GARDP

Global Antibiotic Research & Development Partnership

A joint DND*i* / WHO initiative

ACTIVITY REPORT 2018

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The rise of drug-resistant bacteria is jeopardizing decades of progress and threatening our ability to prevent and treat infections that were once easy to treat. As one of GARDP’s founders, WHO is committed to continue supporting GARDP and its growing ambitions to tackle one of the biggest threats to global health. GARDP is an essential element of delivering the Global Action Plan on AMR.

Dr Tedros Adhanom Ghebreyesus, WHO Director-General

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DND*i* is proud to have enabled GARDP to kickstart its mission to develop and deliver antibiotics to tackle drug-resistant infections. DND*i* and GARDP have a shared vision of public health-needs driven research and development that ensures equitable and sustainable access to affordable treatments. We look forward to a strong collaboration in the future, for the benefit of the people served by the two organisations.

Dr Bernard Pecoul, DND*i* Executive Director

Cover illustration courtesy of Wayne Lee-Sing on Unsplash

Message from

Professor Ramanan Laxminarayan, Board Chair and Dr Manica Balasegaram, Executive Director

2018 has been a landmark year for GARDP. We have built on last year's successes and made significant progress in addressing Gram-negative drug-resistant infections in children, newborns with sepsis, and sexually-transmitted infections. The work we have done this year includes conducting three clinical trials and preparing to launch our first phase III clinical trial for a potential new treatment for gonorrhea. Our discovery and exploratory research, and memory recovery and asset evaluation programme, which has evaluated over 80 assets, gives us the flexibility to expand our current portfolio.

None of this would have been possible without your support.

Partnerships are at the heart of our success in developing new treatments. We are now working with industry, research institutions, governments, civil society and not-for-profit partners in over 16 countries in our efforts to develop antibiotics and facilitate their sustainable access. We have formed partnerships and collaborations that span the drug development lifecycle. These range from screening the chemical compound libraries of Takeda and Eisai for antibacterial activity to preparing the launch a pivotal phase III clinical trial with Entasis Therapeutics. We are already leveraging knowledge and sharing expertise through our strategic partnership with Sandoz, the Novartis generics division, and are collaborating with the University of Liverpool to explore the frequency of resistance of potential antibiotic combinations for newborns with sepsis.

Antibacterial resistance poses a global threat. Many were shocked by data published towards the end of the year. It showed drug-resistant infections are responsible for the loss of 2,300 years of life per 100,000 people every year in Europe. This burden is highest in infants under one and has increased significantly since 2007, and is expected to be even higher in low- and middle-income countries.

Recognizing the role serious Gram-negative bacterial infection plays in child mortality, we are generating data to update treatment guidelines for this vulnerable population, helping us develop new treatments. In July, we held a joint forum in New Delhi with the support of our partners the Indian Centre of Medical Research, Penta, St. George's, University London and WHO. Together, we welcomed over 80 researchers from around the world including Brazil, South Africa, Bangladesh – to kick-off our global observational study for newborns with sepsis.

As GARDP transitions into a legal independent entity, we are grateful for our unique WHO and DND*i* parentage which has allowed us to benefit from their expertise, infrastructure, and capacity. As our incubation comes to an end, we give special thanks to DND*i* and its many individuals – from the DND*i* team to the Board of Directors - who contributed to the establishment of GARDP and for acting as our host during our incubation as well as to the many WHO Departments and staff who have helped us in shaping our programmes. We look forward to continuing our close collaboration with both DNDi and WHO.

AMR remains a priority on the global political agenda with high-level engagement from all quarters. We are at a crossroads. Governments are under pressure to develop and implement national, regional and global action plans on AMR. We, and the rest of global health community, must continue to support them.

Overcoming AMR is key to achieving universal health coverage and delivering the SDGs. But we can only succeed through concrete actions. This includes commitments to public-private partnerships, such as GARDP, and by focusing on R&D and sustainable access of new treatments.

Looking forward to 2019, we are developing a new and ambitious business plan. With an established track record, we are a trusted partner bringing together the public and private sector to drive innovation and access to address public health priorities.

As we continue to make good progress, we thank all of you who made it happen - our donors, our partners, and, of course, our team. We are delighted that all the commitments made at GARDP's first pledging event have been realized. For this we are grateful and look forward to growing our collaboration and engagement in the years to come.

Professor Ramanan Laxminarayan

Dr Manica Balasegaram

About antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) causes more than 700,000 deaths a year[1]. It's clear AMR is a major and rapidly growing global threat to health and development. Infections that are treatable today are once more becoming life-threatening and routine surgery is becoming risky to carry out.

The World Bank estimates that if AMR is left unchecked, the impact on economic growth could be devastating, with up to USD 100 trillion of economic output at risk by 2050[2]. That is the equivalent to twice the annual GDP of the US, Europe, and China combined. Low-and middle-income countries already bear significantly higher resistance rates (40-60% compared to an average of 17% for OECD countries. Addressing AMR is key to deliver the Sustainable Development Goals.

Action is needed now, to ensure old and new antibiotics remain available and effective for generations to come.

Antimicrobial resistance causes more than

700,000

deaths a year

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 The World Bank. (2016). Drug-Resistant Infections: A Threat to Our Economic Future. Available at: http://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

About GARDP -

a public-private partnership approach to address AMR

The Global Antibiotic Research and Development Partnership (GARDP) is driven by a core vision. A world where research and development (R&D) is driven by the needs of the patient. Where effective, appropriate, and affordable antibiotic treatments are available to anyone who needs them.

GARDP is a not-for-profit organization focused on the research and development of new (and improved) treatments needed to address global public health priorities. Through partnerships, collaborations and coordination, we work with stakeholders from across the world to develop new antibiotic treatments, while endeavouring to ensure their sustainable access. Created in May 2016 by the World Health Organization (WHO) and the Drugs for Neglected Disease *initiative* (DND*i*), GARDP is an important element of the WHO's Global Action Plan on Antimicrobial Resistance.

GARDP's R&D programme is identifying drug candidates to treat serious Gram-negative bacterial infections. Through discovery and exploratory research, and memory recovery and asset evaluation, promising candidates are taken forward for development within GARDP's portfolio. GARDP's portfolio currently focuses on developing antibiotics to treat:

GARDP's focus is determined by considering the priority pathogens identified by WHO, and current unmet needs for diseases and key populations. GARDP takes a portfolio approach to its work and can expand its focus based on newly identified priorities. Each programme incorporates sustainable access strategies, endeavouring to ensure treatments are affordable and available to all those who need them.

