R&D for children's antibiotics – a wake-up call

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It is time to prioritize children's needs in the context of antimicrobial resistance (AMR). Children, especially babies and young infants, are particularly vulnerable to the rise in drug-resistant infection and need treatments that are adapted to their specific needs. Yet, there are almost no clinical trials looking into children's antibiotics. This lack of prioritization threatens the attainment of the UN Sustainable Development Goals. The Global Antibiotic Research & Development Partnership (GARDP), Penta, St George's, University of London and global partners are working together to tackle AMR in children. They call on governments, researchers, industry and more – to join them.

AMR has a disproportionate effect on children

Children do not usually feature highly in global discussions around antimicrobial resistance (AMR). Yet, drug-resistant infections hit them particularly hard. This is especially the case for babies and young infants.

Children make up a quarter of the world's population and are prescribed antibiotics more than any other medicine *(1)*. Globally, infectious diseases such as pneumonia and sepsis are the leading cause of death and disability in children under 5-years-old; responsible for more than three million childhood deaths in 2013 *(2)*. Newborn deaths make up nearly half of all deaths in children under-5-years-old *(3)*.

The situation is aggravated by AMR, as the few available treatments are becoming increasingly less effective. Some 214,000 neonatal sepsis deaths were estimated to result from drug-resistant infections in 2015 *(4)*. Although many low- and middle-income countries (LMICs) bear the highest burden of infection and drug resistance, AMR is a global threat; one that affects every country in the world.

This is sharply illustrated by a recent European Centre for Disease Control (ECDC) study. The research found that drug-resistant infections are responsible for 2,300 disability-adjusted life years (DALYs) per 100,000 people each year, in Europe *(5)*. The World Health Organization (WHO) describes one DALY as being equal to "one lost year of healthy life," with the sum of DALYs across a population or disease burden measuring the gap between current health status and a situation where people live free of disease and disability *(6)*.

Startlingly, the study found infants under the age of 1-year-old bear the vast majority of the burden of AMR. This is in Europe, home to some of the wealthiest countries in the world. Thus far, it has not been possible to evaluate this burden in many LMIC settings, where it is expected to be even more severe.

A threat to children's health targets

Studies like this serve as an urgent wake-up call. The public health impact of AMR is here and happening now, with particularly severe consequences for our most vulnerable populations – children.

The threat that AMR poses to children's health also endangers the attainment of internationally agreed-upon goals such as universal health coverage and the UN Sustainable Development Goals (SDGs). It particularly threatens SDG3, which aims to improve health and wellbeing for all.

Under SDG3, there are specific targets to end preventable deaths of newborns and children under 5-years-old by 2030, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1,000 live births and to reduce mortality in the under 5-years-old to at least as low as 25 per 1,000 live births *(7)*.

Need for children's antibiotic clinical trials

One of the biggest challenges in the fight against AMR is the lack of antibiotics in development. This situation is critical for children, who need medicines that are adapted to their specific needs in terms of dosing, formulation and regimen. All too often such treatments are not available.

Although regulatory agencies require pharmaceutical companies to develop paediatric plans to evaluate new antibiotics for use in children, these are not developed until after such drugs are registered for use in adults. Many are delayed for

years after licensing in adults, if they are developed at all. New antibiotic trials made up less than 1% of all registered paediatric clinical trials, in 2017*(8)*. There are also scarcely any trials looking at optimizing the use of existing antibiotics for children.

The very few active trials are often limited in scope, do not recruit a sufficient number of patients, or do not focus on the areas of greatest need. A 2017 rapid review of open clinical trials which found just 76 registered trials looking at antibiotics in children, illustrates some of these issues *(9)*. The majority of the trials were located in North America, with less than a third recruiting patients from LMIC settings; these trials were primarily focused on minor infections, rather than on the most life-threatening conditions; just 23 were recruiting newborns; with only eight including pre-term infants. The review also found that of 37 new antibiotics being developed in adults, just two were being studied in children.

Lack of evidence limits treatment options

The significant lack of studies being performed around the effectiveness of both new and existing antibiotics for children, limits appropriate treatment options. For example, despite increasing rates of resistance to the WHO recommended treatment regimen for neonatal sepsis, which reaches up to 80% in some cases *(10)*, the lack of alternative treatment options means the guidelines recommending them have not been updated for more than 50 years.

This lack of evidence also hinders the development of urgently needed treatment guidelines. In some areas, nearly half of antibiotics prescribed for children have been found to be "off-label" *(11)* – a term that refers to drugs registered fo r a different condition or use (including different age groups, dosing or form) than that for which they are being prescribed. This places enormous pressure on paediatricians and a heavy reliance on specialist knowledge which may be limited, particularly in low-resource settings.

Need to re-frame how we tackle AMR

It is imperative to normalize the conducting of clinical trials in children. In doing so, the risks are reduced as the scientific community gains knowledge and experience. Achieving this in the context of AMR requires a radical shift in prioritization.

In 2017, the WHO published an AMR priority pathogen list which classifies bacteria as being of critical, high, or medium priority for antibiotic research and development (R&D). The multidrug-resistant Gram-negative bacteria that can lead to hospital-acquired serious bacterial infections are ranked as critical *(12)*.

In response, many drug developers started to pursue new antibiotics to treat serious bacterial infections, such as complicated urinary-tract infections and nosocomial pneumonia in adults.

