS Amikacin 15 mg/kg/dose q24h **IV**

Amikacin would mostly be used as a treatment for infections caused by Gram-negative bacteria and when antibiotic-resistant bacteria are suspected

In settings with high prevalence of resistance, particularly for suspected health care-associated infections, a broad-spectrum antibiotic with activity against Gram-negative bacteria should also be considered (e.g. piperacillin+tazobactam)

How and when are babies acquiring these pathogens?

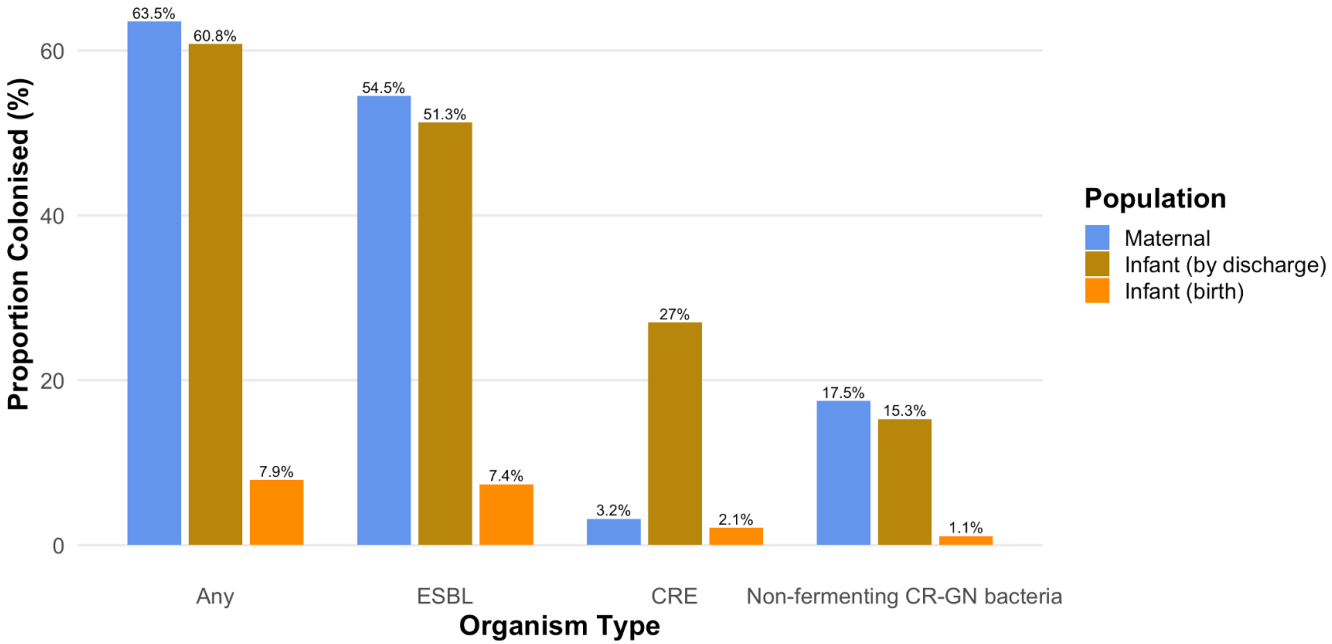


Figure 1 *Overall proportion of maternal and infant colonisation with gram-negative bacteria, by resistance mechanism type.*

Note: ESBL = extended-spectrum beta-lactamase producing; CRE = carbapenem-resistant Enterobacterales; CR-GN = carbapenem-resistant non-fermenting bacteria (*Acinetobacter* spp., *Pseudomonas* spp.)