GARDP works closely with a range of public and private sector partners. The partnerships GARDP creates mitigates the significant risks and costs associated with drug development. A key feature of this model is the ability to enter at any point along the drug development pipeline, all the way to patient access. Critically, sustainable access is built into GARDP's R&D strategies from the beginning.

Since being established, GARDP has secured €66M in funding and requires a further €200M to deliver its current ambitions. With this modest amount of money, GARDP is demonstrating that innovative, collaborative approaches are worth investing in.

2018 highlights and achievements

Jan

- Professor Laura Piddock joined GARDP to lead Scientific Affairs on a secondment from her role as Professor of Microbiology at the University of Birmingham, UK.

PROFESSOR LAURA PIDDOCK

- GARDP welcomed DRIVE-AB's report *Revitalizing the antibiotic pipeline* acknowledging GARDP's role as a pipeline coordinator, and that a combination of ways to apply and attract financial investments in R&D are required to effectively stimulate antibiotic innovation. In its response GARDP highlighted the need for well-designed incentive mechanisms based on public health priorities that ensure sustainable access.

Feb

- GARDP presented its approach and progress made on stimulating R&D for new antimicrobials in the fight against multi-drug resistance to G20 Health Ministers in Argentina.

- A comment on the 'unavailability of old antibiotics threatens effective treatment for common bacterial infections,', co-authored by Dr Manica Balasegaram, was published in The Lancet Infectious Diseases journal. The piece highlights how limited availability, supply shortages, and pricing of current antibiotics is restricting access to effective treatment for common bacterial infections.

Mar

- GARDP started its first phase 1 clinical trial on fosfomycin. The drug was first licenced over 40 years ago but is not yet widely used in newborns with sepsis. The trial seeks to evaluate the safety of the drug and confirm the correct dosage.

1st CLINICAL TRIAL ON FOSFOMYCIN

May

- During the World Health Assembly, the Public Library of Science (PLOS), in partnership with GARDP, launched a dedicated AMR channel encouraging research collaboration between science, policy and public health officials. The channel opens up a holistic approach towards addressing AMR, and allows quick access to updates on a range of cross-cutting issues.

- GARDP was invited to present on a panel 'Ensuring innovation for improved access to tackle antimicrobial resistance' at the meeting 'A Future Free from the Fear of Untreatable Infections': A Civil Society Agenda organized by the South Centre, Third World Network and ReAct.

Jun

- GARDP welcomed Seamus O'Brien, as its first R&D Director. Seamus' appointment completed the recruitment of key R&D positions and enables GARDP to continue delivering its programme ambitions at pace.

SEAMUS O'BRIEN

- REVIVE (GARDP's online space for the antimicrobial R&D community) hosted the first of four webinars, delivering learning to hundreds of participants around the world.

REVIVE
Advancing Antimicrobial R&D

Jul

- Over 80 researchers from 11 countries gathered in New Delhi to kick-off a global observational study for newborns with sepsis. Data generated from the study will be used to evaluate future interventions for this vulnerable population.

+80 RESEARCHERS **11** COUNTRIES

- GARDP was registered as an independent legal entity in Switzerland with a Board of Directors comprising leading international experts in the global health arena.
- GARDP responded to the ad hoc Inter Agency Coordination Group's discussion paper 'Antimicrobial resistance: Invest in innovation and research, and boost R&D and access,' highlighting the need for public led and funded response to AMR, implementation of key public interest principles, and integration of access and stewardship within the R&D process, and a global focus which includes the needs and enhancement of capacity in low- and middle-income countries.

Sep

- GARDP addressed the Council of the European Union on identifying and effectively tackling medical need in research programmes.

EU

- A strategic partnership between GARDP and Sandoz, the Novartis generics division, was announced. The aim of the partnership is to reduce child deaths from drug-resistant infections. It focuses on enhancing generic antibiotics and increasing access for children in low- and middle-income countries.
- GARDP started evaluating two key recovered antibiotics for STIs and neonatal sepsis.

Oct

- GARDP started a food effect trial to inform a phase III clinical trial for a novel, first-in-class oral antibiotic to treat drug-resistant gonorrhoea.

FOOD EFFECT TRIAL

- G20 Health Ministers welcomed the work of product development partnerships and funding initiatives, highlighting the work carried out by GARDP.

G20

Nov

- GARDP signed up to the Ghana Declaration. - a Call to Action on AMR highlighting the global and national action required to address AMR, and endorsed by WHO, the Food and Agriculture Organization, and the World Organization of Animal Health.
- GARDP was invited to discuss its 'bench to bedside' approach in developing antibiotic treatments with UK's Members of Parliament as part of World Antibiotic Awareness Week.

WORLD ANTIBIOTIC AWARENESS WEEK

Dec

- St George's, University of London published the results of its global review of the sales of children's oral antibiotics in 70 high- and middle-income countries. The research was carried out in collaboration with GARDP and found consumption varies widely with little correlation between countries' wealth and the types of antibiotics.
- GARDP announced its first multi-actor partnership with Eisai and Takeda whereby the Institute Pasteur Korea will test chemical compounds on behalf of the two companies in the search for new antibiotics.
- GARDP signed a research collaboration with the University of Liverpool to explore potential antibiotic combinations and improve treatment outcomes for newborns with sepsis.

From innovation to access:

how GARDP is combating AMR

Worryingly, current treatments fail to address the biggest public health threats posed by increasingly drug-resistant Gram-negative bacteria. This was reiterated by the G20 Health Ministers at their first meeting in 2017. The subsequent Berlin Declaration welcomed initiatives, including GARDP, to 'reinvigorate R&D in science and industry for antimicrobials.'

Global collaborations

No country or actor can solve AMR alone. GARDP works collaboratively, building global partnerships with industry, academia and governments to optimize resources and bring the right actors together to accelerate the development of new and improved antibiotics. Notably, GARDP is one of the few organisations working in partnership with a small medium-sized enterprise, Entasis Therapeutics, in the late-stage development of a novel, first-in-class treatment for gonorrhoea.

