Incentivising the development of new antibacterial treatments

Progress Report by the Global AMR R&D Hub & WHO

A tragedy of the commons

Antimicrobial resistance (AMR) is one of the biggest threats to global health and development today. In 2019, an estimated 1.27 million deaths were a direct result of antibiotic-resistant infections, making AMR a leading cause of global mortality at a magnitude comparable to HIV and malaria[1,2]. Regionally, the death rate attributable to AMR resistance was highest in the sub-Saharan Africa and South Asia. In sub-Saharan Africa, countries with a high number of deaths attributed to AMR also see an overall high burden of infectious diseases. The World Bank[3] and the World Economic Forum[4] have singled out AMR as one of the biggest global health risks, with predicted losses of up to 3.8% of gross domestic product (GDP) globally by 2050[2].

Antibiotics are the enduring cornerstone of modern medicine, but are now becoming increasingly ineffective. Resistance to antibiotics threatens the success of modern healthcare with devastating consequences for vulnerable patient populations, such as the 10 million people annually who receive chemotherapy for cancer[2] and other patients undergoing life-saving treatments, such as organ transplants and hip replacements[5].

Today's antibiotics are characterised by an insecure supply chain for existing generic products and a lack of new and innovative products entering the market. Unless action is taken now, we are set to enter an era where routine operations and infections pose a real danger to our lives.

Bringing a new antibiotic to market is a scientifically challenging and resource-intensive endeavour with a relatively low return on investment. As a result, major pharmaceutical companies have backed away from antibiotic development, and the enterprises remaining in the space struggle to sustain their operations. This is reflected in the fact that over the last three decades, no new ground-breaking antibacterial treatments have reached the market for Gram-negative bacteria. According to the World Health Organization's (WHO) most recent report "2021 antibacterial agents in clinical and preclinical development: an overview and analysis"[6], only 79 new antibacterial treatments are in development. But most are derivates of existing antibiotic classes, and the majority are unlikely to make it to the market.

The Global AMR R&D Hub's studies[7] evaluating the scale of the challenge of bringing needed new antibiotics (& diagnostics) onto the market in current economic conditions highlighted the astonishing mismatch between global patient needs and the commercial potential of products. The immediate adaptation of existing national health systems tools in combination with pull incentives was called for to both support innovation and ensure necessary new products are accessible to those with the greatest need around the world.

[1] Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-655. doi:10.1016/S0140-6736(21)02724-0

[2] ReAct Group, May, 2020. Successful cancer treatment relies on effective antibiotics.

[3] Jonas et al. Drug-resistant infections: a threat to our economic future: executive summary (English). HNP/Agriculture Global Antimicrobial Resistance Initiative Washington, D.C.: World Bank Group.

[4] The Global Risks Report 2018 - Reports - World Economic Forum (weforum.org)

[5] Health at a Glance 2021: OECD Indicators (oecd-library.org)

[6] WHO 2021 antibacterial agents in clinical and preclinical development: an overview and analysis, to be published in May 2022.

[7] Global AMR R&D Hub, 2021. Estimating global patient needs and market potential for priority health technologies addressing antimicrobial resistance.

The COVID-19 pandemic has shown the need to strengthen health security and preparedness. In alignment with the German G7 Presidency's key health priorities for 2022[8], a sustainable supply of existing and new antibiotics to meet priority public health needs globally will be a central component of securing a resilient and productive future.

Under the UK G7 Presidency in 2021, Finance Ministers committed to take additional steps to address antibiotic market failure and create economic conditions to preserve essential existing antibiotics and ensure their access, strengthen AMR research and development (R&D), and bring new drugs to market if they meet identified public health needs[9].

The G7 Finance Ministers requested the Global AMR R&D Hub and WHO to support this work and prepare a progress update for G7 Finance and Health Ministers in 2022[9]. This brief is a response to this request. It provides an update on:

- The current antibacterial treatment and vaccine pipelines;
- the financial landscape for developing new antimicrobials, and
- recommendations for future action.

Key action areas

Renew Leadership and Agenda Setting

With over 1.27 million deaths directly attributable to AMR in 2019[1], increasing rates of AMR, and limited progress toward the development of new and novel antibacterial treatments, expedited and ambitious action is urgently required.

Recommendations:

- Broaden AMR awareness of R&D challenges and opportunities by issuing specific calls to action with relevant partners and stakeholders, including:
    - Quadripartite (e.g., AMR Multi-Stakeholder Partnership Platform[10], One Health Global Leaders Group (GLG) on AMR[11])
    - Multilateral health and development organizations (e.g., UNICEF[12], World Bank[13])
    - Global and national industry and public health advocacy groups

Support and Replenish Push Funding for AMR R&D

Despite substantial global investments in antimicrobial R&D, progress toward the development of new and novel antimicrobials is not sufficient.

Recommendations:

[8] G7 Germany, 2022. Policy Priorities for Germany's G7 Presidency in 2022.
[9] G7 UK, 2021. Finance Ministers' Statement on Actions to Support Antibiotic Development - G7 UK Presidency 2021.
[10] https://www.fao.org/antimicrobial-resistance
[11] The Global Leaders Group on AMR: https://www.amrleaders.org
[12] https://www.unicef.org
[13] https://www.worldbank.org/

- Establish global R&D targets based on patient needs for the investment in the development of new antibacterial treatments and encourage countries to make specific national commitments toward these targets
    - Strengthen R&D targeting priority bacterial pathogens to ensure a steady supply of new antibacterials that address urgent public health needs
    - Build on significant investment in early stage product development and further support later stage clinical development
    - Provide coverage across the R&D pipeline and increase the donor base for CARB-X[14] and GARDP[15]

Increase and Coordinate Pull Incentives

Recognising that push incentives on their own are not sufficient to drive the development of new antimicrobials beyond the R&D phase, concerted and ambitious actions are needed for the development and implementation of pull incentives.

