NEONATAL SEPSIS EXPERT MEETING

GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT PARTNERSHIP (GARDP)

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

A joint WHO/DNDi initiative incubated by DNDi in support of the Global Action Plan for Antimicrobial Resistance

Drugs for Neglected Diseases initiative offices,
Geneva, Switzerland / 27-28 June 2016
Background to GARDP

The mission of the Global Antibiotic Research and Development Partnership (GARDP) is to develop new antibiotic treatments addressing antimicrobial resistance and to promote their responsible use for optimal conservation, while ensuring equitable access for all in need. GARDP is a joint initiative of the Drugs for Neglected Diseases initiative (DNDi) and the World Health Organization (WHO) in support of the Global Action Plan for Antimicrobial Resistance.

Launched in May 2016, GARDP is now in its incubation, or start-up phase, hosted by DNDi. This means that until the end of 2017, the Partnership will build up its team, establish a legal entity, and set out its long-term strategy and roadmap. In addition, GARDP aims to have at least two projects that address urgent global health needs ready for implementation by the end of 2016, and two more by the end of 2017.

GARDP will work closely with all stakeholders in the field of antibiotic research and development (R&D) – including pharmaceutical and biotechnology companies, startups, other product development partnerships, academia, civil society, and health authorities – from countries of all income levels – to develop new antibiotic treatments.

It will address global public health and specific needs of low- and middle-income countries; target products that industry will likely not develop due to lack of profitability or other reasons; pilot the use of alternative incentive models delinking cost of R&D from volume-based sales and prices of antibiotics, and embed sustainable access (stewardship, conservation, and access) of antibiotics in its R&D projects.

Objectives of the Neonatal Sepsis Expert Meeting

1. To review and evaluate the neoAMR project proposal.
2. To determine observational study details, notably countries most feasible in terms of laboratory capacity, exportation of isolates, etc.
3. To review in detail work streams and adjust any preparatory work to be done in advance of clinical trials.

Over-arching goal of neoAMR: To determine – and ultimately bring to patients within 5 to 8 years, 1-2 new treatments for the treatment of neonatal sepsis in settings of high prevalence of multi-drug resistant (MDR) and/or extensively drug resistant (XDR) pathogens.

Targeted Outcomes of the Meeting
1. Consensus on the way forward for the neoAMR proposal, including content and financing opportunities.
2. Timelines and work stream required to reach the GARDP Scientific Advisory Group meeting on 12 October 2016.
Background of Neonatal Sepsis

Neonates and young infants are at high risk of severe bacterial infections (SBIs) with significant associated morbidity and mortality. Because of the non-specific presentation of SBI in this patient group, at least initially most treatment is empiric (i.e. covering a range of possible target bacteria). This results in many infants being treated who are unlikely to have a bacterial infection, because neonates with confirmed bacterial sepsis have a high mortality. This balance between potential over-and under-treatment is made more complex by the concern that empiric treatment is increasingly likely to be inadequate in terms of antibiotic cover in settings where there is a high prevalence of antimicrobial resistance (AMR). Multidrug-resistant Gram-negative bacteria (MDRGNB) are a major global health threat, and MDRGNB SBI is associated with a very high mortality amongst neonates and young infants. Several reviews have identified low- and middle-income countries (LMICs) as having high MDRGNB prevalence, but outbreaks and endemicity of MDRGNB have also been described for neonatal units in high-income countries (HIC).

The overall possible SBI (pSBI) incidence in non-premature neonates in Latin America, Africa, and South Asia has been estimated to be around 8%, with a case-fatality risk of nearly 10%, and pSBI is thought to account for over a quarter of deaths in this patient group in sub-Saharan Africa [Seale, 2009]. In HICs, the incidence of early-onset sepsis, one of the most severe forms of neonatal SBI, is around 1 per 1,000 live births. The case fatality risk for these infants is similar to that described for LMICs [Weston, 2011]. Hospital-born babies in LMICs are at particular risk of neonatal SBI (3-20 times higher than in HICs), and GNB account for nearly 60% of culture-proven infections in this group [Zaidi, 2005]. Recent modelling puts annual neonatal sepsis deaths due to resistant organisms in China, India, Pakistan, Nigeria and the Democratic Republic of Congo alone at 215,000 [Laxminarayan, 2016a; Laxminarayan, 2016b].

In HIC settings, guidelines defining the recommended empiric antibiotic regimens are highly variable [Spyridis, 2016], perhaps in response to statements such as those made by the “Surviving Sepsis Campaign” that “antibiotic choices should be guided by local prevalence patterns of bacterial pathogens and susceptibility data” [Dellinger, 2013]. However, data from Europe suggest that broader-spectrum options used in some settings may not necessarily provide better cover when microbiological epidemiology is taken into account [Bielicki, 2015]. In LMICs, a standard regimen of aminopenicillin plus gentamicin is recommended for neonatal SBIs [World Health Organization, 2013]. However, based on the limited available surveillance data, a substantial proportion of neonatal and young infant SBI cases would not be adequately covered with this regimen [Downie, 2013], particularly when considering GNB [Le Doare, 2015]. Together with an increasing proportion of births taking place in hospitals in LMICs, this may explain why meropenem was amongst the antibiotics accounting for the top 90% of prescriptions to hospitalized neonates in Africa, Asia, and Latin America [Versporten, 2016].
Meeting Report

**GARDP (Global Antibiotic R&D Partnership)**

The Global Antibiotic R&D Partnership (GARDP) was presented. The established initiatives predominantly address long-term goals to bring new antibiotics to patients and attempt to implement better stewardship for using existing medicines to extend their use. However, given that the drug discovery process is long—typically taking well over a decade even with sustained funding—and suffers from attrition (the loss of molecules during R&D due to safety, efficacy, or other issues), it is important to address what has been called the “valley of death” in preclinical development [The Boston Consulting Group, 2015] as soon as possible and boost early R&D [Payne, 2015]. The recently launched Global Antibiotic Research and Development Partnership (GARDP) is determined to developing new antibiotic treatments, promoting responsible use, and ensuring access for all.