Searching for new antibiotics for Gram-negative bacteria with Eisai and Takeda

Through its partnership with Eisai and Takeda, GARDP is screening previously untested components from their chemical libraries in the hope of discovering novel compounds with antibacterial activity. The libraries are tested by the Institut Pasteur Korea against bacteria identified as a critical priority for R&D of new antibiotics. Our goal is to identify novel compounds suitable for further optimization and development.

Dr. Wangshick Ryu, CEO of the Institut Pasteur Korea

"We are honoured to collaborate with GARDP on a global project of great importance to find a solution for antibiotic resistance. The world needs global cooperative action to prevent the post-antibiotic era. This work, instigated by GARDP, is an active response to this urgent global demand that connects Institut Pasteur Korea's resources with the technology of global pharmaceutical companies. We believe that together we can achieve much more."

Prioritizing global health needs

GARDP prioritizes developing antibiotics that address public health needs by considering:

- Priority pathogens designated by WHO;
- The needs of specific underserved populations, diseases and syndromes; and
- Those indications currently ignored due to perceived risks, challenges and lack of commercial interest.

While drug-resistant pathogens are found globally, the burden of AMR is higher in low- and middle-income countries. GARDP's work ensures regulatory and public health-orientated studies are undertaken as early as possible.

Working in partnership with South Africa

While the impact of gonorrhoea is truly global, Africa and Western Pacific regions are particularly affected.

As part of its global efforts, GARDP will conduct clinical trials with the South African Medical Research Council (SAMRC) to develop and deliver a new treatment for gonorrhoea and new treatments for neonatal sepsis.

Professor Glenda Gray, President & CEO of SAMRC and member of GARDP's Board of Directors

"We have to be adaptive and rapidly responsive to AMR so as to prevent it from aggravating the quadruple burden of disease in South Africa. Collaborating and investing in new drug development projects such as these is just one of our contributions towards achieving the sustainable development goal to reduce neonatal mortality."

Prof. Adrie Bekker, neonatologist and researcher, Cape Town South Africa

"We're grateful to be part of the observational study. I think it's wonderful that for the first time on a broad scale people will be looking at what is happening to babies with sepsis. We know it's the third leading cause of mortality in neonates, but we actually know very little about what causes it and how we should treat them. It often feels like we're working in the dark. This will be an opportunity to actually give our patients better care."

Addressing stewardship and access

Any effort to tackle AMR, must address the complex issues of stewardship, ensuring access but not excess and reflect the realities of clinical practice. GARDP envisions a world where all infections are treatable everywhere. A world where everyone who needs antibiotics receives effective, appropriate, and affordable treatment, no matter where they live.

New drugs alone will not halt the rapid rise in antibiotic resistance. An integral part of GARDP's R&D process is ensuring the effectiveness of new drugs is preserved through stewardship. GARDP will work with partners, governments, and other agencies to ensure the right policies are in place to ensure that sustainable access – conducting, where necessary, public health studies to identify the best use of new treatments and guide appropriate use. Optimizing the use of existing drugs can protect the efficiency of antibiotics over time as well as ensuring sustainable, equitable, and affordable access for those who need them.

Dr Tedros Adhanom Ghebreyesus, WHO Director-General

"GARDP is developing new treatments on a not-for-profit basis through public-private partnerships. One new antibiotic showing promise is for drug-resistant gonorrhoea, an infection that has failed treatment with last-resort antibiotics in at least 10 countries. If it works, this partnership could be a model for how to increase access to and affordability of medicines, which is key to achieving universal health coverage."

Sustainable investment in R&D

Tackling AMR requires not only a coordinated global effort, but urgent and significant public investment into antibiotic R&D.

GARDP's public-private partnership model means GARDP can work from any entry point along the R&D pipeline through to patient access.

GARDP has the ability to leverage institutional experience in lowering the costs of R&D by using in-kind contributions from partners, linking networks, and building platforms, as well as leveraging funds from bilateral and multilateral entities and governments.

Anja Karliczek, Federal Research Minister, German Federal Ministry of Education and Research

Photo by BMBF/ Laurence Chaperon

"Many people worldwide are suffering from infections that can no longer be treated because the pathogens are resistant to antibiotics. We are also facing this problem in Germany. This is why we are committed to tackling the health challenge of AMR. We need new, effective antibiotics, diagnostics and prevention measures against resistant microbes. We are advocating a better global coordination of AMR R&D activities and extending our support for a number of national and international research initiatives. We are convinced that GARDP's R&D Strategy will provide urgently needed treatments against infections affecting the world's most vulnerable populations."

Building a robust pipeline to address the antibiotic R&D void

Issue

Since the early 1990s there has been a void in the discovery and development of new antibiotics. There are numerous reasons for so few new drugs to treat Gram-negative bacterial infections. These include the challenges of complex science, lack of sufficient return on investment, and regulatory issues and changes in the pharmaceutical sector. Together, these have led to the abandonment of countless antibiotic development programmes.

Today, as drug-resistant infections fast outpace the development of new treatments, there is a growing acceptance that the development of drug resistance to treatments is inevitable. There is an urgent need for renewed antibiotic R&D to build a pipeline of treatments that focus on bacteria, in particular multidrug-resistant Gram-negative bacteria identified as a priority by WHO. Discovery and exploratory research to find novel compounds and formulations is a critical component of this. There is a need for more exploratory research focused on the discovery of novel antimicrobials. Part of the solution may also lie in long-forgotten compounds. It may be possible, with emerging science and technological advances, to further rescue and repurpose under-used or forgotten compounds.

