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The growing crisis in antibiotic R&D: opportunities for G20 member action to support sustainable innovation

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by the Wellcome Trust**

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The growing crisis in antibiotic research and development

Executive Summary

Antibiotics enable all of modern healthcare. Consistent use of infection prevention procedures and vaccines reduce but do not eliminate infections. The inevitable emergence of resistance to antibiotics is now reaching a point where some infections are virtually untreatable – a backward step with significant negative consequences for patients' lives and for the burden on healthcare systems. There is an inescapable need for innovation to deliver new antibiotics as a central part of the wider response to antimicrobial resistance (AMR).

Unfortunately, antibiotic research and development (R&D) has become stagnant over the past 15 years due to the challenging economics of antibiotic development. Significant funding has emerged over the past five years to support new work, re-energising the early stages of antibiotic R&D.

However, continued disinvestment and withdrawals from this area by multinational pharmaceutical companies, and two recent corporate bankruptcies from smaller companies, have made it clear that the current financing environment is inadequate. The (already weak) pipeline of new products – as well as the critical mass of expertise and infrastructure to develop them in the future – are now immediately threatened.

Work underway in a small number of countries points to possible solutions but the policy interventions made by governments so far, while welcome, will not be adequate to prevent further corporate failures and safeguard the antibiotic R&D ecosystem. Avoiding economic failure of the pipeline of nascent innovations is a critical and urgent issue requiring market-shaping interventions across multiple countries. Measured, national-level intervention by G20 members in the near term could play a vital role in securing a supply of antibiotics that meet global needs in the long term, delivering significant public value and benefits to patients around the world.

Antibiotics make modern healthcare possible

Antibiotics have become vital tools which underpin much of modern healthcare.

Society has benefited from having an array of reliable antibiotics since the 1950s. Although challenges remain in ensuring equitable access to antibiotics for those who need them in all countries, the benefits of antibiotics impact patients in every part of the world¹.

But, recent reports from the US CDC² and the ECDC³ in Europe document the progressive emergence of antibiotic-resistant infections to even the best currently available antibiotics.

Resistance has serious consequences, as the availability of effective antibiotics enables all aspects of modern healthcare. The loss of treatment options affect patients in all settings, but low- and middle-income countries (LMICs) where infection burdens are higher will be disproportionately affected by significantly weakening public health and undermining economic growth, as noted by the World Bank⁴.

For serious infections, healthcare providers need to have effective antibiotics immediately at hand, as delays to effective therapy of as little as a few hours measurably increase the morbidity and mortality of patients. Without reliable antibiotics, important surgical interventions and organ transplantation become significantly higher-risk; the ability to offer good care to premature infants is reduced; and the efficacy of some advanced therapies for life-threatening diseases – such as cancer chemotherapy – is substantially undermined.

The global response to AMR must address a wide range of issues, across multiple sectors. These include:

- Strengthened infection prevention and control, and the use of preventive tools such as vaccines.
- Measures to improve access to quality-assured essential medicines in LMICs.
- Improved antibiotic stewardship across human and animal health, to reduce unnecessary use and maintain the efficacy of antibiotics for longer.
- Better surveillance of the global development and spread of drug-resistant infections.

These topics are all rightly the focus of sustained national and global efforts to respond to AMR. But whatever the success of these measures, there is an unavoidable need for new antibiotics and other treatments to ensure that infections can be effectively treated wherever they do occur. A strong and sustainable pipeline of new antibiotics is an essential, foundational element of the world's response to AMR.

