GARDP
Program
Strategy

Neonatal Sepsis: NeoAMR

NEONATAL SEPSIS STRATEGY

Contents

EXECUTIVE SUMMARY

The spread of antimicrobial resistance (AMR) is an urgent, global threat, raising the possibility of a world without effective antibiotics. Among the initiatives being planned to prevent (or at least control) such a crisis, special attention is required for newborn babies (neonates), since their immune system is not yet fully developed, and therefore they are particularly vulnerable to infection. At present, treatments are delivered often without knowledge of optimal dosing, exposure and efficacy of the drugs, off-label use, inappropriate choices given the pathogens and resistance patterns involved, and inadequate formulations. The overall outcomes are: a waste of resources (and costs), poor clinical outcomes and steep community costs in the form of the generation and spread of yet more resistant bacteria.

The current NeoAMR (Neonatal Antimicrobial Resistance) strategy is based on two Target Product Profiles(TPPs) for the treatment of neonatal sepsis, which were built on a consensus among global experts on how to address the most pressing medical needs. These are:
- TPP1 describes an affordable 'empirical' treatment for neonatal sepsis and meningitis in settings with high resistance rates to the WHO first line empiric therapy of ampicillin and gentamicin, where the pathogenic bacteria have not been formally identified.

- TPP2 addresses situations where the presence of Multi Drug Resistant Gram-negative (MDR-GN) pathogens has been identified including K. pneumoniae, P. aeruginosa or Acinetobacter spp., Carbapenem Resistant Organisms (CRO's).

The main activities for the program includes: extended analysis of candidate drugs for TPP1/2 inclusion and constitution of an expert Project Advisory Group; a clinical observation study of neonatal sepsis in the target populations, associated with advanced microbiological analysis; an experimental evaluation of TPP candidates using PK/PD (pharmacokinetic/pharmacodynamic) modeling based on in vivo hollow fibre infection models, allometric scaling and optimized formulation; clinical trials necessary to provide sufficient data to support relevant use and project management.

INTRODUCTION

Disease burden - Global neonatal mortality

Maternal and child deaths have halved worldwide over the past two decades(1). From 2000 to 2013, global under-5 mortality was reduced at an average annual rate reduction (ARR) of 4.1% per year, with most countries making great progress in improving child survival since 2000. In 2015, among the 5.9 million deaths in children under the age of 5 years, 45% died in the neonatal period. This portion exceeds 50 % in several regions(1). In 2012, an estimated 6.9 million (uncertainty range 5.5 – 8.3 million) possible serious bacterial infections (pSBI) occurred in neonates in South Asia, sub-Saharan Africa, and Latin America(2). Reductions in pneumonia, diarrhea, and measles accounted for half of the reduction reported in 2013 versus 2000. The slowest progress though was reported in neonates and included congenital causes, preterm births, neonatal sepsis, and injury(3).

In addition to a substantial mortality burden, pSBI in neonates also account for about 3% of all disability-adjusted life years (DALY(2)). This is likely to be a considerable underestimate, as it does not include long-term impairment in survivors.

Clinical manifestations and diagnosis of Neonatal Sepsis

There are wide variations in the reported incidence of neonatal pSBI, likely due to differences in diagnostic criteria and case definitions, as well as true interregional variability.

An accepted definition of sepsis in neonates is lacking. According to the report on the expert meeting on neonatal and paediatric sepsis of EMA (2010)(4), neonatal sepsis can be defined by the presence of at least two clinical symptoms and at least two laboratory signs in the presence of or as a result of suspected or proven infection (positive culture, microscopy or polymerase chain reaction).

In resource-limited settings with limited and/or intermittent access to laboratory evaluations this definition is not practical. Instead in LMIC it is recommended that initiation of antibiotics is based on the presence of clinical signs, using WHO Integrated Management of Childhood Illness (IMCI) clinical algorithms. IMCI defines:

- danger signs - not feeding well, convulsions, drowsiness or unconsciousness, movement only when stimulated or no movement at all, fast breathing ≥60 breaths/min, grunting, severe chest in-drawing, raised temperature >38°C, hypothermia <35.5°C or central cyanosis)
- priority signs - severe jaundice, severe abdominal distension or localizing signs of infection

Types of bacteria associated with neonatal sepsis

Bacterial pathogens involved in neonatal sepsis vary between High (HIC) and low or middle (LMIC) income countries. In HIC, Gram-positive pathogens are a more common cause of neonatal sepsis than Gram-negative bacteria(8).