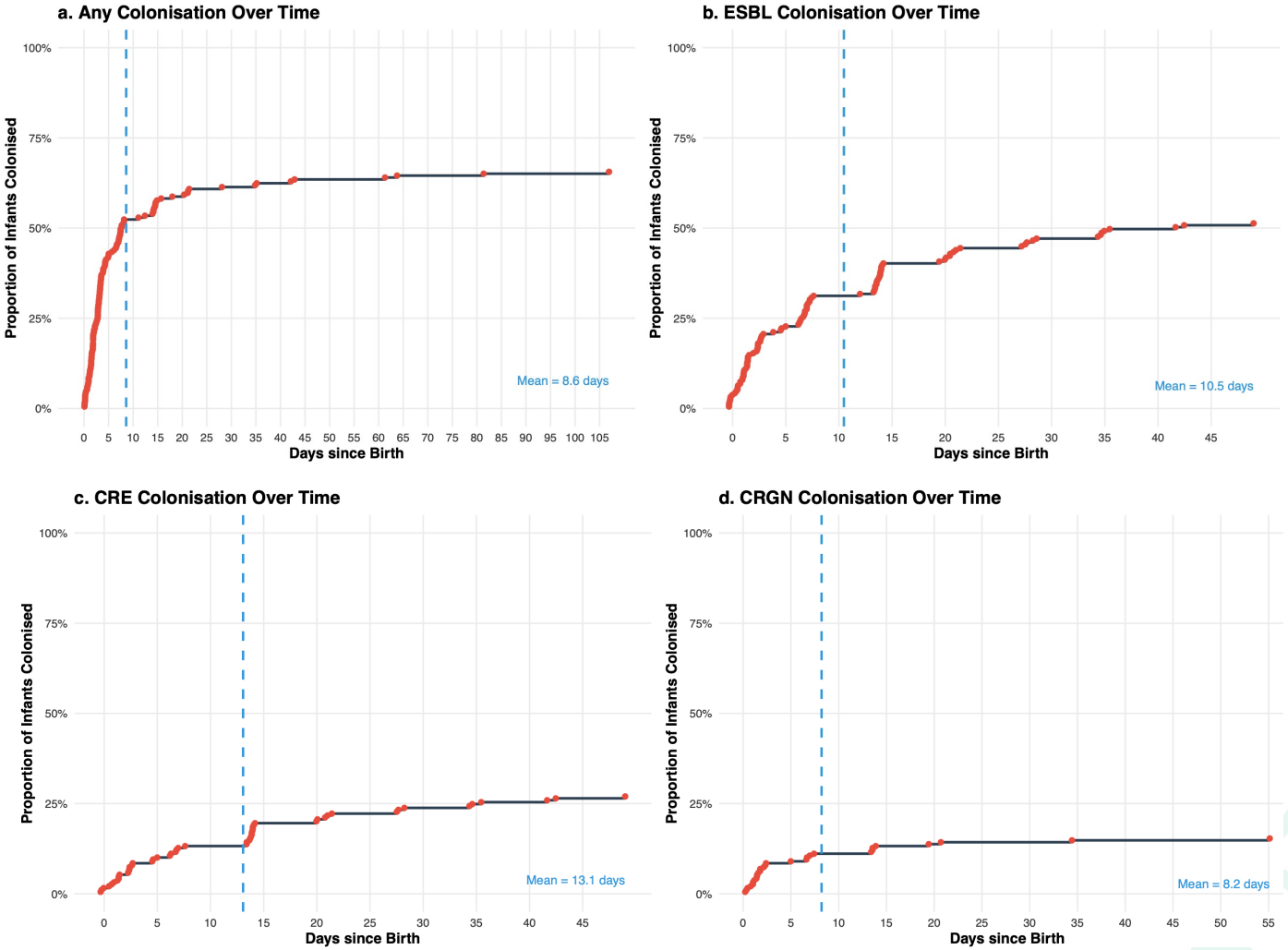
ESBL colonisation is common in mothers at delivery, yet CRE colonisation is rare

Neonates admitted to the NICU quickly become colonised with CREs, with 1 in 4 positive by discharge

n=189 mother-infant dyads swabbed at delivery, then q72-hourly until discharge; tertiary NICU in Jakarta, Indonesia

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific

How and when are babies acquiring these pathogens?



Kaplan–Meier curves summarising the cumulative time to neonatal colonisation of 189 hospitalised neonates, with:

a. any resistant gram-negative bacteria

b. ESBL-producing bacteria

c. carbapenem-resistant Enterobacterales

d. carbapenem-resistant gram-negative (non-fermenting) bacteria (including *Acinetobacter* spp. and *Pseudomonas* spp.)

