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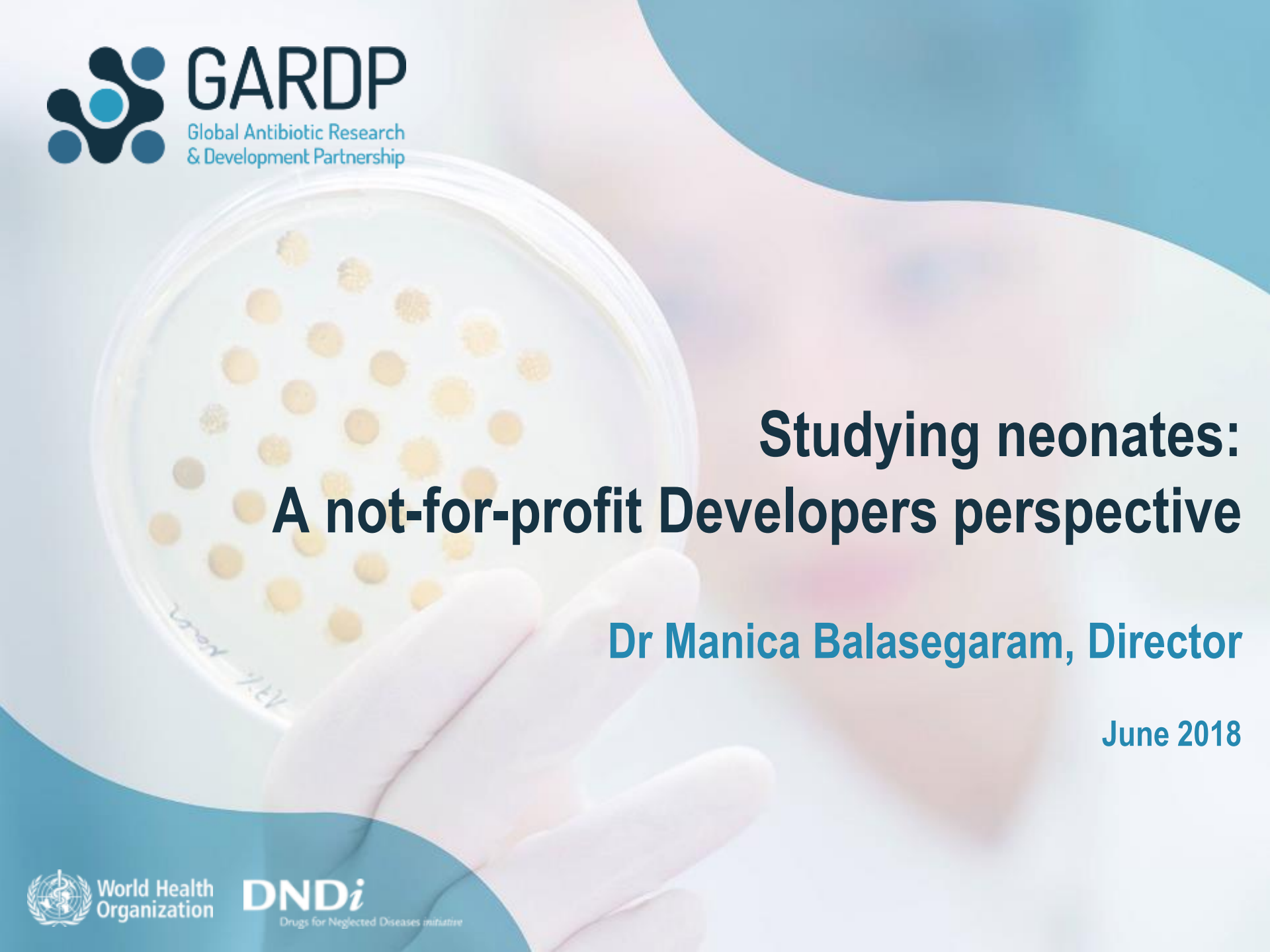

Studying neonates: A not-for-profit Developers perspective

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June 2018

World Health Organization

DNDi
Drugs for Neglected Diseases *initiative*

GARDP – a not-for-profit R&D organization

Focus:

- Drug-resistant bacterial infections for which adequate treatment is not available.
- Address global health priorities that reflect the realities of clinical practice.