In HIC, the most common causes of early onset neonatal sepsis (EONS) are group B streptococcus (GBS) and Escherichia coli (E.Coli). The remaining cases of EONS are caused by Staphylococcus aureus (S. aureus), coagulase-negative staphylococci (CoNS), Listeria

monocytogenes and other Gram-negative bacteria(5). In Late onset neonatal sepsis (LONS), the main pathogens are CoNS, responsible for half of the episodes. Other important etiologic agents are E. coli, Klebsiella spp. and Candida spp. Less common causes of LONS include S. aureus, Enterococcus spp. and Pseudomonas aeruginosa(9,10).

Etiological data from LMIC, particularly from rural, community-based studies, are very limited. Considering existing systematic reviews on this topic, the commonest causes of neonatal bacteremia in LMIC are: S. aureus, E. coli and Klebsiella spp.(11,12). Although some similarities exist between community- and hospital- acquired sepsis, available data is of insufficient quality to be able to draw firm conclusions(5). Acinetobacter spp., for example, appear to be predominant in some regions (13,14), while the incidence is very low in other regions. GBS is responsible for only 2–8% of cases in LMIC.

It is possible that infants with GBS infection are underreported, since this pathogen usually presents very early in life and infected newborns might die or be adequately treated before blood cultures or other relevant microbiological samples are obtained. CoNS is responsible for a lower proportion of hospital-acquired infections compared to HIC(5), and this may be related to the use of invasive medical devices, e.g. central venous catheters.

Current treatment options
The current treatment options for pSBI and neonatal sepsis according to WHO guidelines for the management of common childhood illnesses, 2013(11) are:
- Neonates with documented risk factors for infections - prophylactic intramuscular (IM) or intravenous (IV) ampicillin and gentamicin for at least 2 days and reassess. Treatment should only be continued if there are signs of sepsis (or positive blood culture).
- Infants fulfilling the case definition of SBI - hospitalization and IM or IV antibiotic therapy with a combination of gentamicin and benzylpenicillin or ampicillin for at least 7–10 days in infants aged <2 months.
- Infants deemed at risk of staphylococcal infection - IV cloxacillin and gentamicin

Recommendations for prevention of neonatal infection and for the management of pSBI have not changed since 2005(12). In setting with high levels of resistance other antibiotic regimens are increasingly being used. (13,14)

The threat of resistance

The increasing incidence of MDR Gram-negative bacteria in the neonatal population is of great concern due to the significant morbidity and mortality associated with these infections (15). Among them, E. coli and K. pneumoniae represent key pathogens, being associated with the development of multi-drug resistance and thus limited treatment options in the neonatal population(16). The emergence of extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae represents a major challenge in managing neonatal sepsis. ESBL colonization prevalence of up to 12% for E. coli and 39% for Klebsiella spp have been reported in paediatric intensive care units (PICUs;(17)). Even if still reported to be relatively uncommon in the paediatric population, carbapenem-resistant Enterobacteriaceae (CRE) represent an emerging global public health threat (18). In real-life situations, CRE rates much higher than those published are observed (for example, in South Africa, personal communication 2016).

These highly resistant pathogens hydrolyze carbapenem agents, such as imipenem and meropenem, which are today's treatment of choice for ESBL-producing bacteria(19).

Regional differences in AMR and treatments for neonatal sepsis

Pathogen-specific neonatal AMR rates vary by region and over time, but surveillance is fragmentary. Available sensitivity data is summarized for the WHO first-line empirical antibiotic coverage among neonates and infants in Table 1.

Pathogen	WHO Regions											
	EURO		EMRO		AFRO		PAHO		WPRO		SEARO	
	A[a]	G[b]	A	G	A	G	A	G	A	G	A	G
E. coli	36%	87%	-[c]	-	7%	57%	-	-	-	-	3%	17%
K. pneumoniae	-	74%	-	-	0%	46%	-	-	-	-	6%	31%
P. aeruginosa	-	86%	-	-	-	-	-	-	-	-	85%	81%
S. aureus[d]	83%		-		-		-		-		-	

Table 1: ***Sensitivity to the ampicillin and gentamicin (WHO first-line neonatal sepsis regimen in hospital settings). [a]A: ampicillin; [b]G: Gentamicin; [c]No regional data available; [d]Percentage of methicillin-susceptibility. See for regional acronyms: http://apps.who.int/medicinedocs/en/d/Jwhozip16e/2.html***

In a standardized antimicrobial point prevalence survey (PPS) conducted in 226 hospitals (41 countries) in 2012 within the ARPEC (Antibiotic Resistance and Prescribing in European Children) Project, (20) showed that by far the most-used regimens for neonatal sepsis globally were aminoglycosides, in combination with either ampicillin/amoxicillin or benzylpenicillin; The pooled data from the systematic reviews discussed above demonstrate that around 40% of SBI in neonates was due to pathogens that were resistant to the currently recommended WHO regimens.

