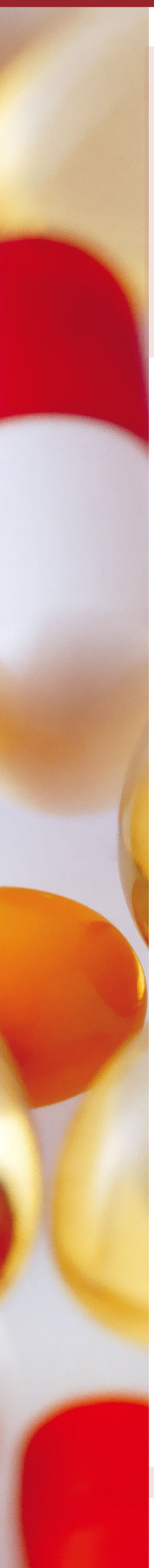
Exploring key bottlenecks and alternative solutions in the antibiotic R&D pipeline

Summary Report from Expert Workshop Discussions

7-8 November 2022, Uppsala University, Sweden

Organized under the ReAct initiative:
Revisiting Effective Models to Advance the Antibiotic Pipeline (REMAAP)



About REMAAP
The initiative *"Revisiting Effective Models to Advance the Antibiotic Pipeline" (REMAAP)* seeks to build evidence and broader political understanding of the core challenges in antibiotic research and development and how to effectively address them.

Within the framework of this initiative ReAct organised an in-person workshop in Uppsala, Sweden on November 7-8th 2022. The workshop aimed to take an "end-to-end" approach to antibiotic R&D (from discovery to patient access), with specific attention given to the early stages (discovery and preclinical) of antibiotic research and development. Discussions focussed on identifying the vulnerabilities, challenges, and potential solutions. The workshop gathered leading experts with knowledge particularly of the early stages of antibiotic R&D with backgrounds ranging from microbiology and chemistry, lab experience and compound development, infectious diseases and clinical medicine, economy, policy and history. This document synthesizes the identified challenges and suggests building blocks of more comprehensive solutions.

Introduction

The burden of antibiotic resistance is steadily increasing worldwide, accounting for 1.27 million deaths in 2019. Meanwhile, compared to other therapeutic areas, the antibiotic development pipeline is very poorly populated. Over the last two decades, the number of large multinational companies with active anti-infective programs has fallen from 18 to just 3 in 2023. Instead, academics and numerous biotech companies, which are smaller and focused on developing only a few compounds mostly with public support, have filled the gap in the early stages of clinical development. We are now well into a third decade of an acutely insufficient number of new antibiotics in development. An effective global response to antibiotic R&D is urgently needed. The existing market-based R&D model is neither appropriate nor effective for developing antibiotics, and it is increasingly clear that more of the same, hence primarily stimulating the end market, will not be the answer. Instead, there is a need for increased public leadership to test new alternative models in order to overcome challenges in an efficient and public health needs-driven way. By building evidence and collective understanding around the key challenges and needed solutions for antibiotic development, the Revisiting Effective Models to Advance the Antibiotic Pipeline (REMAAP) initiative aims to identify the role and purpose of publicly funded and not-for-profit models and entities in tackling the vulnerabilities in the antibiotic pipeline. The initiative aims to generate interest and commitment amongst governments, other policymakers and funders to take strong leadership and concrete steps to support solutions where public and not-for-profit models and entities play a key role.

Approaches and activities

Based on the objectives of the REMAAP initiative, a collaborative analysis and dialogue-based process is being rolled out in a phased manner with the outcomes of each step informing the following activity. The first activity was an in-person workshop held in Uppsala (Sweden) on November 7-8th 2022, which aimed to:

- Explore the vulnerabilities, challenges, roadblocks, and potential solutions in the current antibiotics R&D pipeline, including a focus on the early R&D stages.
- Identify points of consensus and divergence through dialogue and knowledge exchange, based on both the contributions from each participant's pre-existing knowledge and experience, as well as group discussions and brainstorming activities.

The workshop comprised of 15 senior leading experts, academics, and members of civil society in the field of antibiotic R&D, representing nine countries. While the workshop aimed to take an "end-to-end" approach to antibiotic R&D (from discovery to patient access), specific attention was given to the early stages of antibiotic R&D in the first workshop. This focus was also reflected in the multidisciplinary expertise of the participants, ranging from microbiology, chemistry, infectious diseases, as well as academics with backgrounds in economy and history.

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Outline of the workshop

In order to achieve the above-mentioned objectives, the workshop was built around **four main activity blocks:**

1. **Initial mapping exercise:** a social sciences-informed mapping exercise during which participants were asked to reflect on and identify key problem areas within the antibiotic pipeline to produce a "heat map" of challenges.

