The impact of AMR on cancer care – reinvigorating the R&D pipeline

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Antibiotics are a crucial part of modern medicine, but resistance is growing and the development pipeline is waning. Innovation in this sector is required to deliver a steady and sustainable supply of new and novel antibiotics (as well as other antibacterials). Here we outline how antibiotic resistance is impacting cancer care and why a coordinated approach is required to create an innovative ecosystem for research and development and a sustainable market for antibacterials addressing the most critical public health needs.

Global patient needs versus diminishing returns – the pipeline paradox

Antimicrobial resistance (AMR) continues to represent an urgent global health challenge, with growing medical, social and economic impacts *(1–3)*. In 2019, 1.27 million people died as a direct result of antibiotic-resistant bacterial infections *(3)*, more than malaria or HIV, with death rates highest in sub-Saharan Africa and Asia *(3)*. At the current rate of emergence and spread, AMR is expected to lead to 10 million deaths annually by 2050, with associated economic costs of up to US$ 100 trillion *(2)*.

The increasingly rapid emergence and spread of resistance to antibiotics – accelerated in part due to over- and misuse across all One Health sectors (human, animal, environment and plant) – threatens to erode the transformative health and economic benefits of drugs that have become one of the most widely used classes of medication worldwide. Resistance to antibiotics threatens the success of modern health care, with devastating consequences for vulnerable patient populations, such as the close to 10 million people each year – and rising – who receive chemotherapy for cancer as a first-line treatment *(4)*.

Over the last five years, 12 new antibiotics have been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA). However, the majority of these agents (10 out of 12) belong to existing antibiotic classes for which resistance mechanisms are already established, providing limited clinical benefit over already existing treatments. The most recent evaluation of antibacterials in clinical and preclinical development by the World Health Organization (WHO) *(5)* again highlights that innovation must be accelerated to combat AMR and address public health needs.

Despite the growing societal impacts of AMR, the antibacterial development pipeline remains insufficient. This is due to a variety of scientific, regulatory and commercial challenges along the pathway from research and development (R&D) to successful and sustainable market entry of antibiotics. It is scientifically challenging to discover new antibiotics for priority resistant bacteria, the time and financial costs of clearing regulatory hurdles are substantial and the commercial outlook is bleak for new products due to a combination of low prices and lack of return on investment due to restrictions on use, limiting volumes sold *(6,7)* – the pipeline paradox. Given these hurdles, many large pharmaceutical companies as well as small and medium enterprises (SMEs) have exited the field to focus on more lucrative sectors, such as oncology.

As resistance grows and the replenishment pipeline wanes, it is imperative that we stimulate innovation in this sector and ensure a steady and sustainable supply of new and novel antibiotics (as well as other antibacterials), especially for vulnerable patient groups such as cancer patients. Here we summarize how the insufficient antibiotic pipeline and the growing emergence and spread of resistance to antibiotics is impacting the care of cancer patients globally and outline how a coordinated approach is required to create an innovative ecosystem for R&D and a sustainable market for antibiotics addressing critical public health needs.

The impact of antibiotic resistance on cancer care

Although modern cancer care has resulted in increased survivorship globally, cancer continues to be a leading cause

of death worldwide, responsible for almost 10 million deaths in 2020 *(8)*, with a continuously growing burden, including within low- and middle-income countries (LMICs) *(9)*. By 2030, almost three-quarters of cancer deaths are forecast to be in LMICs *(10,11)*.

Antibiotics continue to be a crucial part of the supportive care of cancer patients, especially for those receiving immunosuppressing chemotherapy, hematopoietic stem cell transplantation (HSCT) or novel immunomodulatory therapies. There is growing evidence that antibacterial prophylaxis increases the frequency of blood-stream infections caused by resistant Gram-negative bacteria in HSCT patients *(12)*. Thus, infections caused by resistant bacteria are of major concern; they could increase the likelihood of infections or prolong hospitalization *(13)* and, in severe cases, result in death. Cancer patients are three times more likely to die of infections than non-cancer patients *(14)*. Over one-third (36%) of cancer patients will require surgery, often multiple times, with approximately 5% of these patients developing drug-resistant infections *(15)*. Following chemotherapy, it is estimated that over one-quarter (26·8%) of pathogens causing infections are resistant to standard prophylactic antibiotics *(16)*. A recent study pointed out that 95% of oncologists in the United Kingdom are concerned about the rise of drug-resistant bacteria *(15)*. In addition, the rapid advances of modern therapies directed against autoimmune and malignant diseases, and their widespread use, further increase the number of patients at risk. This has been recognized and acknowledged by infectious disease experts from the scientific community *(17)*.

Studies quantifying the economic impact of AMR on cancer care are scarce, but due to both increasing treatment costs and length of hospitalization, associated costs are expected to rise. For example, hospital stays are prolonged by a factor of three in head and neck cancer patients infected with methicillin-resistant *Staphylococcus aureus* (MRSA) *(18)*.

Without viable antibiotics to prevent and treat infections, key advances made in the care and treatment of cancer patients will be limited due to the risks of severe infections.

