

CARB-X IS A NEW APPROACH TO ACCELERATING PROMISING RESEARCH INTO NEW ANTIBIOTICS, THERAPEUTICS, DIAGNOSTICS, VACCINES AND DEVICES ... AND IT IS MAKING PROGRESS

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CARB-X stands for Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. It is funded by the United States government (through BARDA and NIAID, within the United States Department of Health and Human Services), the United Kingdom government (through the Global AMR Innovation Fund, GAMRIF, in the Department of Health and Social Care), the Wellcome Trust, and the Bill and Melinda Gates Foundation. CARB-X has as its mission to invest more than US\$ 500 million in 2016–2021 to support the pre-clinical development of antibiotics and other therapeutics, rapid diagnostics, vaccines and devices to address the rise of drug resistance.

Since Alexander Fleming's discovery of penicillin 90 years ago this year, antibiotics have been the miracle drugs that revolutionized healthcare and helped produce today's era of modern medicine. No other drug class in human history has been more important in curing disease and extending life expectancy.

Fleming himself warned that we are in a perpetual race against bacteria that develop resistance to antibiotics. Yet today, the world is facing a crisis. Superbugs are developing resistance faster than we can come up with new weapons. We are depleting our supply of antibiotics, according to a recent World Health Organization (WHO) study, and there are only a handful of antibiotics in clinical development to treat the most deadly drug-resistant superbugs. The WHO estimates that 700,000 people die each year from infections and that number is growing. In the United States alone, drug-resistant infections kill 23,000 Americans each year and 14,000 more die from infections triggered by antibiotics that upset the normal microbiome of the human gut.

Imagine the potential toll that drug-resistant bacteria could take in a natural or man-made disaster where there is widespread injury.

The danger isn't only to our health. In 2016, the World Bank projected the economic impact: the "optimistic"

scenario was a 1.1% reduction in global GDP by 2050; the "high-impact" scenario was more than three times worse.

The reasons are well known. Overuse and misuse of existing antibiotics have contributed to the rapid rise of resistance. Limited access to antibiotics in parts of the world where they are most needed also contributes to the spread of deadly bacteria. At the same time, the antibacterial pipeline is very thin. There have been no new classes discovered for antibiotics approved by the FDA for the most serious bacteria – Gram-negative superbugs – since 1962. Drug developers are reluctant to invest in developing new antibiotics to treat Gram-negative bacteria because the science is difficult and returns are low. Unlike other therapy areas where breakthrough medicines can generate billions in sales, the most powerful antibiotics are reserved as "last-resort" treatments for the hardest-to-treat patients. Companies cannot make money on drugs they do not sell.

The economic model for antimicrobials is broken. We can no longer count on private industry to deliver the antibiotics we need.

We need to think differently about how to drive innovation, and we need bold action at the global level to win the war against the rise of superbugs.

Finding long-term solutions for a complex global problem

It is encouraging that world leaders are looking for meaningful solutions. For several years, the WHO has been sounding alarm bells and urging nations to develop action plans to address the crisis. In 2016, the UN general assembly recognised drug-resistant infections as one of the greatest threats facing humanity. And in May 2017, G20 leaders called for national action plans by the end of 2018.

Sweden and the United Kingdom were pioneers in this area. Professor Otto Cars at Uppsala University had long championed the issue, which was taken up when Sweden chaired the Presidency of the EU in 2009. The Chief Medical Officer of England, Dame Sally Davies, also raised the profile of this issue in the United Kingdom and abroad. The United Kingdom government and the Wellcome Trust commissioned an independent review of the issue, chaired by Lord Jim O'Neill. The Independent Review on AMR called for new business models to provide predictable financial incentives to encourage innovation. After an exchange between the United Kingdom's Prime Minister, David Cameron, and President Barak Obama, the United States government accelerated action. In 2015, the United States government launched its National Action Plan on Combating Antibiotic Resistant Bacteria, a multi-pronged effort to slow the spread of drug-resistant bacteria, improve national surveillance, reduce misuse and overuse of antibiotics in animals, crops and humans, and to accelerate research and development of new products including antibiotics, diagnostics and vaccines.

The United States, the Wellcome Trust and Boston University came together to create CARB-X in July 2016, a non-profit global partnership to provide funding and support to early development research projects. CARB-X stands for Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator. It is funded by the United States government (through BARDA and NIAID, within the United States Department of Health and Human Services), the United Kingdom government (through the Global AMR Innovation Fund, GAMRIF, in the Department of Health and Social Care, the Wellcome Trust and the Bill and Melinda Gates Foundation). CARB-X has as its mission to invest more than US\$ 500 million in 2016–2021 to support the pre-clinical development of antibiotics and other therapeutics, rapid diagnostics, vaccines and devices to address the rise of drug-resistant bacteria.

Initially, the goal was to support 20 research projects by the end of Year 5, but that goal was exceeded quickly in CARB-X's first year of operation.