2. **Deep-dive into the early R&D stages** - Challenges: to comprehensively identify the key challenges in the early stages and their key characteristics, as well as select four important challenges to enable an informed and focused discussions about solutions (activity block 3).

3. **Deep-dive into the early R&D stages** - Solutions: to identify the way forward to address challenges identified, with a particular focus on solutions/models in which public not-for-profit actors play a key role

4. **Case study scenario - exploring the end-to-end approach**: Building on the previous activity blocks, to identify the solutions or interventions that would be needed in order to develop and deliver a promising novel antibiotic molecule in a way that ensures equitable access, including in LMICs.

At the start of the workshop, an opening session was organised to spark the thinking and interrogate the understanding of the "antibiotic pipeline". The exercise was led by Dr Claas Kirchhelle (UCD) and Dr Rebecca Glover (LSHTM), and framed as a social sciences-informed mapping exercise during which participants were asked to visualize the pathway from discovery to access and, then, to reflect on and identify key problem areas within the antibiotic pipeline to produce a "heat map" of bottlenecks. Participants were free to opt out, responses were anonymized and the exercise has received ethics clearance from UCD and LSHTM.
Based on the discussions in the four main blocks of the workshop, in a final concluding session, participants were also reflecting on a few key questions regarding the role of public and not-for-profit actors and entities, the involvement of LMICs, as well as key messages for policy makers (see section 4).
The workshop spanned two days and through a series of fast-paced exercises, each segment set out to comprehensively map key challenges and potential solutions in selected areas as well as covering a range of complex questions. The discussions and exercises generated a plethora of insights and ideas, many of which could have become even more elaborate if more time had been available for further discussion and analysis.

Deep-dive into the early stages of antibiotic R&D

The session was introduced by Dr Ursula Theuretzbacher who presented a recent survey[1] of key challenges encountered in the early antibiotic R&D stages, in which four different types of challenges could be identified: scientific, structural, financial and knowledge/expertise related.

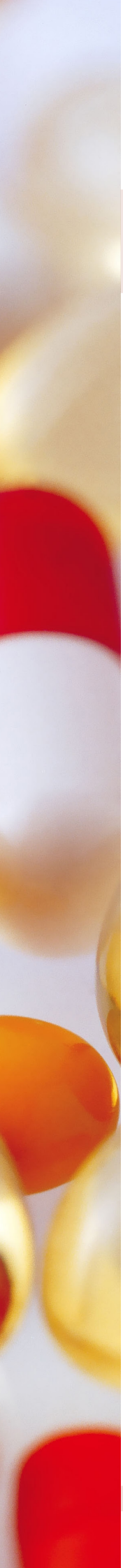
These categories were then used to guide a wide and open brainstorming where participants were asked to identify any kind of challenges they know of or have themselves experienced in the early stages, belonging to either of the aforementioned categories or labelled as cross-category/overarching.

Following the brainstorming of the challenges, the experts sorted, identified, and selected four challenges to be further described and move forward as those best suited for in-depth discussion in the solutions-oriented sessions that followed. While the selection process was deliberately structured to identify one challenge from each of the four categories, the challenges under the category "structural" included the highest prioritised challenges in the selection process.

The four challenges selected for further discussion were:
1. Scientific – Challenges with penetration/efflux in Gram-negative bacteria, and insufficient standardised models for predicting toxicity
2. Structural – Insufficient coordination of different entities and misaligned incentives for universities to get a molecule through the discovery process and ultimately on to the market
3. Financial – Short term unpredictable/unsustainable funding (lack of access to scientific support)
4. Knowledge – Insufficient knowledge sharing and lack of open knowledge & expanded support

Based on a rapid round of discussions in smaller groups to elaborate further on characteristics, causes and effects of each of the four challenges, participants then moved on to discuss possible solutions. Starting with a brainstorming activity, participants submitted individual proposals through an online collaborative brainstorming tool, before identifying and further exploring potential solutions in smaller groups, corresponding to two of the four challenges in each group. This report provides a comprehensive but non-exhaustive summary of the discussions.

1 Theuretzbacher U, Baraldi E, Ciabuschi F, Callegari S. Challenges and shortcomings of antibacterial discovery projects. Clin Microbiol Infect. 2022 Dec 8:S1198-743X(22)00600-0. doi: 10.1016/j.cmi.2022.11.027. Epub ahead of print. PMID: 36503116.