GARDP was launched in May 2016, following the WHO Sixty-eighth World Health Assembly in 2015, which adopted the Global Action Plan on Antimicrobial Resistance (GAP-AMR), requesting the WHO Secretariat to propose:

- Options for the establishment of new partnerships to identify priorities for new treatments, diagnostics, and vaccines to fight resistant pathogens
- To act as the vehicle for securing and managing investment in new medicines, diagnostics, vaccines and other interventions
- To establish open collaborative models of research and development facilitating access to the outcomes of such research.

GARDP is hosted by DNDi and is presently in its set-up phase. GARDP aims to have at least two projects that address urgent global health needs ready for implementation by the end of 2016, and two more by the end of 2017. To date, GARDP has secured seed funding commitments from:

- The Federal Ministry of Health of Germany
- The Netherlands’ Ministry of Health Welfare and Sports
- The South African Medical Research Council
- The United Kingdom Department for International Development
- The Swiss Federal Office of Public Health
- Médecins Sans Frontières

totaling EUR 2.2M out of the projected EUR 3M required for the incubation phase.

DNDi’s partnership model for product development based on the experience gained from the field of neglected diseases will provide an important element in the overall strategy for R&D in the field of antibiotics. It can provide an important alternative to the traditional market-driven pharmaceutical approach, by focusing on products that the pharmaceutical industry will likely not develop by itself for lack of profitability or other reasons.

**Respective roles of DNDi and WHO in incubating GARDP**

Hosted by DNDi, the GARDP team is responsible for developing:

- The GARDP business plan
- Fundraising
- Building the scientific strategy
- Setting up governance and structure
- Preparing for the creation of a dedicated entity
- Building a product pipeline.

WHO will:
- Provide support in priority setting, stewardship, and access
- Report back to Member States
- Secure close collaboration with the AMR Secretariat, relevant WHO departments, the Essential Medicines List team, and the Global Health R&D Observatory
- Provide other technical input where needed.

GARDP’s governance is currently *de facto* embedded into that of DNDi during this start-up phase.

*Activities to date*
- Institut Pasteur scientific meeting (10 Projects reviewed)
- Neonatal sepsis (this Meeting)
- Gonorrhea (expert meeting held in June 2016)
- Drug Combination Platform (expert meeting planned in August 2016)
- The Antimicrobial Memory Recovery initiative (old/unpursued antibiotics, meeting planned in September 2016)

In the Q/A discussion, the need was emphasized to create market incentives so as to engage the industry, as was also a central topic in the final report of the AMR Review [O’Neill, 2015]. GARDP can play a role both in the ‘push’ by pooling resources and the ‘pull’ by facilitating development, such as helping to register drugs in regions where they are needed. One challenge may be to work with companies to market drugs in a differential process (e.g. in private vs. public markets).

*Mapping antimicrobial resistance globally*

Antimicrobial resistance is widespread, a growing concern, and has numerous distinct features, depending on bacterial pathogen and on the specific antibiotic. The frequency of hospital-acquired infections (HAIs) involving MRSA (methicillin-resistant *Staphylococcus aureus*) varies greatly by country. In the EU, MRSA occurrences diminished in six countries from 2010 to 2013, as shown by the 2014 Antimicrobial resistance interactive database (EARS-Net, the European Antimicrobial Resistance Surveillance Network). This success was ascribed to a number of measures taken in these countries.

Vancomycin resistance is described by five phenotypes (VanA-G); the two first are transmissible, yield resistance to the highest concentrations of the drug and concern *E. faecium* and *E. faecalis*. A distinct *E. faecium* subpopulation exists that is associated with nosocomial epidemics. Its clonal complex 17 (CC17), provides high-level vancomycin, ampicillin, and quinolone resistance [Ruiz-Garbajosa, 2012]. An overview was presented of reports that illustrate the increasing number of VRE (Vancomycin-Resistant Enterococci) *E. faecium* outbreaks across Europe. Antibiotics target various Gram-negative bacterial processes (Figure 1).
Figure 1: Mechanisms of Resistance in Gram-Negative Bacteria, and the Antibiotics Affected [Peleg, 2010].

β-Lactamases are divided in four classes (A-D; [Bush, 2010]); class D includes the carbapenemases [Patel, 2011]. Extended-Spectrum β-lactamases (ESBLs) have the ability to hydrolyze and cause resistance to oxyimino-cephalosporins (cefotaxime, ceftazidime, ceftriaxone, cefuroxime and cefepime) and monobactams (aztreonam), but not cephemycins (cefoxitin, cefotetan) or carbapenems (imipinem, meropenem, doripenem, ertapenem). They are inhibited by the ‘classical β-lactamase inhibitors’: clavulanic acid, sulbactam and tazobactam. *K. pneumoniae* isolates are often ESBL producers [Reinert, 2007]. The history and ‘family tree’ of ESBL gene variants was presented [Naas, 2008]; CTX-M is encoded by genes captured by mobile elements from chromosomes of *Kluyvera* spp., whereas CTX-M-15 is a community-acquired *E. coli* variant. This variant ST131, is globally distributed [Nicolas-Chanoine, 2014]. By contrast, *Enterobacteriaceae* producing carbapenemases vary by region for the different variants: KPC, ndm-1, VIM+KPC or OXA-48. [Lee, 2016].

A particularly impressive plasmid is NDM-HK (Figure 2). It confers resistance against β-lactams (bla(TEM-1), bla(NDM-1), Δbla(DHA-1)), aminoglycosides (aacC2, armA), sulphonamides (sul1) and macrolides (mel, mph2) as well as ultraviolet radiation. Bacteria that harbour these plasmids are - in principle - only sensitive to colistin and tigecycline.
NDM-HK, which is easily transmissible between Gram-negative bacteria, harbours a newly identified carbapenemase, ndm-1, which belongs to the group of metalloproteases. Ndm-1 was first identified in India in 2006, but is now found globally.

In summary, the most serious species/strains seen today are the clonally spreading *Klebsiella pneumoniae* ST258 with the KPC gene, the IncL/M plasmid with the OXA-48 gene and the ndm-1 carbapenemase gene on numerous broad-range plasmids. Among carriers for these AMR bacteria are household members and pets, animals (husbandry), travel and food.