Global scope:

Low-, middle- and high-income countries

Joint initiative:

- World Health Organization
- Drugs for Neglected Diseases *initiative*

Priorities:

- Neonatal sepsis
- Sexually transmitted infections
- Memory recovery and exploratory
- Paediatric antibiotics

2023 objectives

Develop 4 new treatments through:

- Improving existing antibiotics
- Developing new chemical entities

Build a robust pipeline of pre-clinical and clinical candidates end to end

Actively support appropriate use of and access to new antibiotic treatments

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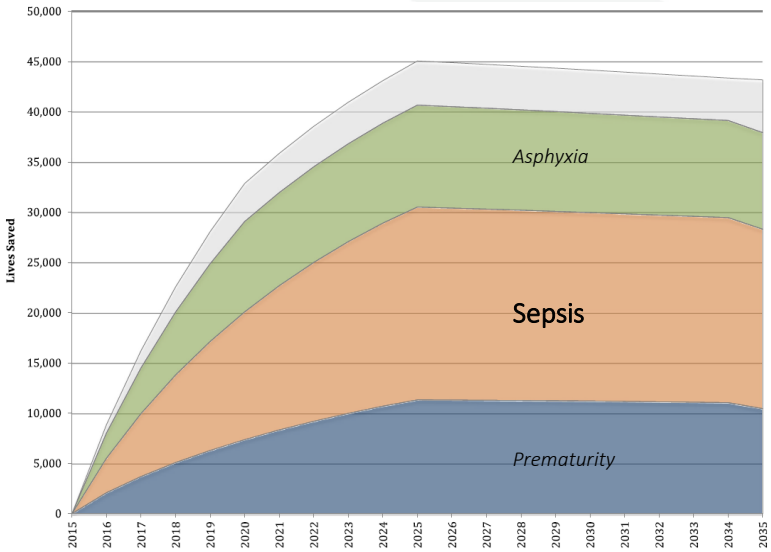
Why prioritize neonates and neonatal sepsis?

Maternal and child deaths have halved worldwide over the past two decades

HOWEVER

- Neonatal mortality remains high with 2.9 million deaths estimated in newborns (<28 days) every year
- Nearly a quarter(23%) of deaths are due to infectious causes
- Estimated that 214 000 deaths were due to AMR



Number of neonatal lives saved annually, and from asphyxia, sepsis and prematurity. Arnesen L, BMC Public Health. 2016

To achieve the SDGs, a high proportion of **neonatal deaths must be prevented** and the **outcome of neonates with sepsis** must significantly **improve**

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Strategy for paediatric/ neonatal programme

Accelerate the development of paediatric antibiotics	• **Expedite development of new & late stage pipeline drugs by collaborating with companies** • Extending use / Improve or optimize formulations of existing antibiotics for use in childhood infections
Evidence-based treatment guidelines	• Support the update of guidelines with evidence, taking into account an evolving epidemiology globally
Paediatric CT Network	• Develop an international neonatal and paediatric clinical trial network, including regulatory work (PIPs, master protocols)

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Neonatal Sepsis Program

Primary objectives: Develop 1-2 new treatments within the 6 years.

1. An *empirical* treatment for babies with possible serious bacterial infection in areas where drug-resistant Gram-negative (ESBL-producing) pathogens are suspected (**TPP1**).

2. A treatment for babies and children where MDR Gram-negative bacterial infection is confirmed (*e.g.* carbapenem-resistant *K. pneumoniae* or *Acinetobacter* spp) (**TPP2)**.

Specificities to consider in the neonatal population

- Relative (im)maturity of organ development; special situations of pre-term babies.
- Predominance of BSIs / sepsis in neonates.
- Signs and symptoms to define presumed SBI (inclusion criteria) and clinical progression (*GARDP is now conducting a global observational study to address this*).