In relation to the following four challenges, examples of solutions are also presented:

1. Scientific – Challenges with penetration/efflux in Gram-negative bacteria, and insufficient standardised models for predicting toxicity

The underestimation over the years (even by drug developers themselves) of the scientific challenges connected with antibiotic discovery, such as penetration/efflux in Gram-negative bacteria, (especially Pseudomonas and Acinetobacter), the lack of reliable models for predicting toxicity, standardisation of in vivo efficacy models, the emergence of resistance due to target mutations, and non-traditional strategies (predictive efficacy models), has left those issues still unresolved. Additionally, the lack of data-, knowledge- and expertise-sharing between academic groups and companies further hinders the progress on addressing such challenges. Research groups are often small and fragmented, and the lack of knowledge-sharing (within the field and across disciplines) leads to repetition of mistakes. The underfunding of some of these key issues pushes the problem downstream to be exposed only at later and more expensive stages of development.

Not least, access to expensive equipment (such as mass spectrophotometers) especially in low- and middle-income countries, represents an issue that needs to be addressed if we want to see sustainable progress.

A contributing factor to this challenge is that the academic system highly incentivises publishing in journals and funders also fail to create incentives for and enforce collaboration and the sharing of knowledge and resources to promote more effective problem-solving. Additionally, short-term (usually 3 years with no option to renew) and less predictable funding discourage new researchers, while expertise, equipment and staff risk being lost when funding ends.
Although this type of technical-scientific challenge will also require scientific solutions, the discussions were oriented towards solutions other than strictly scientific ones, given the overall focus and scope of the workshop. Examples of solutions proposed in the discussions and through individual brainstorming were:

a, Promoting/funding long-term projects where expertise and institutional memory are conserved.

b, Developing incentives for academics to share data and know-how and, in some cases, bacterial strains.

c, Stimulating coordination and sharing expertise/knowledge across disciplines or within fields.

d, Supporting the publishing of negative data.

e, Focusing upcoming projects on two critical scientific barriers, i.e. challenges with accumulation of small molecules (penetration/efflux) in Gram-negative bacteria, and insufficient standardised models for predicting toxicity.

2. Structural – Insufficient coordination of different research entities and misaligned incentives for researchers to get a molecule through the discovery process

Among the major "structural" challenges hindering the drug discovery process, two leading components were identified: the lack of coordination between entities and misaligned academic incentives with the R&D process.

Before multinational pharmaceutical companies exited the antibiotics field knowledge and competencies used to be managed within one single organisation. Over the last two decades, increasingly micro- and small enterprises (including research groups within universities) have taken the lead. The increasing fragmentation of knowledge and expertise in the antibiotic discovery field, coupled with the lack of leadership has created a complex situation with insufficient coordination of different entities involved in antibiotic R&D. These include disparate groups in academia, small biotech companies, Contract Research Organisations (CROs), Product Development Partnerships (PDPs), and public health institutions, all with different agendas.

There can be a lack of political leadership and policy makers may have a poor understanding of their role

in stimulating support for this area, while competing political agendas and disagreement of mandate and priorities prevail. There can also be a lack of political recognition that drug discovery and development is a transnational effort.

In the context of fragmentation, a related challenge is that of misalignment between, on one hand, the academic incentives and structures (such as the expectations to publish in highly ranked journals or the negative perception of translational research among peers), as well as timelines and short-term financing of academic work, and on the other hand, the incentives and resources required for financially sound and medical need-driven drug-development projects designed to advance early drug discovery towards delivering new products. These challenges may lead to duplication of efforts and fewer molecules of good quality likely to progress.

Access and affordability of the end product may also be negatively affected by structural challenges. While some participants considered access to be less relevant or harder to influence at the earlier stages due to the lack of knowledge or time to focus on this, others insisted on the need to clearly allocate the responsibility and address access early on, for example by attaching access conditions to publicly funded research, to be passed on through the next stages in the development process. According to individual proposals and group discussions, solutions proposed to tackle these challenges included:

a, Enforcing pipeline coordinators operating at multiple R&D stages that (i) oversee and/or connects the activities of various R&D stage-specific pipeline coordinators (such as ENABLE2 and CARB-X); (ii) manage broad project portfolios; (iii) award milestone-based prizes; (iv) enable knowledge sharing across projects (representing the whole pipeline "end-to-end"); and (v) take projects through the various stages.

b, Building a sustainably-funded, non-competitive, centralised (virtual) hub/institution/consortium of academic, SME, Pharma partners that can take promising compounds ("leads") produced/validated by academics to the next stage. The organisation would not fund the individual partners, which will need to secure funding elsewhere. All partners are expected to share data, assays, chem libraries etc, while working on individual projects (generally) and would retain IP. All partners would be legally required to respect proprietary data.

c, Maximising sharing, free licence, making knowledge and results openly available and engaging industry to take the molecule into the clinical stages. By doing so, If the research entity decides to leave there will be someone that can continue.

d, Building understanding and trust in the process.

e, Involving organisations such as the African CDC that have close links to the African governments, and other organisations in LMICs which can bring in a different perspective early on in the drug discovery process.

