Groundbreaking clinical trial to improve treatment for newborns with life-threatening sepsis gets underway in South Africa and Kenya

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Geneva - An international clinical trial to evaluate much-needed new antibiotic combinations for newborn babies with sepsis has started in three public hospitals in South Africa and Kenya. The trial will be expanded to other countries and regions in 2024, with a target of recruiting up to 3,000 newborns overall.

The NeoSep1 trial will evaluate new combinations of existing antibiotics and compare them to treatment regimens that are currently used in newborn babies with suspected neonatal sepsis.

Chris Hani Baragwanath Academic Hospital in Johannesburg, Tygerberg Hospital in Cape Town and KEMRI, Kilifi County Hospital in Kenya are involved in the initial stage of the clinical trial.

Neonatal sepsis, a life-threatening infection, affects up to 3 million babies a year globally. This is compounded by the fact that an increasing number of newborns are becoming resistant to WHO-recommended antibiotic treatments, particularly the ampicillin-gentamicin regimen. Over the last decade, AMR has worsened to the point that around 50-70% of common pathogens exhibit a high degree of resistance to available first- and second-line antibiotics. Over 214,000 newborn babies die of drug-resistant neonatal sepsis every year, mostly in low- and middle-income countries (LMICs).

The trial is sponsored by the Global Antibiotic Research and Development Partnership (GARDP) in collaboration with the Medical Research Council Clinical Trials Unit at University College London (MRC CTU at UCL); St George's, University of London (SGUL); and Penta.

"Many babies are dying because of limited treatment options. The NeoSep1 trial is an opportunity to shift this trajectory by identifying new antibiotic combinations that we can tailor to treat neonatal sepsis in settings where there is widespread resistance to current recommended options. This is vital if we are going to address the impact of antimicrobial resistance on the burden of disease related to neonatal sepsis," said Seamus O'Brien, Director of Research and Development at GARDP.

The trial will rank the safety and efficacy of three new combinations of older antibiotics (fosfomycin-amikacin, flomoxef-amikacin, and flomoxef-fosfomycin) against the current standard of care. It will also assess and validate the doses of two antibiotics (fosfomycin and flomoxef) for use in newborns.
A key goal is to find out whether some antibiotic treatments perform better than others for the empiric treatment of babies with neonatal sepsis, particularly in LMICs where highly resistant bacteria are common. The trial will also consider how these combination treatments can best be used in hospital settings with varying levels of antibiotic resistance.

A new way of comparing antibiotic treatments with each other, called the Personalised Randomised Controlled Trial (PRACTical) design, will be used. The novelty of this design is that it allows researchers

to compare many antibiotic treatments for neonatal sepsis. It will also enable doctors to choose treatment regimens that are likely to work well for newborns in their particular hospital settings.

“The development pipeline for new antibiotic treatments is limited and the lack of a universal, effective standard of care creates huge challenges in conducting research to tackle neonatal sepsis. Novel trial designs such as the PRACTical design have been specifically developed to address these challenges in important public health emergencies such as neonatal sepsis,” said Sarah Walker, Professor of Medical Statistics and Epidemiology at the MRC CTU at UCL.

The NeoSep1 trial builds on findings from a global observational study of sepsis in newborn babies, conducted by GARDP and partners in 19 hospitals across 11 countries from 2018 to 2020. GARDP published a report on the study in 2022.

The study found a worryingly wide variation in treatment and frequent switching of antibiotics because of high resistance to treatments.

“Newborns handle medicines very differently to older infants, children and adolescents. Premature or otherwise critically ill babies are at great risk of severe infection or sepsis because of their immature immune systems. The types of bacteria causing newborn infections are not necessarily the same as those found in other patients. For these reasons, it is essential to investigate antibiotic treatments of newborns with sepsis,” said Dr Julia Bielicki, paediatrician and researcher at the Centre for Neonatal and Paediatric Infection at St George’s, University of London.

The trial aims to generate relevant and reliable evidence for doctors who need to make treatment decisions.

“We often have to treat babies with a combination of the antibiotics of last resort. On top of this we are not 100% sure about how to dose these drugs. We’re dealing with fragile newborns, so we need to be aware of the potential toxicity of the antibiotics and dosages we use. This trial will help in giving us confidence that we are delivering more effective treatment. This is critical as we want the best possible outcome for newborns in our care,” said Adrie Bekker, Principal Investigator for the NeoSep1 trial at Tygerberg Hospital, Cape Town, and Professor in the Division of Neonatology, Department of Paediatrics and Child Health at Stellenbosch University.

Expanding the number of suitable, effective treatment regimens could be lifesaving for newborns and could also decrease the risks of neuro-developmental impairment.

“Having the right antibiotics immediately can make the difference between life and death. We are hoping the trial will provide robust evidence that the antibiotic combinations are safe and effective and that this will lead to a change in both WHO and local treatment guidelines,” said Christina Obiero, Principal Investigator for the NeoSep1 trial for the KEMRI-Wellcome Trust Research Programme at Kilifi County Hospital, Kenya.

About GARDP

The **Global Antibiotic Research and Development Partnership (GARDP)** is a Swiss not-for-profit organization developing new treatments for drug-resistant infections that pose the greatest threat to health. GARDP was created by the World Health Organization (WHO) and the Drugs for Neglected Diseases initiative (DNDi) in 2016 and legally founded in 2018 to ensure that everyone who needs antibiotics receives effective and affordable treatment. GARDP is currently funded by the governments of Australia, Germany, Japan, Monaco, the Netherlands, the Public Health Agency of Canada, South Africa, Switzerland, United Kingdom, the Canton of Geneva, as well as the European Union, Wellcome Trust and private foundations. GARDP is registered under the legal name GARDP Foundation. www.gardp.org

About the MRC Clinical Trials Unit at UCL

The **MRC CTU at UCL** is at the forefront of resolving internationally important questions in infectious diseases, cancer and neurodegenerative diseases by delivering swifter and more effective translation of scientific research into patient benefits. The MRC CTU at UCL carries out challenging and innovative studies, and develops and implements methodological advances in study design, conduct and analysis. Furthermore, one of the key goals of the MRC CTU is to build strong networks for capacity building, training and knowledge transfer. The MRC CTU is part of the Institute of Clinical Trials and Methodology (ICTM) which brings together the largest group of trialists in Europe. For more information, see the MRC CTU at UCL website: https://www.mrcctu.ucl.ac.uk/about-us/.

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