Recommendations:

- Implement a coordinated and aligned global pull incentive focusing on urgent public health needs
- Recognising the complexity of agreeing on one concept, countries are urged to prioritise and accelerate efforts to develop and implement economic pull incentives that target priority bacterial pathogens and lead to the development of new and novel antimicrobials
    - Call on the Global AMR R&D Hub to facilitate sharing of lessons learned and to return with recommendations on coordination opportunities to align global pull incentives

Advance Equity and Access Through AMR Development Cooperation

Although the development of new and novel antimicrobials should be prioritised, broadening access to existing antimicrobials is also essential.

Recommendations:

- Access to priority antibiotics should be taken up as a key factor in mitigating the AMR response
    - G7 countries should consider financing the SECURE[16,17] pilot – SECURE is an open model for expanding access to new and existing antibiotics, with potential to act as a pull mechanism for new Reserve antibiotics
- Development cooperation agencies should expand their remits to AMR, including the development of needed new antibacterial treatments (e.g. through the Global Fund to Fight AIDS, Tuberculosis, and Malaria)

[14] https://carb-x.org
[15] https://gardp.org
[16] https://www.who.int/groups/secure-expanding-sustainable-access-to-antibiotics
[17] https://gardp.org/what-we-do/secure/

AMR is a global economic threat

The World Bank estimates that if current approaches addressing AMR are not scaled up, a reduction in global GDP of the magnitude seen during the 2008 financial crisis is impending, with the burden of impact felt most in the poorest of countries (**Figure 1**). By 2050, global GDP is predicted to decrease by up to 3.8%, throwing an estimated 28 million people into poverty. The impacts will be felt across multiple sectors, from reductions in global livestock production (↓7.5%) and global exports (↓3.8%) to increases in health care costs estimated in the range of 1 trillion USD[3].

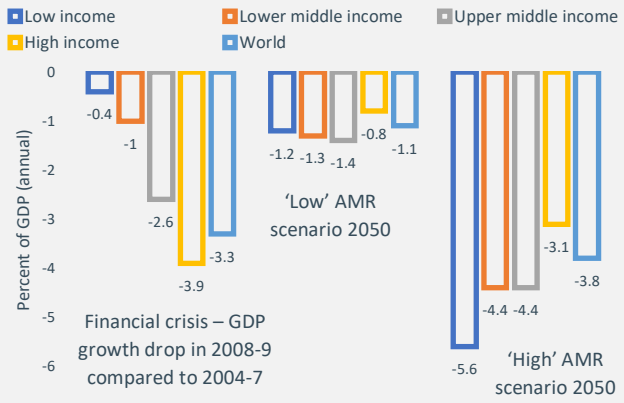


Figure 1: Economic impacts of AMR may be comparable to the 2008 financial crisis. 'Low' and 'high' indicate the severity of impacts. Figure adapted from World Bank 2017[3] .

The economic impact of AMR across countries/regions

EU	**1.5[18] - 9 billion EUR per year**[19,20] - due to increased health expenditure & productivity losses
OECD	**2.9 trillion USD by 2050**[21] - cumulative losses in OECD countries due to AMR
US	**55 billion USD per year**[22] **-** 20 billion USD in excess for direct healthcare costs, plus lost productivity ~ 35 billion USD a year
CANADA	**120 billion CAD in hospital costs, and 388 billion CAD** in lost GDP by 2050[23,24]
JAPAN	**55 - 192.47 billion USD** in losses per year by 2050 [3,25]

EU – European Union; OECD – Organisation for Economic Cooperation and Development; US – United States of America; EUR – Euros; USD – US dollars; CAD – Canadian dollars

[18] European Commission, Factsheet 2017 AMR: a major European and Global challenge.
[19] Llor C & Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf.* 2014;5(6):229–241.
[20] Prestinaci F, Pezzotti P & Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health.* 2015;109(7):309. doi:10.1179/2047773215Y.0000000030
[21] Cecchini M, Langer J & Slawomirski L. OECD, 2015. Antimicrobial Resistance in G7 Countries and Beyond: Economic Issues, Policies and Options for Action.
[22] U.S. Department of Health and Human Services, CDC, 2013. Antibiotic resistance threats in the United States; 2013.
[23] Council of Canadian Academies, 2019. When Antibiotics Fail: The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, Council of Canadian Academies: Ottawa (ON).
[24] Government of Canada, 2022. Challenges in the Antimicrobial Business Model and Potential Incentives to Increase Access and Promote Innovation: Best Brains Exchange Summary Report.
[25] Global Coalition on Aging, 2022. AMR: A Threat to Healthy Longevity and National Security for Japan.

