NeoOBS – Observational Study

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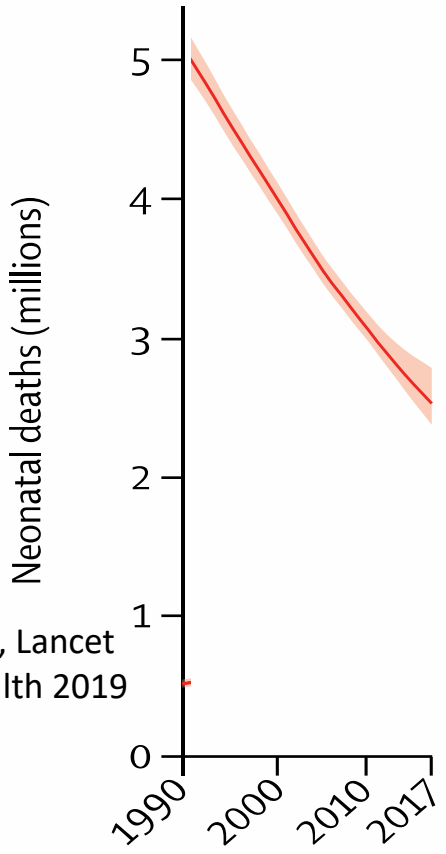
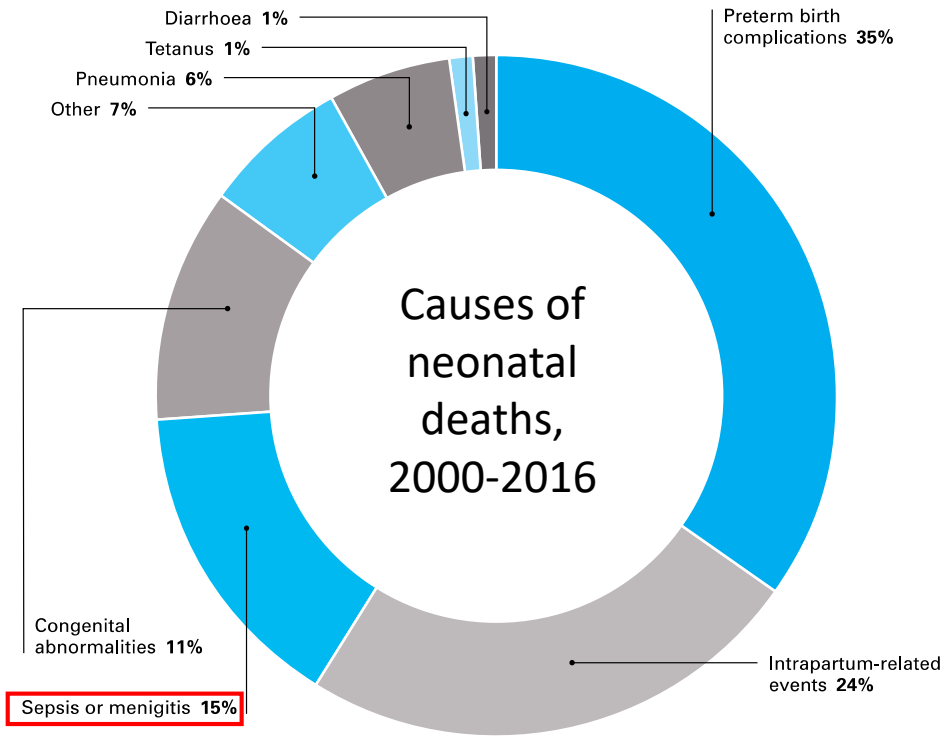
2019

Global neonatal mortality is still high



Hug et al, Lancet Glob Health 2019



Source: WHO and Maternal and Child Epidemiology Estimation Group (MCEE). 2018.

Adequate diagnosis and treatment of infection are crucial for reducing neonatal mortality

Treatment of neonatal sepsis – 2017 WHO guidelines

5. Management of neonatal sepsis

Prophylactic antibiotics for prevention of sepsis

- A neonate with risk factors for infection (i.e. membranes ruptured >18 hours before delivery, mother had fever >38 °C before delivery or during labour, or amniotic fluid was foul smelling or purulent) should be treated with the prophylactic antibiotics ampicillin (Intramuscular – IM – or intravenously, IV) and gentamicin for at least two days. After two days, the neonate should be reassessed and treatment continued only if there are signs of sepsis or a positive blood culture.

