GARDP
Global Antibiotic Research & Development Partnership
A joint DNDi / WHO initiative

Paediatric antibiotics

Antimicrobial resistance (AMR) is a major and rapidly growing global public health challenge. Responsible for more than 700,000 deaths a year[1], it poses a significant threat to achieving the Sustainable Development Goals (SDGs), in particular SDG 3, which aims to ensure healthy lives and promote wellbeing for all[2].

The Global Antibiotic Research and Development Partnership (GARDP) is a not-for-profit research and development organization that addresses global public health needs by developing and delivering new or improved antibiotic treatments, while endeavouring to ensure their sustainable access.

Initiated by the World Health Organization (WHO) and the Drugs for Neglected Disease initiative (DNDi) in May 2016, GARDP is an important element of WHO's Global Action Plan on Antimicrobial Resistance that calls for new public-private partnerships to encourage research and development of new antimicrobial agents and diagnostics.

GARDP's programmes – sexually-transmitted infections, neonatal sepsis, paediatric antibiotics and antimicrobial memory recovery, evaluation and exploratory research – are designed to address global public health priorities. Each programme incorporates sustainable access and stewardship strategies to ensure treatments are affordable and available to all those who need them.

Partnerships are central to GARDP's model and include WHO, pharmaceutical and biotechnology companies, academia, governments, health authorities, philanthropic organisations and civil society from across the world.

Globally, infectious diseases such as pneumonia and sepsis are a leading cause of death and disability in children under-five – responsible for more than three million childhood deaths in 2013[3].

Paediatric populations (newborns, infants and children[4]) are particularly vulnerable to the effects of AMR. In Europe, drug-resistant infections are responsible for an estimated 2300 disability-adjusted-life-years[5] per 100,000 people every year – the majority in infants under 1-year-old[6].

The problem is expected to be higher still in many low-and-middle-income countries (LMICs).

The AMR crisis is exacerbated by a lack of new antibiotics in development, a situation that particularly affects paediatric patients. Children are not small adults – their immune systems are still developing and treatments, including the formulation and dosing of antibiotics, need to be adapted to their specific needs. There is a gap between approval for use in adults and evidence to support their use in children, infants and babies. Evaluation of paediatric use of antibiotics – if it happens at all – only occurs once drugs are approved for adult use. Only an estimated 38 percent of antibiotic paediatric development programmes are completed within seven years of adult registration[7]. The programme has a global focus and aims to develop antibiotics for use in hospitals and the community, for countries with a high burden of drug-resistance in LMIC and high-income settings to develop the evidence needed to ensure regulatory approval and that new treatments meet public health needs.

GARDP'S PAEDIATRIC ANTIBIOTICS PROGRAMME

GARDP's paediatric antibiotics programme aims to expedite the development of new, improved and adapted antibiotics to treat serious bacterial infections in children of all ages. GARDP's paediatric antibiotics programme aims to expedite the development of new, improved and adapted antibiotics to treat serious bacterial infections in children of all ages. Antibiotic treatments will be developed, for use in hospitals and in the community, for countries with a high-burden of drug-resistance in both LMIC and high-income settings; this will enable GARDP to develop the evidence needed to ensure that new treatments meet public health needs and meet standards for regulatory approval.

OBJECTIVES

By 2023

- Develop and deliver up to two paediatric antibiotic projects in clinical development.
- Deliver one optimised paediatric antibiotic treatment ready for use in patients.

The programme will also work to build a global network of experts and inter-connected trial sites with the appropriate capability to deliver antibiotic treatment options for priority paediatric and neonatal bacterial infections.

TO DATE, GARDP HAS

- Identified an antibiotic called polymyxin B as a priority area for paediatric development. Polymyxin B is used to treat serious multidrug-resistant bacterial infections for which treatment options are limited, if available at all.

  Although registered in the USA for about 50 years, there is little evidence about its correct use in children in particular to treat neonatal sepsis. Polymyxin B is not available in many parts of the world, including most of Europe, South Africa and Thailand.

  GARDP is developing a paediatric investigation plan[8] to facilitate initial registration of polymyxin B in Europe, particularly in Italy and Greece and other regions with a high burden of drug-resistance, including in targeted countries in Africa and Asia.

- Started a collaboration with Novartis' generic division, Sandoz, to accelerate the development and availability of antibiotic treatments for children in LMIC settings. In particular to develop heat-stable child-appropriate formulations such as dispersible tablets to treat bacterial infections, including neonatal sepsis and pneumonia.

  GARDP and Sandoz will also share wider knowledge and expertise towards the potential development of other paediatric antibiotic treatments and towards improving the availability of medicines, particularly in under-served areas.

LOOKING AHEAD

In 2019, the paediatric antibiotic programme will

- Submit the paediatric investigation plan to the European Medicines Agency for approval.
- Set up a clinical trial to establish the correct dose of polymyxin B for children of all ages.
- Identify up to two further drug candidates towards improved paediatric antibiotics – that have either been recently registered for adult-use or are in late-stage clinical development and/or repurpose older antibiotics.
- Develop a global paediatric antibiotic development network to build on existing capability within GARDP's ongoing projects and in preparation for future projects.

A GLOBAL COLLABORATION

The paediatric antibiotic programme is made up of an international, multidisciplinary partnership of experts, institutions and research centres from across the world.

Partners include: St George's University, Medical Research Council - Clinical Trials Unit, PENTA-ID foundation, Italy, Chris Hani Baragwanath Hospital, Wits Health Consortium, Stellenbosch University, Tygerberg Hospital, South Africa.

GLOBAL PAEDIATRIC ANTIBIOTIC PLATFORM

The paediatric antibiotics programme is, alongside the neonatal sepsis programme, a building block for a global paediatric antibiotic platform. The platform will include clinical and pre-clinical antibiotic development activities supported by a network of medical, statistical, pharmacokinetic clinical trial design experts. It will support the development of, and conduct, paediatric projects, whereever they are needed.

The platform will

- Collaborate with existing trial networks to build an international network of experts and clinical trial sites focused on paediatric antibiotics, including experts from LMIC settings where the burden of disease is greatest.
- Use the knowledge and experience gained to develop streamlined paediatric plans that are acceptable to regulatory authorities.
- Build on innovative approaches already in place in GARDP programmes, such as starting trials in paediatric populations as early as possible (i.e. not waiting for a drug to have adult approval first) and, where appropriate, use data from adult trials to fast-track antibiotic interventions.
- Develop innovative trial designs to ensure it is possible to conduct clinical trials, including larger-scale more challenging trials that can inform public policy, wherever they are needed.

1 Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired by Jim O'Neill, 2014
2 Sustainable Development Goals sustainabledevelopment.un.org/SDG3
3 Liu L et al (2015) Global, regional, and national causes of child mortality in 2000-13 – The Lancet 385; 430-40
4 European Medicine Agency (EMA) definitions – *newborns including neonates: up to 28-days, infants and toddler: up to 23-months, children 2-11 years-old, adolescents 12 years-old -16-18-years old, depending on region*
5 Disability-adjusted-life-years are a measurement of overall disease burden of years of healthy life lost through ill-health, disability or early death.
6 Cassini, A. et al (2018) Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015 Lancet Infect Dis. 2019 Jan;19(1):56-66
7 Hwang TJ, Tomasi PA, Bourgeois FT (2018) Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: A cohort study PLoS Med 15(3): e1002520
8 *A paediatric investigation plan is a development plan aimed at ensuring that the necessary data are obtained through studies in paediatric populations to support the authorisation of a medicine for use in children and infants.*