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PIDRG Paediatric Infectious Diseases Research Group

GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT (GARD) PARTNERSHIP

Developing new antibiotic treatments, promoting responsible use, and ensuring access for all

Addressing Antibiotic Treatment of Neonatal & Infant SBI in the Context of High Multidrug-Resistant Gram-negative Bacteria

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on behalf of PENTA-ID

INSTITUTE FOR INFECTION & IMMUNITY

Neonatal Infection:
"A major burden with minimal funding"

- Further progress in decreasing child mortality depends on reducing the 2·9 m neonatal deaths each year, around a quarter of which are directly due to infection

- 6·9 m neonates required treatment for possible serious bacterial infection in 2012 in high-burden settings

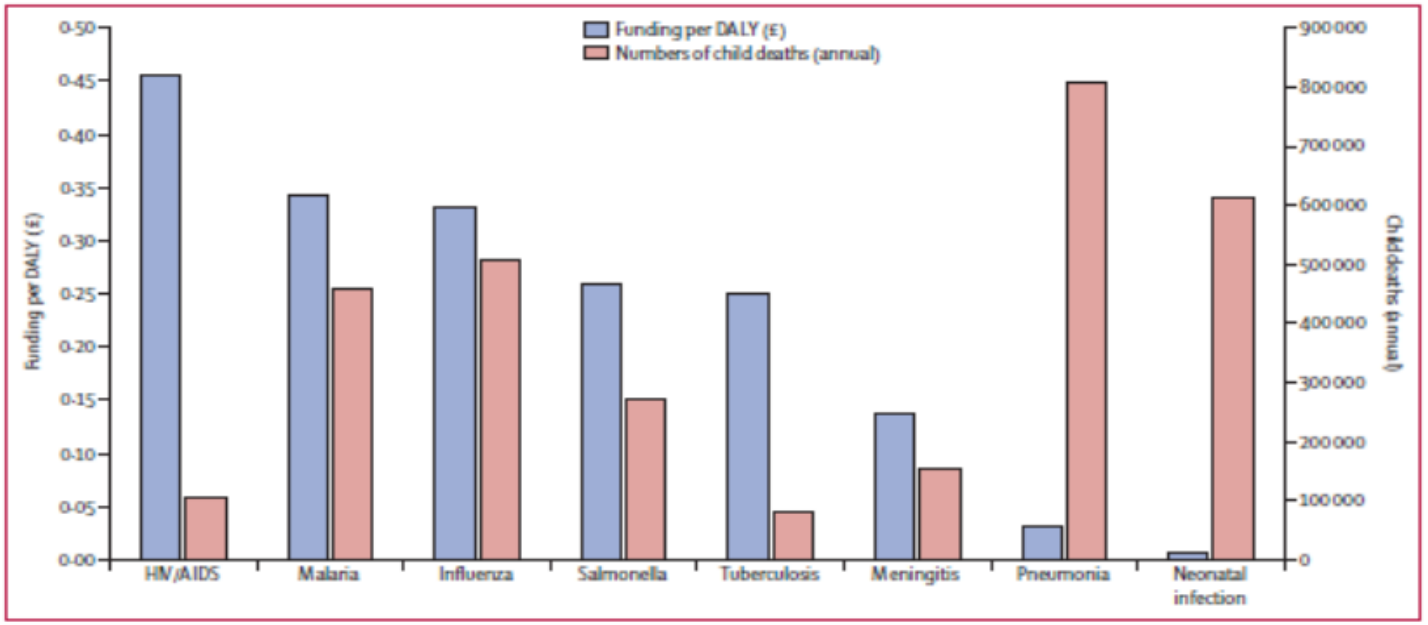

Figure: UK research investment per DALY per year for infections and number of child deaths in a year for those infections
The metric illustrates relative levels of investment for each infection and used the following equation (sum investment 1997–2009 / DALYs 2010[9]) / 13 (number of years of investment included). The number of child deaths are given based on Global Burden of Disease estimates for 2013.[11,10]

Lancet 2015

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Burden of AMR in neonates

Table 2 – Median % Antimicrobial Resistance of Gram-negative bacteria in Neonates in Low/Low-Middle Income Countries