**The global clinical epidemiology of neonatal serious bacterial infection (sepsis)**

The global burden of neonatal sepsis was only recently estimated [Seale, 2014]. Diagnosis for the condition is driven by clinical algorithms that are based on a set of observations, including: difficulty feeding, lack of non-stimulated movement, fever or body temperatures below 35.5°C, high respiratory
rate, severe chest indrawing and history of convulsions (among other observations). The pSBI (possible severe bacterial infection) Investigator Group has surveyed the literature for studies that evaluate the problem. By looking at data from 22 studies, for 259,944 neonates with 20,196 pSBI cases it concluded that pSBI occurs predominantly in sub-Saharan Africa, Latin America and, to lesser extent, in India and Southeast Asia [Seale, 2014]. The overall risk was estimated at 7.6% (with a 95% confidence interval of 6.1-9.2%). The relative risk is higher for males (1.12), and the overall fatality risk is 10%. There was virtually no useable data for impairment amongst survivors of neonatal sepsis. Our view of the problem is obscured by a lack of accurate reporting: absent adequate laboratory structures for blood culture, CSF analyses and molecular biology. The STROBE-NI (STrengthening the reporting of OBServational studies in Epidemiology for Newborn Infection) initiative aims at improving research reporting in this area. Finally, simplified antibiotic regimens are being evaluated for efficacy in the regions where these are needed. In 2015 the WHO issued guidelines for young infants where referral is not feasible [World Health Organization, 2015].

Another presentation looked at neonatal sepsis among hospitalized babies (mostly relating to HICs), predominantly very low birth-weight and pre-term infants. These are vulnerable to infection for a number of reasons including their incapacity to mount a good immune defense. A distinction was made between early-onset sepsis (EOS) <48 hours, and late-onset sepsis (LOS) >48 hours after birth. In hospitals, LOS mostly represents Hospital Acquired Infection (HAI). In these settings Group B streptococci or Gram-negative bacteria (especially E.coli) are responsible for the majority of early-onset sepsis cases, while late-onset sepsis is associated with Coagulase-negative Staphylococci, S. aureus and Enterococci; among Gram-negative bacteria are other enterobacteriaceae (in addition to E. coli), and fungi [Cailes, 2015]. A more detailed age at presentation by individual pathogens was presented from unpublished data from the neonIN (neonatal infection) European surveillance network.

Of particular (and rapidly growing) concern globally are infections with extended spectrum β-lactamase (ESBL)-producing E. coli and Klebsiella pneumoniae [Murray, 2015]. Genes encoding these lactamases reside on genetic elements that shuttle between the bacterium’s central genome and plasmids. The latter are easily transferred horizontally and vertically among Gram-negative bacteria. AMR is estimated to be responsible for over a 100,000 neonatal deaths in India, and other countries are proportionally affected [Laxminarayan, 2016a; Laxminarayan, 2016b]. Resistance frequencies against ampicillin, gentamicin, ceftriaxone, ciprofloxacin and ceftriaxone in E. coli, Klebsiella spp., Enterobacter spp., Acinetobacter spp. and Pseudomonas spp. were presented for Africa and Asia [Le Doare, 2015]. Such data are being used to determine and refine optimal empiric antimicrobial regimens [Bielicki, 2016].

Multi-Drug resistance in neonates in Africa

Overall, available data come predominantly not from areas with the most deaths. Antimicrobial resistance is increasing, but is potentially unrecognized. Specimen collection is variable in Africa, with high contamination values (19%) in Botswana; other issues include laboratory proficiency, and access to biomarkers. AMR surveillance (in South Africa) involves passive surveillance based on public sector laboratory results and recent sentinel site active surveillance from a few, largely academic sites. The latter includes ESBL Gram-negatives, MDR non-enterobacteriaceae, MRSA and (emerging) Azole-resistant fungi, carbapenem-resistance, and colistin resistance.

Fifteen African countries are now reporting on carbapenemase-producing GNBs [Manenzhe, 2015]. Among African countries, South Africa is particularly well-equipped for neonatal care. Quarter-by-quarter bacterial isolate characterizations were shown from a South African ward. K. pneumoniae, A baumannii and P. aeruginosa were the most common, and many were MDRGNs: >95% of Klebsiella were ESBL-producing, many A baumannii were only susceptible to colistin, but colistin-resistant Acinetobacter were
seen in 2016, while many fungi were azole resistant. Neonates are susceptible to *Candida* infection, which is rarely seen in older children. Sensitivity of fungi to antimicrobials varied significantly by geographical area within the country. Increasingly non- *albicans* species are seen as well, and there is limited access to antifungals: often, only fluconazole and/or amphotericin B are used, with almost no access to newer azoles or echinocandins. South Africa has set up standard treatment guidelines:

- **Early-Onset Sepsis:**
  - ampicillin + gentamicin
- **Suspected nosocomial sepsis:**
  - cefotaxime + gentamicin ± metronidazole (2013)
  - piperacillin-tazobactam + amikacin (2016 – draft)
  - ‘3rd-line’: meropenem (2016 – draft)
- **Meningitis:**
  - cefotaxime + ampicillin
- **Necrotizing Enterocolitis:**
  - ampicillin + gentamicin ± metronidazole (2013)

The role of HIV in neonatal sepsis is poorly understood. It is associated with prematurity and low birth weight but it is not clear if beyond these factors HIV contributes a risk by itself. The co-occurrence of other maternal diseases such as tuberculosis and syphilis needs to be evaluated as well. Polymicrobial infections are not uncommon (25%) but are often under-reported.

Paediatric antimicrobial stewardship has seen minimal uptake in Africa; it is largely confined to academic, urban centres, with limited expertise among specialists, subspecialists, nurses, pharmacists and microbiologists. There is resistance to ‘change’ and a lack of reimbursement of additional costs. Yet such programmes can bring significant benefits, as was demonstrated in Senegal [Landre-Peigne, 2011]. There is little oversight of antibiotic use in the private sector, and in South Africa this is an area where AMR is the largest problem.

**MDR in neonates in India**

Mortality among neonates weighing between 1 and 1.5 kg is 38-53% in this region. Small pilot studies have shown that it is possible to reduce mortality in this setting by reducing overcrowding, and avoiding the use of stock solutions [Singh, 1988]. An experiment was carried out in Jaipur to test a set of simple interventions: rational admissions and early discharge, entrusting mothers in care-giving, enforcing asepsis routines, aggressive enteral feeding, abandoning unnecessary interventions, protocol-based management, rational antibiotics and training and empowerment of nurses. This strategy resulted in a two-fold improvement in neonatal survival [Agarwal, 2007].