The development of such antibiotics is important, but it is not enough. These same bacteria are leading to drug-resistant infections, such as pneumonia and sepsis, in our children.

Managing AMR does not only mean developing new antibiotics. To be truly effective, antibiotics – both new and re-purposed – must be usable in different populations. They must be appropriate for use in children. Investment in R&D needs to reflect this. In short, it is time to re-frame how we tackle AMR.

A global children's antibiotic platform

The Global Antibiotic Research and Development Partnership (GARDP) and Penta have entered into a strategic partnership, with key associate partner St George's, University of London (StGeorge's), to address AMR in children.

GARDP is a not-for-profit R&D organization, working with the public and private sectors to develop and deliver new and improved antibiotic treatments where drug resistance is present or emerging, or for which inadequate treatment exists, while endeavouring to ensure sustainable access. It has two programmes dedicated to children's antibiotics, neonatal sepsis and paediatric antibiotics.

Penta, a global leader in the field of paediatric medicines incorporates research, training and education centres across the world. Penta has sponsored 22 clinical trials involving more than 3,000 children, in more than 100 clinical centres in 18 countries worldwide. The paediatric infectious disease research group at St George's is a world-renowned centre for paediatric AMR research.

GARDP, Penta and St George's – together with partners across the world – have collaborated on projects including: a pharmacokinetic clinical trial to assess safety and dosing of the antibiotic fosfomycin in neonates in Kenya; a global observational study to collect clinical information on neonatal sepsis in up to 3,000 newborns in 19 hospitals in 11 countries; and are developing a paediatric investigation plan for an antibiotic to treat multidrug-resistant neonatal sepsis.

Now, together with governments, industry and research institutions from across the world, the partners are entering a new phase. Building on their existing clinical trial networks, they are working to create a global children's antibiotic platform *(13)*.

The aims of the platform include to: develop streamlined paediatric development plans acceptable to regulatory authorities, accelerate regulatory approval of treatments by ensuring children's trials are started as early as possible, and to incorporate innovative designs to maximize the information that can be gained from each trial.

The vision of the platform would not be possible without the global partnerships with academics, research institutions, governments and industry across the world; including in

Bangladesh, Brazil, China, Greece, India, Italy, Kenya, South Africa, Thailand, Uganda, United Kingdom, Vietnam, Zambia and Zimbabwe.

Conclusion

Drug development in the context of AMR is about much more than new antibiotics.

It is about ensuring that antibiotic treatments – both existing and new – are designed to meet global public health needs. Antibiotics are only useful if they are given appropriately – the right drug, right dose, right duration, right delivery and formulation – accessible and affordable to those who need them.

There are reasons to be encouraged, as new initiatives show increased awareness and political will to address children's needs. These include connect4children (c4c), coordinated by Penta and funded by the European Union through the Innovative Medicines Initiative (IMI2) programme. The c4c consortium aims to improve the design and conduct of clinical trials in children through the development of a pan-European paediatric clinical trial network for medicine development and research.

In addition, there is the new European Clinical Research Alliance on Infectious Diseases (ECRAID), for which Penta is the paediatric partner. ECRAID aims to reduce the public health impact of infectious diseases through establishing a sustainable, single-point-of-access, coordinated, pan-European, clinical research network. Although c4c and ECRAID are European projects, they will be linked to global initiatives and networks, including the global children's antibiotic platform being developed by GARDP and Penta, in close collaboration with St George's and partners.

Thus, progress is being made but there is still a long way to go. Further investment is critical to see these initiatives reach their full potential.

It is time to put children front and centre of the AMR debate, of investment and antibiotic R&D. By doing so, we can get on track to meet SDG3 targets; improve children's health and wellbeing and ensure efforts to tackle AMR are focused on the greatest needs.

A global problem requires global collaboration. GARDP, Penta, St George's and partners call on governments worldwide, as well as academics, donors, maternal child health organizations, public institutions, the private sector, scientists and more – anyone with an interest in tackling AMR in children – to join them. ■

Dr Seamus O'Brien is the R&D Director of GARDP, accountable for the strategic direction and operation of all programmes across discovery, development and implementation. Dr O'Brien previously worked with leading pharmaceutical companies Pfizer and AstraZeneca, overseeing R&D collaborations, partnerships and networks to develop treatment options for drug-resistant infections, including the New Drugs for Bad Bugs framework and the COMBACTE-CARE consortium with the IMI in Europe; and an antibiotic portfolio agreement with BARDA in the United States.

Professor Mike Sharland is one of the United Kingdom and Europe's leading experts in antimicrobial prescribing, resistance and healthcare-associated infection in children. Under his direction the Paediatric Infectious Diseases Unit at St George's, University of London has become a Centre of Excellence for clinical care, teaching and research. Professor Sharland is also closely involved in implementation of the UK National AMR Strategy; a member of the WHO Essential Medicines List Committee and Vice Chair of Penta.

Professor Theoklis Zaoutis is Professor of Pediatrics and Epidemiology at the University of Pennsylvania and Chief Scientific Officer of Penta. As CSO, he helps define Penta's scientific agenda and oversees its implementation, leads and coordinates research, and represents Penta in the global scientific community. Dr Zaoutis has served on committees advising the CDC, NIH, AAP, ESPID, and WHO, among other organizations, and is Editor-in-Chief of the Journal of the Pediatric Infectious Diseases Society.

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