	N	Ampicillin Median % resistance (IQ range)	Gentamicin Median % resistance (IQ range)	Chloram-phenicol Median % resistance (IQ range)	Cotrimoxazole Median % resistance (IQ range)	Cipro-floxacin Median % resistance (IQ range)	Ceftriaxone Median % resistance (IQ range)
Asia							
E. coli	89	96.9 (71.2-100)	83.3 (56.1-100)	0 (0-43.8)	31.3 (0-90.6)	4.5 (0-44.5)	80.2 (75.3-100)
Klebsiella	44	93.8 (57.1-100)	68.8 (18.6-95.1)	41.9 (10.0-67.8)	16.7 (0-55.2)	32.5 (15.8-70.6)	84.4 (45.0-95.1)
Enterobacter	78	79.6 (16.7-98.1)	22.2 (0-70.4)	0 (0-44.4)	0 (0-63.0)	5.6 (0-47.2)	74.1 (0-100)
Acinetobacter	98	0 (0-51.7)	38.7 (0-86.7)	0 (0-43.3)	0 (0-35.0)	10.3 (0-43.3)	61.1 (25.0-100)
Pseudomonas	74	15.0 (0-57.5)	9.4 (0-38.1)	0 (0-32.2)	0 (0-57.1)	5.6 (0-24.2)	53.8 (11.9-65.0)
Africa							
E. coli	37	92.9 (0-100)	42.9 (0-68.2)	NR	0 (0-77.3)	0 (0-4.5)	0 (0-50.0)
Klebsiella	109	100 (100)	54.5 (0-68.0)	NR	0 (0-80.0)	0 (0-10.0)	50.0 (0-86.5)

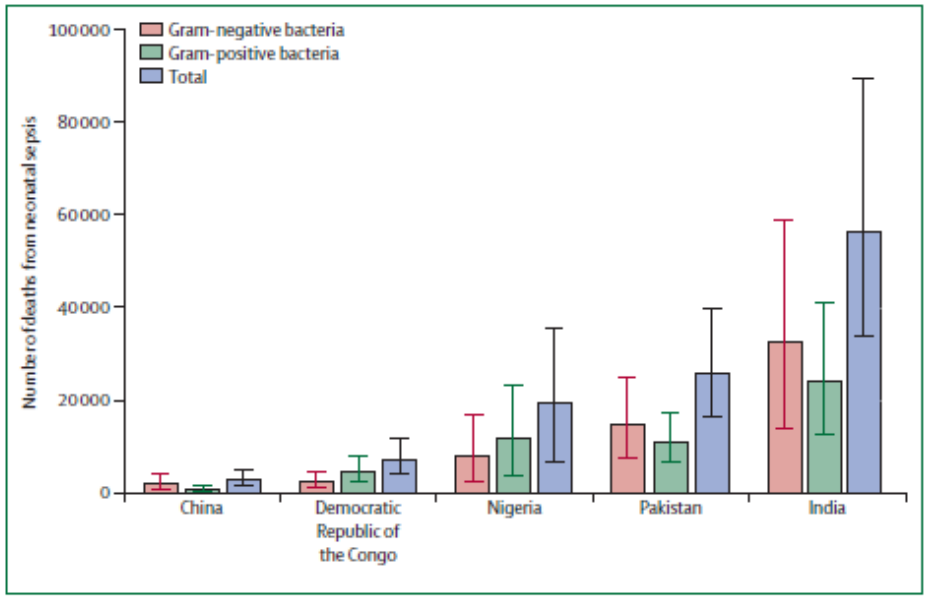

Figure 2: **Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries**

Bars represent maximum and minimum values from Latin Hypercube Sampling model in appendix.

Lancet 2015

- Retrospective observational study, 4 years (2007 – 2010), Kolkata, India:

MDR in **50%**; carbapenem resistance in 30% of Acinetobacter spp; pan-resistance in 5

Paediatrics and International Child Health 2014

- MDRGN: a major cause of **EO** & LO neonatal sepsis in India & widespread in the community.