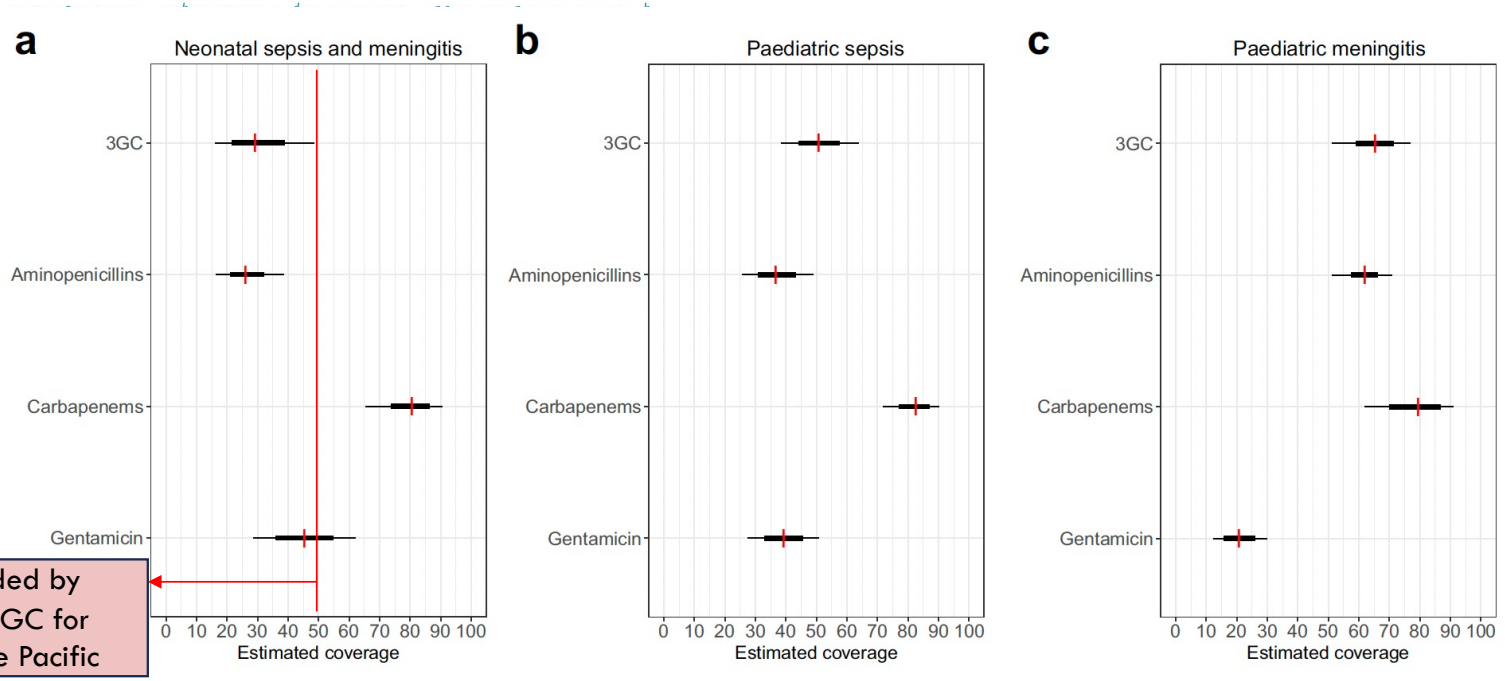
What is the likelihood the currently-recommended empirical regimens are efficacious in treating neonatal sepsis?

Findings from the NeoSEAP study, 2024

Coverage gaps in empiric antibiotic regimens used to treat serious bacterial infections in neonates and children in Southeast Asia and the Pacific

Phoebe C. M. Williams,[a,b,c,*] Mark Jones,[a] Th
Priyali Wijeratne,[b] Anousone Douangnouvon

[a]Faculty of Medicine, School of Public H
[b]Department of Infectious Diseases, Sydr
[c]Sydney Institute of Infectious Diseases (
[d]Department of Infectious Diseases, Roy
[e]Department of Global Health, London S
[f]Lao-Oxford Wellcome Trust Research Ur
[g]Centre for Tropical Medicine and Globa
[h]Cambodia Oxford Medical Research Uni



<50% coverage provided by ampicillin/gentamicin/3GC for neonates in SE Asia & the Pacific

Fig. 2: Coverage estimates by syndrome and antibiotic. Note: 3GC = Third-generation cephalosporins (ceftriaxone, cefotaxime); aminopenicillin incorporates ampicillin and amoxicillin non-susceptibility data, and carbapenem incorporates published non-susceptibility data for both meropenem and imipenem. The thin and thick lines correspond to the 80% and 50% credible intervals.

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We're currently stuck in a perpetuating cycle