3. Financial – Short term unpredictable/unsustainable funding (lack of access to scientific support)

One of the major problems contributing to the extremely low rate by which new antibiotics are discovered and developed is that funding is typically provided in a short-term, dispersed, insufficient and non-strategic fashion. This means that research teams have to invest valuable time and expertise to apply for funds, using resources that could be dedicated to research. Short-term funding also entails the risk of losing valuable institutional memory and expertise, as well as the risk of discouraging more research teams to enter the field.

The insufficient understanding by funders and governments of the drug discovery process and timelines (more than 10 years needed), coupled with the increasing attention to market mechanisms and the focus on return on investments at the expense of the actual research and discovery of new antibiotics, has contributed to a critically dry pipeline of antibiotics. The state of the pipeline and the lack of truly innovative projects is in turn not attracting more investments. It should be a public responsibility to provide stable and sustainable funding and address donor fatigue in the absence of pressure from patient organisations. The lack of targeted funding, the lack of interest by funders/donors willing to invest, and the lack of transparency of the actual costs of antibiotic development by the private sector, as well as the misalignment of funding conditions and drug discovery, are additional causes making available financing not only insufficient but also inadequate for antibiotic development.

Regarding the way that funding is provided, some governments often fail to differentiate and allocate funding between basic science, discovery efforts, pre-clinical and clinical development research. There can be confusion between funding for basic science vs. discovery research and there is an overemphasis on the need for investment in later stage research, while the very early pipeline is often wrongly perceived to be well funded and populated with with new discoveries with potential for drug development. Moreover, as funding tends to be allocated to projects rather than specific organizations, there is a risk of losing not only potentially promising molecules, when a grant is ending, but also the expertise and infrastructure that were painfully gathered to support it.

Consequently, the discovery and delivery of new antibiotics is being seriously hampered by the lack of predictability and sustainability in funding. Additionally, opportunities to better address affordability and access are likely missed as both public or philanthropic funders fail to include related conditions and criteria, to the extent that it could or should best be applied in the early research stages.

Based on individual brainstorming and discussions in smaller groups, solutions proposed to tackle financial challenges included:

a, Aligning R&D endpoints (e.g. the design of clinical studies) with the requirements of regulatory bodies. Funding permanent organizations (and their staff salaries) with attached conditions, such as data and knowledge sharing (including of projects that do not yield novel chemical matter for the pipeline but do add knowledge to the field).

b, Shifting to public (state/EU) clinical trials (which of course requires an ecosystem of early-stage discovery to feed pre-clinical and clinical development). There already similar examples in other infectious disease areas: for priority pathogens/indications one can consider a model similar to ravidasvir (new Hepatitis C drug) which was licensed from an SME in San Francisco by DNDi plus Egyptian and Malaysian generics companies. Clinical trials were funded by Malaysian and Thai governments, plus MSF.

c, Implementing incentives specific to researchers for longer term engagement with realistic milestone setting and recognising that projects require go/no-go decision points.

4. Knowledge – insufficient knowledge sharing and lack of open knowledge & expanded support

In the Knowledge category, the challenge of insufficient and unsupported knowledge sharing was identified as a key challenge. There is limited knowledge about drug discovery, a poor understanding of go/no-go criteria and very few academics have a full end-to-end knowledge and know-how about the R&D process. Insufficient knowledge-sharing in this environment leads to a scattered and fragmented field where failures are repeated, progress stalled and money lost when lessons are not being shared and learned. It also means that projects that are stopped due to financial reasons are not being handed over to those that could take them through the next stage of the pipeline.

Among the main contributing causes behind this challenge identified were the insufficient collaboration between (and within) the parties involved in research and discovery (e.g. academia and industry), coupled with the lack of incentives for experts to remain in the field, or to publish (and or share early on) failed or parked projects. Furthermore, the systemic competition and focus on secrecy around IP at an early stage in the process (by both academia and companies) discourages knowledge sharing. Finally, the lack of understanding among funders of the overall complexity, barriers and disincentives in the field, also contribute to the problem.

An inherent part of this challenge is also the problem of identifying the intended recipients of the knowledge that should be shared and to identify people currently not reached.