GARDP's response

How GARDP is addressing the antibiotic discovery void

Through discovery and exploratory research, and antimicrobial memory recovery and asset evaluation, GARDP

1. **Nominate a candidate for the pre-clinical development of an antibiotic to target serious drug-resistant Gram-negative bacterial infections (such as sepsis).**
2. **Recover assets from companies that work or worked in the antibiotic space in order to find drug candidates which may meet public health needs.**
3. **Identify up-to-two new chemical entities for pre-clinical or clinical development.**
4. **Disseminate knowhow and expertise in antibiotic drug R&D before the knowledge of this generation of experts is lost.**

Results

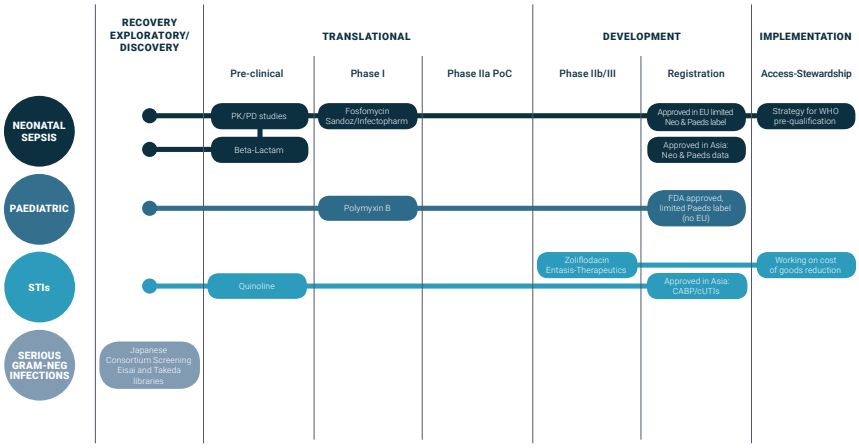
Achievements in 2018:
GARDP established a due diligence process to review old and new candidates for drug development. Through this, more than 80 new and 'recovered' chemical entities have been evaluated, of which:

• Two new assets in late-stage development are being evaluated and discussed with potential partners as possible candidates for GARDP's clinical programmes.

• Two recovered assets, fosfomycin and polymyxin B, have been identified as potential candidates for development in GARDP's clinical programmes.

• Six new assets have been identified as potential candidates for GARDP's pipeline.

GARDP's portfolio up to December 2018



GARDP announced a partnership with Japanese pharmaceutical companies, Eisai and Takeda, to access and screen components of their chemical libraries in the hope of discovering novel compounds with antibacterial activity. The compounds, which have never been screened before, will be tested by the Institut Pasteur Korea.

Dr. Kappei Tsukahara, Senior Group Officer, Head of Human Health Care Data Creation Center, Head of Tsukuba Research Laboratories, Eisai.

Eisai strongly identifies with GARDP's efforts to discover novel antibiotics to treat drug-resistant bacterial infections which have become a threat to human beings and are pleased to provide our compound library for screening. We sincerely hope new medicines will be discovered through this partnership to realize a world in which lives are no longer lost to drug-resistant bacteria."

REVIVE - revive.gardp.org

REVIVE is GARDP's interactive online space which aims to improve, accelerate, and streamline antimicrobial drug discovery and R&D by :

• offering online open-access webinars, blogs, articles in scientific and medical journals, face-to-face workshops, bootcamps and symposia at international conferences.
• connecting people - linking researchers new to the field with more than 120 world-class experts – leading academics, industry experts and healthcare professionals.

During REVIVE's first year, over 1,200 people registered to participate in REVIVE's series of webinars led by experts in their field. The webinars covered topics such as clinical development pathways of antibacterial drugs and safety considerations as a part of antibacterial drug design. REVIVE also hosts monthly blogs to stimulate discussion on cross-cutting topics ranging from financial models to stimulate antimicrobial development, to stewarding new antibiotics.

REVIVE
Advancing Antimicrobial R&D

Addressing the global rise of drug-resistant gonorrhoea

Issue

In 2016, there were approximately 376 million new cases of gonorrhoea, chlamydia, syphilis and trichomoniasis around the world[1]. The rise in drug-resistance is making these sexually-transmitted infections (STI) more and more difficult to treat.

Gonorrhoea – a growing global burden
With an estimated 87 million new cases a year[1], gonorrhoea affects every region of the world. In South Africa, it accounts for up to 90% of cases of urethral discharge in men[2]. It is the second-most frequently reported infectious disease in the USA[3].

If left untreated, gonorrhoea can have serious consequences for reproductive health and fertility. It can cause ectopic pregnancies, spontaneous abortions and stillbirths. Gonorrhoea also increases the risk of contracting and transmitting HIV.[4]

The spread of drug- resistant gonorrhoea is rapidly outpacing the development of new medicines. In a survey of 77 countries, more than 60% report at least one strain that was either resistant or had decreased susceptibility to last-line antibiotics[4]. *N. gonorrhoeae* is classified as being 'high priority' on WHO's list of pathogens representing the greatest threat to human health and most in need of new antibiotics.[5]

Cases of drug-resistant gonorrhoea have been reported across the world from Australia, to France, to Japan. With increased international travel, resistant strains are spreading quickly around the world.

GARDP's response

How GARDP is addressing sexually-transmitted infections
GARDP's dedicated R&D strategy for STIs was published in 2017[6]. The strategy outlines a roadmap to develop a new treatment for drug-resistant gonorrhoea, investigate new combinations of antibiotics to treat STIs, and ensure sustainable access to the treatments.

Starting with gonorrhoea, GARDP's programme aims to develop and deliver at least one treatment that will most impact on public health by ensuring it meets three criteria:

1. **Works against current drug-sensitive and drug-resistant gonorrhoea.**
2. **Is suitable for integration into international and national STI treatment guidelines.**
3. **Can address urogenital and extra-genital infections.**

Results

Achievements in 2018:
GARDP, in partnership with Entasis Therapeutics, is developing zoliflodacin, a new oral antibiotic for uncomplicated gonorrhoea. A multi-site phase III clinical trial will be initiated in 2019.

Results from the phase II clinical trial, sponsored by the US National Institutes of Allergy and Infectious Disease (NIAID), part of the National Institute of Health, were published in the New England Journal of Medicine[7]. They support the therapeutic potential of zoliflodacin to treat uncomplicated gonococcal infections including those resistant to currently used antibiotics.

If zoliflodacin receives regulatory approval, Entasis will grant GARDP an exclusive license with sublicensing rights in 168 low and middle-income countries. Entasis will retain the commercial rights for high-income countries. Both GARDP and Entasis have committed to affordable and equitable pricing in their respective territories.

Preparation for the pivotal phase III clinical trial included a clinical trial to confirm a safe and effective dose of zoliflodacin. Forty-eight patients in the US were enrolled into a phase 1 'food effect' study to investigate the effect of food on a new formulation of zoliflodacin. Results from this study will inform the dose and formulation for the phase III study.

