A NOT-FOR-PROFIT ANTIBIOTIC DEVELOPER – THE GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT PARTNERSHIP

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The Global Antibiotic Research and Development Partnership (GARDP) – a not-for-profit drug developer – addresses global public health needs by developing affordable new or improved antibiotic treatments. Initiated by the World Health Organization (WHO) and the Drugs for Neglected Diseases *initiative* (DNDi) in 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 (R&D) of new antimicrobial agents and diagnostics. GARDP capitalizes on DNDi's track record of developing, delivering and implementing seven new treatments since 2003 for neglected diseases, and a pipeline of new chemical entities, as well as from WHO's technical expertise and leadership.

The increasing resistance of bacteria is outpacing antibiotic drug discovery at an alarming rate. The current pipeline for new antibiotics and biological treatments fails to address the biggest threats posed by increasingly drug-resistant Gram-negative bacteria, as well as tuberculosis *(1)*, identified by the World Health Organization (WHO) as global public health priorities *(2)*. The pharmaceutical industry has largely left the field of antibiotic development and new and remaining players struggle to mobilize financial resources due to the limited return on investment and the scientific challenges. This calls for coordinated support for basic research and early stage discovery, as well as for bringing new drugs through clinical trials *(4)*. There is also insufficient investment to improve access and optimize the use of existing antibiotics.

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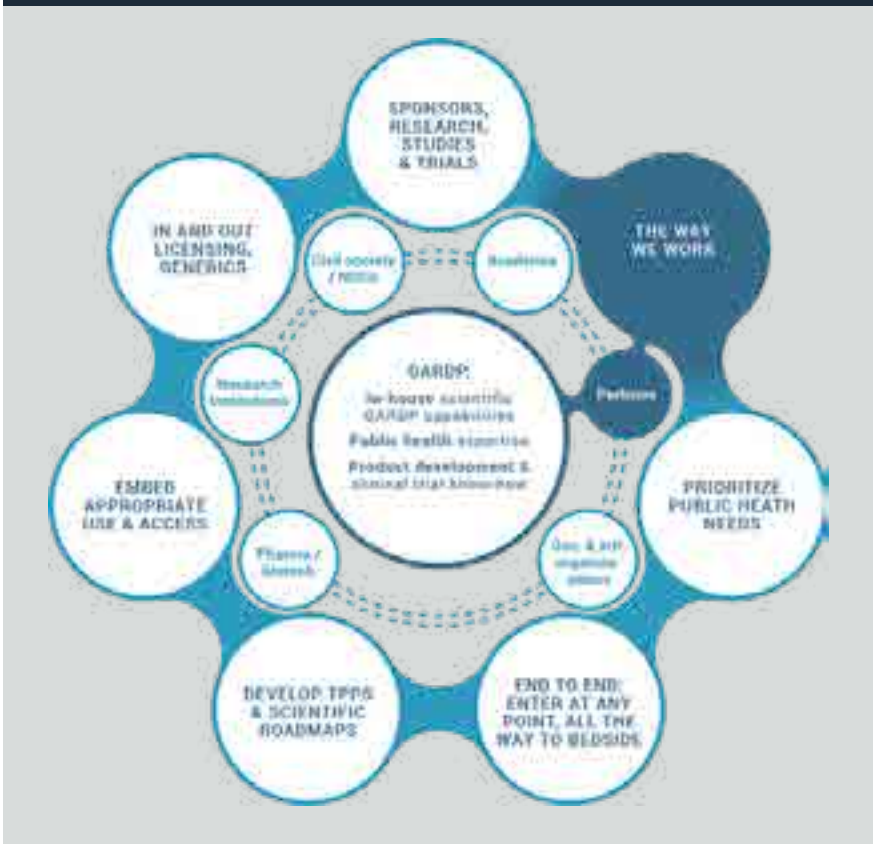
The Berlin Declaration of the G20 Health Ministers in 2017 *(5)*, as well as other UN declarations *(6)* and WHO strategic plans *(7)*, cautioned that success in the fight against antimicrobial resistance cannot be achieved with existing health tools and technologies. The Berlin Declaration welcomed new initiatives, including GARDP, which can "reinvigorate research and development in science and industry for antimicrobials." It recognized the importance of reactivating the R&D pipeline through incentive mechanisms that do not rely on high price/volume combinations and that promote appropriate use of antibiotics. Finally, the Declaration also called for "broadening the voluntary financial support" for such initiatives.