  (Weak recommendation, very low quality evidence) Source

Empirical antibiotics for suspected neonatal sepsis

- Neonates with signs of sepsis should be treated with ampicillin (or penicillin) and gentamicin as the first line antibiotic treatment for at least 10 days.

  (Strong recommendation, low quality evidence Source

- If a neonate with sepsis is at greater risk of staphylococcus infection (e.g. extensive skin pustules, abscess, or omphalitis in addition to signs of sepsis), they should be given cloxacillin and gentamicin instead of penicillin and gentamicin.

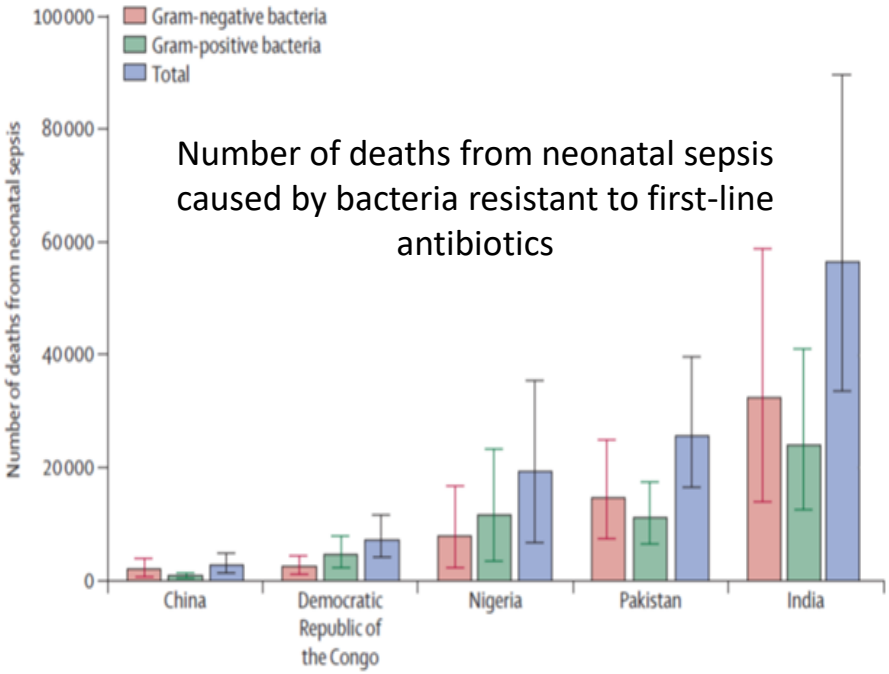
  (Strong recommendation, quality of evidence not graded) Source

- Where possible, blood cultures should be obtained before starting antibiotics. If an infant does not improve in two to three days, antibiotic treatment should be changed, or the infant should be referred for further management.

  (Strong recommendation, quality of evidence not graded) Source

Disease burden: AMR in neonatal sepsis

Nearly half of pathogens causing serious bacterial infections in neonates are resistant to the WHO first-line and second-line treatment



→ AMR potentially responsible for about 30% of all global neonatal sepsis deaths

(Laxminarayan R, 2016)

Antimicrobial Resistance is a major barrier to achieving the goal of **reducing neonatal mortality**

World Health Organization

GARDP
Global Antibiotic Research & Development Partnership

Neonatal Sepsis Program

NeoAMR global consortium

Primary objective: Develop 1-2 new treatments within the next 6 years

1. An *empirical* treatment for babies with possible serious bacterial infection in areas with a high prevalence of drug-resistant Gram-negative pathogens.

2. A treatment for babies when MDR Gram-negative pathogens are confirmed.

NeoOBS

NeoAMR Global Neonatal Sepsis Observational Study: A Prospective Cohort Study Of Sepsis In Hospitalised Neonates

Chief investigators: Mike Sharland and Paul Heath
St. George's University of London

Lead microbiologist: Herman Goossens
University of Antwerp / COMBACTE-LAB-Net

World Health Organization

PENTA - ID www.penta-id.org

GARDP Global Antibiotic Research & Development Partnership

NeoOBS – Protocol

- Prospective, multinational, multicenter, observational cohort study of infants with significant clinical sepsis

- Designed to <u>evaluate the management of neonatal sepsis in different countries:</u>

  1. Use of healthcare resources
  2. Current clinical practice
  3. Outcomes
  4. Risk factors for poor outcomes

  etc.