Very concerning data from the Delhi Neonatal Infection Surveillance (DeNIS) Network (including both inborn and out born) demonstrated that unlike historical data, the most commonly seen organisms are now *Klebsiella* spp., *E. coli*, and *S. aureus*, followed by *Acinetobacter* spp. and group B streptococci. The first three showed nearly universal resistance to ampicillin, cefotaxime, and gentamicin. Very high levels of carbapenem resistance were observed in *Acinetobacter, E. coli and Klebsiella*.

India has set up a Neonatal Sepsis Registry and Molecular Epidemiology of Bacterial Isolates (2010-5). The first phase (2Q2011) was preparation, standardization, training, etc.; phase 2 was surveillance until hospital discharge (July-2011-Feb-2014) and phase 3, molecular typing (2014-May 2015). Among the queries to the large dataset (13,530 births) are a distribution of pathogens in sepsis. Fairly evenly distributed among *Acinetobacter, E. coli, S. aureus and Klebsiella* in the inborn cohort. AMR
was very high among all species (typically around 30-70%). For the out born cohort (2,058 births), sepsis occurred in 55%, with *Candida* predominating (various species). AMR was even higher, between 80 and 90% for *Acinetobacter* and *Klebsiella*. The latter often harbored the ndm-1 plasmid (81%).

There is literature data on the occurrence of hospital-based ESBL* Klebsiella (27-87%) and *E. coli* (64-73%), MRSA (56-70%), VRSA (0-36%) and carbapenem resistance (0-25%). An overall conclusion for India is that MDR *Acinetobacter* has emerged as a dominant pathogen, and that 60% of sepsis cases occur within 72 h after birth. The rise of AMR is alarming, with the frequent occurrence of ndm-1 in *Klebsiella* and Oxa in *Acinetobacter*. A surprise finding was the predominance of fungi in referred infants.

**Global Neonatal Networks**

In HICs a number if networks are active:

- iNEO (The International Network for Evaluating Outcomes in Neonates)
- eNewborn (European Neonatal Benchmarking and Evaluation Programme)
- VON (Vermont Oxford Network)
- INC (International Neonatal Consortium)
- neonIN (European neonatal infection network)

The EU-funded GRIP (Global Research in Paediatrics) survey is reporting on existing neonatal networks outside the EU. This identified in addition:

- **North America**
  - NICHD: Paediatric Trials Network (Duke)
  - iACT (Instant Acceptance and Commitment Therapy): non-profit with seed funding from industry
    - Multipurpose site funding including neonates
    - Global interoperability

- **Europe**
  - European Paediatric Clinical Trials Research Infrastructure (on ESFRI Road Map)
  - Potential IMI2 call for site management network
    - Multipurpose site funding including neonates
    - Global interoperability

- **Central/South America**
  - SIBEN (Iberoamerican Society of Neonatology)
  - NeoCosur (Chile)
  - BNRN (Brazilian Neonatal Research Network)

- **Africa**
  - Egyptian Neonatal Network
  - South Africa (in development)

- **China**
  - The Chinese Neonatal Network

- **India**
  - (in development)

- **Middle East**
  - NCPNN (The National Collaborative Perinatal Network- Lebanon)

- **Australia and New Zealand**
  - ANZNN (The Australian Paediatric Network)
  - The Maternal and Neonatal Clinical Network

It was recognized that there are no global neonatal networks with clinical trial capacity. Virtually all networks reflect only a limited number of countries and generally conduct observational studies.
Previous clinical trials in neonatal sepsis (especially in LMICs) have been conducted in the community setting. The group could identify no previous global trial of neonatal sepsis conducted in the hospital setting.

Regulatory aspects of drug discovery for neonatal sepsis

The main (stringent) regulatory authorities, namely the US FDA, the EU EMA (European Union Medicines Agency) and Japan follow the International Council for Harmonisation (ICH). In parallel there are the Agencies in Switzerland, Canada, and Australia. The situation in LMICs is quite variable, for instance such agencies do not exist in Rwanda.

In terms of guidelines, the US FDA has issued PSP (Paediatric Study Plans), and for Clinical Pharmacology in Paediatrics a Neonatal supplement will likely soon be issued in the form of an INC White Paper. The EMA has issued PIP (Paediatric Investigation Plan) templates, Neonatal guidelines, and set up an EnprEMA (European network of paediatric research-European Medicines Agency) Working Group.

Thus, there are no global guidelines for the clinical development of antibiotics for neonates. Trial approval involves a national competent authority, an ethics committee, and site approval. This is a country-by-country affair that may be difficult in countries that are particularly risk-averse for neonates; the risk for not doing research in this area is often under-estimated (the omission bias).

The recommended strategy is, first, to develop a ‘regulators-independent’ global clinical development plan. Then to: (1) aim for an integrated dialogue with regulators; (2) treat regulators independently; and (3) develop relationships with regulators.

Experience with neonatal sepsis trial designs

The MRC Clinical Trials Unit at UCL

The trial design should be driven by the scientific question. Trials in this area should always be adaptive to some degree, and the sponsors should provide explicit guidance to the Data Monitoring Committee about what to consider as triggers for adaptation (e.g. control group event rates, compliance deviations) as well as early stopping for efficacy/safety reasons. Given that the opportunity to do paediatric trials is so limited, sponsors need to be creative when such an opportunity presents itself.

The key goal is to develop new empiric antibiotic regimens for the treatment of neonatal sepsis in settings of high AMR prevalence. The main caveat is that the design is as good as the data it is based on: resistance prevalence, and hence appropriate empiric options to test, and PK/PD models that determine the optimal regimen.

