GLOBAL AMR R&D HUB

A SHARED DIALOGUE ON PULL INCENTIVES

Global AMR R&D Hub & Stakeholder Group

Joint Meeting Report

April 2023

OVERVIEW

Antimicrobial resistance (AMR) continues to be one of the world's major health challenges, associated with nearly 5 million deaths in 2019[1]. But the research and development (R&D) pipeline for new antimicrobials is insufficient and access to new and existing therapeutics remains a challenge in many countries worldwide.

It is widely recognized that pull incentives will have a transformative impact on the development and access to novel antimicrobials addressing unmet needs in AMR. However, aligning the mechanism(s) and principles for implementing such incentives within national health system frameworks is still an open question for many countries.

The Global AMR R&D Hub's (Hub) 17 member countries and the European Commission (EC) are all at different stages in developing AMR strategies, including the approach to pull incentives for incentivizing the development of and access to new antimicrobials (see Annex I)[2].

The Hub members agreed that an informal platform for discussing the topic of pull incentives was crucial for making progress in this area. The Pull Incentives Working Group was established in April 2022, comprised of the Hub's Board Members (and technical representatives) & Observers, to share lessons learned and challenges faced across countries.

Over the last year the working group has engaged in an open and informal dialogue between member countries and other Hub Members and Observers, with a key focus on the topic area of 'valuation' of new antimicrobials. A range of different approaches currently being implemented or evaluated by countries have been explored via case studies and expert presentations followed by discussion sessions.

The working group has forged a broader awareness and recognition of similarities and differences in approach between countries and encouraged exchanges to discuss respective approaches to pull incentives and AMR strategy in general.

[1] Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022 Feb 12;399(10325):629-655. doi: 10.1016/S0140-6736(21)02724-0.
[2] Global AMR R&D Hub & WHO, May 2023, Incentivising the development of new antibacterial treatments: G7 Progress Report

On the 27th April 2023, the Hub convened a virtual meeting to discuss the progress of this working group and gain feedback from the Hub's Stakeholder Group (see Annex II) on a range of guiding questions (Annex III) to help shape the working group's future direction. The feedback from the Stakeholder Group on the questions posed was provided during the meeting and in written format following the meeting.

Feedback from the Hub's Stakeholder Group on questions posed is summarized below.

DISCUSSION SUMMARY

The key themes discussed and responses from across the Stakeholder Group are summarised below.

Pull Incentives – appropriate size & valuation principles

- The appropriate size of a pull incentive was a topic of great interest among the group, with a concensus among stakeholders that the incentive needed to be of 'sufficient size' and duration to drive the development of a robust and sustainable R&D pipeline for novel antimicrobials, and that the model needs to be delinked from revenue to ensure appropriate use.

- A range of estimates for a global pull incentive were highlighted: (i) PASTEUR ACT, which intends to offer a fully delinked annual revenue in the range of USD 750 million to 3 billion per successful antimicrobial over 10 years. This leads to a global pull size in the USD 1.6 – 6.5 billion range; (ii) Estimates from Boluarte & Schulze 2022[3] for a subscription model for a novel antibiotic lie in the range of USD 2 – 3 billion; (iii) The UK pilot's fully delinked subscription model of GBP 10 million/year for 10 years, converts to a global pull size in the range of USD 1.9 billion; (iv) A number of contributors pointed to the work of Prof. Kevin Outterson[4] - Estimating the appropriate size of global pull incentives for antibacterial medicines - which outlines a 10-year end-to-end fully delinked subscription model, at USD 4.2 billion per antibiotic on average, as providing a reasonable estimate of cost.

- The size of the UK's subscription model was regarded as lying in the lower range of what an effective pull incentive would be, but the group noted that the current criteria for this model are being evaluated with the maximal cap likely to be raised.

> "It's important to create an incentive with a meaningful size and to create a sustainable ecosystem for innovation.

> "For any pull incentive, it is critical that a global perspective is pursued.

[3] Boluarte & Schulze 2022 "The Case for a Subscription Model to Tackle Antimicrobial Resistance": https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance [accessed 1st June 2023]
[4] Outterson K. Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. Health Aff (Millwood). 2021;40(11):1758-1765. doi: https://doi.org/10.1377/hlthaff.2021.00688

- The topic of 'fair share' contributions to a global pull incentive was touched upon with the discussion highlighting the leading role of the Group of 7 (G7) and the European Union (EU), in providing financial inputs.

- Stakeholder members also emphasized the need to reflect on how incentive models within high income countries would actually translate into possibilities for low income countries.

- Top level considerations for an incentive framework that were highlighted included aspects such as, "incentivising innovation and appropriate use", "value for money", "predictability", "feasibility", "access", "average research and development investments", "costs of production", and "reasonable profits" for companies.