CARB-X is making a difference

By June 2018, CARB-X had 33 innovative projects in

seven countries in its portfolio and had announced more than US\$ 87 million in non-dilutive funding awards to the product developers, plus an additional US\$ 118 million for those projects if milestones are met. Among the projects are nine projects that are new classes of antibiotics, many non-traditional therapeutics, projects to boost the body's microbiome, a vaccine, and six rapid diagnostics that will enable doctors to treat patients more quickly. All these projects target antibiotic-resistant bacteria on the Bacterial Pathogen Threat List prepared by the US Centers for Disease Control and Prevention (CDC) or on the Priority Pathogens list published by the WHO. Planning for responsible use of existing antibiotics and equitable access, particularly in low-income countries where need is greatest, are also a condition of CARB-X funding.

With CARB-X support, the companies in the portfolio have made solid progress in just a year: five projects have advanced into clinical Phase 1 trials, several have achieved major milestones on the path to clinical development and the rest of the projects in the pipeline are moving forward on schedule. In the Powered by CARB-X portfolio, one project has been stopped due to negative toxicity studies and another has been parked while the company restructures. The goal is to support projects through the early development phases and Phase 1 clinical trials so that they will attract additional private or public support for further clinical development. This is a vital mission because pre-clinical research is often where projects are abandoned because of lack of funds or expertise.

CARB-X launched two new funding rounds for 2018, inviting applications from around the world. The new rounds are focused on increasing the number of new classes of antibiotics in the portfolio and increasing the numbers of novel therapeutics, rapid diagnostics and other approaches to address the rising threat of drug-resistant bacteria. Hundreds of product developers have applied for CARB-X funding.

CARB-X is also expanding its global network of accelerators – companies and organizations that partner with CARB-X to provide scientific and business support to the projects in the Powered by CARB-X portfolio. It plans to add accelerators in several locations to improve the global footprint, bringing CARB-X closer to the companies it partners with to support innovative projects. A global RFP was conducted in 1Q 2018. New accelerators will be announced in 3Q 2018.

In addition to creating the world's largest early development antibacterial pipeline, one of CARB-X's main distinguishing features is that it is highly entrepreneurial in its approach, lean and effective. It has a small team based at Boston University; 94% of CARB-X's annual budget is invested directly into support for projects. Since it was established, CARB-X has averaged 1.5 funding announcements every month.

Research is a high-risk endeavour and some of the projects in the portfolio are likely to fail. But if only a handful of these innovative projects go on to be approved and to reach patients, that will represent a major victory in the battle against drug-resistant bacteria.

The CARB-X advantage

In addition to providing valuable funding and support to promising research projects around the world, the CARB-X experiment is producing other benefits that can help in the fight against drug-resistant bacteria. It is strengthening the global network of antibacterial product developers, providing expertise, communication channels and access to funding opportunities that may not have existed before.

For governments and funding organizations, CARB-X is a turn-key opportunity to invest in the best science and antibacterial innovation in a meaningful and impactful way at a global level. CARB-X is actively seeking support from other governments, industry and civil society to expand its ability to fund the best science around the world to get the new life-saving treatments so urgently needed. While the funding provided by CARB-X is important, companies are also offered a host of business, technical and regulatory support services from CARB-X and its accelerator network.

But much more is needed. Urgently.

The recent DRIVE-AB report, published earlier last year by 16 public-private partners supported by the European Innovative Medicines Initiative (IMI) and seven major pharmaceutical companies, called for almost doubling the amount of money invested in funding organizations like CARB-X and GARDP, which is supported by DNDi and the WHO. Increased funding would produce increased numbers of new antibiotics and other approaches to address drug resistance.

Grant funding, known as 'push' funding, is not enough. DRIVE-AB also recommended 'pull' funding – a big US\$ 1 billion market-entry reward for companies for each new antibiotic approved to attract more private investment antibacterial research. This prize would be in addition to any sales revenues. Others, including the O'Neill Review, has also urged 'pull' incentives to achieve a significant acceleration in the speed of drug development.

Long-term commitment from governments is also needed. It takes years to develop new medicines and so long-term financial commitments from government is also part of the solution. The study suggests that the G20, through its member countries, would be ideally positioned to take the lead globally on public funding of R&D and coordinating efforts to ensure a predictable supply of antibiotics over the next 30 years. The measures proposed by DRIVE-AB would cost an estimated

US\$ 36 billion and produce some 20 new antibiotics over the next 30 years, which would go a long way to saving lives and battling the rise of superbugs.

The challenge for world leaders is how to make this a reality at a global level. One country acting on its own, or one initiative like CARB-X no matter how impressive the achievements, cannot solve this problem on its own – any meaningful solution must involve concerted, sustainable long-term global action.

CARB-X is making solid progress and is demonstrating that it is essential to stimulating innovation to address the superbug threat. Much more is needed. With so much at stake, and so many lives in the balance, we must act together to find sustainable and meaningful solutions. ■

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