GARDP Neonatal AMR STRATEGY PROPOSAL

Gaps
The key information gaps that we have are:
- very limited data on MDR neonatal infections in LMIC, including resistance to last-resort antibiotics such as carbapenems
- limited information on which antibiotics have the potential to be used in neonates as part of empirical regimens in settings with a high prevalence of MDR, especially MDRGNB
- lack of any trial evidence to inform the use of antibiotic regimens for the treatment of neonatal infection in such settings

Overarching goal
The aim of the NeoAMR (neonatal AMR) programme is to develop new, improved treatment regimens for the management of neonatal sepsis in settings with high prevalence of multi-drug resistant (MDR) and extensively drug resistant (XDR) pathogens.

Targeted outcome

To develop improved and adapted treatment options for neonatal sepsis including:

- An affordable 'empirical' treatment in settings with high resistance rates to the WHO first line empiric therapy of ampicillin and gentamicin, where the pathogenic bacteria have not been formally identified (TPP1).
- Treatment where the presence of Multi Drug Resistant Gram-negative (MDR-GN) pathogens including Carbapenem Resistant Organisms (CRO's) have been identified including K. pneumoniae, P. aeruginosa or Acinetobacter spp., i.e. that is affordable and adapted for neonates (TPP2).

The NeoAMR platform will provide enablers (PK, PD, analytical methods, formulations, genotypic/phenotypic global neonatal sepsis microbiology) for the identification of the candidate drug/drug combinations to be tested. Consideration will be given to the identification and development of appropriate formulations for candidate agents. All these enablers will thus allow for the evidence-based development and evaluation of new and improved treatments for neonatal sepsis.

Proposed R&D Strategy

Based on the gaps identified above, and in line with the overall objectives, GARDP has developed a comprehensive R&D strategy that consists of collection and evaluation of data that addresses the gaps that have been identified, including collection and evaluation of clinical epidemiological data and treatments used as standard in resource limited settings, together with microbiological data including evaluation of resistance, pharmacokinetic modelling of existing antibiotics, in vitro pharmacodynamic modelling and assessment of development of resistance for currently available antibiotics or combination of antibiotics, development of formulations and /or packaging appropriate for use in neonates. This information will all be utilized to inform the design of future pivotal clinical trials evaluating potential treatment that meet the criteria defined in TPP1 and TPP2 (see appendix 1).

Component 1: Collect and evaluate observational clinical and microbiological data to inform development of adapted treatment regimens

Complete a detailed situational analysis on the prevalence of AMR in neonatal sepsis, including conduct of an observational study to prospectively characterize the routine clinical presentation, management, and outcomes of SBI in neonates hospitalized on NNUs globally, together with collection of clinical isolates for national/central species determination to evaluate the microbiological epidemiology, and antimicrobial susceptibility patterns.

This could include sites in: Greece, Kenya, South Africa, India, Cambodia, China, Thailand and Argentina. The aim is to develop a network of centres that can obtain high-quality observational clinical and microbiological data in order to:
- *(i)* inform the design, choice of regimens and conduct of relevant clinical trials evaluating antibiotics as potential empirical treatment agents and for optimal antibiotic regimens to treat confirmed drug resistant infections
- *(ii)* support conservation of antibiotics through on-going surveillance.
- *(iii)* further develop the optimal approach for selection of empiric antibiotic regimens to treat neonatal pSBI in settings with variable AMR epidemiology,
- *(iv)* to determine the current phenotypic and genotypic resistance profiles of invasive and colonizing GN isolates from NNUs participating in observational study

(v)   Determine an appropriate method of determining MICs (minimum inhibitory concentrations) of the candidate drugs within the LMIC setting

(vi)   Identify a representative network of microbiology laboratories able to conduct analysis of SBI and CSF isolates for resistance to key drugs

(vii)   Collaborate with existing networks including Combatting Bacterial Resistance in Europe (COMBACTE) laboratory network and (LAB-Net) isolates to collect clinical data from routine neonatal blood and CSF cultures.