- For assessing the value of antimicrobials, the importance of STEDI (Spectrum, Transmission, Enablement, Diversity, Insurance) values were underscored.[5,6]

- There was recognition that countries will want to prioritize interventions that address their own needs, but that co-ordinated efforts and priorities globally, would help support developer predictability.

> "Although countries have their own priority needs & burden, alignment across countries will help support predictability.

AMR R&D targets

- There was general agreement on the need for realistic and collective targets for the development of new antimicrobials, especially antibiotics, that are informed by public health needs.

- The setting of targets was seen as being a way for both developers and governments to agree on R&D priorities and design incentives needed to attract the required investment and secure a sustainable future pipeline of innovative drugs.

> "How much of a pipeline does the world need?

[5] J. Rex. Pull Incentives For Antibiotics: How Much And Why? - A Literature Survey, 2020.
[6] G7 UK. G7 Shared Principles for the Valuation of Antimicrobial Therapeutics, 2021.

- The multi-stakeholder nature of this effort was underlined and that the most-up to date evidence on the emergence of resistance regionally, nationally and globally would be required to ensure these targets would have the most impact on public health.

- The open question of a normative process to identify how many new "high-impact" antibiotics are needed per decade – six being mentioned as a starting point – was raised, to faciliate budget planning and determine the upper limit of drugs that could qualify for a pull incentive over the next decade.

- Developers highlighted the importance of incremental progress towards 'high value' breakthroughs (i.e. new mode of action/new class/targeting an urgent unmet clinical need) and that all new antibiotics (not just 'breakthroughs') should be rewarded commensurate with their clinical benefit, with incentives rewarding innovation calibrated to reflect their value.

- Although the WHO[7] and CDC[8] priority lists were regarded as a good starting point to inform R&D targets, the importance of setting targets in a way that considers both present and future threats was underscored, to ensure the ability to respond to emerging and unknown threats. However, one stakeholder highlighted the unintentional side effect of the priority lists triggering a shift to development of pathogen-specific drugs, rather than indication specific drugs, the former potentially requiring sophisticated diagnostic infrastructure.

- Developers emphasized the collective nature of pull incentives - that they would only work if multiple countries implement them.

Equitable access to new and existing antimicrobials

- The critical need to ensure equitable access to antimicrobial treatments that are required globally and that this access is guided by appropriate stewardship principles was broadly acknowledged.

> "Companies will chase the target only when G7 or other countries collectively set a target.

> "How do these high income based models translate into possibilities for low income countries?

[7] WHO Bacterial Priority Pathogen Priority List
[8] Centre for Disease Control Priority Pathogen List

- From a developer's perspective, the main barrier to ensuring equitable access was seen to be economic and that reimbursement reforms that recognize the societal value of antibiotics addressing critical unmet public health needs would be required to encourage broader product launches and reliable access.

- Procurement models that aggregate demand across multiple, smaller or lower income markets, strongly grounded in stewardship principles, were proposed as an avenue for ensuring access across a broader geographical range. However, the challenges existing even when a product is registered in a country, regarding local distribution and prescribing were highlighted.

- SECURE[9] was provided as an example of a mechanism to accelerate access to existing and new antibiotics (with clear stewardship measures) in low and middle income countries. SECURE is currently working with governments to define what the optimal economic tools would be to ensure access.

- Transparency throughout the end-to-end process of the development of and access to new antibacterials was regarded by some stakeholders as being important. Transparency on R&D costs was seen by some as a requirement to participate in any of the potential pull incentive schemes. However, some developers pointed to the difficulty of determining investment in R&D for a single product due to fixed costs that are common to a whole company, and shared services across the R&D value chain. The existence of credible estimates for the development of antibiotics were highlighted[10]. Timely publication of clinical trial data, sharing key provisions underpinning agreements for the development of an antibacterial, and transparency to strengthen both supply and demand, including appropriate disclosure for product registration and transparency of demand volumes were all encouraged.

> "Building in stewardship & access into pull incentives at an early stage is helpful.

[9] www.secureantibiotics.org
[10] J. Rex. What Does An Antibiotic Cost To Develop? What Is It Worth? How To Afford It? AMR.Solutions, 2020.

Development of antibacterials & alternatives in the animal health sector

- Stakeholders highlighted regulatory restraints - restricting exploration of certain classes and compounds based on their use in human health - as a key barrier to developing novel antibacterials for use in animal health.

- Actors in both the animal and human health field called for more co-ordination in these fields, for example, to explore drugs that work in animal species but failed in humans to be considered for animal use.

Next steps

- Keeping the focus on the topic of antimicrobial pull incentives and appropriate use was seen as integral to achieving concrete next steps. However the better incorporation of diagnostics into treatment guidelines and treatment protocols, development of new diagnostic tests and alternatives to antibiotics were seen as integral to the AMR toolkit.