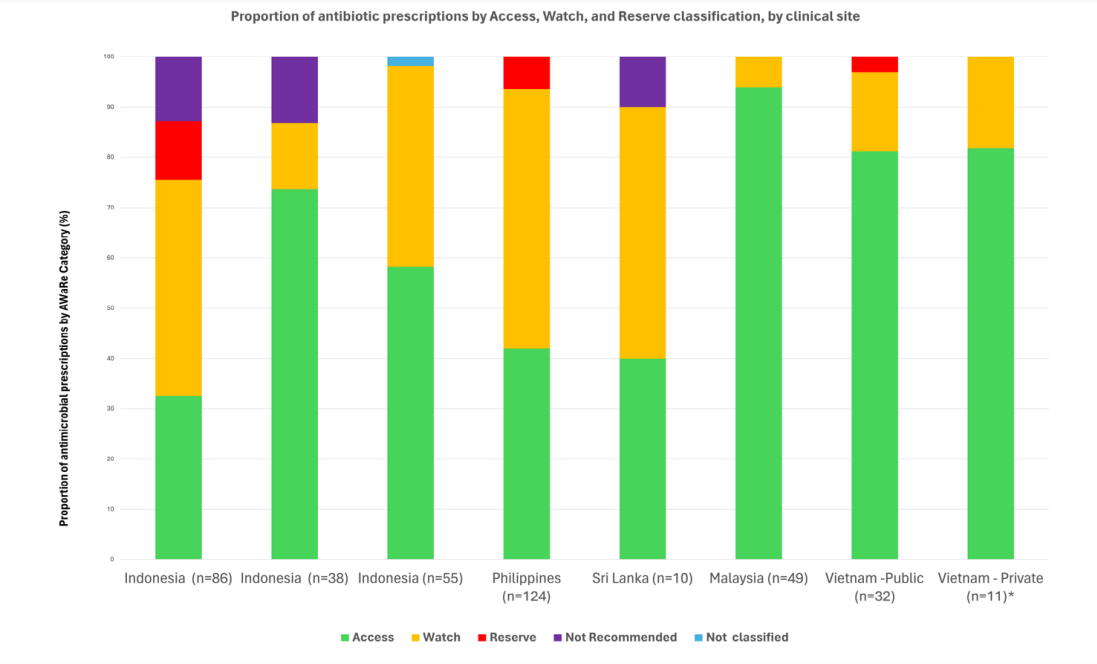
Rapidly rising prevalence of MDR gram-negative bacteria causing neonatal sepsis

→ High rates of broad-spectrum empiric antibiotic use

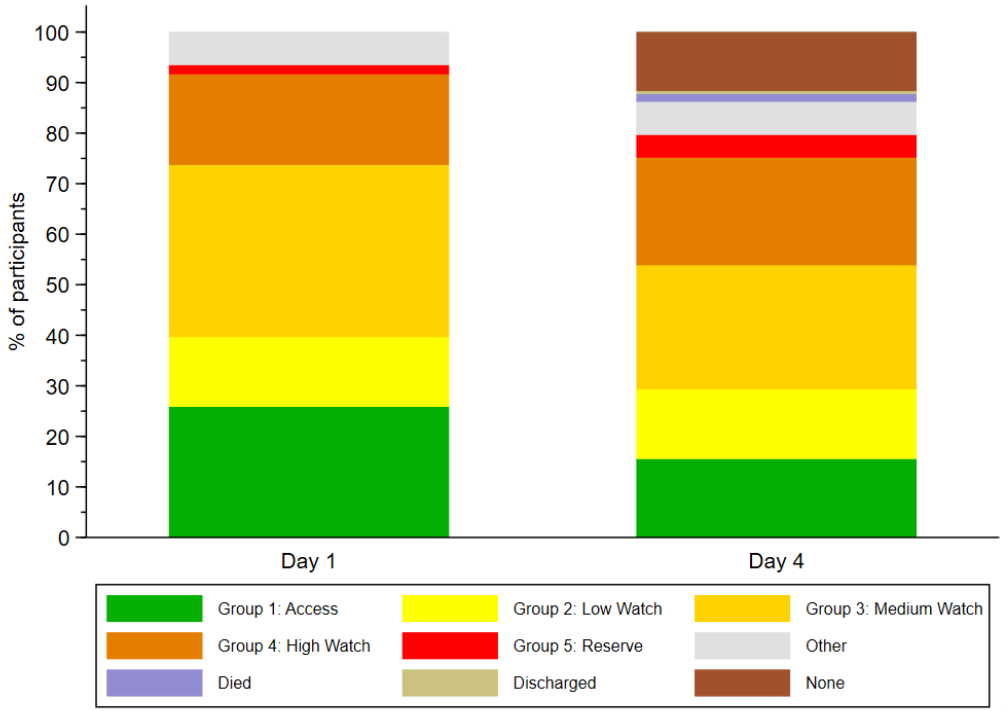
→ Drives selection pressure

→ Further propagates AMR

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific



Supplementary Figure 3. Proportion of antibiotic prescriptions by AWaRe Classification by clinical site.
*Vietnam private hospital data pooled secondary to low prescribing frequency.



NeoSEAP study

- High rates of 'Watch' and 'Reserve' antibiotics prescribed
- Evolving carbapenem resistance & colistin resistance in gram-negative pathogens

NeoOBS study: Escalation was common; de-escalation was rare

- Most common empirical therapy combinations prescribed:
  1. Meropenem+vancomycin (n=438, 14%)
  2. Ceftazidime+amikacin (n=435, 14%)
  3. Piperacillin/tazobactam+amikacin (n=410, 13%)

Harrison et al 2025 PIDJ; Russell et al. PLOS Medicine 2023.


What can we do now
and what can we aim for in the future
to stop babies dying from infections?