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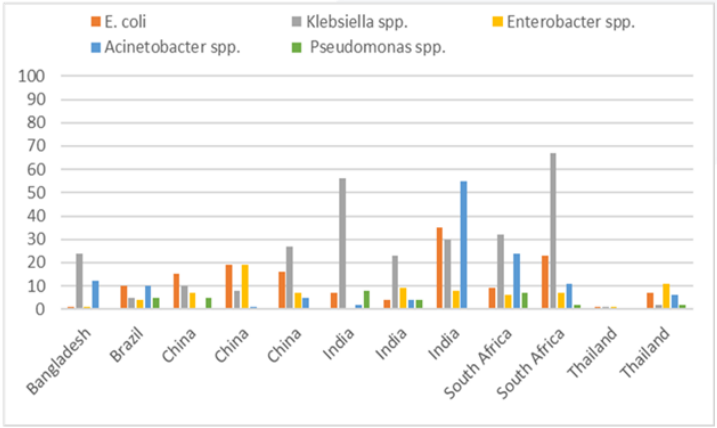
GARDP Feasibility study

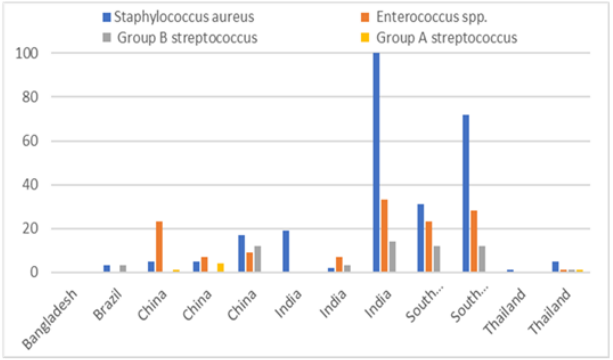
Feasibility data on current antibiotic regimens used to treat late onset neonatal sepsis are extremely varied

	EOS	LOS
Ampicillin/Benzyl Penicillin+ Gentamicin	12	2
Ceftazidime/Cefotaxime + Amikacin	1	4
Ampicillin / Cloxacillin / oxacillin + Amikacin	5	2
Ceftazidime+ Ceftriaxone	2	0
Ceftazidime / Cefepime+ Co Amoxiclav	2	1
Benzyl penicillin + Ceftriaxone/Ceftazidime	2	2
Piptazo + oxacillin		1
Meropenem +/- Vancomycin		5
Cefepime + Vancomycin		1
Ciprofloxacin + Amikacin		1
Meropenem + Amikacin		1
Cefotaxime+ Vancomycin		1
Piptazo+ Amikacin		2
Ampicillin + Cefotaxime		1

Gram-negative



Gram-positive



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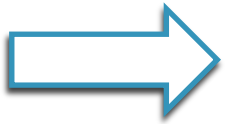
Summary of the problem

- Children and neonates are disproportionately affected by AMR; gram negative infections are a major issue; Low and Middle income countries are bearing the brunt of the burden.
- Few antibiotic paediatric trials being conducted, EVEN fewer neonatal trials (**Thompson et al.** 2017: while 2/3 were not-for-profit sponsored only 2 of the 37 in the Pew Ab pipeline were recruiting in 2016).
- Many paediatric studies required under regulation have not been completed due to delays (**Hwang et al.** 2018: 38% completed after 7 yr follow up).
- Lack of 'regulatory' and 'strategic trials'= off label use and outdated guidelines.
- Recruitment & feasibility remain a challenge: recent experience.



- Conduct trials in relevant populations and geographies.
- Develop drugs for children that can appropriately address the relevant infections.
- Conduct feasible regulatory trials (and have a viable and clear pathway for developers).
- Be able to conduct pragmatic 'strategic trials' for policy and use.
- Develop a global network of trial sites.
- *Develop common or standardized protocols per indication: inclusion/ exclusion criteria, diagnostic criteria, end points, PK methodology, safety reporting, pooled controls, pooled data (meta-analyses)..*

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The experience from HIV and TB

- FDA guidance for Industry, Paediatric HIV infection (May 2018):
  - Based on consistency of dosing recommendations for ARVs in adults and children: can we make same assumption for antibiotics?
  - Include adolescents (12-16) in initial phase III trial/ or parallel trial.
  - Commence Paediatric formulation development once adult dose selected (end phase II).
  - For children of 4 weeks- 12 yrs: enrol cohorts in parallel rather than in series (use PK modelling based on adults and adolescent data for dose selection; apply this across parallel weight bands). Notes that there may be circumstances to start neonatal development then.
  - Approval of new paediatric formulations could be based on BA/BE equivalence studies in adults.