The global antibacterial pipeline

Recently approved antibacterial agents, and those in clinical development, are insufficient to address AMR. Vaccines for some priority pathogens are already on the market or in development, but it is unlikely that they will be the solution for many of the most critical Gram-negative pathogens

WHO has been tracking the antibacterial development pipeline against the WHO bacterial priority pathogens[26] since 2017. In 2021, for the first time, WHO conducted a systematic identification of the vaccines in development against the same bacteria.

Addressing public health needs

To maximise their impact, any publicly financed R&D initiatives must focus on the most pressing public health needs. It is for that reason that in 2017 the WHO launched its first bacterial priority pathogens list (BPPL)[26]. The BPPL aimed to guide private and public R&D investments through the identification of R&D priorities. The BPPL includes 13 of the most critical drug-resistant bacterial pathogens. Since the WHO BPPL was launched, WHO has regularly used the list to analyse the antibacterial development pipeline. WHO is creating a similar list of fungal priority pathogens of public health importance. It is important that global, regional or national R&D incentives focus on identified public health needs to make the best use of public funds.

The antibacterial treatment pipeline

WHO gathers data and analyses all traditional[27] and non-traditional[28] antibacterial agents in development globally. It evaluates to what extent the present pipeline addresses infections caused by priority pathogens and whether drug candidates meet a set of predefined criteria for innovation[29].

[26] World Health Organization, 2017. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. (WHO/EMP/IAU/2017.12).
[27] Direct-acting small molecules, e.g. antibiotics
[28] Non-traditional agents include bacteriophages or phage-derived enzymes, microbiome-modulating agents, immunomodulating agents and miscellaneous agents.
[29] World Health Organization, 2021. 2020 Antibacterial agents in clinical and preclinical development: an overview and analysis.

Key Facts

Preclinical Pipeline

217

Number of antibacterial agents in development by 121 entities (commercial /non-commercial)

~34%

Turnover year on year – projects & developers

Focused activity against **>1** pathogen is common (narrow spectrum agents)

Clinical Pipeline

79

45 traditional antibiotics

34 non-traditional agents

57%

Traditional antibacterials

27 (60%) are active against the WHO bacterial priority pathogens.
- 6 designated as innovative
- 2 active against **≥1** critical multidrug resistant (MDR) Gram-negative bacteria

13 (28%) are active against *M. tuberculosis* and 5 **(11%)** against *C. difficile.*

43%

Non-traditional antibacterials

6 Antibodies
9 Phages/phage-derived enzymes
11 Microbiome-modulating agents
2 Immunomodulating agents
6 Miscellaneous agents

Current pipeline is insufficient to address the challenge of AMR

The 2021 WHO review of antibacterial agents in clinical and preclinical development[6] concluded that recently approved antibacterial agents, and those in the different stages of clinical development (**Figure 2**), are still insufficient to address antimicrobial-resistant infection emergence and spread. Since 2017, **12 new antibiotics have been approved** by either the US Food and Drug Administration (US FDA) or the European Medicines Agency (EMA). But the majority of these newly approved agents have limited clinical benefit over existing treatment. 10 out of 12 belong to existing antibiotic classes for which resistance mechanisms are established.

Among the recently authorised antibacterial agents, only one compound, cefiderocol, is intended for use against the WHO critical pathogens CRAB (carbapenem-resistant *Acinetobacter baumannii*) and CRPA (carbapenem-resistant *Pseudomonas aeruginosa)* in addition to carbapenem-resistant *Enterobacterales* (CRE).

The **current clinical antibacterial pipeline** contains 79 antibiotics and/or combinations that include at least one new therapeutic entity. Of the 45 traditional antibiotics, 27 (60%) are reported to be active against the WHO bacterial priority pathogens, 13 (28%) against *M. tuberculosis* and 5 (11%) against *C. difficile* (**Figure 3**).

The analysis of the 27 antibiotics under development against WHO bacterial priority pathogens finds that:

- 6 fulfil at least one of the WHO innovation criteria;
- of these 6 “innovative compounds”, only 2 are active against at least one multidrug-resistant (MDR) Gram-negative bacterium from the “critical” category (i.e., CRAB, CRPA, CRE); and over 40% (13/27) are β-lactam and β-lactamase inhibitor (BLI) combinations

Of the 45 traditional antibacterials, 7 new products entered the clinical pipeline since the last report[29], and 6 were either discontinued or there was no recent available information about them.

Of the 34 non-traditional antibacterials, 6 are antibodies, 9 are bacteriophages or phage-derived enzymes, 11 are microbiome-modulating agents, 2 are immunomodulating agents and 6 are grouped as miscellaneous agents.

There are 121 commercial and non-commercial entities developing 217 antibacterial agents that are in the **preclinical stage**. Turnover of projects and developers from one year to another is generally high with about one-third of developing projects being stopped and one-third of new projects coming in. Overall, the preclinical pipeline is diverse and is benefitting from initiatives such as CARB-X. However, most of these projects will fail due to economic and scientific challenges, in particular for the new innovative approaches.

Figure 2: Traditional and non-traditional antibacterials by clinical development phase (phases 1–3 and NDAs). NDAs: New Drug Applications.