Dr Manica Balasegaram, Executive Director, GARDP spoke on BBC World radio following news of a man in the UK reported to have caught the world's "worst-ever" case of super-gonorrhoea. In a report issued by Public Health England, this was the first time in the UK that the infection could not be cured with first-line antibiotics.

What appears to be unusual from the Public Health England report is that this gentleman has a strain highly resistant to both antibiotics recommended by WHO, and that is of great concern because these drugs are now the mainline treatment for gonorrhoea. Gonorrhoea has developed resistance to many classes of antibiotics, so this is indeed troubling news. We are working to develop a new drug that is going to work against drug-resistant gonorrhoea. We have tested this drug in the lab, and we are now in clinical development for this drug. We hope to have this drug developed in the next few years."

1 World Health Organization (WHO), Report on globally sexually transmitted infection surveillance 2018
2 Sentinel Surveillance, STI South Africa, Communicable Disease Communique, February 2016
3 The US Centers for Disease Control and Prevention (CDC): Sexually Transmitted Disease Surveillance.
4 Wi, T. et al. (2017). Antimicrobial resistance in Neisseria gonorrhoeoe. Global surveillance and a call for international collaborative. PLoS Medicine. Jul 7;14(7)e1002344
5 WHO priority pathogens list for R&D of new antibiotics – February 2017
6 Alirol E, Wi TE, Bala M, Bazzo ML, et al. (2017) Multidrug-resistant gonorrhea: A research and development roadmap to discover new medicines. PLoS Med 14(7): e1002366
7 Taylor, S, Marrazzo, J, Batteiger, B et al. (2018) Single-Dose Zoliflodacin (ETX0914) for Treatment of Urogenital Gonorrhea, The New England Journal of Medicine,

Prioritizing children: a hard-to-study and hard-to-treat population

Issue

Infectious diseases, such as pneumonia and sepsis, are a leading cause of death and disability in children under five and responsible for more than three million childhood deaths in 2013[1]. Newborns, infants and children[2] are particularly vulnerable to the effects of AMR.

Children are not small adults – their immune systems are still developing. Any treatments, including antibiotics, need to be adapted to their specific needs. Evaluation of antibiotics for use in children, only occurs years after treatments are approved for adult use. It is estimated that only 38% of antibiotics approved for adults go through paediatric development programmes[3].

Carrying out clinical trials in children, particularly babies and young infants, involves highly complex ethical, regulatory and study-design issues. Active trials are often of poor quality, without enough patients. They do not focus on the most important childhood infections and aren't being conducted in areas with high risk or incidence of drug resistance. This inadequate research means child-friendly antibiotic treatment options are often limited.

GARDP's response

How GARDP is addressing lack of appropriate antibiotics for children

GARDP's paediatric antibiotics programme aims to accelerate the development of new, improved and adapted antibiotics to treat serious bacterial infections in children of all ages.

By building clinical research capability and expertise, GARDP will be able to ensure new treatments meet public health needs and standards for regulatory approval. Specifically, the programme will:

1. **Develop and deliver up to two paediatric antibiotic projects in clinical development.**

2. **Deliver one optimised paediatric antibiotic treatment ready for use in patients.**

Results

Achievements in 2018:
Polymyxin B has been registered in the USA for about 50 years and is used to treat serious multidrug-resistant bacterial infections in adults for which there are limited or no treatment options. There has been little research into the use of polymyxin B in treating neonatal sepsis caused by multi drug-resistant bacteria. GARDP is developing a paediatric investigation plan to facilitate initial registration of polymyxin B in Europe, as a gateway for access in regions with a high burden of drug resistance.

In September, GARDP entered into a strategic partnership with the Novartis generic division, Sandoz. The partnership aims to accelerate the development and availability of generic antibiotic treatments for children in low- and middle-income countries. The partnership will target the development of heat-stable, paediatric formulations against bacterial infections in a bid to reduce child deaths from drug-resistant infections.

GARDP supported the global review of Consumption of oral antibiotic formulations for young children according to the WHO's Access Watch and Reserve (AWaRE) categorization for the prioritization of antibiotic use. Findings of the report showed consumption of children's antibiotics varies widely with little correlation between countries' wealth and types of antibiotics prescribed. Of concern is the relatively low-level use of amoxicillin, an antibiotic used to treat the most common childhood infections. The review also found the sale of antibiotics on the 'Watch' list (those which have a higher risk of developing bacterial resistance) accounted for 20% of total antibiotic consumption.

Generating such data is an important first step to help countries tackle overuse of antibiotics. It provides country policymakers evidence on what antibiotics are being prescribed in their country. This, in turn, will help countries deliver their National Action Plan on AMR and ensure antibiotics remain available and effective for generations to come.

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

Build clinical research capability in regions where the burden of disease is greatest.

Work alongside existing trial networks to build an international team of experts and clinical trial sites focused on paediatric antibiotic development.

Use the knowledge and experience to develop streamlined paediatric plans acceptable to regulatory authorities.

Build on innovative approaches already in place in GARDP programmes, such as starting trials in children 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 Liu L et al (2015) Global, regional, and national causes of child mortality in 2000-13 – The Lancet 385; 430-40
2 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
3 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

Sepsis in newborns: a growing global concern

Issue

Although significant progress has been made, the number of preventable deaths in newborns (babies up to 28-days-old, or neonates) remains unacceptably high. Globally, deaths in newborns account for 44 percent of all deaths in children under five[1].

Newborns are at significant risk from serious blood-stream infections, such as sepsis, as well as other serious bacterial infections such as pneumonia and meningitis. The situation is aggravated by AMR, as currently available treatments become less effective. Globally, 214,000 newborns die from sepsis due to drug-resistant infections each year[2].

Drug-resistant sepsis in newborns is often associated with high-mortality rates in hospital settings. When healthcare systems are overwhelmed, hospitals may not have sufficient resources to ensure medical care, let alone infection control. In such settings, the bacteria which lead to drug-resistant infections can thrive.

A major challenge is the knowledge gap, as there is very little evidence to support the appropriate treatment of serious, including drug-resistant, infections in neonates. Despite increasing rates of resistance to the WHO recommended treatment regimen, the lack of evidence on potential alternatives means the guidelines have not been updated for more than 50 years.