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1. Improve our surveillance data

i. To ensure our empiric guidelines remain efficacious; and

ii. To reduce broad-spectrum empirical prescribing clinicians are needing to utilise, without better guidelines

The literature currently predominates with:

- Data from high-income countries
- Biased towards reporting of hospital-acquired infections

To truly understand neonatal sepsis, we need:

- Data from resource-constrained healthcare settings
- Community-acquired infections

2. Cease antibiotics as soon as possible

- Cultures before any empirical treatment
- Reduce redundant (double) coverage
- Stop antibiotics after 5 to 7 days if culture-negati and clinically improving
- Target therapy where possible

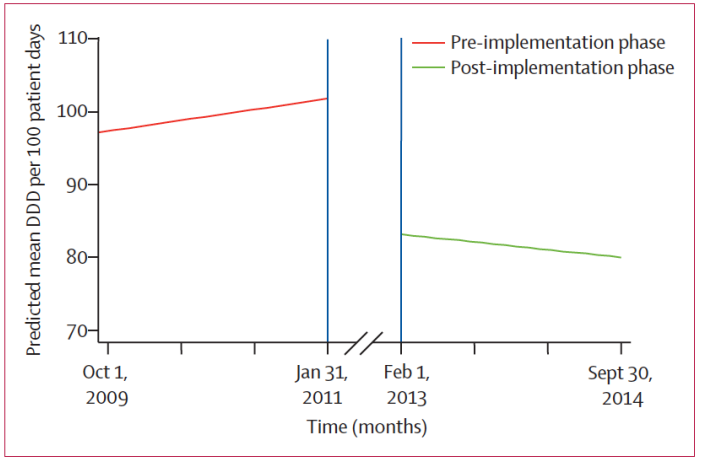


***Figure 3*: Predicted mean antibiotic consumption for the pre-implementation and post-implementation phases**
Mean antibiotic consumption is measured in defined daily doses (DDDs) per 100 patient–days. More detail is available in the appendix.

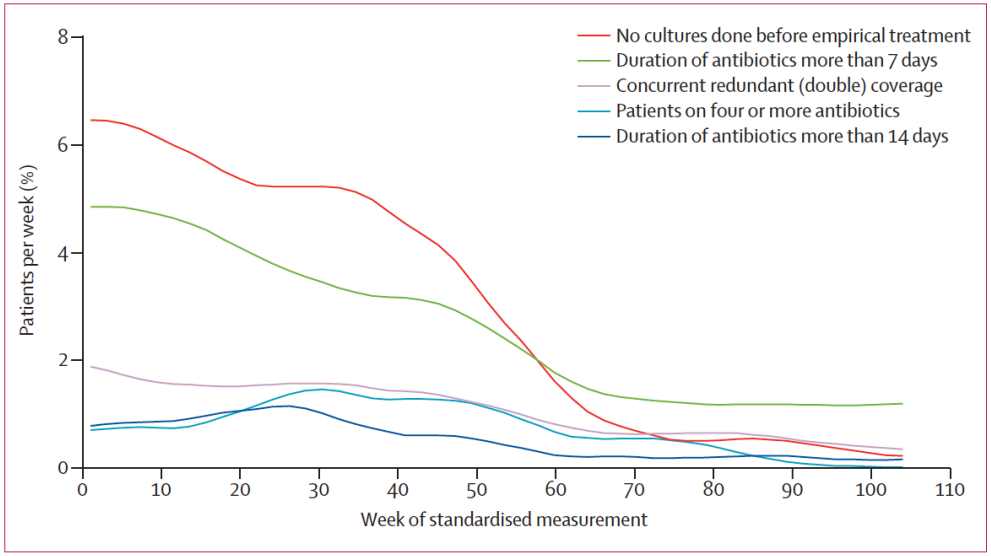


***Figure 4*: Local polynomial smoothed curves for the five parameters targeted for improvement (weeks 1–104)**
More detail is available in the appendix.

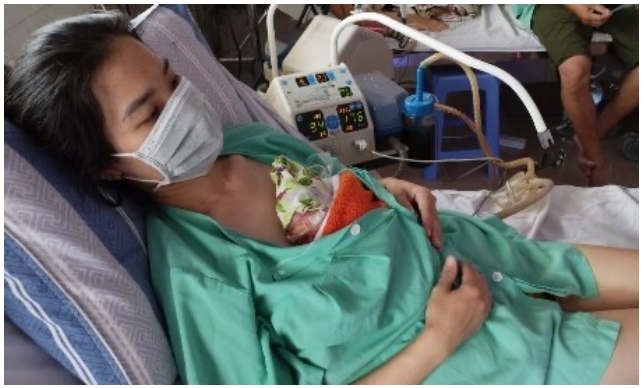
Antimicrobial stewardship across 47 South African hospitals: an implementation study