- Tuberculosis expert opinion (Nachman et al; LID, June 2015):
  - Also calls for paediatric development starting in early development, and occurring in parallel (rather than post-approval); prioritize according to defined TPPs.
  - Proposes a range of age groups and need for diverse ethnic backgrounds.
  - Proposes SD PK evaluation as first step, or/ and mini (n=6=) multi-dosing cohort.

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Considerations and assumptions for Neonates

- Draft addendum for paediatric bacterial infections (under consultation)- EMA/CHMP/187859/2017
  - Extrapolation from adult data considered possible for most infections (***sepsis not specifically mentioned***).
  - Knowledge of DDIs required when co-administration expected
  - Safety profile driven by dose and systemic exposure: additional data required only if emerging concerns from non clinical / adult clinical data (e.g. FQ age specific AEs).
  - PK data needs to be generated in neonates owing to rapid developmental changes in ADME: PK studies can be conducted in parallel where no age or maturation related differences are expected.
  - Acknowledgement that it is often impossible to determine primary site of infection in neonates: obtain PK data from suspected or late onset sepsis with no known primary focus.
  - For MD PK studies, recommend to us age-appropriate internationally agreed diagnostic criteria for specific IDs.
- We should start paediatric and neonatal development when we have sufficient adults safety and efficacy data, i.e. end of phase IIB for KEY pipeline drugs (e.g. unmet need it fills for babies/ young children, adult PK and safety profile, DDIs).
- This assumes an appropriate extrapolation on safety and hence MoA / dose can be made (e.g. Pansa et al, 2017: AEs are class specific and broadly predictable; nothing unexpected seen in neonatal group).
- Assume we use diagnostic criteria noted in the EMA report on the Expert meeting on Neonatal and Paediatric Sepsis (EMA 477725/ 2010).
- Timing and approach: When exactly do we start neonatal PK studies? NCEs v label extensions of old drugs.
- Neonatal studies: MD essential? Single arm? Pooled control? Randomized Controlled? This depends on safety profile?

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Old versus New drugs: significant difference?

- Older antibiotics
  - Dossier may not meet current requirements (nonclinical, CMC, clinical data), so may need to conduct additional studies
  - May need to develop an appropriate presentation or formulation
  - May need to do SD and MD studies
  - May still need to conduct strategic trials, including use in combination
- NCEs
  - Start work on appropriate presentation and formulation after phase II in adults
  - Start neonatal trial after paediatric trials
  - Start with SD study to confirm dose
  - May still need to conduct strategic trials, including use in combination after registration