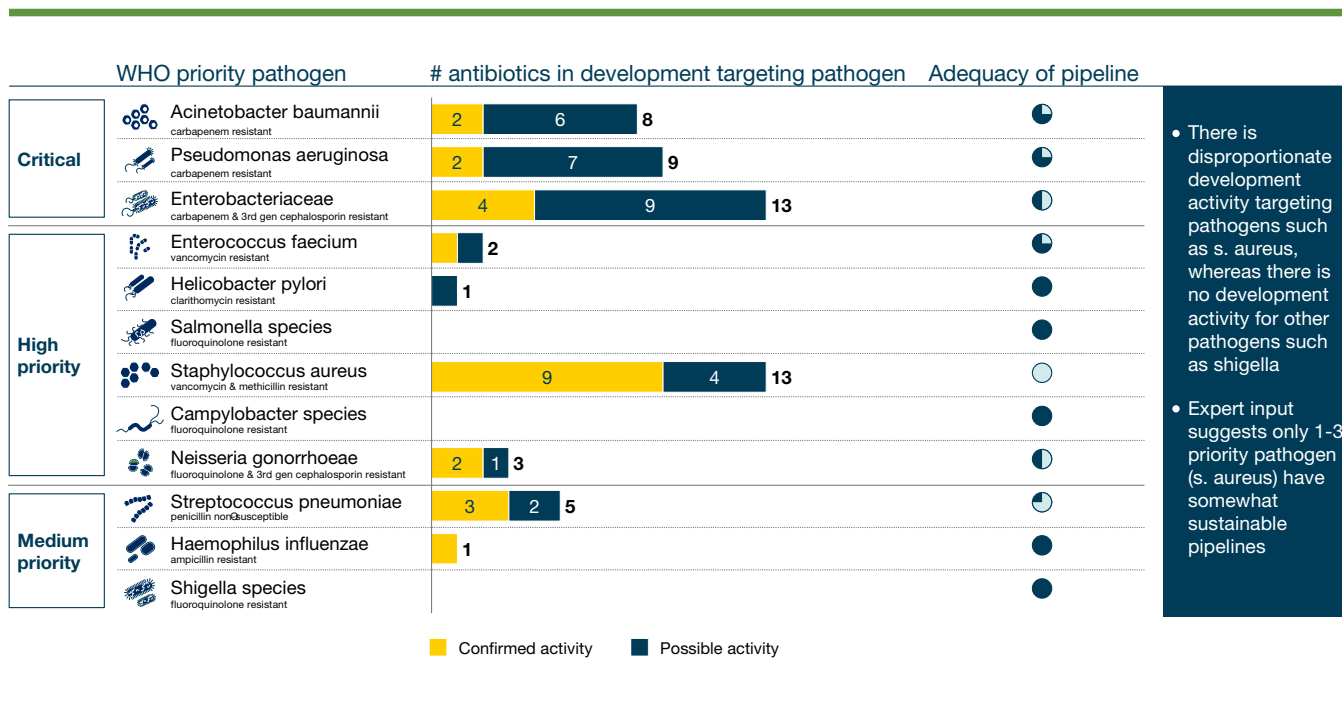
The pipeline of new antibiotics is currently too weak to meet the threat of rising rates of drug resistance

Despite this necessity, and the rising threat, a long-term decline in antibiotic R&D means that the antibiotics pipeline does not contain enough – or the right types of – products to meet these mounting needs.

Recent analysis finds that there are 33 antibiotics currently in clinical development⁵. This may appear superficially promising, but it will be many years before any of them appear as products on the market. Furthermore, the high-risk nature of all drug development is such that this pipeline will ultimately likely produce fewer than 10 new antibiotics. In simple numbers terms, this pipeline is far more limited than those of other therapeutic areas, with the number of antibiotics in development being only a tiny fraction of the hundreds or even thousands of products in

clinical development in other disease areas. The immunology pipeline, for instance, currently contains more than 1,500 products in clinical development.⁶ The critically important antibiotics pipeline is insufficient to address *current* unmet medical needs and offers little protection against the rising rates of drug-resistant infections.