NeoOBS – Protocol

19 Sites in 11 countries:

Europe: Italy
Greece

Asia: Bangladesh
China
India
Thailand
Vietnam

Africa: Kenya
South Africa
Uganda

South America: Brazil

Ribeirão Preto – HCFMRP-USP
São Paulo – Santa Casa

NeoOBS – Protocol

Primary Objective

- To characterise mortality rates in infants treated for clinical sepsis

Secondary objectives

- Characterise the clinical presentation, mortality risk factors and outcomes of infants with sepsis
- Collect information on antibiotic dose and duration to inform AMR stewardship practices
- To collect isolates from routine blood/CSF for species determination and susceptibility
- Update data on the prevalence of AMR in neonatal sepsis
- Collect a cohort of babies with infection by carbapenem-resistant Gram-negative pathogens

NeoOBS Endpoints

Primary Endpoint

Mortality at 28 days after enrolment

Secondary Endpoints

1. Daily physiological observations of infants treated for significant sepsis

2. Frequency of readmissions, need for change or subsequent courses of antibiotics

3. Incidence of culture-positive and culture-negative sepsis

NeoOBS study

Clinical sepsis cohort

Microbiology cohort

Inclusion Criteria:

- Current in-patient in the hospital
- <60 days of age
- Informed consent from parent / guardian

Clinical team

Microbiology team

-High clinical suspicion of sepsis & planned treatment with IV antibiotics
-2 or more clinical signs or laboratory investigations

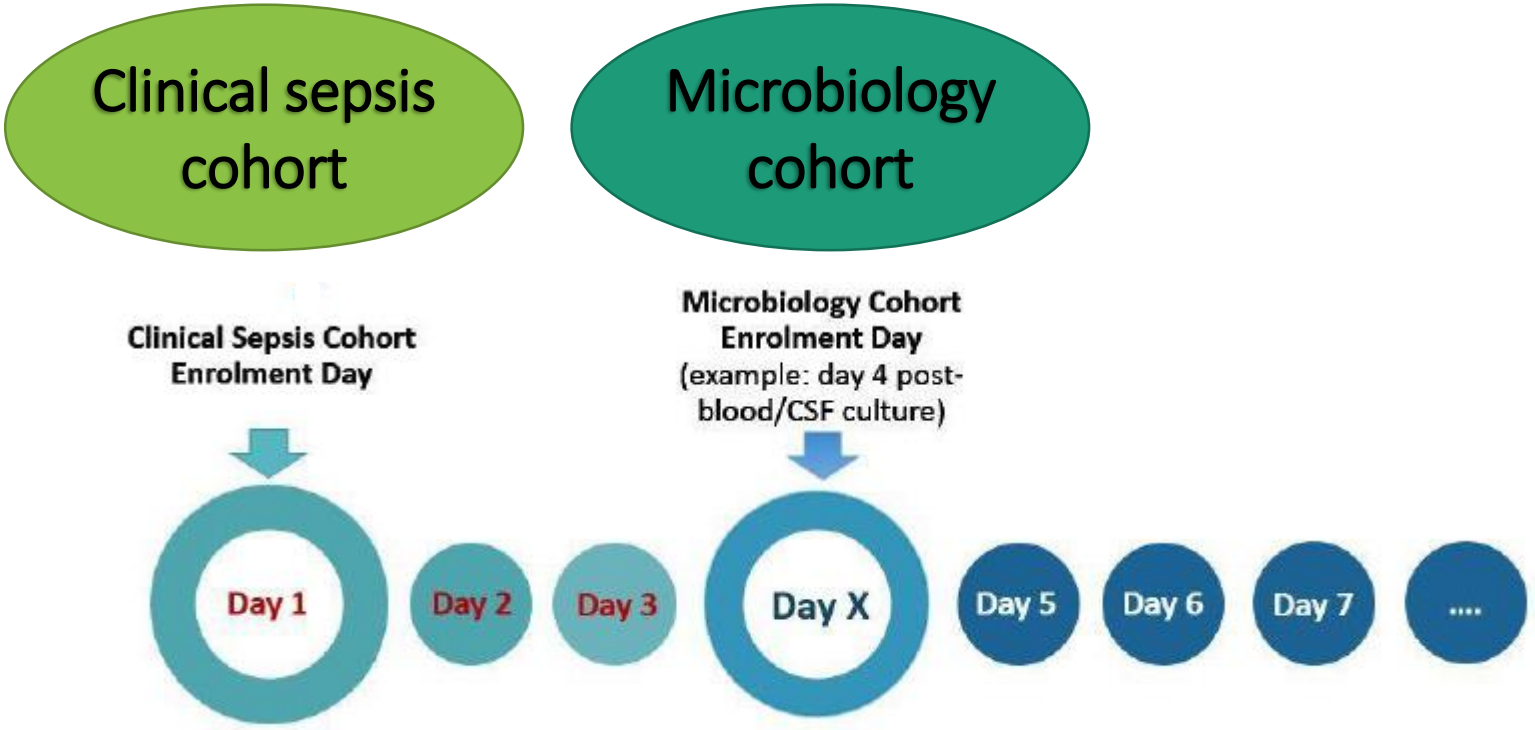
New episode of infection with:
-*Candida* species isolated from blood culture OR
-Carbapenem-resistant organism isolated from blood culture OR
-Confirmed bacterial meningitis