*Adrian J Brink, Angeliki P Messina, Charles Feldman, Guy A Richards, Piet J Becker, Debra A Goff, Karri A Bauer, Dilip Nathwani, Dena van den Bergh, on behalf of the Netcare Antimicrobial Stewardship Study Alliance**

Summary

3. Immediate and continuous Kangaroo Mother Care (KMC)

especially for premature and LBW neonates



Open access Original research

BMJ Open Quality

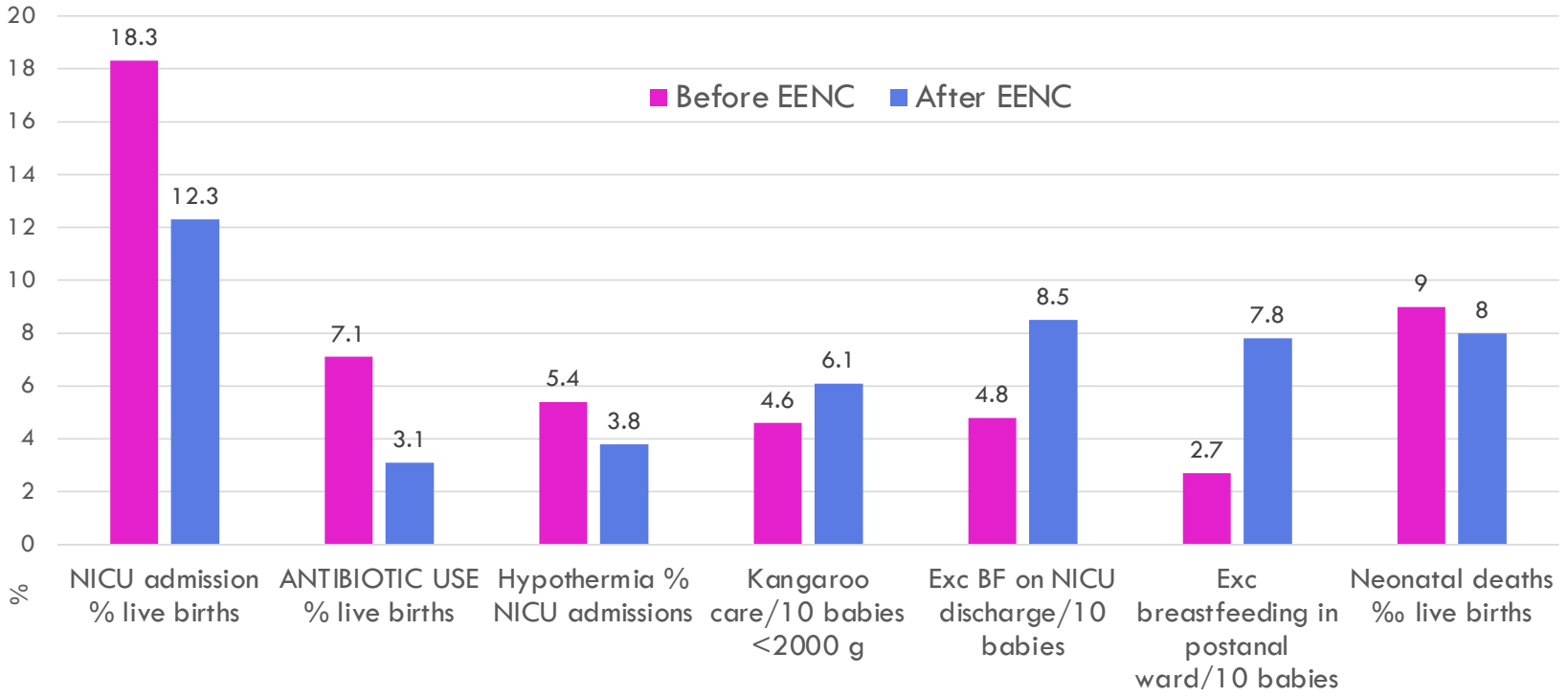
Early essential newborn care is associated with improved newborn outcomes following caesarean section births in a tertiary hospital in Da Nang, Vietnam: a pre/post-intervention study

Hoang Thi Tran ,[1,2] John Charles Scott Murray,[3] Howard Lawrence Sobel,[3] Priya Mannava,[3] Le Thi Huynh,[1,2] Phuong Thi Thu Nguyen,[1,2] Hoang Thi Nam Giang,[2] Tuyen Thi Mong Le,[4] Tuan Anh Hoang,[5] Vinh Duc Nguyen,[5] Zhao Li,[3] Nga Thi Quynh Pham[6]