Given the high rates of ESBL+ GN bacteria at potential sites, an ampicillin/gentamicin trial may not be suitable at all sites. Currently two groups are envisaged:

- a fosfomycin-based regimen (possibly fosfomycin plus amikacin)
- a meropenem regimen (representing the only widely available β-lactam regimen that would cover ESBL-producing Gram-negative bacteria)

Because of different formulations, routes and dosing, trials will be open-label. The strategic questions that need to be dealt with are:

- Efficacy vs effectiveness
- Outcomes, particularly primary
- Changes to management/compliance with strategy
- Hypothesis (superiority vs non-inferiority)
- Other set of overlapping questions relating to
  - Population – when to recruit
  - Duration of antibiotics to compare
A particular problem is how to count/assess patients who change treatments. Randomized strategy has to cover both initial and subsequent management. The other variable is treatment of drug-sensitive vs AMR infections, and at what frequency they occur. Other benefits to measure in outcomes include a shortened hospital stay/costs.

**The PENTA experience**

The PENTA (Paediatric European Network for Treatment of AIDS) Network, founded in 1991 manages clinical trials, cohort studies collaboration, pregnancy studies and training/ educational programmes. A large number of PENTA trials were (are being) conducted in infants and children. In 2010, the Network morphed into PENTA-ID, into the broader area of paediatric infectious diseases, with an emphasis on neglected and complex diseases. Among its activities are a number of antimicrobial trials:

- **NEOmero/vanc:**
  - NEOMERO-1: *Efficacy, pharmacokinetics and safety of meropenem in infants ≤90 days with clinical or confirmed late-onset sepsis: an European multicentre randomized phase 3 trial*
  - NEOMERO-2: *A European Multicentre Phase I-ii Clinical Trial Of Meropenem In Infants <3 Months With Bacterial Meningitis*
  - NeoVanc: *Treatment of late onset bacterial sepsis caused by Vancomycin susceptible bacteria in neonates and infants aged under three months*

- **COMBACTE**
- **PREPARE**
- **(G)ARPEC**
- **EPeMyn**
- **RESCEU**

The first three trials were described in detail, as well as the PENTA-ID structure, funding sources and key people.

**Landscape analysis of old drugs to treat infections with MDR Gram-negatives**

There is a renewed interest in ‘forgotten’ antibiotics. A recent analysis for HICs [Pulcini, 2012] found that few antibiotics are marketed globally, due to economic reasons (small market size) and regulatory issues (Figure 3). The situation has worsened since 2011. A similar study would be needed in LMICs.
For such a drug to be of interest to a world that is increasingly populated by resistant pathogens it should:

- Be active against ESBL-producing *Enterobacteriaceae* and/or CROs (Carbapenem resistant organisms)
- Have significant cerebrospinal fluid exposure (mandatory)
- Be available in oral, rectal, intramuscular, and intravenous formulations (if possible)
- Allow optimized PK/PD administration (e.g. prolonged infusion for β-lactams)
- Have a limited impact on microbiota.

In this context some candidates were presented:

- Temocillin (i.v.), which is not active against non-fermenting Gram negatives, and kills CRE (carbapenem-resistant *enterobacteriaceae*) and ESBL. However, there is limited clinical data, and CNS exposure is unknown.
- Mecillinam (i.v) and pivmecillinam (oral). For these there is some ESBL activity, but limited clinical data. For mecillinam this will only be useful if there is a low MIC (minimum inhibitory concentration) and low inoculum. CSF exposure may be low. These drugs may possibly be used with association with clavulanic acid.
- Colistin (polymyxin E) could be used single or in combination therapy, but it has poor CNS exposure. Moreover, *Serratia marcescens* and *Proteus* sp. are usually resistant.
- For Polymyxin B the situation is similar as to polymyxin E.
- Fosfomycin (i.v and p.a.) has excellent CSF exposure. It could be used in combination to avoid selection of resistance. On the downside, *Morganella morganii*, *Stenotrophomonas* spp. and *Acinetobacter* spp are resistant.
• Tobramycin /Amikacin target ESBL and CRO, depending on the epidemiology. Tobramycin is more active against *P. aeruginosa*, but has poor CNS exposure.

Finally a set of second-tier ‘revival’ candidates were discussed: Piperacillin – tazobactam, chloramphenicol and thiamphenicol, cefoxitin, cefoperazone-sulbactam, aztreonam, cefepime, cephalosporins, and clavulanic acid.

A case was made for the revival of colistin. This is an old antibiotic (introduced in 1959) that was not used in human medicine because of nephrotoxicity and neurotoxicity, though it is used to treat diarrhea in weaning piglets and calves. It is now being re-introduced in human medicine to treat infections due to carbapenemase-producing *Enterobacteriaceae*. Until recently no transferable resistance had been reported, but in 2016 plasmid-mediated colistin resistance was discovered [Coetzee, 2016; Elnahriry, 2016; Liu, 2016; Piffaretti, 2016; Zeng, 2016]. The gene that mediates this resistance, mcr-1, was found first in retail meat in 2011, and appeared in infected patients in 2012. In chicken, mcr-1-carrying strains can be traced back as early as the 1980s, with a rapid increase from 2009 [Liu, 2016]. The gene is distributed globally [Xavier, 2016]. It is often co-expressed with CTX-M (72%) and (to a lesser extent) with other resistance markers. Recently a second colistin-resistance gene was identified, mcr-2, also carried on a plasmid [Xavier, 2016].

It was noted (Q&A) that these plasmids, even when large, appear not to confer significant fitness costs to the carrier. Thus, even a global ‘antibiotic holiday’ would not likely result in the disappearance of these strains. The general problem is that safety for these drugs in infants is unknown.

**The neoAMR**

The introduction to this topic re-emphasized the challenge of the spread of MDR (multi-drug resistant) Gram-negatives (especially ampicillin/gentamycin), and noted that the WHO Pocket Book of Hospital Care for Children generic recommendations lists only eight major antibiotics for the treatment of all SBI (Serious Bacterial Infections) in neonates and children. The spread of MDR is especially facilitated in hospital settings, and the increasing numbers of preterm babies being delivered in such centres follows the worldwide trend in urbanization (seen for all regions). Problems in care for SBI in LMIC were listed: limited diagnostic lab capabilities, missing surveillance data, variable access to antibiotics because of the ir costs (especially to new ones, which may cost 5-10 k$ for a seven-day course), and problematic off-label use.