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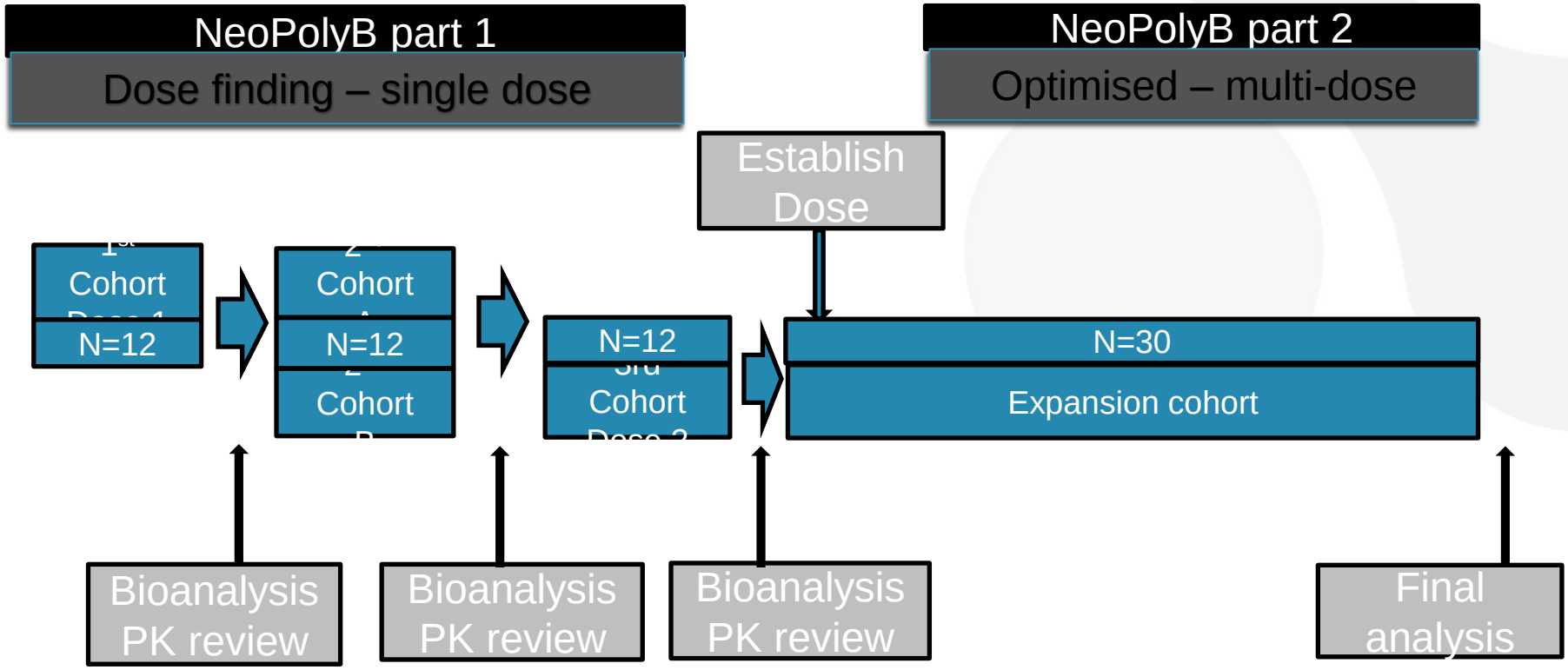
NeoPOLI Current Study design



- **Second cohort A -** if an optimal dosing regimen **can** be defined from the first cohort, an additional 12 subjects will be recruited to collect sparse PK data and to assess the safety.
- **Second cohort B** if an optimal dosing regimen **cannot** be defined from the first cohort a new dose will be proposed and another 12 subjects with complete PK data will be recruited.

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Potential paediatric development project for antibiotic in late stage clinical development

Neonate and Paediatric programme – Same project in development

Children

Neonates

Pharmacokinetics – Single dose

- Cohort 1 12-16yrs
- Cohort 2 2-11yrs
- Cohort 3 28 days-23 months

PK– Multiple dose

- Cohort 6 12-16yrs
- Cohort 7 2-11yrs
- Cohort 8 28 days-23 months

- Cohort 4 Term - 28 days
- Cohort 5 Preterm
- Cohort 9 Term - 28 days
- Cohort 10 Preterm

Modelling and Simulation
Extrapolation

Questions

Current PK study ?Timing – overlap vs Sequence
? Single dose and Multi dose required

Other studies required:

- ? Efficacy
- ? Safety

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Summary for neonates

- Consider if all assumptions and extrapolations made do hold.
- Ensure all relevant preclinical and clinical studies required done.
- Clarify which agents we focus DDI studies.
- Start after generation of initial SD data for paediatric trial done.
- Priority Indication: BSIs/ Sepsis caused by MDR gram negatives.
- Consider conduct of a seamless SD followed by MD study (dose finding and optimised dosing).
- After label extension: a comparative study against SOC using safety as outcome.
- Superiority design in this scenario? Will depend on SOC. Future SOCs with NCEs incorporated in may be difficult to attain.
- Invest in the development of an international trial network (especially for younger age groups).
- Need for clear regulatory harmonisation here: developing countries where need is greatest need clarity.