<u>Da Nang Women and Children's Hospital, Vietnam:</u>

Immediate KMC care is now routine for **all** neonates

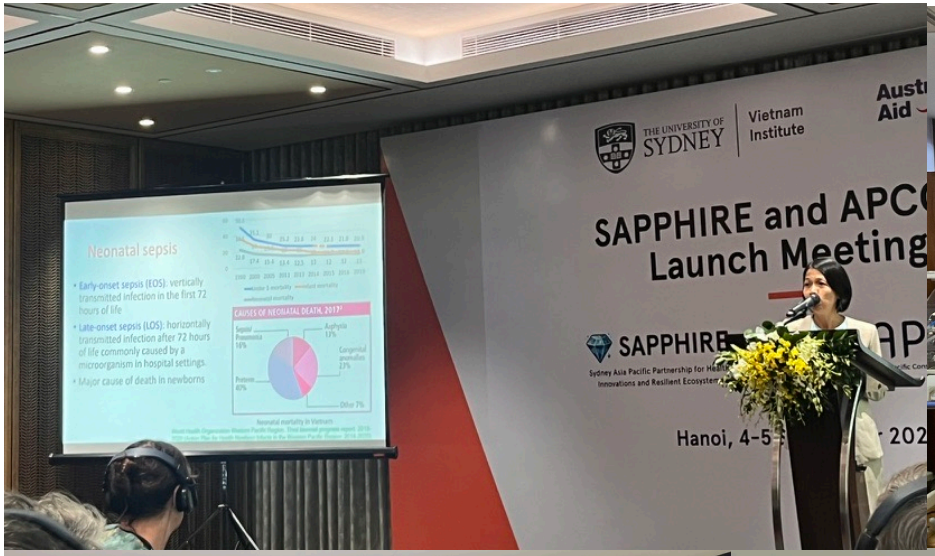
- ⇩antibiotic use
- ⇩NICU admission
- ⇩sepsis incidence
- ⇩neonatal mortality
- ↑ Excl breastfeeding (Immunoglobulin, microbes, cytokines → promotes neonatal immune development



Immediate and continuous Kangaroo Mother Care (KMC)

especially for premature and LBW neonates

NEOSEAP
Neonatal Sepsis in Southeast Asia and The Pacific



4. Focus our research efforts on the licensing of antibiotics that will treat the pathogens causative of neonatal sepsis

ie, with coverage against MBLs

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 Nis 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

Antibiotics needed to treat multidrug-resistant infections in neonates

Phoebe CM Williams,[a] Shamim A Qazi,[b] Ramesh Agarwal,[c] Sithembiso Velaphi,[d] Julia A Bielicki,[e] Sumathi Nambiar,[f] Carlo Giaquinto,[g] John Bradley,[h] Gary J Noel,[i] Sally Ellis,[j] Seamus O'Brien,[j] Manica Balasegaram[j] & Michael Sharland[e]

Table 3. **Potential neonatal priority antibiotics for accelerated development, 2022**

Priority antibiotic in development	Priority pathogens against which activity is anticipated	Development stage and clinical indication	Other benefits	Limitations
Cefiderocol – a siderophore cephalosporin that forms a complex with iron which is actively transported into the bacterial cell via iron receptors	• Activity against ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* • Activity against carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, although warnings exist against its use for the latter infections in critically ill patients • Activity against gram-negative carbapenemases, including class B MBLs	• Phase III trial in adults (complicated urinary tract infection and hospital- and ventilator-acquired pneumonia in adults) – complete • Phase II trial in children > 3 months – recruiting	• Likely cerebrospinal fluid penetration • Predictable pharmacokinetic profile[34]	Requires infusions over 3 hours, three times a day
Cefepime + taniborbactam – anti-pseudomonal fourth-generation cephalosporin plus a new cyclic boronate β-lactamase inhibitor	• Activity against ESBL-producing *E. coli* and *K. pneumoniae* • Activity against gram-negative carbapenemases, including clinically relevant class B MBLs • Activity against carbapenem-resistant *P. aeruginosa*	• Phase III trial in adults – complete (complicated urinary tract infection)	• Likely cerebrospinal fluid penetration	Possible neurotoxicity effects associated with cefepime
Sulbactam + durlobactam – dual β-lactamase inhibitor combination therapy	• Activity against MDR *A. baumannii* complex • Activity against class A, C and D β-lactamase producing Enterobacteriaceae	• Phase III trial in adults – complete	• Likely cerebrospinal fluid penetration	Requires infusions over 3 hours, four times a day

ESBL: extended-spectrum β-lactamase; MBL: metallo-β-lactamase; MDR: multidrug resistant.

5. Ensure the research is conducted in the regions where the burden is greatest

"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 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 might the future (need to) hold to reduce the ongoing burden of neonatal sepsis?