The information gathered as part of the observational study will provide the key features for designing the randomized controlled study in which the candidate treatments will be tested.

Component 2: Identify potential treatment regimens based on available, pharmacokinetic, pharmacodynamics data.

Evaluate available PK, PD, analytical methods, formulations, for the identification of the candidate drug/drug combinations to be tested. Consideration will be given to the identification and development of appropriate formulations for candidate agents. This will allow for the evidence-based development and evaluation of new and improved treatments for neonatal sepsis.

Pharmacokinetics

There is limited pharmacokinetic data in neonates, in order to address gaps in knowledge selected bioavailability study(ies) will be conducted via the oral and intravenous routes. This will utilize a population sampling strategy to minimize number and volume of samples collected. This study will be designed to apply innovative pharmacometrics and optimal design to maximize the leverage from existing neonatal clinical and PK data for study design. In addition, this approach will be used to justify the dose and optimal sampling schedules for larger phase 3 trials. PK will be measured as a secondary endpoint in these trials.

Pharmacodynamics

The pharmacodynamics will be evaluated using a Hollow Fiber Infection Model (HFIM(21) Neonatal PK will be simulated based on existing literature or data generated from this programme. The antibacterial effect and the emergence of AMR will be used as study endpoints. The neonatal regimen that results in maximal killing and prevents the emergence of AMR will be determined. If the optimal regimen exceeds current safety bounds, then this will indicate that *e.g.* fosfomycin needs to be used in combination with another agent. This approach allows testing various combination of drugs, supported by PK/PD modeling and other rational considerations. Consideration will be given to the optimal dosing to prevent the emergence of resistant sub-populations.

Formulation identification and development

Formulation development: GARDP/DNDi will coordinate all formulation activities, including work undertaken by scientific and manufacturing partners with the aim of ensuring that new and appropriate formulations are developed according to international standards. This will include:

- Defining the neonatal needs in terms of drug formulations. For existing antibiotics Investigate the opportunities to manipulate or to modify existing drug products to identify potential formulations that are appropriate for neonatal use in terms of the

formulation (eg low sodium content for intravenous formulations) or can easily be adapted for neonatal use.

- If the outcome of this study is that the manipulation or modification of a licensed product cannot be further supported, the development of new products will be initiated. This could include a new drug formulation for systemic use in neonates which comes with a specific vial with drug powder or granules to be constituted before use. Another concept could be single-dose syringes for single-use.

If feasible and the quality can be ensured, the technology will be transferred to a contract manufacturing organization (CMO) to produce GMP batches for the clinical trials.

Component 3: Develop 'empirical' treatment in settings with high resistance rates to the WHO first line empiric therapy of ampicillin and gentamicin.

Using the data generated during components 1 and 2 identify potential treatment(s) and conduct the relevant formulation development, clinical trials and registration activities. For example, with potential treatments that already have a neonatal indication such as fosfomycin and amikacin, confirm the doses and formulations are appropriate for use in neonates and conduct the necessary clinical trial(s) including but not limited to pivotal phase 3 trial(s). Potential candidates that could be used to take forward in formal clinical trials are listed in Annex 2

Component 4: Development of a treatment for MDR-GN pathogens have been identified including K. pneumoniae, P. aeruginosa or Acinetobacter spp., Carbapenem Resistant Organisms (CRO's) that is affordable and adapted for neonates.

Using the data generated during components 1 and 2 identify potential treatment for MDR-GN pathogens have been identified including K. pneumoniae, P. aeruginosa or Acinetobacter spp., Carbapenem Resistant Organisms (CRO's)and conduct the relevant formulation development, and conduct the necessary clinical trial(s) including but not limited to pivotal phase 3 trial(s). Potential candidates that could be used to take forward in formal clinical trials are listed in Annex 2.

Conduct of Clinical Trials for components 3 and 4.

The pivotal clinical trials will be Sponsored by DNDi and the conducted by DNDi /GARDP/ PENTA /Medical Research Council Clinical Trials Unit (MRC-CTU) each with defined roles and responsibilities in planning, conducting, analyzing and reporting of the trial. It will be planned as global trial(s) and could include clinical trial sites in Argentina, Cambodia, Greece, India, Kenya, South Africa. Clinical trial sites will be identified as part of the epidemiological study.