Any new approach must address the complex issues of stewardship, as well as sustainable, equitable and affordable access to existing and new antibiotic drugs. These must meet patients' needs globally and take into account the diversity of national health systems' challenges and levels of economic development.

[1] This contribution has been prepared strictly in a personal capacity and reflects the view of the author. The views expressed must not be attributed to the WHO, its Secretariat, or its Member States.

It is vital that all new tools are designed from inception to meet health priority needs, reflect the realities of clinical practice, and ensure access but not excess. GARDP has committed to explore concrete ways to address this challenge both through its business model and programmes.

Figure 1: **GARDP's business model and operating principles**



GARDP's model

GARDP is a not-for-profit drug developer that focuses on filling R&D gaps identified by WHO. GARDP's business model is different as its ultimate objective – to facilitate access to new treatments and their appropriate use – is built into the R&D process from the beginning. GARDP's programmes not only support public health needs but have the flexibility and capacity to enter at any point from early exploratory to preclinical and clinical studies all the way through to patient access. Its R&D strategies are based on global health priorities, clear target product profiles (TPPs) and R&D roadmaps. This approach creates a favourable environment for equitable access by developing a sustainable and fair pricing system. Partnerships are key to GARDP programmes and include contractual arrangements with pharmaceutical companies, research institutions, and academic partners.

Since its formation, GARDP has built up a skilled team with expertise from a range of sectors and backgrounds, notably public health, clinical infectious disease, industry, academia and working in developing country experience. Furthermore, GARDP has benefited from its unique WHO and DNDi parentage. The incubation period hosted by DNDi gives GARDP access to an international network as well as DNDi's R&D expertise, while WHO's technical departments provide expertise in the different disease areas as well as guidance on priority setting.

GARDP's business model and operating principles

Prioritization process

Prioritization is crucial and should take into consideration the intersection between priority pathogens; specific populations' health needs; and individual diseases and broader syndromes. It is essential that recommendations are evidence-based, and that data also supports access and appropriate use. This ensures any new health tools are designed from the start to address priority needs. GARDP's choice of initial programmes follows these principles and has been supported by expert reviews and input from WHO (including priority pathogens, pipeline *(8)* and landscape analyses). GARDP's work is global in focus, while paying particular attention to the needs of developing countries.

R&D programmes launched

Three programmes have been launched by GARDP in 2017:

- The antimicrobial memory recovery and exploratory programme recovers the knowledge, data, and assets of forgotten, abandoned, or withdrawn antibiotics as well as seeking new treatments. Through REVIVE – an online platform (http://revive.gardp.org) for the antimicrobial R&D community to learn, connect and share good practice on conducting antimicrobial drug R&D *(8)*. This will help improve, accelerate, and streamline antimicrobial drug discovery, and R&D. So far, more than 100 experts have engaged with REVIVE. An exploratory strategy is being developed to support early stage research. This will include building a long-term portfolio of therapeutic interventions necessary to address the unavoidable development of resistance to any novel compound that will be brought to patients.
- The sexually-transmitted infections programme aims to develop treatment for gonorrhoea patients with drug-resistant infections by accelerating the development of

at least one new drug *(9)*. In July 2017, GARDP entered its first partnership agreement with biotech company Entasis Therapeutics *(10)* to co-develop the antibiotic zoliflodacin *(11)* for gonorrhoea. GARDP and Entasis are collaborating to develop the product globally. Phase III clinical trials are being planned in Europe, South Africa, Thailand, and the United States. Should zoliflodacin receive regulatory approval, Entasis will grant GARDP an exclusive license with sublicensing rights in 168 low- and middle-income countries, while retaining commercial rights in high-income markets. The licence also contains provisions on affordability and sustainable access. In addition to zoliflodacin, a review of back-up candidates is underway via, but not limited to, GARDP's memory recovery programme. The investigation of combinations of existing antibiotics, as well as exploring the development of fixed-dose combinations, is also underway.