- The inclusion of more voices from the global south, including patients and government representatives in the dialogue, was seen as being crucial to developing solutions that work for all.

> “We need more patient voices from around the world, including LMICs, in all exercises like this.

CONCLUSION

The Global AMR R&D Hub Members, Observers and Stakeholder Group entered into an open dialogue on pull incentives that highlights a strong appetite for the creation of solutions to incentivise the development of antimicrobials that will actually work for all stakeholders involved. There was a shared appreciation that solutions should keep unmet public health needs, the societal value of antimicrobials and the global nature of the AMR challenge in the centre. The ability to build on country-level experiences and engage with key stakeholders provides a pathway to help optimize thinking and shape - potentially international - collaborative pull incentive mechanisms and ultimately set the tone for a future and sustainable pipeline of antimicrobials that address the most critical public health needs. We look forward to our next shared dialogue to exchange ideas and perspectives to create impact.

Acknowledgements

The Global AMR R&D Hub warmly thanks its Stakeholder Group for this shared dialogue on pull incentives and for helping highlight a number of crucial issues that require collaboration to find global solutions.

Annex I

List of Board Members

- → Australia
- → Bill & Melinda Gates Foundation
- → Canada
- → China
- → European Commission (EC)
- → France
- → Germany
- → India
- → Italy
- → Japan
- → The Netherlands
- → Norway
- → Russia
- → Spain
- → Sweden
- → Switzerland
- → Turkey
- → United Kingdom
- → United States of America
- → Wellcome Trust

Observers

- → Africa CDC
- → Food and Agriculture Organization of the United Nations (FAO)
- → Organisation for Economic Co-operation and Development (OECD)
- → World Health Organization (WHO)
- → World Organisation for Animal Health (WOAH)

Annex II

Members of the Global AMR R&D Hub Stakeholder Group

NGO / civil society

- → **Access to Medicine Foundation (ATMF)**
- → European Patients' Forum (EPF)
- → The Pew Charitable Trusts (PEW)
- → World Alliance Against Antibiotic Resistance / AMR Think Tank (WAAAR)
- → **World Farmers' Organization (WFO)**

Industry

- → **AdvaMedDx, division of Advanced Medical Technology Association (AdvaMed)**
- → **Biotechnology Innovation Organization (BIO)**
- → **BEAM Alliance (BEAM)**
- → **HealthforAnimals (HfA)**
- → **International Federation of Pharmaceutical Manufacturers Association (IFPMA)**

International research funding initiatives

- → **Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)**
- → **Global Antibiotic Research and Development Partnership (GARDP)**
- → **Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)**
- → Innovative Medicines Initiative (IMI)
- → UNITAID

Academia

- → African Association for Research and Control of AMR (AAAMR)
- → European Public Health Association (EUPHA)
- → **European Society of Clinical Microbiology and Infectious Diseases (ESCMID)**
- → **International Society for Infectious Diseases (ISID)**
- → **International Network for AMR Social Science (INAMRSS)**

Members in **bold** were present at the meeting**.**
Written feedback on questions discussed was received from BEAM, BIO, CARB-X, GARDP, HfA and IFPMA.

Annex III

Questions discussed

1. How should economic value be ascribed to priority antibacterials addressing public health needs? Does the UK's Netflix model provide a reasonable level of guaranteed revenue to ensure a sufficient supply guarantee? Can this model be applied for incentivising the development of new antimicrobial treatments? How many countries would need to implement subscription models such as the Netflix model in order to promote R&D of new antibiotics? In this context, is having many different incentive models a challenge for stakeholders. What are your views on the current discussions on 'fair share'.
2. Do you think the implementation of R&D targets for the development of antibiotics addressing priority needs (e.g., six 'high impact' antibiotics in the next decade) would be beneficial for developers and other stakeholders? Which targets are realistic and who can contribute to setting these targets?
3. Provided there are adequate funding and financing mechanisms in place, pharmaceutical companies should align their R&D programs to address unmet needs defined under the WHO Priority Pathogen List, and assure equitable and sustainable access to new and existing antibiotics. Which aspects could be streamlined/aligned to increase effectiveness? Feedback on implementing this from developers would be helpful.
4. What are the main challenges and gaps for the development of antibacterials and alternatives to antibacterials for use in the animal and other health sectors.
5. Where next? The conversation has been on valuation of antimicrobials, especially antibiotics within the respective health systems. Do we need to broaden the topic to diagnostics and alternatives to antibiotics and how to ensure uptake of these tools?
6. Should full transparency on R&D cost be a requirement to participate in any of the potential pull incentive schemes that are under consideration?
7. To what extent should pull incentives address the needs of the participating countries in terms of unmet medical need, or should a global perspective be pursued?

(Questions 6 & 7 were provided to the Stakeholder Group during the meeting).

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.

www.globalamrhub.org

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