GARDP's response

How GARDP is addressing sepsis in newborns
GARDP's neonatal sepsis programme aims to develop new antibiotic treatments and provide an evidence base for the use of antibiotics, both old and new, in newborns with confirmed or suspected sepsis by:

1 **Developing and delivering a new first-line antibiotic treatment for clinically-diagnosed neonatal sepsis in areas experiencing high levels of drug-resistance.**

2 **Developing evidence-based treatment regimens for neonatal sepsis caused by multidrug-resistant Gram-negative pathogens.**

Results

Achievements in 2018:
GARDP started a global observational study to increase understanding about neonatal sepsis. The study is collecting clinical information on suspected (clinically-diagnosed) sepsis in up to 3,000 newborns in hospitals and / or neonatal units in 11 countries.

Outcomes such as antibiotic use, duration of treatment and mortality rates will be recorded and analysed. The study will help to build the evidence base needed to evaluate future interventions that could be used to treat neonatal sepsis.

GARDP developed a target product profile (TPP) to re-purpose an existing antibiotic for use in the treatment of clinically diagnosed neonatal sepsis. GARDP has identified fosfomycin as an initial development candidate to assess, in combination, with other existing antibiotics as potential components of an improved empiric regimen for newborns with sepsis.

GARDP developed a second TPP for an antibiotic to treat confirmed or highly-suspected neonatal sepsis caused by multidrug-resistant Gram-negative bacteria.

GARDP completed the patient phase for a single dose pharmacokinetic and safety evaluation of fosfomycin in newborns. This clinical trial, conducted in Kenya, is in the analysis and reporting phase. The results will support dose selection of fosfomycin as a possible component of the revised empiric treatment regimen for newborns with sepsis.

Researchers gather in New Delhi to kick off global observational study for newborns with sepsis
The Honourable Minister for State, Ministry of Health and Family Welfare, Ms Anupriya Patel, joined over 80 researchers from 11 countries at a launch event co-hosted by the Indian Council of Medical Research and WHO. The event marked the kick-off of GARDP's global observational study to understand clinical management of sepsis in newborns, including current antibiotic prescribing practices.

The study is being run in partnership with St George's, University of London and Penta (the paediatric infectious diseases research network). Data will be used to develop and deliver new antibiotic treatments for newborns with drug-resistant bacterial infections.

The study will generate a robust evidence based on how neonatal sepsis is managed which can be used as a basis for evaluating future interventions in this vulnerable population. Outcomes of interest will include mortality, antibiotic use and duration of antimicrobial therapy.

Ms Anupriya Patel, the Honourable Minister for State, Ministry of Health and Family Welfare, India.

"AMR is one of the biggest threats to global health, food security and development today. It is a major and rapidly growing public health problem, globally, with estimates of up to 700,000 deaths per year. AMR is threatening to compromise the gains we made as a country to control infectious diseases such as malaria, and tuberculosis. The National Health Policy 2017 identifies AMR as a critical priority and calls for effective action to address it. The ministry of health and family welfare identified AMR as one of the top 10 priorities for the ministry's collaborative work with WHO."

1 Reducing Child Mortality Factsheet, World Health Organization, September 2018
2 Laxminarayan, R. et al. (2016). Antimicrobials: access and sustainable effectiveness 1 Access to effective antimicrobials: a worldwide challenge. Lancet: 387: 168-75.

Income

GARDP continues to seek a broad range of funding from both public and private donors.

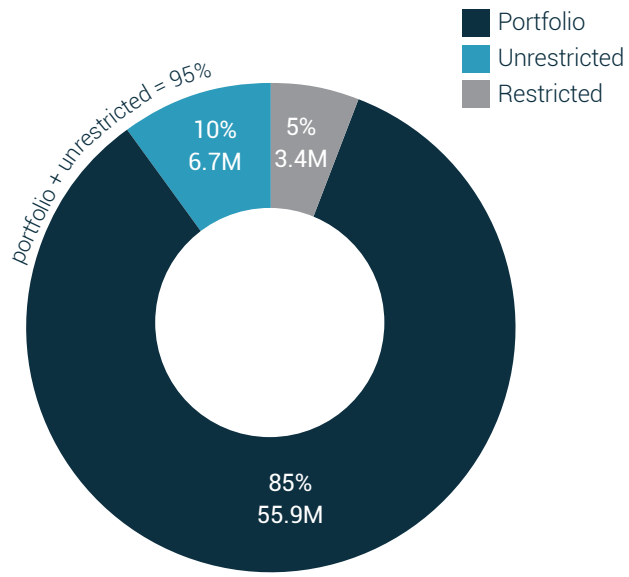
Five new donors were added in 2018:

• Two public institutions: German Federal Ministry of Education and Research (BMBF) and UK Department of Health and Social Care (DHSC).

• Three private contributions: Bill and Melinda Gates Foundation, Leo Model Foundation and Wellcome Trust.

• 95% of the EUR 53.8M in new funding in 2018 was granted by public institutions.

84% portfolio funding
GARDP aims to maintain a balance between restricted and unrestricted grants. However, a strong trend of portfolio funds puts GARDP in a good position to respond quickly to research opportunities within a broad portfolio of projects and provides flexibility in funding these diverse initiatives. 84% of portfolio funding plus 10% of unrestricted funding provides high flexibility to GARDP in delivering its priorities.



Public contributors 2016 - 2022	
German Government (BMBF and BMG)	EUR 54.1M
UK Government (DFID and DHSC)	EUR 4.6 M
Dutch Government (VWS)	EUR 2.5 M
The Swiss Government (FOPH)	EUR 0.8 M
South African Medical Research Council	EUR 0.6 M
Grand Duchy of Luxembourg	EUR 0.1M

Private contributors 2016 - 2022	
Bill & Melinda Gates Foundation	EUR 1.7M
Wellcome Trust	EUR 1.1M
Others: Médecins Sans Frontières, Leo Model Foundation	EUR 0.6M

Expenditure

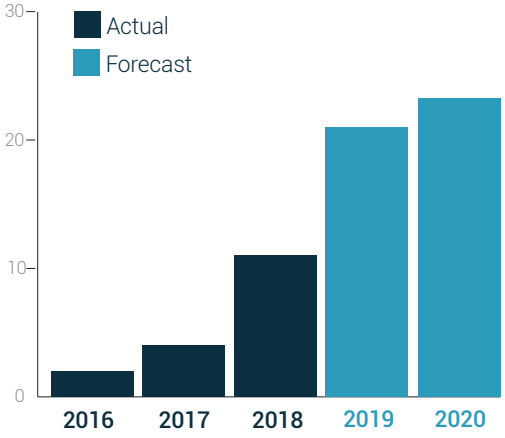
Steady growth in spending, concentrated on R&D

• Expenditure totaled EUR 11.2M in 2018, an increase of 164% (+EUR 6.9 M) compared to 2017.