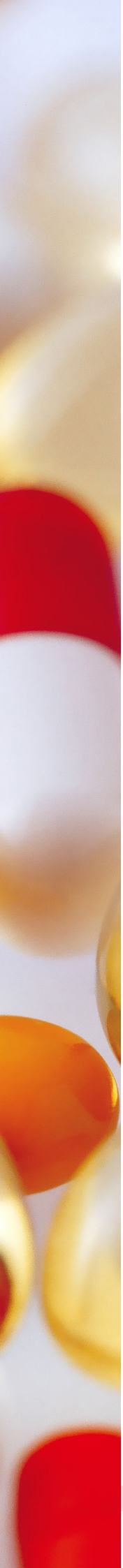
According to the individual contributions and workshop discussions in smaller groups, the solutions to tackle the challenge of insufficient knowledge sharing may be tackled by, included:

a, Open-access to knowledge, data (similar to the COVID-19 response), expertise/experts (creating a map -expert flows, e.g. via centre(s) for universities and/or small companies to access specialised expertise, equipment and/or funding). A model similar to the Canada's Centre for Drug Research and Development (CDRD).

b, Better integrate existing knowledge between different expertise/experts.

c, Funding should encourage collaboration and provide infrastructure; public/philanthropic funding should also have conditionalities to make results available in the public domain.

d, Institutional memory – to maintain knowledge, strains, and open information on failures, as well as the connection with experts that leave the company/project.



Group discussions on potential solutions

During more in-depth group discussions regarding solutions, participants elaborated further on specific solutions or approaches and models that could be applied to tackle the challenges.

Group 1 discussed potential solutions to address both the selected scientific and structural challenges and focused on elaborating an approach designed specifically to address the scientific challenges. Described as a **centralised network of R&D hubs** (or centres of excellence), a key solution would consist of centres that include scientists experienced in drug discovery, with additional support provided for decision making. The network would be developed over the longer term and built to be sustainable, operate at global level, and include hubs in LMICs to promote access aspects. Funding would be needed for infrastructure and salaries, to support a new ownership model which promotes data and knowledge sharing (including publishing of failures). The network would share a common goal, i.e. focusing on drug discovery and solving scientific problems, and could provide incentives to academic institutions other than that of publishing.

The solution would counter the trend of pharmaceutical companies moving away from investing in drug discovery (not just in antibiotics), and it builds upon a recognition of the limitations of academic institutions in drug discovery. The role of the hub would be to take on compounds that academic institutions have identified and help move them forward into the next stage.

The participants debated whether the network needed to be physically centralised, but it was argued that unlike institutes like the European Organization for Nuclear Research (CERN) for example, it would not need to be. Creating a dynamic "network of centres of excellence" could also stimulate innovation better than (more static) centralised models. However, a central "off-loading" point may be needed for research going into the preclinical stages. Alternative solutions discussed included the option to build a centralised institution or better map and support the existing drug discovery centres in the current system.

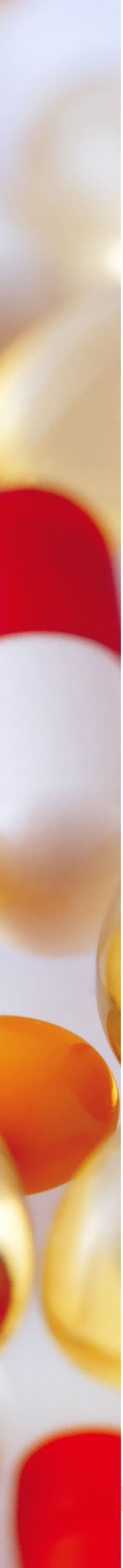
The political barriers for this model to move forward include the reality that the topic is low on the political agenda in the global north and the need to explore and capture emerging discovery projects and political interest (following COVID-19 pandemic) also in the global south. Issues regarding the control and ownership of the scientific results would need attention and funding would need to be leveraged from governments including through matching funds.

Group 2 discussed approaches to address financial and knowledge related challenges through a set of interlinked solutions, with several aspects being similar to those discussed in Group 1. To address the challenge of insufficient knowledge sharing, lessons should be learned from examples of open knowledge-sharing during COVID-19. While expertise largely exists, the challenge is rather about how to connect the experts with the right information and provide guidance on how to proceed with their promising ideas. Academic research teams/SMEs tend to work in isolation and do not necessarily have a tradition of collaboration and cooperation.

By using primarily existing (global) structures (including the WHO), the approach aims to make information more available. It would accelerate progress in drug discovery by first focusing on **collecting and matching ideas with the right expertise**, and secondly to **connect the expertise to the beneficiaries**. Several initiatives already exist, such as GARDP's REVIVE and JPIAMR-VRI (Virtual Research Institute). This would also be a space for sharing failures and to map the "expert flow"; to identify where experts go when a project fails and where they go to get the information and funding they need.