Arch Dis Child Fetal Neonatal Ed 2012;97:F182–7

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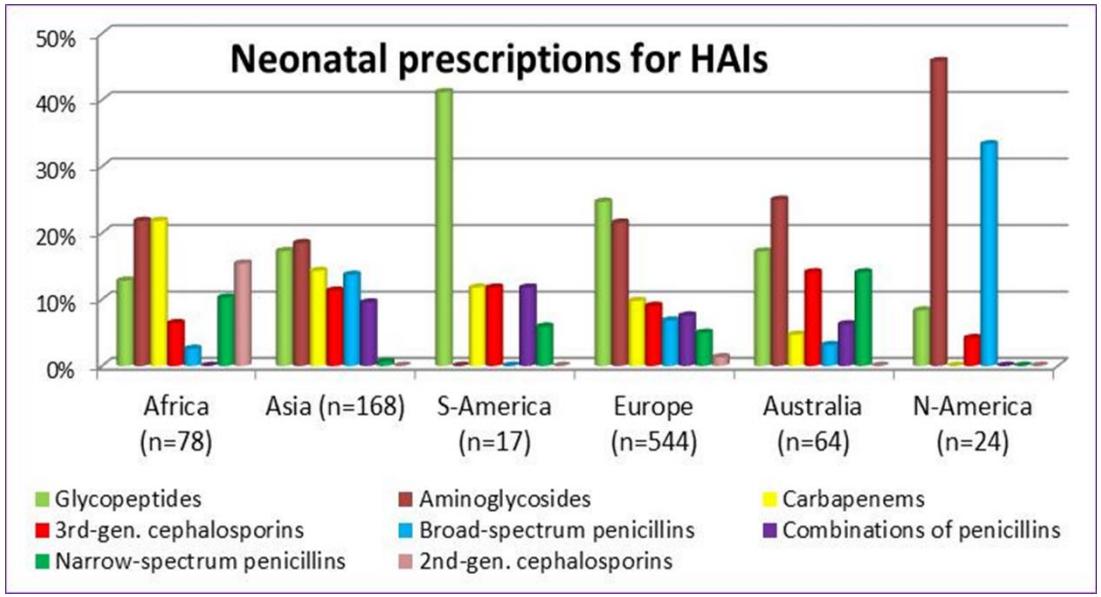
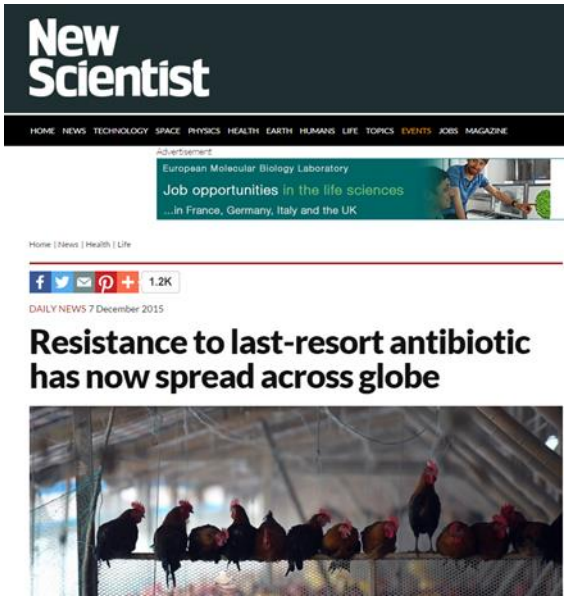


ARPEC point prevalence survey in 2012 – 41 countries



Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics—systematic review and meta-analysis

Lilian Downie,[1] Raffaela Armiento,[1] Rami Subhi,[1] Julian Kelly,[1,2] Vanessa Clifford,[2] Trevor Duke[1]

Arch Dis Child 2013;98:146–154

- **only 57%** of isolates susceptible to benzylpenicillin/ampicillin & gentamicin and **only 56%** susceptible to 3rd-gen cephalosporins

- main gaps in antibiotic coverage were due to **enteric Gram-negative bacilli, particularly Klebsiella**

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Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC)

A global surveillance network focused on collection of data on neonatal and paediatric antimicrobial prescribing and resistance.