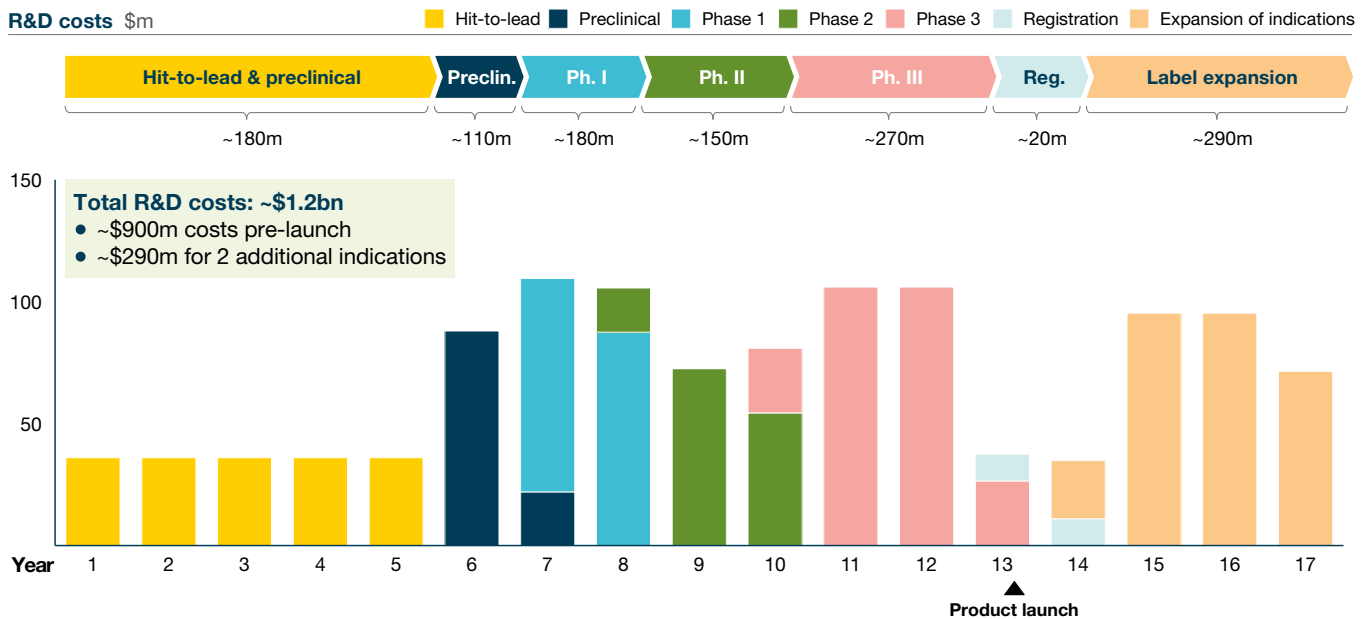
Added to this, the range of products in development does not match the types of emerging drug-resistant infections posing the greatest cause for concern. In particular, the pipeline is currently dominated by products focused on Gram-positive bacteria, rather than Gram-negative bacteria, which currently pose the greatest cause of concern. And many of these products are redevelopments or refinements of existing, known compounds. In summary, this means that fewer than half of the priority pathogens identified by the WHO currently have anything approaching an adequate range of products in development to counter them.



The weakness of the pipeline is primarily the result of the unattractive economic returns on antibiotic development – rather than scientific barriers

The costs involved in supporting antibiotic development are significant. When the costs of failed R&D products are taken into consideration, each successful antibiotic launched requires up to \$1.19bn in direct R&D costs

(excluding any cost of capital)⁷. The greatest costs fall in the later stages of development and commercialisation: Phase 3 trials, requiring the enrolment of hundreds or thousands of patients (and the final stage before regulatory approval), can cost \$130-\$170m per product, and even once launched an antibiotic requires further trial expenditure of \$250-300m to ‘expand its label’ from the narrow ‘launch’ indication for which first regulatory approval is obtained.



Currently, an antibiotic would need to be expected to achieve peak global sales of \$700m for a company to rationally invest in antibiotic its development as a commercial proposition⁸. This level of revenue is well below the sales achieved by innovative, new-to-market products in most other areas of the pharmaceuticals industry, yet as has been summarised in reviews by DRIVE-AB¹⁴, for the German Federal Ministry of Health⁹, and the UK AMR Review¹⁰, significant sales volumes for new agents are generally unlikely. Those antibiotics which have reached market in recent years (since 2000) have averaged peak global sales of only \$260m, with many products (particularly those used as ‘reserve’ antibiotics) recording sales of substantially less than that¹¹.

Multiple drivers for the weakness of antibiotics markets have been identified in reviews to date:

- **Limited market volumes.** Developers of antibiotics perceive that new-to-market products will capture only very limited market share. Some innovative, breakthrough

products may be subject (appropriately) to robust stewardship measures by health authorities to preserve their efficacy. Even in the absence of these ‘active’ stewardship measures, prescribers will naturally seek to use older, cheaper antibiotics wherever possible, reserving newer and more expensive products only for those patients for whom other treatments have failed.