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Thank you

Global Antibiotic R&D Partnership (GARDP)
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TPP1

Descriptors	Criteria	Minimum TPP	Optimum TPP
Populations	Neonates (< 2 months)	Neonates (premature and term, early and late onset)	
Disease	Bacteria	Severe bacterial infections	
Diseases/ syndromes	Sepsis, (meningitis)	Sepsis, (meningitis)	Sepsis, meningitis, pneumonia, UTI, IAI, (enteric fever)
Pathogens	Gram negative / Gram positive bacteria	Klebsiella, Enterobacter, E. coli, S. aureus, group B streptococci	Acinetobacter, Pseudomonas
Resistance	ESBL and other resistance profile	ESBL, aminoglycoside^{R}, methicillin^{R}	ESBL, aminoglycoside^{R}, methicillin^{R} carbapenemase producers,
Efficacy		Comparable clinical activity to amoxicillin/gentamicin or ceftriaxone/gentamicin in claimed indication	
Syndrome status	Unconfirmed by microbiology	Empiric	Empiric
Co-medication	HIV (AZT, nevirapine)	Manageable co-medication	No interference
Clinical safety	Adverse events	Low propensity for resistance development, large therapeutic window (hepato-, nephro-, CNS-, and cardio-toxicity)	Low propensity for resistance development. No AE related monitoring required
Predicted dose for neonates	Case by case basis	N/A	N/A
Route of administration	IM, IVpush, IVinfusion	IVpush	IVpush, (oral)
Dosing schedule	2-3 x daily	2-3 x daily	1 x day
Treatment duration	5-14 days	up to 14 days (21 for meningitis)	5 days
Price/day therapy	Average ex-factory price at launch:	Low	Low
Current reccommeded treatment	Amoxicillin/gentamicin or ceftriaxone/gentamicin		
Key countries	Global or regional (ie SE Asia or Africa)	Regional	Global

TPP2

Descriptors	Criteria	Minimum TPP	Optimum TPP
Populations	Age	Neonates and children < 12 years of age	
Disease	Bacteria	Severe bacterial infections	
Diseases/syndromes	Sepsis, meningitis	Sepsis	Sepsis,meningitis, pneumonia, UTI, IAI
Pathogens	Carbapenem-resistant Gram-Negatives	Klebsiella, Enterobacter, E. coli	Klebsiella, Enterobacter, E. coli, Acinetobacter, Pseudomonas
Resistance	Carbapenemase		All classes of Carbapenemases
Efficacy	Comparable clinical activity to existing options in claimed indication	Activity against carbapemen-resistant bacteria	Activity against MDR/XDR Gram-negative bacteria
Syndrome status		Strong clinical suspicion or confirmed by microbiology	Strong clinical suspicion or confirmed by microbiology
Co-medication	Malaria, TB, HIV	Manageable co-medication	No interference
Clinical safety	Adverse events	Low propensity for resistance development, large therapeutic window concerning hepato-, nephro-, CNS-, and cardio-toxicity	Low propensity for resistance development, No AE related monitoring required
Predicted dose	Case by case basis	N/A	N/A
Route of administration	IV-push/IV-infusion/oral	IV-push / IV-infusion	IV-push
Dosing schedule	2-3 x daily	2-3 x daily	1 x day
Treatment duration	5-14 days	up to 14 days (21 for meningitis)	5 days
Price/day therapy	Average ex-factory price at launch:	£X / course	£X / course
Current treatment	Colistin-based combinations		

Paediatric Investigation Plan

- Indication
- Paediatric age sub-sets
- Information on CMC
  - Paediatric formulation development e.g. age-appropriate pharmaceutical form, formulation, strength or new route of administration compatibility with paediatric administration systems, taste and palatability
- Non clinical studies
  - Planned or ongoing non –clinical studies or justification if not required e.g. *repro tox and* juvenile animal studies if appropriate
  - Safety signals which could impact on development in children
- Clinical
  - PK, Pop PK and PK/PD, consider Receptor maturation, simulations for Paediatric age groups
  - Clinical, Efficacy and Safety - in relation to the existing adult data and the potential to extrapolate to paediatric populations
  - Modelling and simulation
  - Extrapolation studies
- Timelines

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