• Spending on social mission equated to 92% of the 11.2M with R&D expenditure totalling EUR 9.8M.

• GARDP expenditure totals EUR 16.5M since the start of its incubation within DNDi in 2016.

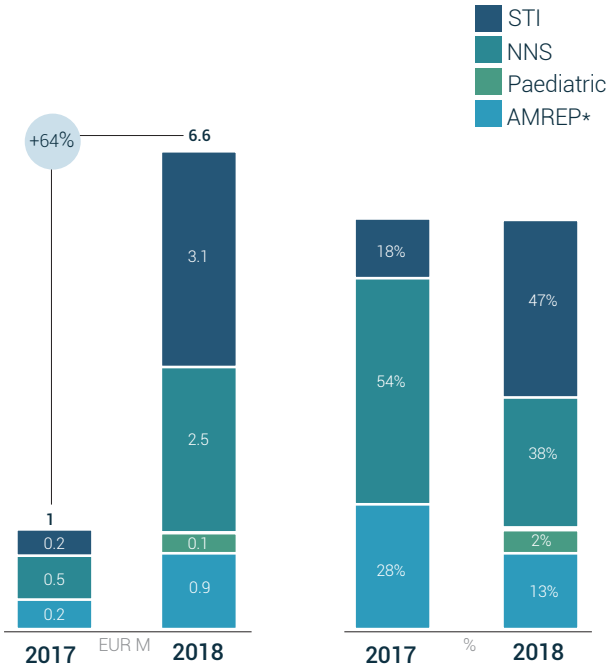
Actual expenditure 2016 – 2018 and forecast 2019-2020 in million EUR



R&D expenditure per programme

R&D spending per programme increased (+EUR 5.7M) significantly over 2017 with the largest proportion being spent within the neonatal sepsis and sexually-transmitted infections programmes.

R&D expenses per programme in million EUR



* Antimicrobial Memory, Recovery and Exploratory Programme

Interim combined financial statements

STATEMENT OF OPERATIONS

At 31 December 2018 with comparative figures

	2018	2017
INCOME (EUR)		
Total public institutional funding	**10'213'611**	**3'937'635**
Total private funding	**965'963**	**324'975**
Other income	1'406	3'307
TOTAL INCOME	**11'180'980**	**4'265'917**
SOCIAL MISSION EXPENDITURE		
Research & development expenditure:		
Antimicrobial Resistance R&D coordination & supervision	3'215'581	2'570'219
Antimicrobial Memory Recovery & Exploratory	862'708	261'104
Neonatal Sepsis	2'480'991	471'275
Sexually Transmitted Infections	3'065'379	180'242
Paediatric Antibiotics	138'022	-
Total research & development expenditure	**9'762'681**	**3'482'840**
International Network Expenditure	**485'350**	**329'870**
TOTAL SOCIAL MISSION EXPENDITURE	**10'248'031**	**3'812'710**
NON-SOCIAL MISSION EXPENDITURE		
Fundraising and general administration	931'544	449'900
Total non-social mission expenditure	**931'544**	**449'900**
TOTAL EXPENDITURE	**11'179'575**	**4'262'610**
Operating surplus / (loss)	1'405	3'307

Extracted from GARDP '2018 Financial and Performance Report' audited by Deloitte. The full audited report will be available from July 2019 on GARDP's website www.gardp.org

A word of thanks

No single actor can tackle the problem of antimicrobial resistance alone. GARDP relies on the experience, knowledge, and support of a wide range of donors and partners. Thank you for your loyal commitment and collaboration. Together, GARDP and its partners are working towards a world where anyone, anywhere can have access to the treatments they need.

Federal Ministry of Education and Research

Federal Ministry of Health

UKaid from the British people

saMRC advancinglife

LE GOUVERNEMENT DU GRAND-DUCHÉ DE LUXEMBOURG

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Ministry of Health, Welfare and Sport

MEDECINS SANS FRONTIERES

BILL & MELINDA GATES foundation

Leo Model Foundation

A global collaboration

Partnerships with governments, academia, research centres and industry are at the heart of GARDP's work. Without the support of partners, GARDP would not have been able to make the progress it has made so far.

Belgium

- University of Antwerp

Denmark

- REPAIR Fund

India

- The All India Institute of Medical Sciences
- The Indian Council of Medical Research

Italy

- Penta

Japan

- Eisai
- Takeda

Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)

Kenya

- Kenyan Medical Research Institute

Korea

- Institut Pasteur Korea

The Netherlands

- Department of Infectious Diseases, Public Health Service Amsterdam

South Africa

- National Institute for Communicable Diseases
- South African Medical Research Council
- Stellenbosch University
- University of KwaZulu Natal
- Wits RHI, University of Witwatersrand
- Wits Health Consortium

Spain

- European Society of Clinical Microbiology and Infectious Diseases

Sweden

- WHO Collaborating Center for STIs, University Hospital Örebro

Switzerland

- Foundation for Innovative New Diagnostics (FIND)
- Sandoz, the Novartis generics division

Thailand

- Bureau of AIDS, TB, and STIs
- Department of Disease Control
- Thai Ministry of Public Health
- Thailand US CDC Collaboration
- Thai Red Cross AIDS Research Center
- University of Mahidol, Tropical Medicine Hospital

United Kingdom

- British Society of Antimicrobial Chemotherapy
- St George's, University of London
- The Medical Research Council – Clinical Trial Unit at University College, London
- The University of Liverpool
- The Wellcome Trust

United States

- American Society of Microbiology
- CARB-X
- Entasis Therapeutics
- National Institute of Allergy and Infectious Diseases
- National Institutes of Health
- Pew Charitable Trusts
- University of Alabama
- University of Florida

Research centres collaborating with GARDP on specific studies in the following countries

Bangladesh, Brazil, China, Greece, India, Italy, Kenya, The Netherlands, South Africa, Thailand, Vietnam, and Uganda, United States.