There are substantial differences in HAI patterns in neonates and children as compared to adults (data presented at the 33rd Annual European Society for Paediatric Infectious Diseases (ESPID) Meeting, Leipzig, 2015), with a prevalence of 4.2%. It was noted that ototoxicity, vestibulotoxicity and nephrotoxicity risks for neonates treated with aminoglycosides for MDR Gram-negatives appear to be low. However, ototoxicity risks appear higher with prolonged treatment, or when co-administered with loop diuretics. Furthermore, genetic predisposition may determine risk. But overall, toxicity risks appear lower than for other classes of antibiotics. A number of studies have looked at treating carbapenemase-producing *Klebsiella* infections. Different antibiotics combinations are being looked at as well as increasing dosage and extended infusion to maintain exposure above the MIC for longer. The problem is that neonates are typically not included in trials for new Gram-negative antibiotics, so information is lacking: Among 56 trials registered with clinicaltrials.gov as ‘active’, only two include neonates with sepsis. And an ESCMID (European Society of Clinical Microbiology and Infectious Diseases) review of 33 older antibiotics found that only six have a neonatal license, for example fosfomycin.

The neoAMR’s overall aims (Figure 4) are:
- To deliver globally applicable empiric and targeted antibiotic treatment regimens for neonatal sepsis
- To develop an expert group to elaborate consensus statements about key issues in the development of empiric treatment regimens for the treatment of neonatal sepsis
- To set up a global network of neonatal infection and other expert centres to design and conduct studies on the optimal use of off-patent antibiotics, and other strategies, for effective management of MDR and XDR (extensively drug-resistant) neonatal disease (including epidemiological, microbiological, in vitro and formulations investigations).
- To design and conduct pharmacokinetic, observational and interventional studies to determine efficacy and safety of new regimens compared to existing therapies for neonatal disease.
- To develop a conservation strategy for novel treatment regimens, including a stratified risk-based method for appropriate use of empiric/targeted antibiotic regimens for neonatal sepsis management in settings with varying prevalence of MDR and XDR neonatal disease.

**Figure 4: Overview of neoAMR work areas**

The project is divided in a set of Work Streams (WSs).

The WS1 objectives are to provide expert input to the consortium with respect to:

- the selection of potential agents to be taken forward for further evaluation;
- the preparation and conduct of studies; strategies for implementing novel empiric antibiotic regimens for the treatment of pSBI in settings of high prevalence of resistance to current regimens;
- develop an active advocacy and engagement strategy with relevant stakeholders, including the lay public.
Discussion focused for WS1 on the neoAMR governance structure, with the Funders-DNDi-Consortium hierarchy. It was recommended to highlight the programme’s output (new drug discovery and development programmes).

The **WS2** objectives are:
- To review the emerging global data on current prevalence of AMR in neonatal sepsis, including any clinical outcome and microbiological data
- To prospectively characterize the microbiological epidemiology, clinical presentation, management and outcomes of SBI; and to collect bloodstream infection (BSI) and CSF microbiology isolates
- To determine existing policies, procedures, guidelines and workload of NNUs of partner countries
- To use data from 1) and 2) to identify potential clinical sites for a phase III RCT (regulatory clinical trials) of empiric and targeted antibiotic regimens for neonatal sepsis
- To develop, refine and evaluate a decision tree-based model for the appropriate positioning of different empiric/targeted antibiotic regimens within settings of varying prevalence of MDR pathogens.

Discussion highlighted the challenge of observational studies and RCTs. How do we decide what is a representative geographical set of sites? How do we engage the clinicians, and access molecular biology resources? It was recommended to exploit existing networks. It was also mentioned that innovative formulation and combinations will extend the useful lifetime of existing drugs.

The **WS3** objectives are:
- To conduct a literature review of the molecular mechanisms of resistance globally of candidate drugs (e.g. fosfomycin)
- To determine an appropriate method of determining MICs of the candidate drugs within the LMIC setting
- To identify a representative global network of microbiology laboratories able to adequately conduct analysis of BSI and CSF isolates for resistance of key drugs
- To use validated questionnaires to identify appropriate levels of laboratory capacity
- To develop and conduct appropriate training packages to enhance local laboratory capacity
- To centralize where possible and appropriate BSI and CSF isolate DNA from both the observational and interventional WSs for Whole Genome Sequencing.

It was noted that molecular methods are well described. Networks exist where samples results are databased centrally. It was also noted that it is preferable to send DNA across borders rather than biological samples.

The **WS4a** objectives are:
- To conduct a pharmacokinetic meta-analysis to identify published models on target antimicrobials in neonates, identifying gaps in the literature
- For agents with adequate published PK, to use these models combined with *in vitro* PD for clinical trial simulation to define optimized dose and schedules
- For selected agents with appropriate formulations already available, to perform an optimally designed population three-way bioavailability study for oral, intramuscular, and intravenous routes of administration in neonates, including premature neonates
- To design optimal sampling schedules for PK secondary analysis in the main clinical trial
- To collaborate with industry partners to identify agents for which the development of formulations appropriate for use in the neonatal population is necessary.
The **WS4b** objectives are:

- To **define the neonatal test drug** regimen when administered as monotherapy that results in bacterial killing and prevents the emergence of resistance.
- To define the **nature and extent of the interaction of combination-based combination regimens** involving the key test drug(s) that prevent the emergence of drug resistance and result in maximal antibacterial activity.
- To define the **optimal combination regimens** for the key test drug(s) concerned.
- To identify **potential synergy between a range of potential test drugs**: e.g. amoxicillin (+/- clavulanate), gentamicin/amikacin and fosfomycin versus a range of MDRGNB organisms.
- To quantify concentrations of identified candidate antimicrobial combinations which optimize synergy or efficacy.

It was noted that for none of the compounds listed in the ‘forgotten drugs’ section adequate neonatal PK data exist. Yet a quick PK study requires only 50 babies. Moreover such a sample is sufficient to quantify exposure for a set of antibiotics, using HPLC. We need rapidly to get an idea on what drugs to move forward. Combination efficacies can be evaluated *in vitro*, and early PK/PD using the hollow fibre infection model. For these, the top pathogens can be selected.

**WS5a** will provide the general framework for the management of the clinical trials across different geographical settings:

- The coordination of activities related to the **regulatory and ethical issues** of the trial, ensuring that all relevant rules are complied with.
- The **identification of clinical sites** within collaborative partnerships and PENTA ID Networks.
- Creation and maintenance of a web-based Virtual Learning Environment (VLE) to facilitate the **development of the observational and interventional trial procedures** with specific distance learning modules to be used across different geographical settings.
- Development and implementation of **training modules** for the trial investigators and staff to ensure harmonized procedures compliant with GCP, GLP and the defined protocols.