- **Low prices.** New-to-market antibiotics typically command modest prices compared to other breakthrough drugs. This may be driven by ‘competition’ with cheap generic products. In healthcare systems using health technology assessment (HTA) processes, though, antibiotics may be systematically under-valued, as established methodologies do not adequately reflect the full value of a novel, effective antibiotic¹².
- **Reimbursement barriers.** In healthcare systems that use prospective (i.e. tariff-based) reimbursement for inpatient care, the inclusion of antibiotic costs within a given tariff can act as a disincentive against the use of novel antibiotics, even where doing so is clinically appropriate.

Because of these issues, multinational companies have steadily left the area, with the (self-reported) annual AMR-focused R&D expenditure of global pharmaceutical companies declining from \$1.75bn in 2016 to \$914m in 2018¹³.

Much of the effort to reinvigorate antibiotic R&D has therefore been led by small companies progressing lean programmes, yet these are also now struggling in the face of an adverse market, with bankruptcies occurring at Achaogen and Melinta Therapeutics in 2019. Despite having five recently approved antibiotics between them, these two companies were not able to generate the level of sales needed to offset the burden of financing the high costs of late-stage clinical trials, and the significant costs associated with bringing newly approved drugs to a global market.

Push incentives and other policy interventions have helped re-ignite early-stage R&D, but do not address the full range of challenges along the pipeline

Reflecting the mounting concern about the extent and impact of the rise in drug-resistant infections, significant public funding has begun to flow to support the early phases of antibiotic R&D. Such funding falls largely into the category of *push incentives* and is proving an effective tool for encouraging R&D in a target area.

Approximately \$500m/year from public (i.e. government and philanthropic) funders is now being delivered globally through push incentives, much of this being new funding in the past five years. As well as increases in AMR-focused resources through new and existing public funding programmes – such as the US NIH, and the Joint Programming Initiative on AMR (JPIAMR) – significant new standalone initiatives have been launched to provide new platforms to support antibiotic R&D. Most notably, these include:

- **CARB-X** – launched in 2016 as a joint venture between the US government and the Wellcome Trust, supporting pre-clinical and Phase I antibiotic R&D, this now includes support from the UK and Germany, as well as the Bill & Melinda Gates Foundation. Now supporting more than 50 projects across the US, Europe and Asia, with a total funding envelope of \$550m over five years.

Push incentives is the phrase used to describe public or philanthropic funds that go directly to support current work (e.g., a grant).

Pull incentives is the phrase used for rewards offered for success (e.g., a market entry reward, enhanced reimbursement).

- **Global Antibiotic Research & Development Partnership (GARDP)** – established by WHO and the Drugs for Neglected Diseases Initiative (DNDi) in 2016, GARDP operates as a public-private partnership guiding development of new antibiotic treatments to meet key unmet global health needs. The leading funder is the government of Germany, with additional funding from the UK, Switzerland, France, Japan, South Africa, and a number of charitable funders.
- **Action by regulators**, including the FDA and EMA, to remove barriers to the regulatory approval of antibiotics, including fast-track review for qualified antibiotic products, and market exclusivity extensions.

These interventions have been particularly effective at targeting and stimulating early-stage research, much of it being driven within smaller biotechs across the world. However, the global policy response to date is imbalanced, with less focus so far on the challenges of later-stage antibiotic development and commercialisation. This means we now face an emerging cliff edge, with promising products stimulated by early-stage funding mechanisms having no dependable path through late-stage development and onto global markets.

The nature of the problem and the range of plausible and possible solutions is well known

The economic challenges of new antibiotics and the possible role of novel incentive structures for antibiotics have now been extensively reviewed by such groups as DRIVE-AB¹⁴, the UK AMR Review¹⁰, and the Duke-Margolis Center for Health Policy¹⁵. DRIVE-AB's review is particularly detailed, with 35 different models having been examined at length.