The proposed solution is also linked to solutions for funding-related challenges, with a structure also having a mandate to coordinate targeted funding, acting as a coordinating **"forum for funders"**. While funders tend to prefer to direct their own funding, the forum (or consortium) could provide data sheets with information on relevant funders, as well as guiding researchers how to fill knowledge gaps. Funders could come together to share strategies and information about what they are not funding and help researchers by pointing to other sources. It would also be possible to apply conditions to funding provided to promote access and/or requirements to share data. Alternative incentives to academics to that of publishing could also be introduced via this forum.

There could also be a link to clinical trials networks which are already evolving, and to explore aligning emerging platforms across diseases and countries, and potentially introduce a (non-political) body to coordinate trials and establish knowledge sharing (also open for use by the private sector). This body could also align end-points of trials with regulatory bodies.



Exploring the challenges and solutions throughout the antibiotic pipeline ("end-to-end" case study)

Following the deep-dive into the early stages, a separate session was organised with the intention to harness the views and expertise from the group on the challenges and possible solutions in the later stages of the R&D chain and to ensure an end-to-end approach is taken into account. Participants were also asked to think especially about the way that equitable and sustainable access may be ensured.

To help inspire the conversation, the group was also presented with a few "debatable statements" as follows:

— "*Only big pharma can successfully conduct clinical trials or ensure distribution channels*". A majority of participants thought that this is incorrect.

— "*Financial challenges are the main issue blocking a molecule to move forward*". Participants were more divided on this statement, with about half of the group agreeing and half disagreeing.

— "*The industry antibiotic pipeline is populated enough by promising molecules*". Most participants disagreed with this statement.

To help focus the group discussions in this session, participants were presented with a fictional case study, described as follows:

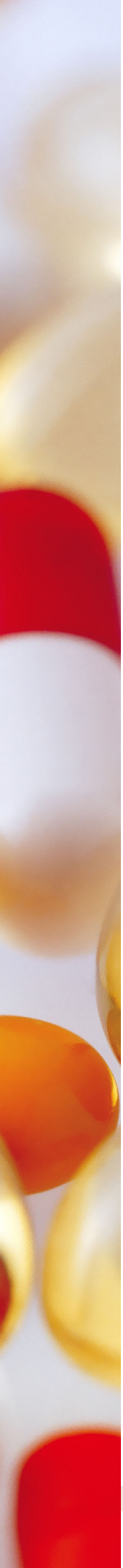
You know of a micro-size SME or an academic group that has managed to bring a promising novel antibiotic molecule – Remapsin – through the early stages of development. The antibiotic is intended for treatment of sepsis in children caused by multidrug resistant organisms. The finished drug would probably be placed in the 'Watch' or 'Reserve' group of antibiotics. Considering the key challenges to overcome in the stages following pre-clinical development (clinical phases 1-3; regulatory approval and market launch; manufacturing; access and distribution), what solutions or interventions would be needed in order to advance the drug through these stages, in a way that ensures equitable access, including in LMICs? Discussion in two groups – you may select the phases/challenges that best suit your expertise in the group.

The exercise was thus to discuss how to shepherd this molecule through the later stages in the pipeline, while taking into account equitable access and affordability.

Key highlights from the discussions

Among the key challenges identified in the group discussions when trying to move a molecule through the later stages were:

- First, many pointed out that the case description, even though inspired by an existing WHO TPP, would not be feasible to follow. In reality, it is impossible to develop an antibiotic for first use in children. This because the drug would have to be **approved and provided first for adults** before testing in children/ neonates and then expanding the indication.
- Several pointed out the need to **clearly define a target product profile** and the indication of the drug. Depending on whether it is intended to treat a wide range of paediatric infections or be narrowly focused on neonatal sepsis, the development pathway would differ.
- Challenges with the **lack of guidelines and a viable market** given the lower incidence of neonatal sepsis in HICs. Paediatric indications of new drugs are supposed to be developed but, in many cases, companies do not do this.
- A challenge is **conducting neonatal clinical trials** across different patient populations, including different ethnicities, ethical aspects, and the cost associated with bigger trial populations. The lack of diagnostics, especially in LMICs, can be an additional problem of clearly defining a neonatal sepsis case.
- **Challenges would differ in different settings,** as LICs and HICs, and in fact different regions, each have their different set of challenges when it comes to both development of a drug and access to it.
- The challenge of **how to define equitable access**. The concept involves many different aspects such as affordability, availability, timely access, global access, and access to quality antibiotics. The question about local capacity to ensure equitable distribution must also be considered.
- **The need for stewardship can create difficult ethical problems,** when restrictive use and price can excessively limit access.



Among the potential solutions discussed in the groups to address some of the challenges along the different stages were:

- Given the challenges in even interpreting the TPP, participants pointed out that **TPPs need to be clearly** written with no ambiguity, and that it was key to have 'the right people in the room' to give feedback before it is finalised.