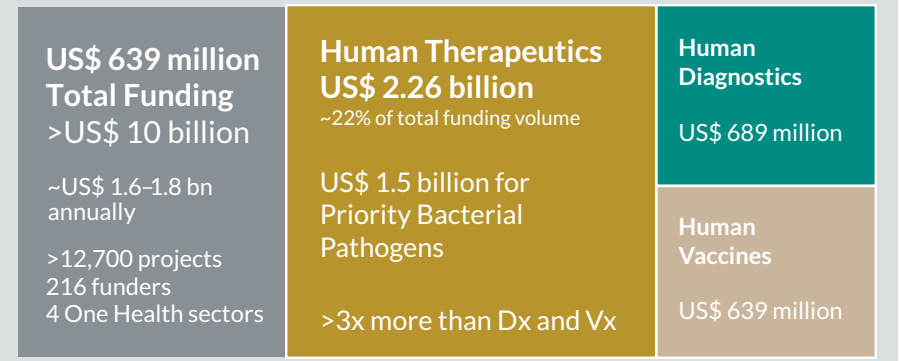
The financial landscape for developing antibiotics

The development pathway for antibiotics is extremely challenging. It is a time-consuming and expensive process, comprising up to 15 years, US$ 1–2 billion and high attrition rates – on average, only one in 15 (existing antibiotic classes) and 30 (new classes of antibiotics) preclinical candidates will reach patients *(19)*.

Although not an unfamiliar story when it comes to developing medicines – 90% of all clinical drug development fails *(20)* – the fact that the use of new and novel antibiotics is restricted to patients with resistant infections means that there is limited potential for developers to recoup their costs. The market for these so-called "Reserve" *(21)* antibiotics is challenging, with the return on investment failing to cover the costs companies incur along the pathway from R&D, regulatory clearance, commercialization and distribution. This has led to an unstable supply chain for existing antibiotics and a lack of novel and innovative antibacterial drugs entering the market *(5,7)*. The dire commercial outlook has resulted in many larger pharmaceutical companies exiting the field, leaving the academic spin-outs and SMEs – major innovators in the antibacterial sector accounting for 81% of all antibacterial programmes in the preclinical stages *(22)* and 75% of all late stages of development *(23)* – struggling to sustain their operations.

Based on data from the Global AMR R&D Hub's Dynamic Dashboard *(24)*, funding for R&D of therapeutics tackling human infections totalling ~US$ 2.6 billon (as at August 2022) has been invested by public and philanthropic sources since 2017. In comparison, this funding volume is >3x greater than for R&D of AMR diagnostics or vaccines (Figure 1). A significant fraction of this total investment – US$ 1.54 billion – is for the development of therapeutics targeting priority pathogens *(25,26)*, including the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*), many of which are known as resistant pathogens in cancer patients *(15)*. Globally, public and philanthropic funders, including the National Institutes of Health

Figure 1: Global AMR R&D Hub – Dynamic Dashboard for AMR R&D funding. The Dynamic Dashboard provides collated information on public and philanthropic funding globally for AMR R&D since 2017. From over 12,700 projects in the Dynamic Dashboard totalling US$ >10 billion, ~22% target the development of human therapeutics, >3x more than investment in human AMR Diagnostics (Dx) or Vaccines (Vx). US$ = United States Dollar



Public/Philanthropic AMR R&D funding since 2017 – August 2022
dashboard.globalamrhub.org

Box 1: **Push and pull incentives**

Push incentives

Push Incentives are government or regulatory interventions which support R&D by directly lowering the costs of development.

These tools are input-based.

Examples include research funding grants, contracts, public and private partnerships and tax incentives.

Push mechanisms target current work and reduce a developer's cost and risk of researching and developing new products either by lowering the costs, decreasing the barriers to participation or by sharing the costs/risks across multiple parties.

Pull incentives

Pull incentives are policy tools to reward the successful development of a product by increasing or ensuring future revenue. Can be achieved through market-making (financial) tools or market-shaping (lego-regulatory policies) rewards.

These tools are output-based.

Examples include subscription models, which de-link revenues from volumes sold, higher reimbursement, market entry rewards, transferrable exclusivity extensions and accelerated approvals.

Each incentive – alone or in combination – has varying impacts on innovation, sustainability, stewardship and access.

See refs *7*, *30*, *31* for information on pull incentives and their different features.

(NIH), the Biomedical Advanced Research Development Authority (BARDA) and the Bill & Melinda Gates Foundation, are continuing to invest in and support the R&D of new therapeutics, including new and novel antibiotics *(26)*, across the spectrum from basic research to clinical trials. In tandem, public-private partnerships such as the Innovative Medicines Initiative (IMI), Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antibiotic Research and Development Partnership (GARDP) are further boosting the field by funding and supporting product development and clinical trials. There has also been renewed commitment to stimulate antibiotic development in the form of the AMR Action Fund – a US$ 1 billion initiative, primarily financed by the private sector, that is committed to the development of 2–4 antibiotics by 2030, focused on helping candidates through the later clinical phases of development. However, on their own these so-called "push incentives" (see Box 1) are still not enough to mitigate the multiple challenges associated with the development and post-market entry of antibiotics.