- Unique global surveillance system
- Uses customised online tool to collate information about neonatal and paediatric prescribing, including microbial culture data and AMR patterns
- Administrative base at St George's, University of London
- 12 paediatric centres participating, covering 6 continents
- Full roll-out Q1 2016 following successful pilot in 2015

Expert Rev Anti Infect Ther 2014
Cochrane Database Syst Rev. 2011
Pharmacotherapy 2015

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Optimising management of MDRGNB infections

- Neonatal studies generally show **lower** rates of toxicity for most antimicrobials
- Recent re-evaluation of dosing strategies e.g. targeting Cmax with gentamicin: use higher doses
- **Combination therapy** with 2 or more active drugs **associated with increased efficacy**: use new combinations
- Role for co-amoxiclav in neonatal infections: use new formulations

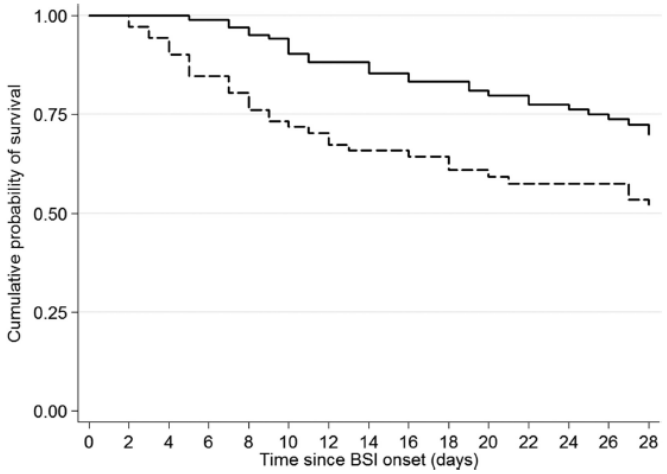

FIG 1 Kaplan-Meier survival estimates of patients with carbapenemase-producing *K. pneumoniae* bloodstream infections according to treatment regimen: combination therapy (continuous line) versus monotherapy (dotted line). $P = 0.003$ (log rank test).

Key issues

- Aminoglycosides appear to have low rates of ototoxicity and nephrotoxicity in neonates.
- No studies are available that report vestibulotoxicity in neonates.
- Ototoxicity is more likely when aminoglycosides are given concomitantly with loop diuretics.
- Ototoxicity is more likely with prolonged courses of aminoglycosides.
- Genetic predisposition accounts for a small proportion of aminoglycoside-induced deafness; practical methods to identity such neonates before administering aminoglycosides are not yet available.

Antimicrob Agents Chemother 2014
Clin Infect Dis 2012

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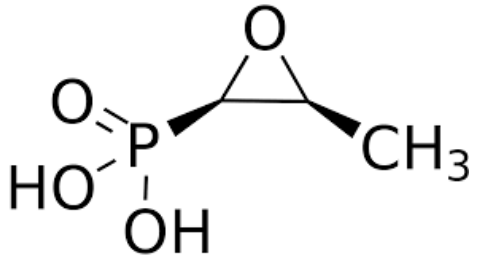