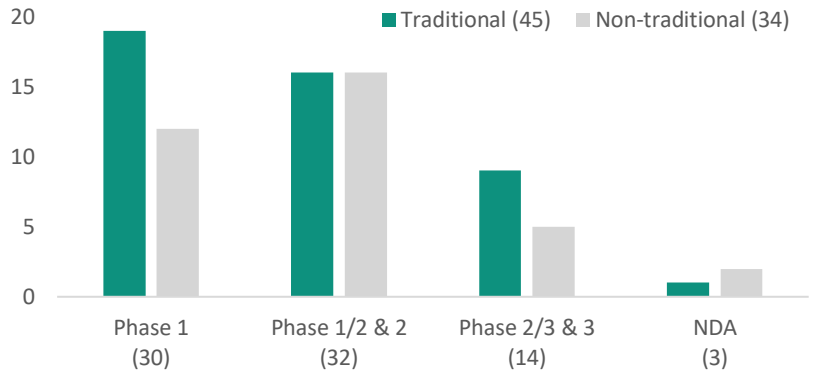
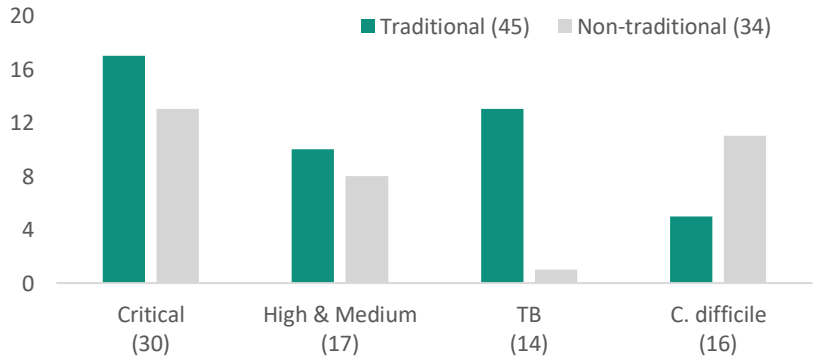


Figure 3: Traditional and non-traditional antibacterials in clinical development (phases 1–3 and NDAs) by the intended target. NDAs: New Drug Applications. TB = Tuberculosis



Antibacterial vaccines in development

63 candidates in CLINICAL development

95 candidates in PRECLINICAL development

targeting 2017 WHO Bacterial Priority Pathogens + *Clostridioides difficile* and *Mycobacterium tuberculosis*.

Vaccines can be highly effective tools in combating AMR as they reduce the incidence of both resistant and susceptible infections as well as reduce inappropriate use of antibiotics by preventing other (viral) infections. The forthcoming WHO report on vaccines against WHO bacterial priority pathogens provides a clear picture of what vaccines are in development and for which pathogens one can realistically expect to see vaccines coming to the market soon.

Vaccine Feasibility Class A (very high): Constitutes AMR priority pathogens for which licensed vaccines already exist. This includes: *Salmonella enterica* ser. Typhi*, S. pneumoniae*, and *Haemophilus influenzae* type b (Hib).

Recommendation: Global coverage of authorised vaccines should be increased in line with WHO immunisation targets to maximise the impact on AMR.

Vaccine Feasibility Class B (high): Constitutes AMR priority pathogens for which a vaccine candidate is in late-stage development (phase 3) and vaccines would be suitable to target AMR infections caused by these priority pathogens in the coming years. This includes: ExPEC (extraintestinal pathogenic *Escherichia coli*)*, S. enterica ser.* Paratyphi A, *N. gonorrhoeae, M. tuberculosis*, and *C. difficile*.

Recommendation: Accelerate the development of a vaccine for these pathogens.

Vaccine Feasibility Class C (moderate): Constitutes AMR priority pathogens for which a vaccine candidate has either been identified in early clinical trials, or been identified as a feasible vaccine target during expert review. For these pathogens, vaccines may be feasible solutions to target AMR infections. These pathogens are associated with moderate feasibility of vaccine development and include ETEC (enterotoxigenic *Escherichia coli*), *K. pneumoniae*, NTS (nontyphoidal *Salmonella*)*, Campylobacter* spp.*,* and *Shigella* spp.. Given the early stages of development, no vaccine will be available on the market soon.

Recommendation: Continue the development of a vaccine for these pathogens and expand knowledge of the potential for vaccine use and impact and other tools to combat the AMR threat.

Vaccine Feasibility Class D (low): Constitutes AMR priority pathogens for which no vaccine candidate has been identified in clinical development and therefore vaccines are not a feasible solution to target AMR infections in the foreseeable future. These pathogens are associated with low feasibility of vaccine development and include the priority pathogens *A. baumannii*, *P. aeruginosa*, *Enterobacter* spp., *E. faecium, S. aureus,* and *H. pylori*. Research and investment should explore alternative methods of control, including treatments and effective infection prevention, and should ensure access to clean water, and adequate sanitation and hygiene facilities. This is even more urgent as the drug development pipeline for *A. baumannii* and *P. aeruginosa* is also currently insufficient to adequately address the burden posed by these critical pathogens.

Recommendation: Focus on other prevention and control tools to combat AMR threats linked to these priority pathogens.

Overall, the G7 countries should work towards increasing the coverage of existing vaccines globally and foster and invest in vaccine development for the Class B pathogens in particular using existing mechanisms and organisations. For some of the most critical Gram-negative pathogens such as *A. baumannii* and *P. aeruginosa,* investing in the prevention and development of new treatments currently is more promising than the vaccine pathway.