- The neonatal sepsis programme will provide an evidence base for the use of antibiotics, both old and new, in neonates with serious bacterial infections. A feasibility survey conducted in 2017 has already confirmed high levels of drug resistance in some settings with significant variation in treatment protocols in different countries. Two TPPs have been developed to guide the development of an alternative first-line treatment for clinically diagnosed neonatal sepsis and a new treatment for new-borns with confirmed multidrug-resistant infection. GARDP currently evaluates potential treatment candidates, including through pharmacokinetic trials, to inform on appropriate dosing regimen. Clinical trials are to follow these studies.

GARDP is also exploring ways to optimize current paediatric treatments and accelerate the development of new antibiotics for children through improvements in dosing, treatment duration, drug formulation, or new drug combinations.

Access, innovation, and incentives

One of the key components of GARDP's model is a tailored approach to ensuring sustainable access – embedding stewardship and conservation within an access approach. Sustainable access is an integral element throughout all of GARDP's programmes. This includes building in access and appropriate use considerations in the TPPs; optimizing use of existing antibiotics; ensuring affordability of new antibiotics; and improving formulations and drug profiles. GARDP also includes clauses that ensure affordability and appropriate use of any new products developed by GARDP in any partnership agreement.

With this approach, not-for-profit antibiotic developers such as GARDP can strongly stimulate innovation while promoting global access and appropriate use. While developers can and should play a part in sustainable access, there remains a crucial role for governments, WHO and other agencies to set the appropriate polices and standards at the national, regional and global level.

Antimicrobial resistance R&D in the global landscape

As the current global R&D pipeline is very weak, three key areas are in need of targeted support: basic research and discovery, clinical development of new drugs, and optimization of existing drugs. But any support to R&D and to sustainable access should take an integrated approach, focusing on an intersection of pathogens, diseases and syndromes, and specific populations. Given the scarce data following registration of future antibiotics, post licensing monitoring to further support public health is extremely important.

It is also important that all stages of antimicrobial R&D can be supported, so it is crucial that any new incentives are appropriately designed to reflect the reality of the research landscape *(12)*. To ensure a public return on public investment, any such incentive should include a contractual relationship between payer(s) and recipient(s) with strong governance, definitions around what constitutes innovation (based on public health priorities), and a clear agreement on sustainable access and appropriate use provisions. It is important to remember that access to quality antibiotics remains critical *(11)*. Surveillance activities not only serve epidemiological purposes, but should link to R&D efforts in a mutually reinforcing way – country- or regional-specific R&D programmes should address the resistance profiles and can feed back into surveillance efforts.

While discussions around R&D today often revolve around possible new financial incentives, it is important to prepare the necessary ground for effective use of public money through existing and possible future R&D mechanisms. The R&D pipeline cannot be seen in segmented parts but must be considered as a continuum that flows from beginning to end. If public money is invested, it is important to ensure that it focuses on priority areas. Undertaking the following activities is key, as is strong public leadership:

- Setting public health priorities includes understanding needs and gaps, identifying priorities and how they evolve. WHO has provided leadership by developing and publishing the Priority Pathogens List in 2017 which is already widely used. Priorities, however, include not just pathogens, but also specific population needs and specific medical indications (e.g., populations disproportionally affected where treatments are last line or not evidence based, such as the case with antibiotic use in neonatal sepsis).
- Landscaping analyses also need to take place in order to collect data for evidence-based decisions. WHO has

already provided an analysis of the clinical antibacterial pipeline. This exercise needs to be done on an annual basis to monitor further developments and should be expanded into the pre-clinical area and include alternative approaches. Importantly, surveillance data on antimicrobial resistance (e.g., WHO GLASS and GASP) must be taken into account, as well as monitoring antibiotic consumption and use, to have a better understanding of how to improve use of antibiotics. A first WHO global report on antibiotic consumption data is anticipated for end 2018. Based on this data and identified priorities, WHO has a role to play in developing general target product profiles reflecting the most urgent public health needs, as well as reviewing the funding landscape via the WHO Global Observatory.

- Directing investment into public health-driven R&D can support optimizing the use of existing antibiotics and the R&D of new antibiotics. Risk-taking can be greater where the gaps have been identified. Such investment should stipulate embedment of stewardship and access provisions and, appropriately, support all relevant sectors. Ensuring public return for such investments is crucial. Regulatory strengthening is also required to clarify and streamline processes for new (relevant) drug development, as well as ensuring appropriate quality and use.