2 or more from the following list of clinical signs and/or laboratory abnormalities:

Difficulty feeding	Feeding intolerance	Convulsions
Abnormal posturing	Hypotonia	Irritability
No movement or movement only when stimulated	Lethargy / Drowsiness	Reduced urinary output
Bulging fontanel	Diarrhea (watery stools)	Pus from umbilical stump
Abnormal temperature / Abnormal heart rate (>180 / min or <100 / min)	Severe chest in-drawing or increased O_2 requirement / ventilation support	CRT> 3 sec or impaired peripheral perfusion
Grunting	Apnea	Cyanosis
Multiple (>10) skin pustules	Abdominal distension	Petechial rash

WBC count <4,000 or >20,000 x 10^9 cells/L	Acidosis (BE <–10 mmol/L or blood lactate >2 mmol/L)
ANC<1500 mm3	Immature -to-total (IT) polymorph ratio of > 0.2
CRP>10 mg/dL or >1 mg/L	

NeoOBS study - Enrolment



Assessments during the study

1. Baseline information (mother, labor, delivery)
2. Diagnoses at admission
3. Presence of neonatal infection risk factors
4. Clinical signs of infection
5. Daily clinical record: vital signs, supportive measures and devices
6. Daily antibiotic record: dose, route, frequency and reason for stopping antibiotics
7. Microbiology/ laboratory results
8. Final diagnoses and outcome at Day 28

Microbiology Procedures

- **Local routine procedures:**
  - Culture
  - Identification
  - Antimicrobial susceptibility testing
  - Reporting to the clinician

- **Study-specific procedures:**
  - Storage of strains
  - External Quality Assurance (EQA) panel of 20 strains – following local routine procedures

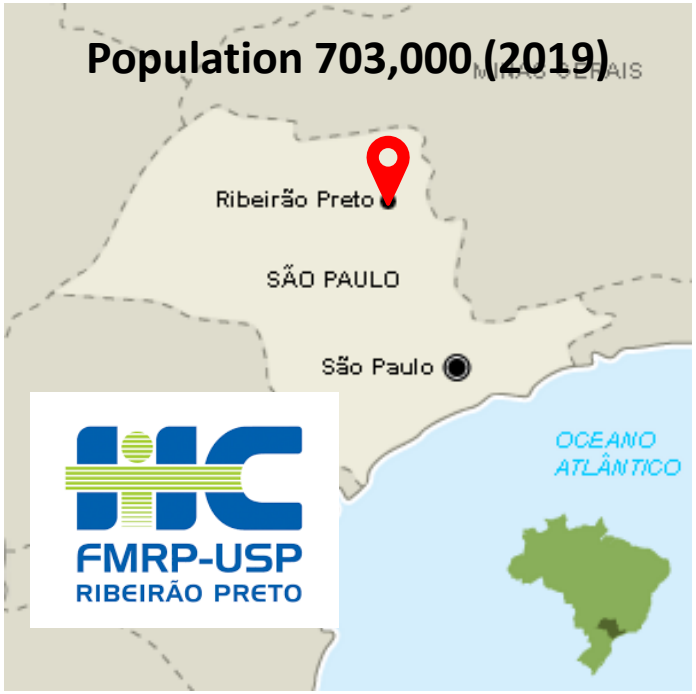
Study Treatment

All treatment and management of the baby will be as **local standard of care**

Starting, stopping, changing antibiotics and all other medicines is entirely decided by the local clinicians.

