SERIOUS BACTERIAL INFECTIONS

ACCELERATING THE DEVELOPMENT OF A NEW ANTIBIOTIC

Every year, drug-resistant infections are responsible for over 700,000 deaths worldwide; without urgent action this number is projected to increase exponentially[1]. The impact of these infections is often worst in healthcare facilities, where bacteria spread easily and can enter the body through wounds, surgery sites, ventilators and catheters, leading to disability and death of adults, children and babies.

The elderly, people with weakened immune systems and young children are particularly vulnerable to serious bacterial infections. Babies are especially vulnerable to infection, with more than three million childhood deaths resulting from infectious diseases, such as pneumonia and sepsis every year.

In Europe, hospital infections are responsible for 37,000 deaths and contribute to an additional 110,000 deaths every year[2]; in the United States, they are responsible for more than 98,000 deaths[3]. The burden of health care-associated infection is significantly higher in low- and middle-income countries, particularly in patients admitted to adult and neonatal intensive care units. The World Health Organization (WHO) estimates the rate of hospital infections among newborns in low-income countries is up to 20 times higher than in high-income countries[4].

CARBAPENEM RESISTANCE

Serious bacterial infections, which have increasingly become resistant to commonly used 'first-line' antibiotics, are often treated with carbapenems, reserved for the most serious and multidrug-resistant infections, including lung, urinary tract, abdominal and bloodstream infections. However, since the introduction of the carbapenem class of antibiotics in the 1980s, pathogens have progressively become resistant to them.

The World Health Organization has identified carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) as 'critical-level' pathogens posing the greatest threat to global health and urgently requiring new treatments[5].

Carbapenem resistance is a growing problem across Europe, North America and the Indian sub-continent.

LACK OF INVESTMENT

Declining private investment and lack of innovation in the development of new antibiotics are undermining efforts to combat drug-resistant infections. According to the WHO, two recent reports revealed a weak pipeline for antibiotic agents. Amongst the 60 products in development (50 antibiotics and 10 biologics), very few target the most critical resistant bacteria (Gram-negative bacteria). While pre-clinical candidates (those in early-stage testing) are more innovative, it will take years before they reach patients.

Most pharmaceutical companies are no longer developing new antibiotics. The discovery and development of antibiotics is time consuming and expensive. New antibiotics that are approved for use typically have a short treatment duration and controls in place to slow the emergence and spread of resistance, which limits their profitability.

Most pharmaceutical companies have left the field altogether, leaving it essentially up to small and medium-sized enterprises to invest in research and development. These companies have difficulties raising sufficient capital to complete clinical trials and bring their compound on the market due to the lack of financial upsides. It is therefore critical to ensure that novel antibiotics responding to global unmet needs are reaching people in need, and this endeavour requires mobilizing resources from the public and private sector.

[1] O'Neill J. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations. The review on antimicrobial resistance. December 2014
[2] ECDC: Antimicrobial Resistance and Healthcare-associated Infections Programme / [3] Infection and Drug Resistance: Health care-associated infections – an overview
[4] WHO: Health care-associated infections Fact Sheet / [5] WHO publishes list of bacteria for which new antibiotics are urgently needed

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THE GARDP RESPONSE

GARDP is bringing together partners in the public and private sectors to address critically underfunded and unfilled gaps in the development of treatments for drug-resistant bacterial infections, and ensure that the antibiotic research and development ecosystem does not collapse. While this includes partnering to support early-stage exploratory activities, GARDP prioritizes late stage clinical and pharmaceutical development of treatments, with a focus on sustainable access. GARDP's work on serious bacterial infections includes ensuring new treatments are evaluated for use with children, who are too often overlooked during the development of treatments.

GARDP AND VENATORX COLLABORATION: MEETING AN UNMET NEED

Driven by a shared vision to address the growing threat of drug-resistant serious bacterial infections, GARDP and Venatorx Pharmaceuticals have joined forces to accelerate the development of a critically needed new treatment to fight antibiotic-resistant, hospital-associated infections in adults and children. We are committed to working together to ensure this treatment is available to everyone who needs it, wherever they live.

The collaboration will focus on the further development of an investigational combination of an approved antibiotic, cefepime, and taniborbactam, a novel, broad-spectrum beta-lactamase inhibitor (BLI), to enhance the activity of cefepime against carbapenem-resistant bacteria, including CRE and CRPA. Taniborbactam is of specific interest to GARDP because the BLI also targets a particularly difficult beta-lactamase class to inhibit, the metallo-beta-lactamases (MBLs). Clinical trials will be conducted in adults with multi-drug-resistant infections, alongside additional trials and development activities to ensure the treatment is safe and effective for use with children and babies with serious bacterial infections, including neonatal sepsis.

In August 2019, Venatorx initiated its first efficacy trial, with a phase 3 trial of cefepime-taniborbactam in patients with complicated urinary tract infections and expects top-line results by early 2021.

PAEDIATRIC TREATMENT TO FIGHT SERIOUS BACTERIAL INFECTIONS

One of the main objective's of GARDP's paediatric programme is to accelerate the development of new, improved and safer antibiotics to treat drug-resistant infections in children, including sepsis in babies. Traditionally it has taken seven to ten years after an antibiotic has been registered for use in adults for the paediatric formulation to be made available.