Considering these steps ensures a focus based on public health needs and gaps. Ultimately GARDP and other initiatives will rely on broader political will and public leadership for success. Collaboration between all existing and new AMR R&D-related initiatives is also essential to maximise the effort directed towards stimulating R&D for new antimicrobials in the fight against multi-drug resistance. ■

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Peter Beyer, a trained lawyer, is a Senior Adviser with WHO in Geneva where he is responsible for the development of a global development and stewardship framework to combat antimicrobial resistance and for developing new innovative funding mechanisms for pharmaceutical research and development. Previously, he was a legal adviser to the Swiss Federal Institute of Intellectual Property where he negotiated bilateral free trade agreements for the European Free Trade Association.

Jean-Pierre Paccaud, a trained molecular and cellular biologist, leads GARDP business development and corporate strategy activities, including opportunity identification, contract structure and negotiations, and alliance management. Previously, he founded and led Athelas SA, a start-up active in the anti-bacterial drug discovery field, until its merger with Merlion Pharmaceuticals. Before taking on entrepreneurial challenges in industry, he spent more than 18 years in academia, working in immunology, diabetes, and cell biology, and was tenured at the University of Geneva School of Medicine.

References

1. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, Guerin PJ, Piddock LJ: Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016, 387:176-187.
2. World Health Organization: Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1 2017.
3. Zignol M, Dean AS, Falzon D, van Gemert W, Wright A, van Deun A, Portaels F, Laszlo A, Espinal MA, Pablos-Mendez A, et al: Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. *N Engl J Med* 2016, 375:1081-1089.
4. World Health Organization: The selection and use of essential medicines. *World Health Organ Tech Rep Ser* 2014:i-xiv, 1-219, back cover.
5. G20 Germany 2017: Berlin Declaration of the G20 Health Ministers. https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G20-Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf. 2017.
6. United Nations General Assembly Draft political declaration of the high-level meeting of the General Assembly on antimicrobial resistance. https://www.un.org/pga/71/wp-content/uploads/sites/40/2016/09/DGACM_GAEAD_ESCAB-AMR-Draft-Political-Declaration-1616108E.pdf 2016, 16-16108 (E).
7. World Health Organization: Global action plan on antimicrobial resistance. http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/ 2015.
8. World Health Organization: Antibacterial agents in clinical development. http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/ 2017.
9. Alirol E, Wi TE, Bala M, Bazzo ML, Chen XS, Deal C, Dillon JR, Kularatne R, Heim J, Hooft van Huijsduijnen R, et al: Multidrug-resistant gonorrhea: A research and development roadmap to discover new medicines. *PLoS Med* 2017, 14:e1002366.
10. Global Antibiotic Research & Development Partnership: Entasis Therapeutics and the Global Antibiotic Research & Development Partnership (GARDP) to develop a new treatment for drug-resistant gonorrhea. Press release, https://www.gardp.org/2017/news-resources/press-releases/entasis-therapeutics-and-gardp-to-develop-new-treatment-for-drug-resistant-gonorrhea/ 2017.
11. Damiao Gouveia AC, Unemo M, Jensen JS: In vitro activity of zoliflodacin (ETX0914) against macrolide-resistant, fluoroquinolone-resistant and antimicrobial-susceptible Mycoplasma genitalium strains. *J Antimicrob Chemother* 2018.
12. Luepke KH, Suda KJ, Boucher H, Russo RL, Bonney MW, Hunt TD, Mohr JF, 3rd: Past, Present, and Future of Antibacterial Economics: Increasing Bacterial Resistance, Limited Antibiotic Pipeline, and Societal Implications. *Pharmacotherapy* 2017, 37:71-84.
13. Tangden T, Pulcini C, Aagaard H, Balasegaram M, Hara GL, Nathwani D, Sharland M, Theuretzbacher U, Cars O: Unavailability of old antibiotics threatens effective treatment for common bacterial infections. *Lancet Infect Dis* 2018, 18:242-244.
14. Laxminarayan R, Matsoso P, Pant S, Brower C, Rottingen JA, Klugman K, Davies S: Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016, 387:168-175.