1 Improved laboratory capacity

in resource-constrained healthcare settings

2 Enhancing our understanding of the microbiome, and how this relates to clinical outcomes

- Identify risk factors and protective factors to promote a healthy neonatal microbiome at reduced risk of sepsis

3 Culture-independent diagnostics

- Rapid point-of-care testing
- Validation of multiplex PCR panels – and ensuring affordability and accessibility (and stewardship)
- WGS for outbreak tracing
- Metagenomics to distinguish bacterial vs viral sepsis & non-infectious conditions

4 Standardised sepsis definitions

- to improve surveillance data and clinical trials
- Validated Bayesian decision-support tools to assist with both sepsis diagnosis *and* understanding the need to prescribe broad-spectrum antibiotics in neonates at higher risk of an MDR infection

5 Improved prevention

- Vaccines against GBS, *E coli* and *Klebsiella* spp.
  - Supported by the Gates Foundation

6 Access to effective drugs to treat MDR sepsis

- Affordable for all healthcare settings
- With accompanying stewardship programs

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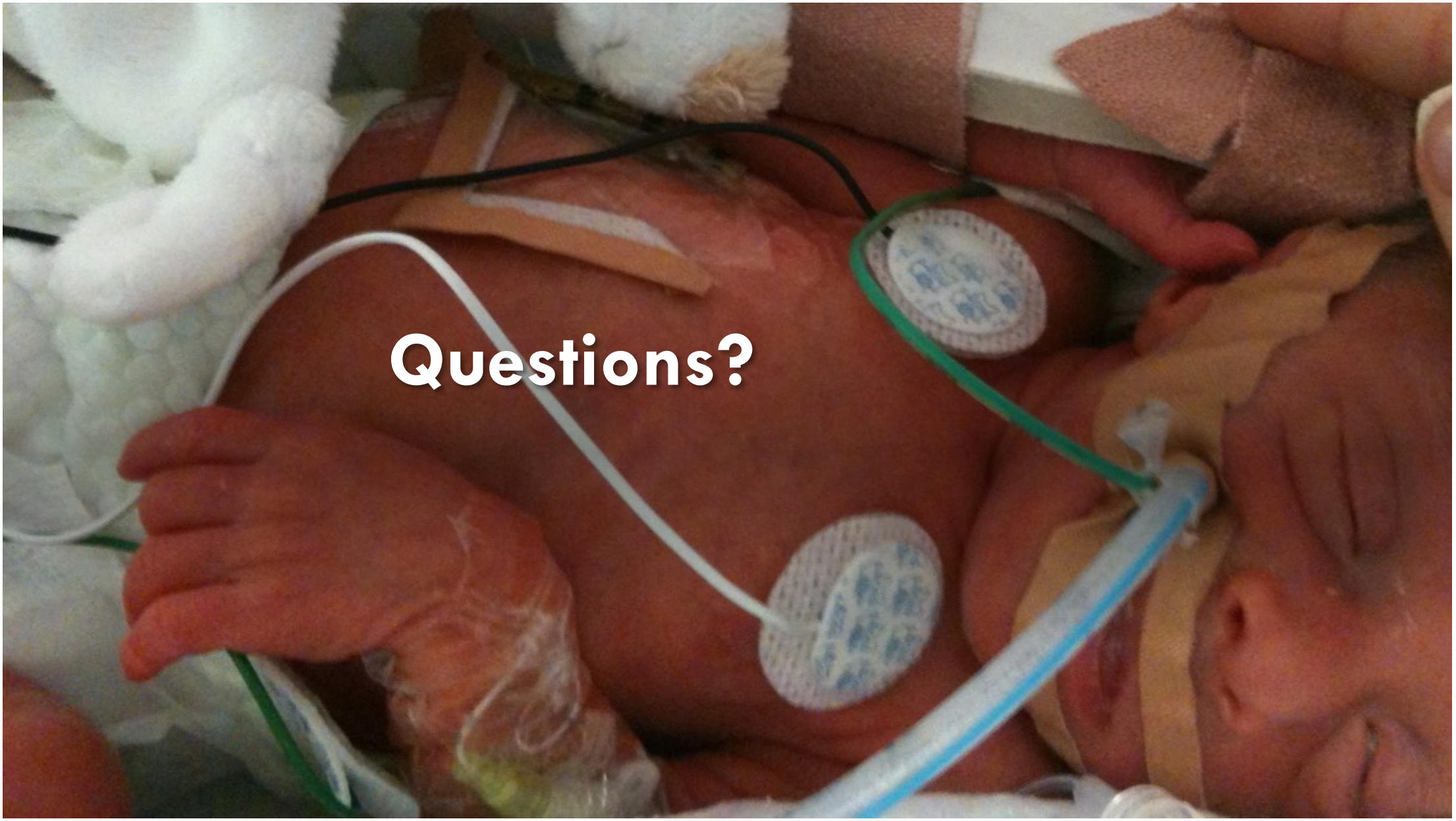
Questions?