The financial landscape for developing new antibacterials

Pushing towards innovation

Since 2017, public and philanthropic investments in AMR R&D globally have reached >9 billion USD[30]**.** A sizeable fraction (41%, 3.8 bn USD) has been directed towards product-related R&D[31] – with a focus on therapeutic products (e.g., antibiotics), which attracts up to three times more public funding than diagnostics and vaccines[32] – despite their acknowledged and integral role in the AMR response[33].

With respect to public funding, the G7 is a leading financial contributor to product-related AMR R&D (65% of the total, ~2.5 bn USD; ~90% incl. EU), including supporting a range of initiatives to accelerate the development and market entry of needed new antimicrobials (e.g., through CARB-X, GARDP & InnovFin[34]). Contributions to CARB-X and GARDP alone are dominated by G7 countries (97% of funding[30]), with the United States of America (US), United Kingdom (UK) and Germany (DE), providing the highest financial contributions.

Current barriers to R&D and market entry of antibacterials

- High cost of research and clinical development for complex research (diverse pathogens involved)
- Scientifically challenging to find new sustainable ways to tackle Gram-negative bacteria
- Low return on investment from sales of new Reserve antibiotics
- Unclear market potential for antibacterials

[30] Values based on data from the Global AMR R&D Hub's Dynamic Dashboard (>12,300 AMR R&D projects)
[31] Product-related = therapeutics, diagnostics, vaccines, promotants, preventatives
[32] 'Therapeutics', also includes therapeutic vaccines – see Global AMR R&D Hub categories.
[33] Micoli F, Bagnoli F, Rappuoli R et al. The role of vaccines in combatting antimicrobial resistance. *Nat Rev Microbiol* 19, 287–302 (2021). https://doi.org/10.1038/s41579-020-00506-3
[34] European Investment Bank Group, InnovFin – EU Finance for Innovators: https://www.eib.org/en/products/mandates-partnerships/innovfin/index.htm

Private sector funding of AMR-related R&D is estimated at ~1.8 bn USD annually[35], but due to the lack of dependable returns and high development costs associated with antibiotics (1-2 bn USD per antibiotic, including the cost of failure), more profitable areas are favoured. This is exemplified by the sizable venture capital interest in oncology, with 17 times more funding for oncology companies as compared to antibacterial investment over the last decade (26.5 bn USD vs 1.6 bn USD – US only)[36]. Initiatives such as the AMR Action Fund[37] signal a commitment by the pharmaceutical sector, but even with the substantial proposed investment of ~ 1 bn USD – plus further public and philanthropic support – only two to four antibiotics are expected to reach the market by 2030 – a number that is insufficient to mitigate the growing AMR challenge we are facing globally[1].

All countries are called upon to support and replenish push funding for AMR R&D, including extending the donor base for CARB-X and GARDP

Push incentives across the pipeline have contributed significantly to mitigating the challenges associated with antibacterial development, but are not sufficient as long as the market does not sustain new Reserve antibiotics (based on the WHO Access, Watch, Reserve categorisation[38]). Policies are required that reward successful R&D and stimulate a sustainable and innovative ecosystem.

Recommendation: All countries need to strengthen R&D targeting priority bacterial pathogens to ensure a steady supply of new antibacterial treatments or agents that address public health needs. The significant investment in early stage product development should be leveraged and later stage clinical development further supported. To achieve coverage across the R&D pipeline, the donor base for CARB-X and GARDP should be expanded ensuring a more sustainable source of funding.

Pushing & pulling in the same direction?

Stakeholders across the development continuum are calling for mechanisms that would create a more viable market for new antibiotics through market incentives – so called pull mechanisms[35,36,39,40]. Extensive literature has highlighted the importance that such incentives should not be linked to volume of sales, but to delink revenue from volumes sold – due to the need to use new Reserve antibiotics sparingly to avoid the development of resistance.

International alignment on how the public sector should reward successfully developed products that address urgent public health needs remains a challenge. While there is a need for a global pull incentive, the heterogeneity of health systems seems to preclude a singular global solution at this moment in time. A second-best option would be sizeable aligned national or regional pull incentives. G7 countries and others are in various stages

[35] AMR Industry Alliance, February 2022. Progress Report: AMR Industry Alliance 2021 Survey.
[36] Thomas D, CFA & Wessel C. BIO Industry Analysis, 2022. The State of Innovation in Antibacterial Therapeutics.
[37] AMR Action Fund: https://www.amractionfund.com
[38] WHO 2021, 2021 AWaRe classification: WHO access, watch, reserve, classification of antibiotics for evaluation and monitoring of use.
[39] IFPMA, 2021. Policy Position: Global Principles on Incentivizing Antibiotic R&D.
[40] BEAM Alliance, 2022. Pull incentive mechanisms suitable for SMEs developing AMR products in Europe.

of proposing, testing and implementing such measures – from higher pricing mechanisms to subscription model pilots. A summary of the key characteristics of the different models piloted and proposed, plus stakeholder perspectives collated by the Global AMR R&D Hub, is provided in **Table 1**.