- It would be important to **identify the key countries needing the drugs** and to enable setting up clinical trial networks in LMICs, which would also lower trial costs.

- **Pooling demand globally and establishing regional procurement, and local production.** This to understand the total patient population that would be in need of the drug, and where these patients are localised. Production, with proper conditions, could be out-licensed to middle income countries with production capacity.

- Understanding the demand side better could help facilitate **pooling of governmental (HIC and LMIC) and philanthropic funding** including also LMICs governments early on to create ownership.

- **Investigating how a public or non-profit entity** (such as GARDP, DND*i*, or MMV) could be engaged in discovery and development of needed drugs may be the way forward, as an alternative to solely provide incentives to the pharmaceutical industry. Costs of each path should be compared.

- To address the issue with companies not developing paediatric indications of new antibiotics, an option could be to **explore march-in rights** for drugs that are not being developed within a certain time-frame. This and other conditions could for example be considered when drugs are registered.

- Important **lessons on equitable access must be learned from COVID.** A licence and access pool may be needed for new antibiotics, and SECURE was mentioned as an important initiative to test an access model. In the current debate about pull incentives for antibiotics, access considerations are usually lacking or very weak.

- The case study also generated discussions about the **importance of communication**. To ensure precision in language within the research community, but also simplicity when talking to policy makers to ensure the messages are well understood and to formulate the problem as something that can be solved.

Trying to summarise the proposed solutions, and bringing the session discussions into a consistent pathway, led to the development of a regional-based model:

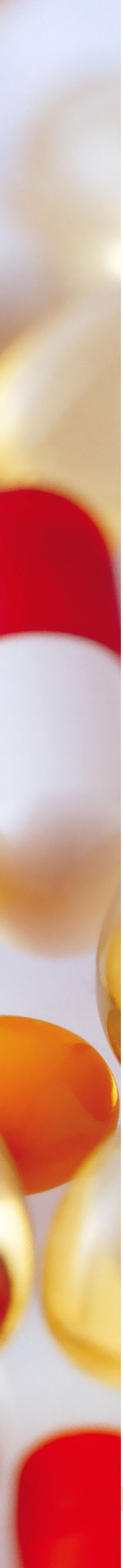
- Moving away from the current "global north"-first model, and exploring if a new drug **could first instead be developed for and by another region.** The example of, Ravidasvir, an antiviral developed by DNDi was highlighted[2]. DNDi established an innovative partnership between the Ministry of Health in Malaysia, the Ministry of Public Health in Thailand, Pharco Pharmaceuticals in Egypt, and Pharmaniaga in Malaysia to jointly develop ravidasvir that would be made accessible and affordable to all.

- This would include **involving regional stakeholders, including e.g.** the Africa CDC, the emergent ASEAN CDC, the African AMA, the AU and many others, to identify local needs (to match with promising molecules), coordinating clinical trials, setting up networks of (local) manufacturers, coordinating procurement, as well as developing integrated stewardship/access policy guidance. Building regional clinical trials and regional collaboration on registration and production can also make the development cheaper.

- **To coordinate the work, a regional coordination body** might be needed to create an end-to-end knowledge model. The aspect of investing for longer lasting solutions (e.g. regions dictating their own legal licensing frameworks) and building a critical mass at regional level to generate longer term spin-off innovation and manufacturing was also raised.

- On access and stewardship, the key takeaway is that there is a need to move away from HICs "giving access" to LMICs, and instead shift the power balance, **to build local ownership and encourage initiatives and partnerships.** This would likely also increase chances for success and sustainability. While striking a balance between access and stewardship will still be a challenge, it was emphasised that for any model to work, local ownership and locally thought-out solutions are what is needed.

2 https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00357-0/fulltext



Reflections on the role of public and not-for-profit actors, involvement of LMICs and key messages for policy makers

In a final session of the workshop, participants reflected on a few key questions regarding the role of public and not-for-profit actors and entities, as well as the key question of the involvement of LMICs. The discussion also involved a short brainstorming around key messages that should be shared with policy makers.

Which are the low-hanging fruit vs. more complex solutions, or rather short/medium term solutions?

Applying for research funding in antibiotic discovery can be a long and cumbersome process and chances of projects being rejected are quite high. When a proposal is rejected from a funder it can be that the same proposal is presented to a different funder prior to implementing the feedback received from the first application process. This causes (i) further delays in improving critical steps in advancing antibiotic research, and (ii) higher chances that other research groups will repeat the same mistakes.

Among the proposals put forward by the participants to overcome this challenge were: (i) funders to act as "honest brokers", incentivising collaboration between research groups, and (ii) create a repository with key information for antibiotic development.