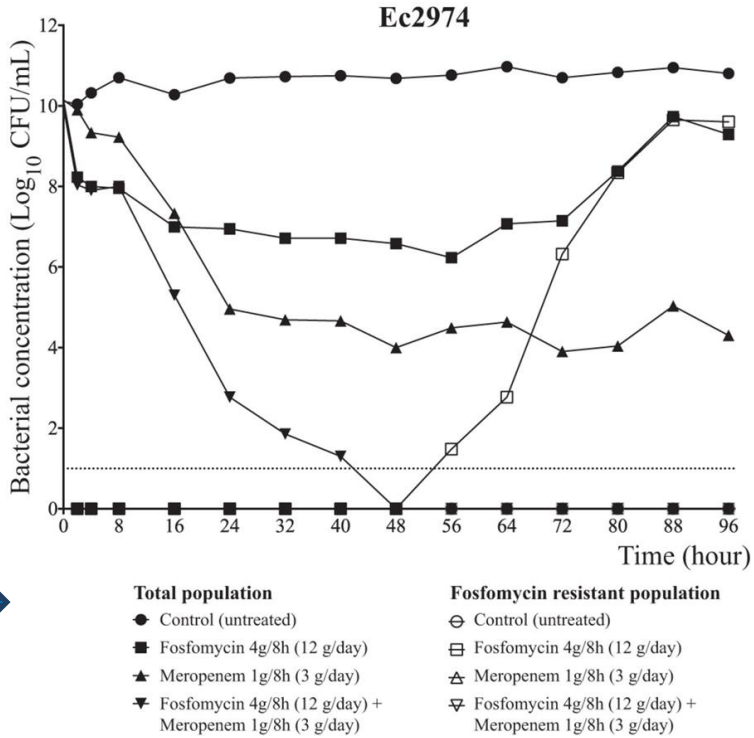
Review of "older agents": Fosfomycin

Pharmacokinetics

- can be taken **orally as well as intravenously and intramuscularly**
- good penetration of tissues with favourable side effect profile
- *in vitro* susceptibility of MDRGNB is high:
  - MIC susceptibility breakpoint of 64 mg/L:
  - 97% of 1657 ESBL-producing *Escherichia coli* isolates susceptible
  - 81% of 748 ESBL-producing *Klebsiella pneumoniae* isolates susceptible

Lancet Infect Dis. 2010 Jan;10(1):43-50

- *in vitro* data suggests synergy with some antibiotic agents



Access to Fosfomycin

- Licensed for use IV in Europe

AAC 2015

1. Pharmacological and pharmaceutical stream

J Antimicrob Chemother
doi:10.1093/jac/dkv451

Journal of Antimicrobial Chemotherapy

Pharmacodynamics of vancomycin for CoNS infection: experimental basis for optimal use of vancomycin in neonates

V. Ramos-Martín[1], A. Johnson[1], J. Livermore[1], L. McEntee[1], J. Goodwin[1], S. Whalley[1], F. Docobo-Pérez[2], T. W. Felton[3], W. Zhao[4], E. Jacqz-Aigrain[4], M. Sharland[5], M. A. Turner[1] and W. W. Hope[1]*

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Objectives: CoNS are the most common cause of neonatal late-onset sepsis. Information on the vancomycin pharmacokinetics/pharmacodynamics against CoNS is limited. The aim of this study was to characterize vancomycin pharmacokinetic/pharmacodynamic relationships for CoNS and investigate neonatal optimal dosage regimens.

Methods: A hollow fibre and a novel rabbit model of neonatal central line-associated bloodstream CoNS infections were developed. The results were then bridged to neonates by use of population pharmacokinetic techniques and Monte Carlo simulations.

Results: There was a dose-dependent reduction in the total bacterial population and C-reactive protein levels. The AUC/MIC and C_{max}/MIC ratios were strongly linked with total and mutant resistant cell kill. Maximal amplification of resistance was observed *in vitro* at an *f*AUC/MIC of 200 mg·h/L. Simulations predicted that neonates <29 weeks post-menstrual age are underdosed with standard regimens with respect to older age groups.

Conclusions: The AUC/MIC and C_{max}/MIC ratios are the pharmacodynamic indices that best explain total and resistant cell kill in CoNS infection. This suggests that less-fractionated regimens are appropriate for clinical use and continuous infusions may be associated with increased risk of emergence of antimicrobial resistance. This study has provided the pharmacodynamic evidence to inform an optimized neonatal dosage regimen to take into a randomized controlled trial.

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Novel combinations: fosfomycin

Fig. 3 SFR Shake Flask Reader with mounted clamps and SFS on a shaker tray

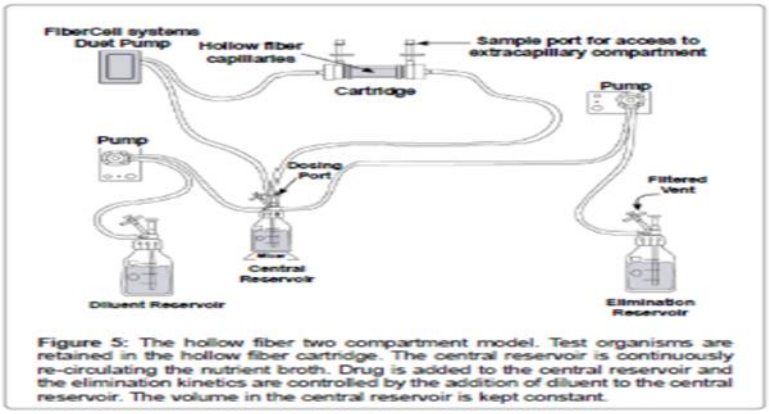

Figure 5: The hollow fiber two compartment model. Test organisms are retained in the hollow fiber cartridge. The central reservoir is continuously re-circulating the nutrient broth. Drug is added to the central reservoir and the elimination kinetics are controlled by the addition of diluent to the central reservoir. The volume in the central reservoir is kept constant.