A recent study entitled, 'The Case for a Subscription Model to Tackle Antimicrobial Resistance'[41] has rated a range of pull incentive models – *Subscription Model, Market Entry Rewards & higher Monetary Prizes, Ongoing Revenue Incentives, Exclusivity Extensions and Accelerated Approval & Priority Review Vouchers* – against six key success factors. The study was conducted by the Boston Consulting Group and mandated by the World Economic Forum, Wellcome, and the Novo Nordisk Foundation. Their evaluation concluded that the **Subscription model** – which guarantees a minimum revenue for a set period or fixed annual revenue delinked from sales volume in return for a sufficient supply guarantee – shows many advantages and is an option to create a viable and sustainable system for the development of new antibiotics. The key recommendations from this study cover a call for countries to progress their efforts to identify feasible national mechanisms to implement pull incentives, including the necessary legal and health technology assessment (HTA) frameworks, and obtaining a collective understanding across nations on paying for access as opposed to volume. Moreover, the study proposed a minimum pull incentive per novel antibiotic of between 2 bn and 3 bn USD, paid out over five to ten years. This aligns with recent work[42] that estimates a combination of push and pull incentives totalling several billion USD per antibiotic are required globally. For a fully delinked subscription programme – such as the UK's subscription model[43] – the study by Outterson and colleagues[42] suggests that an optimal amount of between 2.2 bn and 4.8 bn USD is required, with a best estimate of 3.1 bn USD[42].

In addition, the Global AMR R&D Hub's studies of available national health system tools[44] and modelling of global patient needs and market potential of priority antibiotics and diagnostics[7], provide a quantitative basis to guide current thinking on activities to support the development of antibiotics (and diagnostics). Resulting recommendations from these studies include a call to adapt existing health system tools e.g., national-level reform of pricing and reimbursement, in combination with additional pull support measures, such as a revenue guarantee, to reach the scale of return on investment attractive to private developers and investors (**Figure 4**).

Other options to multiply the impact of pull incentives have also recently been suggested, including a blended capital fund offering financing adjusted to the changing capital needs of an antibiotic as it moves through development, and an 'antibiotic bond', in which committed subscription payments would provide the capital to pay back investors. See [45] for further information. The benefits of these mechanisms have not been assessed for this report.

[41] Boluarte T & Schulze U. BCG, 2022. The Case for a Subscription Model to Tackle Antimicrobial Resistance.
[42] Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Aff (Millwood)*. 2021 Nov;40(11):1758-1765. doi: 10.1377/hlthaff.2021.00688. PMID: 34724432.
[43] NICE, 2022. Models for the evaluation and purchase of antimicrobials: https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials
[44] Global AMR R&D Hub, 2021. Novel Policy Options for reimbursement, pricing and procurement of AMR Health Technologies.
[45] Milken Institute, 2022. Models for Financing Antibiotic Development to Address Antimicrobial Resistance.

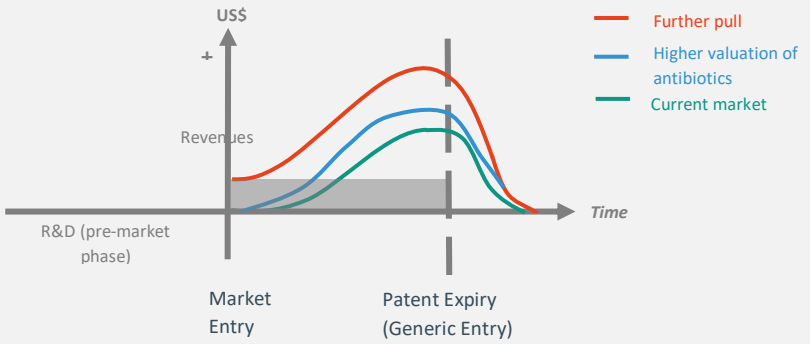


Figure 4: Market potential of priority antibiotics. See ref. 7. Economic modelling of priority antibiotics indicates supplementary market intervention is required to both bolster and secure the market – higher pricing of antibiotics alone is likely to be insufficient to reach scale of revenue attractive for investors. Revenue/volume guarantee could have merit as a supplementary intervention. Epidemiological forecasts of MDR Gram-negative blood stream infections & pneumonia conducted within this study also highlight growing access issues in areas of highest patient need. *Conceptual representation only.*

Ensuring access to priority antibiotics

The Global AMR R&D Hub's studies[7] also highlighted a worsening access gap, whereby effective antibiotics are not available in the parts of the world at scale, where the need is most dominant and growing most rapidly. With need spread thinly across many national markets, access is forecast to be precarious in low and middle income countries (LMICs), but also in some high-income countries (HICs). There is the need therefore for cooperation and further engagement across countries, donor agencies and private-public partners to ensure access to priority antibiotics (and diagnostics) to those with the greatest need. The SECURE[16] initiative has recently been proposed as a mechanism for expanding sustainable access to antibiotics (see Info box).

SECURE - Expanding Sustainable Access to Antibiotics

SECURE[16,17], a collaborative initiative developed by GARDP and WHO with the support of other international organisations, aims to accelerate access to new and existing antibiotics. It aims to act not only as an access mechanism but also to strengthen the current market for antibiotics and expand the evidence base for clinical utility of new antibiotics. The more countries that join and support SECURE, the more it will act as a pull mechanism for new Reserve antibiotics. The model is open, which means countries would not need to change their national systems, but would allow pooling of demand and expanded access to new antibiotics.