Governance and management

Board of Directors

GARDP's Board of Directors is the ultimate policy and decision-making authority and includes leading international figures in global health. The Board determines GARDP's strategic goals and ensures the management works efficiently to meet these goals. GARDP is grateful to DND*i*'s Board of Directors who provided GARDP's governance until the end of June 2018, as part of hosting GARDP during its incubation.

DND*i* Board Members (January to June)

Marie-Paule Kieny, Chair, Institut national de la santé et de la recherche médicale (INSERM), France

Suerie Moon, Secretary, The Graduate Institute, Switzerland

Derrick Wong, Treasurer, Non-profit management consultant, France until February 2018.

Marcel Tanner, Interim Treasurer, University of Basel, Switzerland, February 2018 onwards.

Rashmi Arora Indian Council of Medical Research, India

Jorge Bermudez Fundacao Oswaldo Cruz, Brazil

Stewart Cole Institut Pasteur, France, from February 2018

Noor Hisham Abdullah Ministry of Health, Malaysia

Joanne Liu Médecins Sans Frontières International

Alwyn Mwinga Patient representative; Zambart, Zambia

Bernhards Ogutu Kenya Medical Research Institute, Kenya

Bennett Shapiro PureTech Ventures, USA

John Reeder Permanent observer, WHO

GARDP Board Members (July to December)

Ramanan Laxminarayan, Chair, Centre for Disease Dynamics, Economics and Policy, USA

Marie-Paule Kieny, Vice-chair, Institut national de la santé et de la recherche médicale, INSERM, France

Glenda Gray South African Medical Research Council, South Africa

Marcel Tanner, Treasurer, University of Basel, Switzerland

Joanne Liu Médecins Sans Frontières International

Observers

Bernard Pécoul DND*i*

Soumya Swaminathan WHO

Scientific Advisory Committee up to end of December

GARDP's Scientific Advisory Committee, is made up of scientists with expertise in various disciplines within infectious diseases and microbiology. They provide independent expert advice to GARDP's Board of Directors. The Board of Directors approves the selection of members.

The Scientific Advisory Committee assesses GARDP's scientific strategy and projects and provides guidance and medical and scientific expertise to GARDP's programmes.

Members

Jutta Heim, Chair, University of Basel, Switzerland

Rashmi H Barbhaiya, Advinus Therapeutics, India

Anthony Coates, St George's University, UK

George Drusano, Institute for Therapeutic Innovation, University of Florida, USA

Mark J Goldberger, formerly Food and Drug Administration, United States

MN Herman Goossens, Antwerp University Hospital, Belgium

MN Shabir A Madhi, National Institute for Communicable Diseases, South Africa

Marc Mendelson, University of Cape Town, South Africa

Malcolm Page, formerly Basilea, Switzerland

David Shlaes, formerly Case Western Reserve University, USA

MJ Kazuhiro Tateda, Toho University, Japan

MF Kazuki Hoshino, Daiichi Sankyo Biotech Co., Ltd., Japan

Kamini Walia, Indian Council of Medical Research, India

Nicholas White, Mahidol University, Thailand

Observers

Graeme Bilbe, DND*i*

Karl-Heinz Altmann, Swiss Federal Institute of Technology, Switzerland

ON Patrice Courvalin, Institut Pasteur

Prabhavathi Fernandes, Cempra, Inc., USA.

Nicola Magrini, WHO

OS Lúcia Martins Teixeira, Federal University of Rio de Janeiro, Brazil

Lufuno Rudo Mathivha, Chris Hani Baragwanath Hospital, South Africa

ON Robert Gurny, University of Geneva, Switzerland

OS Yonghong Xiao, Zhejiang University, China

GARDP Leadership Management Team

Manica Balasegaram, Executive Director

Seamus O'Brien, Research & Development Director

Jean-Pierre Paccaud, Business Development and Corporate Strategy Director

Jennifer Katz, External Affairs Director

Laura Piddock, Scientific Affairs Director

Pierre-Yves Delhez, Finance & Administration Director

International network

GARDP, through DND*i*, has a global presence with offices in several countries, including Africa, North America, Latin America and South Asia. This network has allowed GARDP to develop local activities during its incubation. In-country implementation of GARDP's programmes will continue to be supported by these offices and a joint DND*i* GARDP office in Southern Africa.

Carol Ruffell, Head of Joint DND*i* GARDP Office Southern Africa

Rachel Cohen, Executive Director, DND*i*, North America (affiliate office)

Joël Keravec, Director, DND*i*, Latin America

Michel Lotrowska, Interim Director, DND*i*, Latin America

Jean-Michel Piedagnel, Director, DND*i*,South-East Asia

Suman Rijal, Director, DND*i*, in India

Monique Wasunna, Director, DND*i*, Africa

Daisuke Imoto, Head of Office, DND*i*, Japan

MJ Member up to June
MN Member up to November
ON Observer up to November
OS Observer up to September
MF Member from June

GARDP
Global Antibiotic Research & Development Partnership

A joint DND*i* / WHO initiative

Global Antibiotic R&D Partnership (GARDP)
15 Chemin Louis-Dunant
1202 Geneva
Switzerland

t: +41 22 555 19 90
e: contact@gardp.org
w: www.gardp.org

Following another successful year, GARDP's priorities for 2019 include:

- Launching a multi-site phase III pivotal clinical trial for a novel, first-in-class oral antibiotic to treat gonorrhoea.
- Launching GARDP's new 2020-2025 business plan and securing engagement and support to deliver in a timely manner.
- Bringing together stakeholders to identify practical access and stewardship interventions to move from principles to action.
- Completing and publishing data from GARDP's first clinical trial confirming the correct dose and evaluate the safety of fosfomycin for use in newborns with sepsis.
- Completing a global observational study to understand sepsis in newborns, evaluating this, other published and non-clinical data to select which antibiotic candidates to take forward into a large-scale clinical trial to evaluate an empiric treatment.
- Setting up a clinical trial to establish the correct dose of polymyxin B for children.
- Identifying up-to-two more drug candidates for use in children.
- Developing a global children's antibiotic network to build on GARDP's existing capability and prepare for future projects.