All of these reports come to the same core conclusions: (i) both *push* and *pull* incentives are needed and (ii) the pull incentives need to provide some form of reward for successful product approval that is not dependent on the number of patients needing therapy with that antibiotic. Stated differently, whilst maintaining current levels of push funding, it is also necessary to identify new reimbursement models that more fairly reflect the value of antibiotic innovation, and which support better access to and stewardship of the novel products.

Models of improved pull incentives for novel antibiotics commonly identified in the literature include:

- **Lump-sum payments** or prizes for new-to-market antibiotics.
- **'Subscription' models**, where governments or health systems pay an agreed annual sum to access an antibiotic, regardless of the amount consumed.

Beyond these types of pull incentives, there is also increasing exploration of measures to support and incentivise later-stage antibiotic development, such as:

- **Regulatory mechanisms** that expedite or simplify approval for antibiotics and consequently reduce costs of late-stage development and shorten time to enter the market.
- **Administrative measures** to ensure that novel antibiotics are not in price competition with cheaper, generic antibiotics, skewing prescribing decisions.
- **Alternative business models** to improve the efficiency of late-stage antibiotic development and support increased private sector financing.

Aligned interventions at a national level can be effective at strengthening the global market

The R&D ecosystem for antibiotics is inherently global, and a cooperative, collective effort by countries to address the challenges of new drug development is required. However, this does not mean that new incentive models need to be agreed and administered at a multi-national or global level. While no single country can sustainably solve the challenges of antibiotic R&D by acting alone, targeted, concerted efforts at a national (or regional) level by the world's leading economies to improve incentives for antibiotic development can deliver a vital stimulus to the global market.

Some notable national efforts are currently underway to create such models:

- The UK Department of Health and Social Care is working with the National Institute for Health & Care Excellence (NICE) and National Health Service (NHS) in England to implement a pilot project in which two novel antibiotics will be purchased on a fixed commitment basis for several years. This level of reimbursement would embody an agreed definition of the value to society of an effective novel antibiotic.¹⁶
- The Public Health Agency of Sweden is working to implement a tendering process for the annual purchase of several antibiotics.
- In the US, The Centers for Medicare and Medicaid Services (CMS) have modified reimbursement for antibiotics in a hospital setting by allowing new, designated antibiotics to qualify for a New Technology Add-On Payment.¹⁷ CMS also modified the diagnosis-related groups (DRGs) reimbursement system, which now provides an increased payment for patients with a drug resistant infection. This is not a volume-independent reimbursement scheme, but it is expected to provide some increase in return to innovators.
- Initiatives are also underway in Germany to change the reimbursement status of antibiotics, while early efforts have also been reported in Japan.

It would seem unlikely that the level of reimbursement by the pilot projects in these countries will be sufficient to stabilise the global antibiotic R&D ecosystem, but each of them provides a valuable case study and a model for future actions. Indeed, the diversity of these projects is notable: the UK is examining a model well-suited to a country with a single national payer, the Swedish model examines ways to support long-term availability of specific antibiotics, and the US model seeks to create an above-market model that addresses the complexity of a multi-payer insurance system. All of these models are being designed and implemented to deliver value to healthcare systems and better outcomes to patients, while also unlocking better and more predictable reimbursement for antibiotic developers.

Intervention is urgently needed, and the G20 membership can collectively play a leading role in delivering this

The availability of a steady stream of innovative antibiotics is fundamental to maintaining public health and enabling the miracles of modern medicine in all parts of the world. As a central part of the wider response to AMR, sustained and predictable reimbursement models are needed to ensure that novel antibiotics will come to the global market in a sustainable fashion and be accessible to patients who need them. Only by addressing the challenges of antibiotic innovation can global access to lifesaving treatments be improved over the long term.

Progress in addressing these problems is needed urgently if we are to avoid further irreversible damage to the global antibiotic R&D ecosystem. There is a pressing need to now build on earlier statements by the G20 which have acknowledged the challenges of antibiotic innovation.

A firm commitment from each G20 member to now urgently explore opportunities to implement novel reimbursement measures for antibiotics within their own national healthcare systems would deliver a major boost to innovation efforts currently being led by small companies around the world, and strongly complement wider efforts to tackle AMR through improved access to and stewardship of antibiotics, and better infection prevention and control. Such measured, national action today can deliver a lasting, global legacy.

Endnotes

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