Recommendation: Overall, a global pull incentive would be preferable. However, the complexity of aligning on one concept is recognised and countries are urged to pursue their own initiated efforts to implement new innovative delinked models, such as the UK subscription model pilot[43] or as proposed within the US Pasteur Act[46]. Reimbursement reforms, including those in France and Germany (see **Table 1**), are positive developments, but provide lower financial incentives as they don't overcome the challenge of low

[46] S.2076 – PASTEUR Act of 2021, 117th Congress (2021-2022), USA. Available online: https://www.congress.gov/bill/117th-congress/senate-bill/2076/text

volumes of Reserve antibiotics. Aligned efforts are strongly recommended, based on shared insights and experiences across countries. The Global AMR R&D Hub could be used as a platform to facilitate sharing of lessons learned and co-ordination of these activities. In terms of access to new and existing antibiotics, the G7 should consider financing the SECURE pilot project.

Cooperation is key

Further engagement across the existing global health and AMR architectures, such as the Global Fund and the GLG on AMR, will facilitate further strengthening of collective efforts to mitigate the AMR challenge. Existing capacities and infrastructure, such as those available for HIV, tuberculosis and malaria, should be leveraged in this context. In tandem, the remit of development cooperation agencies can be expanded to encompass AMR, including the development of antibiotics. In particular, the GLG (see below) advocates for multi-sectoral collaboration to enhance R&D of new antimicrobials (particularly antibiotics). This includes seeking specific commitments from governments on push and/or pull incentives with defined timelines.

Recommendation: Make AMR a development cooperation issue.

Global Leaders Group on AMR – Priority on AMR R&D

- Increased, effective and affordable innovations across all sectors and stakeholders;
- A sustainable pipeline;
- Specific commitments by governments and the private sector to advance policies that attract sustainable, long-term R&D investments;
- Mechanisms that recognise the value of novel antimicrobials and systems that enable appropriate patient access;
- Increased government commitments to specific push and/or pull incentives; and
- **Ask to G7 Presidency to support financial incentives and mechanisms, with a defined timeline.**

Key Asks to G7 Presidency:

1. Commit to fully fund their own national action plans on AMR;
2. Contribute to fund multi-sectoral national action plans of resource limited countries through support to existing financial structures;
3. Financially support the Multi-Partner Trust Fund for AMR;
4. Support financial incentives and mechanisms for the development of new antimicrobials (particularly antibiotics), vaccines, diagnostics, waste management tools, and safe and effective alternatives to antimicrobials, with a defined timeline; and
5. Follow through on their existing AMR commitments and monitor their progress annually.

Thinking Ahead – Acting Together

There is a range of successful initiatives across G7 countries to strengthen antibiotic R&D and bring new drugs to market[9]. Some progress has been made to overcome the economic challenges following the approval of new antibiotics and to keep them alive on the market. However, these efforts remain ad hoc, small scale and initiated by just a few countries globally, and they are not yet sufficient to create a healthy market for new antibiotics. Leveraging the momentum gained during the UK's G7 Presidency[9], and aligning with the German Presidency's priorities[8], the time is now to increase these efforts.

See page 2-3 for an overview of key action areas and recommendations from the Global AMR R&D Hub & WHO.

Table 1: Summary of selected market incentive models/reimbursement mechanisms & Key stakeholder perspectives

Stakeholders were interviewed by an external contractor as an extension to the Global AMR R&D Hub's commissioned study '*Estimating Global Patient Needs and Market Potential for Priority Health Technologies Addressing Antimicrobial Resistance*'[7]. A transparent process was taken with all interviewees informed of the contracting partner. Stakeholders were selected from both within and external to the Global AMR R&D Hub stakeholder group to ensure a wide coverage of perspectives.

*A non-exhaustive outline of models and reimbursement mechanisms and legislation provided. Viewpoints stated are not representative of the Global AMR R&D Hub's Board of Members. The collated comments are for information only.

Country/ Sponsor	Model type/ Mechanism	Status	Key Goals		Provisions		Volume (per drug)	Level of Delinkage	Time Point (dev. pipeline)	Complexity of implementation	Overview of key aspects + stakeholder comments* *Comments are collated from interviews of 13 stakeholders from Industry (pharma & SMEs), governmental and non-governmental organisations, and key opinion leaders in the field.*
			STIMULATE R&D & INNOVATION	ACCESS - EXISTING Abs	ACCESS - LMICS	STEWAR-DSHIP					
WHO/ GARDP	**SECURE**[16,17]	**Not active** Pre-pilot phase 2022 Pilot phase 2023-2025	✗	✓	✓	✓	Business model in development				▪ Initiative welcomed by stakeholders ▪ Global approach to access pursued, which includes aggregating demand for HICs - difficult for industry to agree to ▪ Funding still required and details unclear, e.g., how to sustainably address access for LMICs on a grander scale and how to link existing models in HICs
UNITED KINGDOM (UK - England)	**Subscription model**[43]	**Pilot active** QALY[47]-based values for each antibiotic released 11.04.2022	✓	✓	✗	✓	**Max. 10 mn GBP /yr for 3-10 yrs (total max. 100 mn GBP) -** QALY[47] -based values indicate~GBP 11-19mn per year per drug	**Full** (fixed revenue)	**Late** (post approval)	**Very high** - new Health Technology Assessement (HTA), reimbursement & procurement processes	▪ Unclear how value to society will be addressed via HTA ▪ Low risk for government due to late stage approval ▪ Full delinkage - use can be guided by clinical need alone ▪ Max. capped value at the upper range of a 'fair share' for England – as measured by global pharma sales or GDP among G20 ▪ Max. capped value insufficient recognition of the true value of antibiotics (industry representatives) ▪ Likely result in greater overall costs than 'normal' procurement based on negotiated unit price
SWEDEN (SE)	**Subscription model**[48]	**Pilot active until the end of 2022**	✗	✓	✗	**?**	**4 mn SEK per yr (~0.4 mn Euro)**	**Partial** (min. guaranteed revenue)	**Late** (post approval)	**Low**	▪ Success story in terms of improving access to existing antibiotics in SE. Five antibiotics included. 2nd-best access to new antibiotics in Europe (1=UK) ▪ Not considered by industry to be a pull incentive that could stimulate innovation and drive R&D given its small size
UNITED STATES OF AMERICA (US)	**PASTEUR ACT**[46] (Subscription model)	**Not active** (Submitted to US Congress in June 2021)	✓	✗	**partial**	✓	**0.4-3 bn USD (3-5 awards – total max. 11 bn USD/ 10 yrs)**	**Partial** (min. guaranteed revenue)	**Early**	**High**	▪ Early designation is seen as helpful for SMEs ▪ $11bn/10 yrs is seen as a significant step to stimulate innovation & to represent a 'fair share' of the US among HICs ▪ Ability to incentivise innovation will depend on the contract criteria ▪ Unclear of how to harmonise with pull incentives in other HICs
GERMANY (DE)	**Changes in §35 SGB V &**	**Since 2017** **Active**	✓	✓	✗	✓	Enables higher unit prices	**NA**	**Late** (post approval)	**Low** (based on existing regulation of innovative	▪ Reimbursement exemption from internal price reference groups for antimicrobials addressing certain resistance patterns (as added therapeutic value)