NeoOBS – Ribeirão Preto site

- Tertiary university center
- 745 beds
- Children's Hospital:
  - 173 beds (68 neonatal)
  - 1840 live births
    - 27% <37 weeks
    - 26% <2500g



HC criança RIBEIRÃO PRETO

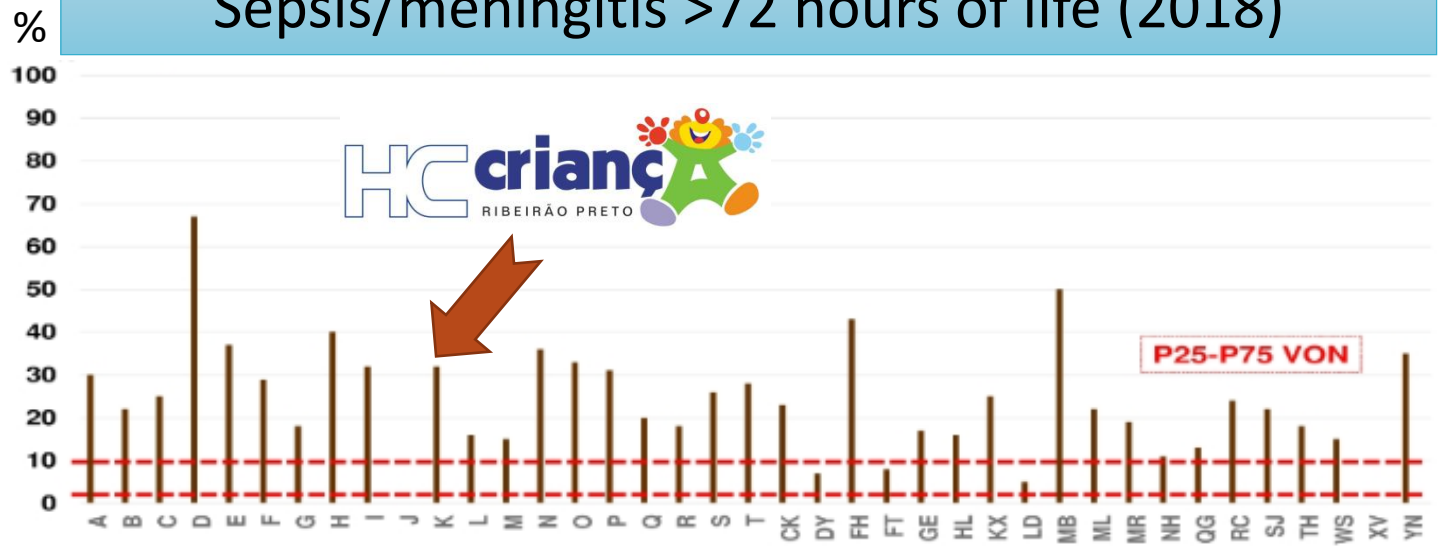
Brazilian Neonatal Network
Vermont-Oxford Network