• The relevant Ethics Committee and Competent/Regulatory Authorities approvals will be sought in compliance with relevant clinical trial regulations such as the EU Directive 2016/680. If the involvement of European countries and/or future European marketing authorization is sought, this will include engagement with the Paediatric Committee (PDCO) at the EMA for the agreement of a PIP.

• Pharmacovigilance (PV) activities. At the end of the trial the activity of SAEs reconciliation will be carried out and the SAEs database transferred to the Partner responsible for the analysis.

- A Trial Steering Committee (TSC) and an Independent Data Monitoring Committee (IDMC) will be established to oversee and advise on the scientific aspects of the trial, and safeguard patients' wellbeing, respectively.
- Harmonization of practices throughout the participating centers will be promoted by implementing SOPs to address the critical issues:

Trial design and protocol development

At present, it is envisaged that hospitalized neonates with sepsis (based on clinical signs and restricted laboratory criteria) will be recruited.

Potential trial designs under consideration are:

(i) a 2x2 factorial non-inferiority trial comparing 1) a novel regimen (e.g., fosfomycin plus aminoglycoside) v.s. standard of care (e.g. β-lactam plus aminoglycoside) and 2) shorter duration of treatment (6 +/- 1 day) v.s. longer duration (12 +/- 2 days). This would address TPP1 in a setting where microbiological evaluations were not being routinely undertaken.

(ii) A sequential multiple assignment randomized trial (SMART) testing the following clinical management strategy: First stage randomization comparing the same regimens as above (TPP1) with a second stage randomization to a novel regimen v.s. standard of care tailored on identification of MDR organisms (ESBL or CRE, depending on prevalence at trial sites) (TPP2). Among others, the following aspects will need to be defined based on observational data, microbiological information and advisory input from the expert group on:
  - pragmatic clinical criteria for sepsis in the LMIC setting;
  - clinical criteria for changing antibiotics (both escalating and de-escalating based on microbiology results and clinical progress);
  - management of sepsis in NNUs with a high prevalence of carbapenem resistance.

Protocol implementation and trial coordination

This activity includes coordination of the trial clinical operations' tasks and will be delegated by the sponsor to third parties such as PENTA-ID/MRC-CTU, with the support of subcontractors.
- Site management and monitoring: includes all the monitoring activities required by GCPs during the study start-up, study conduction and study closure.
- Data management: electronic data capture will be promoted in those centers with stable internet facilities. QC procedure will be in place to ensure data cleaning and submission and to evaluate the consistency of the dataset.
- Drug management: IMP (Investigational Medicinal Product) test and controls will be supplied and managed from release to disposal according to the quality standards appropriate to their intended use. SOPs (standard operating procedures) for the management of supply, drug handling.

Statistical analysis plan, data analysis and statistical report

The final statistical analysis plan will be developed by MRC-CTU and approved by the sponsor during the protocol preparation and finalized after the trial has opened, before any interim analyses are conducted.

Component 5: Access Strategy

While the development of new antibiotics / combinations is important, it has to go hand in hand with a sound access strategy and stewardship framework. GARDP will work with WHO, pharmaceutical companies and regulatory authorities to ensure the newly developed antibiotics/combinations are globally accessible and that they are not "lost" to resistance within a few years after their introduction

Product Registration: GARDP/ DND*i* in partnership with the relevant manufacturing partner(s) will develop a regulatory strategy for any new paediatric formulations developed. This will ensure any additional studies required be undertaken, as well as ensure the relevant activities described above, such as the clinical trials will integrate appropriate design, activities and standards to ensure product registration.

Sustainable Access: A specific objective of NeoAMR will be to ensure sustainable access to all new products and regimens developed. This will be done through a range of activities that are integrated through the whole project and includes:

i) development and evaluation of evidence-based treatments

ii) development of appropriate formulations

iii) ensuring, where relevant, registration of key drugs and new formulations are undertaken, prioritizing high burden countries in the first wave

iv) promoting affordability of new treatments developed

v) promoting guideline and policy change and international and national level based on evidence generated from NeoAMR

vi) promoting the development of new diagnostics that can facilitate appropriate use of the new treatments developed to treat neonatal sepsis

It is anticipated that additional post-trial activities will need to be conducted, including pilot implementation, pharmacovigilance, training and monitoring use of new treatments. All these activities will be primarily the responsibility of the global Sponsor, GARDP/DND*i*.