Studies commissioned and conducted by the Global AMR R&D Hub *(27,28)*, evaluating and quantifying the scale of the challenge facing new health technologies – including priority antibiotics – under current market conditions, highlighted the limited ability of market tools such as pricing, volume and patents to improve revenues and attract investors and developers back to the field, and that market interventions which de-link revenues from volumes sold are required. These studies, and others (e.g., 29), also recommend that the societal value of antibiotics – being at the core of well-functioning health systems – should be integrated into value assessments by governments (e.g., via Health Technology Assessments). Notably, the Global AMR R&D Hub's studies also raise the issue of access, in which effective antibiotics are not available at scale in the parts of the world where the need is most dominant and growing most rapidly – predominantly in LMICs *(27)*.

Recognizing that push incentives on their own are not sufficient to drive the development of new antibacterials beyond the R&D phase, the Global AMR R&D Hub and World Health Organization (WHO) jointly called on the Group of Seven (G7) countries for concerted and ambitious actions for the development and implementation of "pull incentives", policy tools that reward the successful development of antimicrobials by increasing or guaranteeing future revenues (see Info Box and refs *7*, *30*, *31*).

Some progress is being made in this direction (see Table 1 in ref. *7*), with the United Kingdom implementing, and the United States proposing, innovative delinked economic models for antibiotics. The United Kingdom is the first country in the world to pay drug companies (Pfizer, USA; Shionogi, Japan) a fixed fee (£10 million per year) for supplying antibiotics, and there is growing bipartisan support for The Pioneering Antimicrobial Subscriptions To End Upsurging Resistance Act of 2021 (PASTEUR Act) in the USA – a bill authorizing

the Department of Health and Human Services to enter into subscription contracts for critical-need antimicrobial drugs.

A sustainable R&D ecosystem for AMR?

The ongoing commitment to supporting a sustainable and buoyant innovation ecosystem for cancer innovation from both the public and private sector has resulted in prevention programmes, diagnostics and treatment advances that are saving the lives of millions of cancer patients globally *(32,33)*. In 2020, there were over 1,300 cancer medicines in development and more than 1,200 clinical trials initiated *(33)*. In comparison, the most recent analyses from WHO *(5)*, integrated within the Global AMR R&D Hub's Dynamic Dashboard, shows that there are currently only 27 new antibiotics in clinical development against WHO priority pathogens, with the majority of these in the early phases of clinical development (i.e., Phase I or II). Without an effective pipeline of new antibiotics – and antibacterials in general – outcomes for cancer patients are set to be negatively impacted and the recent gains in cancer outcomes endangered. The projected growth of cancer in LMICs *(10,11)* and the worsening gap in terms of access to antibiotics *(27)*, further intensifies the critical and global nature of this health challenge.

The scale and severity of the growing and urgent threat of AMR highlights the need for immediate, concerted and coordinated action across the push and pull continuum to redefine the pathway from R&D of antibacterials to innovative products, their sustainable commercialization and subsequent equitable access and prudent use. Incentivizing the development of new antibacterial treatments addressing public health needs requires renewed leadership and agenda-setting, further support and replenishment of push funding for AMR R&D, increased and coordinated pull incentives and advancement of equity and access through AMR development cooperation *(7)*.

Antibiotics are a central component of cancer care and an R&D ecosystem that encourages innovation and rewards success is crucial for a sustainable pipeline of new and novel drugs. Their development and use, however, needs to be placed in the framework of the full AMR toolkit, which also includes diagnostics and vaccines *(2)*. Effective diagnostics that can rapidly and accurately identify bacterial infections are key to reducing inappropriate use of these life-saving drugs. In tandem, vaccines are crucial tools for potentially preventing and curbing the spread of infection, thus reducing the dependency on antibiotics and helping to mitigate the risks posed by the current insufficient antibacterial pipeline. Renewed efforts in supporting R&D of effective, affordable and rapid diagnostics, alongside the development of vaccines against the most critical pathogens *(34,35)*, as well as incentives to ensure their uptake *(27)*, are key tools in our global response to combatting the threat of AMR and protecting vulnerable patient populations.

About the Global AMR R&D Hub

The Global Antimicrobial Resistance (AMR) Research and Development (R&D) Hub is a global knowledge centre for AMR R&D, fostering evidence-based decision-making and enhancing collaboration and coordination across the One Health continuum. The global partnership, launched in May 2018 following a call from G20 leaders, currently consists of 17 countries, the European Commission, the Wellcome Trust and the Bill & Melinda Gates Foundation, as well as Observers from the World Health Organization (WHO), Organization for Economic Co-operation and Development (OECD), World Organization for Animal Health (WOAH) and the Food and Agricultural Organisation (FAO).

The Global AMR R&D Hub's Strategic Pillars are to:

- Guide and support evidence-based decision-making;
- Enhance collaboration and coordination;
- Promote awareness, knowledge and visibility.

For more information, visit www.globalamrhub.org ■

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