The **WS5b** objectives are:

- To **design a randomized controlled trial** to evaluate the efficacy, safety (and impact on gut colonizing bacteria) of novel antibiotic regimens for the hospital treatment of Gram-negative neonatal bacterial sepsis in settings of high MDR prevalence.
- **To conduct the randomized controlled trial** in multiple neonatal unit sites in lower and middle income countries and in some high income countries with high MDR prevalence in accordance with Good Clinical Practice guidance and applicable international regulatory and legal frameworks.

It was noted that this activity will require a ‘pre-trial’ setup, involving education, as there is little experience. The expertise exists, but needs to be spread further.

WS1-4 can be seen together, collectively aimed at proposing possible new treatments to be tested. Again it was emphasized that WS1 is critical; this is the structure that drives the whole process and it must be constructed well to ensure proper governance.

It was emphasized that the project is still at its inception, and that all input (including after the Meeting) is welcome. The goal is to have a draft by Oct. 2016, with input from Business Development. In parallel, a funding strategy is to be developed.
Draft Target Product Profiles (TPPs)

The USFDA has provided guidelines on how to draft Target Product Profiles (TPPs). These were made available in 2007 but are still under review (feedback). The FDA has stated that ‘A TPP is a format for a summary of a drug development program described in terms of labeling concepts’. A TPP is voluntary but highly recommended, and the FDA will ask for it in discussions. TPPs have been in use for much longer in the Pharma industry, and are typically drafted at the target proposal stage (i.e. very early in the R&D process). They can be updated over time (e.g. in the light of the changing clinical landscape) and provide go/no-go decision guidance to drug developers. In the area of neglected diseases, TPPs have been published by the community for malaria [Burrows, 2013] and other such diseases [Katsuno, 2015].

Below is a list of the FDA recommended key sections for TPPs, but not all sections in the FDA template are required in all drug development projects.

- Indications and usage
- Dosage and administration
- Dosage forms and strengths
- Contraindications
- Warnings and precautions
- Adverse reactions
- Drug interactions
- Use in specific populations
- Drug abuse and dependence
- Over dosage
- Description
- Clinical pharmacology
- Nonclinical toxicology
- Clinical studies
- References
- How supplied/storage and handling
- Patient counseling information

Checklists, sections and examples for TPPs for antibiotics were presented. For neonatal sepsis two TPPs are being proposed. Both TPPs as presented here are to be considered as drafts for further discussion.
TPP1 represents an alternative to the gold standard amoxicillin/gentamycin or ceftriaxone/gentamycin in hospitals of high prevalence of resistance, as a carbapenem-sparing therapy. This may include repurposed drugs (some with neonatal/paediatric) indication such as: fosfomycin, temocillin, mecillinam, nitrofurantoin, minocycline, chloramphenicol. It covers monotherapies and combinations.

**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/gentamycin or ceftriaxone/gentamycin in claimed indication

**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)

**Pharmacoeconomics**
Reduction of intensive care unit and hospitalization days (modelling).

**Main Competitors**
amoxicillin/gentamycin or ceftriaxone/gentamycin

TPP2 represents therapy in hospitals of high prevalence of carbapenemases, for proven *Klebsiella, Pseudomonas* or *Acinetobacter* infection (*Enterobacteriaceae*). Candidates are: Colistin [Jajoo, 2011]; A β-lactam + avibactam: ceftazidime/avibactam, ceftaroline/avibactam or meropenem/avibactam (?). In addition, forgotten or modern aminoglycosides (alone or in combination): plazomycin and netilmicin and potentially others may be included. May also include drugs currently in clinical trials for other indications.

**Indication**
Neonatal sepsis, where MDR Gram-negative pathogens have been demonstrated, including *K. pneumoniae, P. aeruginosa* or *Acinetobacter* spp. Including CRO’s

**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

**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)

**Pharmacoeconomics**
Reduction of intensive care unit and hospitalization days (modelling).

**Main Competitors**
Colistin monotherapy
Both TPPs are part of the neoAMR proposal. There was discussion over pricing; new drugs should be affordable, at least in LMICs, at prices below those for current drugs. There was concern about the upward trend in pricing of existing drugs, which does not seem to relate to manufacturing costs (market-driven). It was also observed that the drug discovery pipeline for the TPP2 is currently empty.

**Sustainable access**

Sustainable access includes addressing innovation, access, conservation and stewardship. A key challenge is how to navigate a wide range of contexts in HIC and LMICs. GARDP will need to go beyond the traditional PDP approach, especially considering its broad geographical and country income contexts and varying TPPs. In general, GARDP could consider the following: i) hosting an incentive mechanism; ii) responsible and fair licensing and pricing with potentially some market segmentation; iii) supporting registration in priority countries; iv) phase IV and implementation studies; v) promoting policy change with the support of WHO; and vi) promoting and supporting the set-up of a Global Drug Facility (GDF)-type procurement mechanism for certain specialized antibiotics. Practical measures could also be implemented at country level ranging from training, building local capacity in key areas, monitoring studies with pilot programmes, and use of appropriate packaging. Further work needs to be done on how engagement with local private practitioners can support sustainable access.

Specific to the neoAMR project, a number of practical steps were discussed that can be taken to achieve the ambitious goals. Among the many examples given are a support to register drugs in priority countries, working with the WHO to ensure policy changes/guidelines, ensure fair and sustainable pricing, supporting Phase IV post marketing studies, designing country level strategies, supporting lab capacity building, health personnel training, health promotion and education.