Long-term sustainability and education in optimal antimicrobial prescribing: This task will provide education and training (teaching courses) for external stakeholders. DND*i* and PENTA-ID/MRC/SGUL (St George's, University of London) will review the potential utility of developing a short online training for optimal prescribing and AMR in neonates and children for a range of healthcare practitioners. The contents will be derived from the training developed for internal stakeholders under the previous task and will work closely with the implementation of the WHO Essential Medicine List for children (EMLc). Training will include both stewardship activities and local guideline development.

Diagnostic development: A key part of ensuring appropriate use of antibiotics is the availability of user-friendly diagnostics. GARDP will use the opportunity of NeoAMR to seek out partners who can take the lead in developing such diagnostics. The priority will include diagnostic technologies that:

i) Can rapidly diagnose presence of important bacterial infections and hence initiate use of empirical treatment (or conversely not)

ii) Can detect presence of drug resistance

iii) Are affordable

iv) Are appropriate for use in LMIC settings

GARDP will seek out partners that may include other product development partnerships, Medical Research Institutions and manufacturers. It can be anticipated that the observational study, microbiology and clinical trial(s) can be used to piggyback additional studies including evaluation and validation of diagnostic technologies.

International partners

DND*i/*GARDP with the support of WHO have obtained clear commitment to participation in NeoAMR from multiple partners worldwide. These include, among others, from Africa, the Tygerberg Children's Hospital, Cape Town, South Africa, the KEMRI - Kilifi County and Mombasa District Hospitals in Kenya. In Asia there are six Hospitals in China, the AIIMS (All India Institute Of Medical Science), New Delhi, India, and Hospitals in Cambodia, Vietnam, Thailand, Indonesia and Bangladesh. Participants from Europe include the University of Antwerp (Belgium), the Fondazione PENTA; University College London; St. George's University of London and University of Liverpool, United Kingdom, and the Hippokration Hospital, Thessaloniki, Greece. Participants from the Americas include Hospitals in South America.

CONCLUSION

The rise of antimicrobial resistance (AMR) is outpacing new drug discovery at an alarming rate. In this looming crisis, newborn babies (neonates) are a particularly vulnerable group where new treatments are most urgently needed to save lives and, conversely, where most gains can be made in a cost-effective manner in the short term.

The key deliverables of NeoAMR are one or more new empirical treatments (TPP1), plus one new treatment for MDRGN bacteria (TPP2) based on the established local threat. This includes formulations, along with PK/PD knowledge that is specifically adapted to newborn babies. Coordination with WHO, industrial partners, governments, and other key stakeholders will be crucial to the success of this project and also the future access of any new treatments.

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ANNEXES

TPP 1:

Indication	Empiric treatment of neonatal sepsis, including meningitis (premature and term, early and late onset)
Patient Population	Neonates with pSBI in settings of high prevalence of resistance to first line WHO empiric therapy
Route of Administration	*i.v.* (intravenous), 30-120 min infusions
Dosing Schedule	2-4 x daily
Efficacy	Comparable clinical activity to amoxicillin/gentamicin or ceftriaxone/gentamicin in claimed indication
	Clinical activity in pathogens resistant to amoxicillin/gentamicin or ceftriaxone/gentamicin
Treatment duration	5-28 days
Safety / Tolerability	Low propensity for resistance development, large therapeutic window concerning hepatotoxicity, nephro- and CNS-toxicity, no QT-prolongation
Drug Interactions	Comparable to competitors
Key Countries	Europe, the Americas, Asia, Africa
Price / Day of Therapy	Average ex-factory price at launch: low/DOT (directly observed therapy)

TPP 2:

Indication	Neonatal sepsis, where MDR Gram-negative pathogens have been demonstrated, including *K. pneumoniae*, *P. aeruginosa* or *Acinetobacter* spp. Including CROs Neonatal meningitis
Patient Population	Hospitalized neonates with severe infections, failure on optimal current treatment and proven microbiology
Route of Administration	*i.v.*, 30-120 min infusions
Dosing Schedule	2-4 x daily
Efficacy	Comparable clinical activity to existing options in claimed indication
	Clinical activity in pathogens resistant to carbapenems
Treatment duration	5-28 days
Safety / Tolerability	Low propensity for resistance development, large therapeutic window concerning hepatotoxicity, nephro- and CNS-toxicity, no QT-prolongation
Drug Interactions	Comparable to competitors
Key Countries	Europe, the Americas, Asia, Africa
Price / Day of Therapy	Average ex-factory price at launch: tbd/DOT (directly observed therapy)