March 2019

Background briefing note

GARDP and Penta partnership

Strategic collaboration to develop global children's antibiotic platform

There is an urgent need to prioritise antibiotics to treat drug-resistant infections in children. Infectious diseases, such as pneumonia and sepsis, are a leading cause of childhood death, responsible for more than three million deaths worldwide in in 2013[1]. The situation is aggravated by antimicrobial resistance (AMR).

The Global Antibiotic Research & Development Partnership (GARDP) and Penta (the paediatric infectious diseases research network), have joined forces to respond to this need. This strategic collaboration aims to accelerate paediatric development of antibiotic treatments including: clinical trials designed to meet regulatory requirements; and trials with a focus on public health interventions to inform treatment guidelines.

Who we are

The Global Antibiotic Research and Development Partnership (GARDP) is a not-for-profit research and development (R&D) 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* (DND*i*) 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 R&D of new antimicrobial agents and diagnostics. GARDP's programmes - sexually-transmitted infections, neonatal sepsis, paediatric antibiotics and antimicrobial memory recovery and evaluation - are designed to address global public health priorities and incorporate sustainable access and stewardship strategies.

First established in 1991, Penta initially started as a collaboration between paediatric HIV centres in Europe. Today, the PENTA-ID network (coordinated by Penta Foundation) is a leader in paediatric development for HIV and infectious diseases. To date, it has more than 100 clinical centres globally and has sponsored more than 20 major trials involving more than 3,500 children. Penta also coordinates conect4children (c4c) a large European paediatric clinical trial network funded by the EU through the Innovative Medicines Initiative (IMI) programme. This public-private partnership includes 33 public institutions and 10 pharmaceutical companies. In addition, Penta sponsors trials aimed at developing an optimal dosing regimen, and minimum treatment duration for off-patent antibiotics in neonates while reducing the impact of drug resistance and toxicity. Penta is also responsible for developing the paediatric component of several EU funded projects (COMBACT, ECRAID, Value-Dx).

[1] Liu, L. et al (2015) Global, regional, and national causes of child mortality 2000-13– The Lancet 385; 430-40. doi: 10.1016/S0140-6736(14)61698-6.

The need for child-friendly antibiotic treatments

Globally, an estimated 214,000 neonatal sepsis deaths result from drug-resistant infections[2]. In Europe, drug-resistant infections are responsible for an estimated 2300 disability-adjusted-life-years (DALYs) per 100,000 people every year, the vast majority in infants under one-year-old[3]. Tackling AMR and its effects on children is critical to the attainment of the Sustainable Development Goals (SDGs), in particular the children's health targets under SDG 3, which aims to ensure healthy lives and promote wellbeing for all[4].

Scarce evidence means child-friendly antibiotic treatment options are often limited. Evaluation of antibiotics for use in children, only occurs years after treatments are approved for adult use. It is estimated that just 38% of antibiotic paediatric development programmes are completed within seven years of adult registration[5].

The lack of evidence stems from the fact that carrying out clinical trials in children, particularly babies and young infants, involves highly complex ethical, regulatory and study-design issues. The few active trials are often of poor quality, including not recruiting enough patients, not focusing on most important childhood infections and not being conducted in areas with high risk and / or incidence of drug resistance. There are also very few trials looking at optimising (ensuring best use of) existing antibiotics for use in children. The lack of evidence hinders the development of appropriate treatment guidelines, urgently needed by clinicians worldwide.

A global children's antibiotic platform

The strategic collaboration consolidates plans for a children's antibiotic platform, which will include clinical and pre-clinical antibiotic development activities supported by a global network of expertise in the design, conduct and interpretation of paediatric antibiotic clinical trials.

This will include trial methodologists and statisticians from the UK Medical Research Council's Clinical Trial Unit, and uniquely, clinicians from low and middle-income (LMIC) settings, where the burden of disease is greatest. The knowledge and experience gained will be used to develop master protocols and streamlined paediatric plans that are acceptable to regulatory authorities.

Building on innovative approaches already in place in GARDP and Penta's programmes, the platform's activities will include:

- Starting trials in children as early as possible (i.e. as soon as safety data and information for dosing derived from adults is available) to fast-track antibiotic interventions for drug-resistant infections.
- Developing innovative trial designs to ensure that it is possible to both conduct regulatory compliant clinical trials and to address the challenge of providing evidence to support treatment decisions.
- Working with partners to develop child-friendly formulations and implement registration and access strategies to ensure treatments are affordable and available where they are needed, as quickly as possible.

[2] Laxminarayan R et al. Access to effective antimicrobials: a worldwide challenge. The Lancet. *2016*; 387:168–175. doi: 10.1016/S0140-6736(15)00474-
[3] 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 19(1):56-66
[4] Sustainable Development Goals - sustainabledevelopment.un.org/SDG3

Building on current efforts

The platform builds on the already strong relationship between GARDP and Penta. Recent collaborations include a pharmacokinetic (PK) clinical trial to assess safety and dosing of the antibiotic fosfomycin in neonates, which recently completed enrolment; and a large-scale global observational cohort study to collect clinical information on neonatal sepsis in up to 3,000 new-born babies in 19 hospitals in 11 countries.

Further plans in development include:

- The creation of a paediatric investigation plan to facilitate initial registration of polymyxin B in countries with a high burden of drug resistance in Asia, Africa and Europe. Polymyxin B is a last-resort antibiotic 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 much of the rest of the world – including most of Europe, South Africa and Thailand. Two trials will be conducted: one to establish the optimal dose for children; and a second trial to further evaluate its safety.

- Preparation for the PediCAP trial sponsored by Penta which intends to optimise antibiotic treatment for children aged 12-weeks to 10-years who have been hospitalised due to severe or very-severe community-acquired pneumonia. A randomised clinical trial will be carried out in sites in South Africa, Uganda, Zambia and Zimbabwe. Innovative trial design will be used to determine both: the effectiveness of two oral step down (switching from injectable-use to oral-use of the same antibiotic) treatments; and to establish the best treatment duration options, that can achieve high cure rates while minimising length of hospital stay, toxicity, and the development of further AMR.

- Evaluation of potential drug candidate(s) – both existing and new antibiotics - that can be repurposed and developed for use in settings experiencing high levels of resistance to the current WHO standard-of-care treatment for neonatal sepsis (ampicillin and gentamicin). Despite increasing rates of resistance to the regimen, up to 80 percent in some cases, the lack of alternatives means the guidelines have not been updated for more than 50 years.

Global partnerships

A global problem requires global collaboration. The work is only made possible through the strong relationships GARDP and Penta have built across the world including with Bangladesh, Brazil, China, Greece, India, Italy, Kenya, South Africa, Thailand, Uganda, Vietnam, Zambia, and Zimbabwe. GARDP and Penta gratefully acknowledge this support.

Further engagement from academics, donors, governments, maternal child health organizations, public institutions, the private sector, scientists, and more, will be critical to the success of GARDP and Penta's efforts to accelerate the development of antibiotics to treat serious bacterial infections in children. GARP and Penta invite anyone interested in tackling AMR in children to join them.

For more information: www.gardp.org and www.penta-id.org