**Conclusions**

As for other infectious diseases, alarming multi-drug resistance in neonatal sepsis is on the rise, rapidly outpacing drug and novel regimen discovery. A concerted effort is required to better manage the use of existing drugs through innovative combinations and/or formulations, and feeding the pipeline with innovative NCEs. A number of ‘forgotten’ antibiotics exist and their suitability for neonatal use is to be explored urgently. In order to be successful this requires better surveillance of the state of AMR among the relevant species associated with neonatal sepsis, which in turn dictates which combinations or drugs are to be tested in trials. In addition, PK data for promising candidate drugs (both old and new) need to be established in neonates, and PK/PD parameters for drugs, formulations and combinations that may be tested in clinical trials. Such trials need to be designed with meaningful and practical endpoints in an adaptive design with clear upfront decision points. Existing networks and organizations (PENTA-ID, molecular biology labs and others) are to be employed optimally in these endeavors. The neoAMR work packages were reviewed. There was a clear recommendation to have a well-defined management structure (WS1 & 6) that will help drive WS2-5 toward the development of novel treatments for neonatal sepsis. Overall, the group was supportive of and highly engaged in the project.

**Attendees**

Anna Seale  
London School of Hygiene & Tropical Medicine, UK

Anthony Costello  
World Health Organization, Geneva, Switzerland

Aparna Narendrua  
GARDP/DNDi

Bernadette Cappello  
World Health Organization, Geneva, Switzerland

Carlo Giaquinto  
PENTA-ID: Paediatric European Network for the Treatment of AIDS and Infectious Diseases, Italy

Céline Pulcini  
University of Lorraine, CHU Nancy, France

Gabrielle Landry  
GARDP/DNDi
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gary Reubenson</td>
<td>Rahima Moosa Mother and Child Hospital, University of the Witwatersrand, South Africa</td>
</tr>
<tr>
<td>Herman Goossens</td>
<td>University Antwerp, Belgium</td>
</tr>
<tr>
<td>Jean-Pierre Paccaud</td>
<td>GARDP/DNDi</td>
</tr>
<tr>
<td>Jean-René Kiechel</td>
<td>DNDi</td>
</tr>
<tr>
<td>John van den Anker</td>
<td>University Basel, Switzerland</td>
</tr>
<tr>
<td>Julia Bielicki</td>
<td>St George's, University of London, UK</td>
</tr>
<tr>
<td>Jutta Heim</td>
<td>GARDP</td>
</tr>
<tr>
<td>Leila Quinodoz</td>
<td>GARDP</td>
</tr>
<tr>
<td>Liz Tayler</td>
<td>World Health Organization, Geneva, Switzerland</td>
</tr>
<tr>
<td>Manica Balasegaram</td>
<td>GARDP</td>
</tr>
<tr>
<td>Mark Turner</td>
<td>University Liverpool, UK</td>
</tr>
<tr>
<td>Mike Sharland</td>
<td>St George's, University of London, UK</td>
</tr>
<tr>
<td>Paul Heath</td>
<td>St George's, University of London, UK</td>
</tr>
<tr>
<td>Pauline Berra</td>
<td>GARDP</td>
</tr>
<tr>
<td>Ramesh Argawal</td>
<td>AIIMS Hospital, India</td>
</tr>
<tr>
<td>Rob Hooft van Huijsduijen</td>
<td>GARDP</td>
</tr>
<tr>
<td>Samir Saha</td>
<td>Child Health Research Foundation at the Bangladesh Institute of Child Health, Dhaka Shishu Hospital in Dhaka, Bangladesh</td>
</tr>
<tr>
<td>Sara Walker</td>
<td>Medical Research Council Clinical Trials Unit, UK</td>
</tr>
</tbody>
</table>

**Abbreviations**

(p)SBI, (possible) severe bacterial infection; (S)AE, (Serious) adverse event; AMR, antimicrobial resistance; AMR, antimicrobial resistance; ANISA, Aetiology of Neonatal Infection in South Asia; ANZNN, The Australian Paediatric Network; ART, Antiretroviral therapy; BNRN, Brazilian Neonatal Research Network; BSI, bloodstream infection; cIAI, Complicated Intra-Abdominal Infections; CRE, Carbapenem-resistant *enterobacteriaceae*; CRO, Carbapenem resistant organisms; CSF, Cerebrospinal fluid; cSSSI, cSSSI (complicated skin and skin structure infection); cUTI, Complicated urinary tract infections; DeNIS, Delhi Neonatal Infection Surveillance; DNDi, Drugs for Neglected Diseases initiative; DOT, Directly observed therapy; EARS-Net, European Antimicrobial Resistance Surveillance Network; EMA, European Union Medicines Agency; eNewborn, European Neonatal Benchmarking and Evaluation Programme; EnprEMA, European network of paediatric research-European Medicines Agency; EOS, early-onset sepsis; ESBL, Extended spectrum β-lactamase; ESBL, Extended-Spectrum β-lactamase; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESPIDM, European Society for Paediatric Infectious Diseases; EU, European Union; FDA, Food and Drug Administration; GARDP, Global Antibiotic Research And Development; GARPEC, Global Antimicrobial Resistance, Prescribing, and Efficacy Among Neonates and Children; GCP, Good Clinical Practice; GLP, Good Laboratory Practice; GRIP, Global Research in Paediatrics; HAI, Hospital Acquired Infection; HIC, high-income countries; iACT, Instant Acceptance and Commitment Therapy; ICH, International Council for Harmonisation; INC, International Neonatal Consortium; tNEO, The International Network for Evaluating Outcomes in Neonates; LMICs, Low/Middle Income countries; LOS, late-onset sepsis; MDR, multi-drug resistant; MDRGNB, Multidrug-resistant Gram-negative bacteria; MIC, Minimum inhibitory concentration; MRC, Medical Research Council; MRSA, Methicillin-resistant *Staphylococcus aureus*; NCE, New chemical entity; NCPNN, The National Collaborative Perinatal Network; neonIN, neonatal infection surveillance; PD, Pharmacodynamic; PENTA, Paediatric European Network for Treatment of AIDS; PIP, Paediatric investigation plans; PK, Pharmacokinetic; PSP, Paediatric Study Plans; RCT, regulatory clinical trial; SIBEN, Iberoamerican Society of Neonatology; STROBE-NI, STrengthening the reporting of Observational studies in Epidemiology for Newborn Infection; TPP, Target Product Profile; UCL, University College London; VAP, Ventilator-Associated Pneumonia; VLE, Virtual Learning Environment; VON, Vermont Oxford Network; VRE, Vancomycin-Resistant Enterococci; WHO, World Health Organization; WP, Workpackage; XDR, extensively drug resistant.

**References**