Stage 1. *Defining the extent and nature of the interaction against Gram negative pathogens*

- 5 strains of: *Pseudomonas aeruginosa*, *Enterobacteriacae* (*E. coli and Klebsiella pneumoniae*) and *Acinetobacter baumannii* (wild-type and defined mutants)
- fosfomycin-based combinations: (1) + amikacin; (2) + ciprofloxacin; (3) + aztreonam, (4) + meropenem
- study combinations against each of the 15 strains (60 experiments) in shaking flasks: estimate the temporal changes in total bacterial density and the resistant subpopulations
- The interactions will be classified as additive, synergistic or antagonistic and ranked in terms of magnitude and their ability to suppress the emergence of drug resistance
- The leading 3-4 regimens that result in killing and prevent the emergence of drug resistance will be studied in the Hollow Fibre Infection Model (HFIM)

Stage 2. *HFIM to define PK-PD relationships of fosfomycin-based regimens*

- Experimental models will be conducted for up to 14 days to provide a study duration that is clinically relevant and will provide a robust test of combination chemotherapy
- Human-like (neonatal) PK will be simulated in the HFIM.
- Relationship between drug exposure (i.e. PK) and the antimicrobial effect (bacterial killing and the emergence of drug resistance) will be described using mathematical models.

Antimicrobial Agents and Chemotherapy 2015

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2. Clinical Trial stream

Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection (STROBE-NI): An extension of the STROBE statement for neonatal infection research

Dr Elizabeth J A Fitchett[1] MBBCh, Dr Anna C Seale[1,2] DPhil, Dr Stefania Vergnano[3] FRCPCH, Professor Michael Sharland[3] FRCPCH, Professor Paul T. Heath[3] FRCPCH, Professor Samir Saha[4] PhD, Dr Ramesh Agarwal[5] PhD, Dr Adejumoke I. Ayede[6] MBBS, Professor Zulfiqar A. Bhutta[7] FRCPCH, Professor Robert Black[8] MD, Dr Kalifa Bojang[9] PhD, Professor Harry Campbell[10] MD, Professor Simon Cousens[1] DipMathsStat , Professor Gary L. Darmstadt[11] MD, Professor Shabir A. Madhi[12] PhD, Dr Ajoke Sobanjo-ter Meulen[13] MD, Professor Neena Modi[14] FRCPCH, Dr Janna Patterson[15] MD, Dr Shamim Qazi[16] PhD, Dr Stephanie J Schrag[17] DPhil, Professor Barbara J. Stoll[18] MD, Dr Steve Wall[19] MD, Professor Robinson Wammanda[20] FWACP Paed, Professor Joy E Lawn[1] FRCPCH, on behalf of the SPRING (Strengthening Publications Reporting Infection in Newborns Globally) Group

NeoMero

Summary

- This proposal aims to develop a strategic pharmacometric, microbiological and clinical trial network for optimising existing antimicrobial options and rapidly and efficiently re-entering older antimicrobials into routine clinical practice. It recognises that currently a large number of neonates and infants cannot access appropriate antibiotic treatment for MDRGN serious bacterial infections

  - address key gaps in knowledge about current management of neonatal sepsis in the context of endemic rates of MDRGNB and in LMIC settings
  - strengthen pre-clinical and clinical evidence base with regard to empirical regimes for treatment of neonatal sepsis
  - support *in vitro* studies of novel antimicrobial combinations, with a focus on fosfomycin
  - develop new standardised definitions for conducting neonatal antimicrobial trials and define the optimal design for neonatal sepsis clinical trials in the context of current regulatory requirements & LMIC settings
  - conduct a phase 1 trial based on new pre-clinical data