[47] QALY – Quality-adjusted life year

[48] The Public Health Agency of Sweden, 2020. Availability of antibiotics: folkhalsomyndigheten.se

Country/ Sponsor	Model type/ Mechanism	Status	Key Goals		Provisions		Volume (per drug)	Level of Delinkage	Time Point (dev. pipeline)	Complexity of implementation	Overview of key aspects + stakeholder comments* *Comments are collated from interviews of 13 stakeholders from Industry (pharma & SMEs), governmental and non-governmental organisations, and key opinion leaders in the field.*
			STIMULATE R&D & INNOVATION	ACCESS - EXISTING Abs	ACCESS - LMICS	STEWAR-DSHIP					
	Act for Fair Competition Among Health Insurance Funds in the Statutory Health Insurance Sector - GKV-FKG[49]	**1x Ab assessed -** Cefiderocol (Fetcroja)								medicines – Pharmaceuticals Market Reorganisation Act (AMNOG)	▪ Allows higher unit prices for selected antibiotics ▪ Backs development and production of generic antibiotics
FRANCE (FR)	**Price renegotiation for medicines at risk of shortages**	**Since 2015**	✗	✓	✗	✗	Enables higher unit prices	**NA**	**Late** (post approval)	**Low**	▪ Reimbursement exceptions ▪ Allows higher unit prices for selected antibiotics ▪ Does not explicitly encourage innovation
NA	**Transfer Exclusivity Vouchers (TEEs)**[45,50,51]	**Not active**	✓	✓	✗	✓	Full details to be determined			**Low**	▪ Legal right to extend the monopoly period of any other patented drug in exchange for successful regulatory approval of a specified drug. Vouchers are transferable & saleable ▪ Potentially very expensive for payors & no longer-term obligations expected from developers. Some industry-near stakeholders argue against this as (i) the overall required size of incentive is independent of incentive type, (ii) TEE cost would occur 'in future', & (iii) at least some countries (e.g., UK and Italy have national medicine budget caps - extra costs are rebated back to payors) ▪ Strongly advocated by bigger pharma companies/associations as a potential approach for EU-wide pull incentive – as part of a **Hybrid model: TEE + Subscription model**
Key aspects for success that are typically mentioned: (i) size of the incentive needs to be sufficient, (ii) set the right targets, (iii) use delinked approach to address stewardship needs (but not all stakeholders agree that stewardship in HICs is an issue), (iv) aim for annual payments to ensure predictability for stakeholders, (v) include an 'early designation' element as is crucial for investors at the early stage vs. rewards only at approval or launch stage.											

[49] Ministry of Health, BMG, Germany. Gesetz für einen fairen Kassenwettbewerb in der gesetzlichen Krankenversicherung - GKV-FKG.
[50] Rome BN & Kesselheim AS. Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. *Clin Infect Dis*. 2020 Oct 23;71(7):1671-1675. doi: 10.1093/cid/ciz1039.
[51] Boyer B, Kroetsch A & Ridley D. Duke Margolis Center for Health Policy, 2022. Design of a Transferable Exclusivity Voucher Program.

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Global AMR R&D Hub

The Global AMR R&D Hub is a partnership of countries, non-governmental donor organisations and intergovernmental organisations to address challenges and improve coordination and collaboration in global AMR R&D using a One Health approach. The Hub was launched in May 2018 and is steered by a Board of Members.

GLOBAL AMR R&D HUB

World Health Organization

The WHO is committed to shaping the public health R&D priority setting agenda to combat antimicrobial resistance and will continue to review the preclinical and clinical antibacterial pipeline annually. In addition, WHO is expanding its pipeline analyses to include a review of the antifungal pipeline. As a first step to achieve this, WHO is currently developing the first global fungal priority pathogens list.

World Health Organization