REDE BRASILEIRA DE PESQUISAS NEONATAIS

<1500g

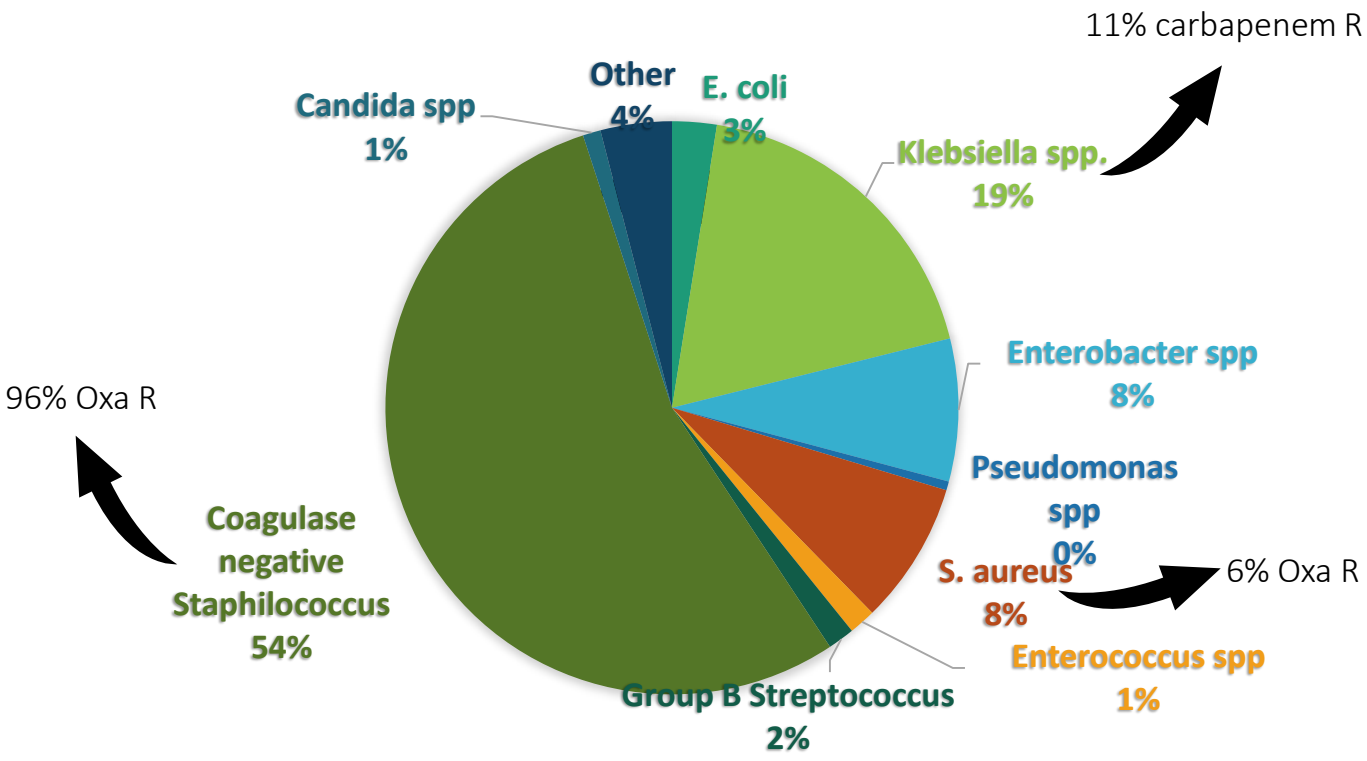
VON Vermont Oxford NETWORK

Sepsis/meningitis >72 hours of life (2018)



NeoOBS – Ribeirão Preto site

- Newborns with positive blood cultures: 199 (10.8%)



Recruitment status in NeoOBS to date:

Country (Number of sites)	Clinical Cohort	Microbiology Cohort	Overall Total
Bangladesh (1)	163	24	187
Brazil (2)	19	0	19
China (3)	323	7	330
Greece (1)	25	0	25
India (3)	405	35	440
Italy (1)	39	1	40
Kenya (1)	130	2	132
South Africa (3)	541	53	594
Thailand (2)	361	3	364
Uganda (1)	121	0	121
Vietnam (1)	150	18	168
Total (19)	2277	143	**2420**

Study Duration

- **12 months** of data collection OR until **31 December 2019**
- Sites who had a late start in 2019 will have an extension of enrolment until end of February 2020
- Participants will be **followed up until 28 days after enrolment** and start of treatment with IV antibiotics

Next steps

Based on information obtained from NeoOBS study:

- Design a strategic empiric treatment trial to evaluate new empiric treatment regimen for use in settings where there is significant antimicrobial resistance, including:
  - Current patterns of antibiotic utilization (comparator(s) regimens)
  - Mortality rate of babies with clinically diagnosed sepsis
  - Inclusion and exclusion criteria, eg. which clinical signs / symptoms and /or lab parameters will be used to define the study population
  - Develop a new sepsis score using daily clinical observations collected as part of NeoObs study
- It is anticipated that the treatment will be based on antibiotics such as Amikacin and Fosfomycin (neonatal indication and good evidence-based dose)

Thank you!

www.gardp.org

Global Antibiotic R&D Partnership (GARDP)
Drugs for Neglected Diseases initiative
Geneva | Switzerland