GARDP will collaborate with Venatorx and other key partners such as the Penta Foundation – a global paediatric infectious diseases research network based in Italy – to conduct the clinical trials required by regulatory authorities such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to gain paediatric approval. The information generated for EMA and FDA will facilitate registration in other settings including low- and middle-income countries. In addition, the collaboration will aim to conduct any strategic public health-focused trials on the appropriate use of cefepime–taniborbactam to treat children and babies.

The first pediatric activities are planned to start by the first half of 2021.

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TERMS OF THE COLLABORATION

Venatorx is responsible for the clinical development and the ongoing phase 3 trial of cefepime-taniborbactam in patients with complicated urinary tract infections (cUTI). GARDP is financially contributing to the phase 3 trial in order to support an initial registration in the United States, to be followed by a registration in Europe.

GARDP will bring financial resources and expertise to accelerate the clinical development of cefepime-taniborbactam, with emphasis on paediatric development and generating clinical evidence for use in carbapenem-resistant infections in adults.

The paediatric drug product development for cefepime-taniborbactam will be led by GARDP in accordance with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) regulations. GARDP will also co-lead a clinical study to demonstrate the safety and efficacy of cefepime-taniborbactam in adult patients infected with carbapenem-resistant pathogens.

GARDP will contribute up to US$35 million in the development collaboration with Venatorx.

ENSURING AFFORDABILITY & ACCESS

GARDP and Venatorx have committed to provide affordable access of cefepime-taniborbactam in patients globally including for underserved populations and geographies, and to ensure its preservation through adapted and implementable stewardship measures.

Access in low and lower middle-income countries will be addressed through the following mechanisms:

- GARDP will aim to make cefepime-taniborbactam and its paediatric formulation available in all low-and lower middle-income countries:
  - Directly through an exclusive commercialization/distribution license for use in the treatment of gram-negative infections in 67 countries (see annex A); countries with the highest burden will be prioritized, with the aim to reach eventually all patients within GARDP's territories;
  - Collaborating with Venatorx on the commercialization strategy in other lower middle-income countries through a Joint Strategic Committee.
  - Working with Venatorx to ensure registration and access outside its territories. Contractual measures have been agreed to ensure GARDP can also ensure this occurs in particular in key GARDP donor countries (Germany and UK).
- GARDP will be responsible for access, including distribution and sale of the adult and paediatric treatment, in India and South Africa.

COVID-19 AND ANTIBIOTIC RESISTANCE

The link between COVID-19 and drug-resistant infections is more troubling than many realize. Antibiotics, while not effective against viruses, are being used frequently in people with COVID-19 to prevent or treat suspected or confirmed secondary bacterial infections. According to an early study from China, secondary infections causing bacterial pneumonia, bloodstream infections, sepsis and hospital-acquired infections were present in half of all deceased COVID-19 patients [6].

However, many of these infections are increasingly resistant to existing treatments.

Just like COVID-19, antibiotic resistance is a health security crisis that moves silently and doesn't stop at national borders. No single country, company or organization can fight drug resistance alone. It can only be done in partnership.

[6] *The Lancet: Clinical course and risk factors for mortality of adult patients with COVID-19 in Wuhan, China: a retrospective cohort study*

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ANNEX A – ACCESS TERMS: LIST OF COUNTRIES

UPPER MIDDLE INCOME

South Africa *(public market)*

LOWER MIDDLE INCOME

Angola
Bangladesh
Bhutan
Bolivia
Cabo Verde
Cambodia
Cameroon
Congo, Rep.
Côte d'Ivoire
El Salvador
Georgia
Ghana
Honduras
India *(public market)*
Kenya
Kiribati
Kosovo
Lao PDR
Lesotho
Mauritania
Micronesia
Mongolia
Myanmar
Nicaragua
Nigeria
Pakistan
Papua New Guinea
São Tomé
Solomon Islands
Sri Lanka
Swaziland
Timor-Leste
Vanuatu
Zambia

LOW INCOME

Afghanistan
Benin
Burkina Faso
Burundi
Central African Republic
Chad
Comoros
Congo, Dem. Rep
Eritrea
Ethiopia
Gambia, The
Guinea
Guinea-Bissau
Haiti
North Korea
Liberia
Madagascar
Malawi
Mali
Mozambique
Nepal
Niger
Rwanda
Senegal
Sierra Leone
Somalia
South Sudan
Syrian Arab Republic
Tajikistan
Tanzania
Togo
Uganda
Yemen, Rep.
Zimbabwe

These 69 countries are among the low-and lower middle-income countries (LMICs), except for South Africa which is upper middle-income[7]. The remaining LMICs were already licensed by Venatorx to other partners.

[7] source: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519

ABOUT GARDP

The Global Antibiotic Research and Development Partnership (GARDP) is a not-for-profit organization developing new treatments for drug-resistant infections that pose the greatest threat to health. Established by the World Health Organization (WHO) and the Drugs for Neglected Disease initiative (DNDi) in 2016, GARDP is a core element of WHO's Global Action Plan on Antimicrobial Resistance.

We were created to ensure that everyone who needs antibiotics receives effective and affordable treatment, no matter where they live. We aim to develop five new treatments by 2025 to fight drug-resistant infections, focusing on sexually transmitted infections, sepsis in newborns and infections in hospitalized adults and children. GARDP is funded by the governments of Germany, Luxembourg, Monaco, Netherlands, South Africa, Switzerland, United Kingdom, Médecins Sans Frontières, as well as private foundations.

www.gardp.org