(i) Funders to act as "honest brokers"

Project reviewers and funders, such as CARB-X, sit on information that is not made available to applicants, due to a confidentiality agreement with the involved parties. Nonetheless, in order to synergize efforts and potentially accelerate the discovery process, such funders can take on the responsibility to promote and incentivize connections and/or cross-program portfolio between both groups working on similar and/or complementary projects, and to other funders. As one of the participants mentioned, "generating ideas is easy, but implementing them is harder". On the other hand, research groups should be open to share knowledge and expertise for the overarching goal of sustainably implementing high-quality antibiotic research and development. The latter could be achieved by both promoting openness and transparency, as well as by adding conditions to fundings.

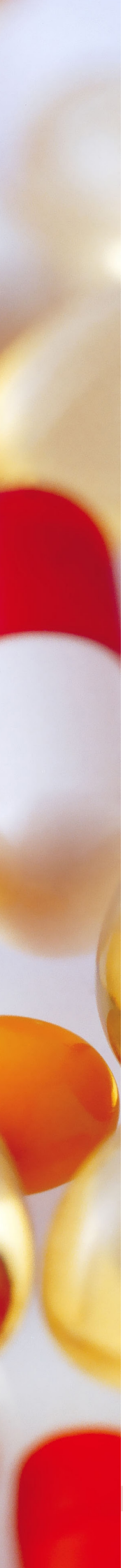
(ii) Create a repository with key information for antibiotic development

Among the major advantages of involving public and not-for-profit actors in the antibiotic development process are (a) making publicly available key information from failed/rejected projects, including institutional R&D memories and strains, particularly antibiotic producers, as well as (b) creating a public guide, roadmap or handbook describing do's and don'ts as a living document, comprehensive of needs of different models for different R&D stages as well as pitfalls to avoid in antibiotic discovery. This would help upcoming and even ongoing projects to not repeat the same mistakes, and it could troubleshoot potential roadblocks. Additionally, establishing a dynamic network between funders, research groups, developers, and experts will be conducive to (i) identifying AMR-specific funding, (ii) matching calls with experts, (iii) creating a roadmap guiding each involved party.

What actors/entities would be best placed to work on operationalizing solutions? What is needed to make the proposed solution sustainable?

The participants reflected on actors and/or entities which already have and/or could potentially have a key role in implementing the proposed solutions.

Most of the stakeholders named during this session were already mentioned in previous group discussions. As for the solutions exercise, regional actors such as the Africa Centres for Disease Control and Prevention and The Association of Southeast Asian Nations were broadly mentioned. From a global perspective, the World Health Organization (WHO) and the United Nations General Assembly High-level meeting on AMR in 2024 (UNGA HLM 2024) were key elements in the discussion. The participants acknowledged WHO as an important stakeholder, especially when it comes to drafting and releasing target product profile (TPP) for supporting and stimulating the development of antibiotics urgently needed. The approach taken by CARB-X, in developing its guide to stewardship and access plans should be taken into account and lessons should be learned from this initiative,as well as other initiatives such as GARDP, a non-profit R&D organisation, and ENABLE 2.



It was proposed that beyond creating new entities, additional resources could be allocated to existing organisations, somewhat expanding their mandate and bridging the gaps. As for the UNGA HLM 2024, the summit could represent a valuable opportunity for further involving LMICs in taking leadership and building a global alliance of developed and developing countries.

Finally, it was concluded that, in order to have a clear picture of all actors involved in the different steps of antibiotic R&D, experts could build a public roadmap listing the names of the entities involved along the pipeline, as well as the intended short- and longer-term targets.

What elements discussed at this workshop do you think are the most important for policymakers to know about?

- **Funding:** One key message that is important to convey to policy makers is the need for more funding, especially for drug discovery. Such funding should have stricter conditions and specific support, with a substantially greater degree of coordination. Additionally, in order to better link funding to actions, an improved approach in estimating the cost of AMR interventions is needed.

- **Ownership/accountability:** Governments and policy makers need to own the processes and problems, and therefore the solutions. Hence, in order to address the solutions, it is fundamental that governments understand the long-term outputs from drug discovery (up to 10 years), in relation to their political mandate (can be in office for as little as five years).

- **Narrative: Communication is key, especially when engaging policy makers.** The AMR narrative needs more clear examples and stories from patients whose lives have been critically affected by AMR. AMR, in contrast with other health related issues and diseases, is a longer-term challenge. Hence longer-term solutions are needed. One participant cautioned against communicating AMR as an emergency, as it risks leading to an emergency fatigue. The narrative should lean towards a positive, longer-term oriented message (e.g. how to create capacity building), while using innovative, simple, and effective communication platforms.

How can we better involve LMICs in this initiative?

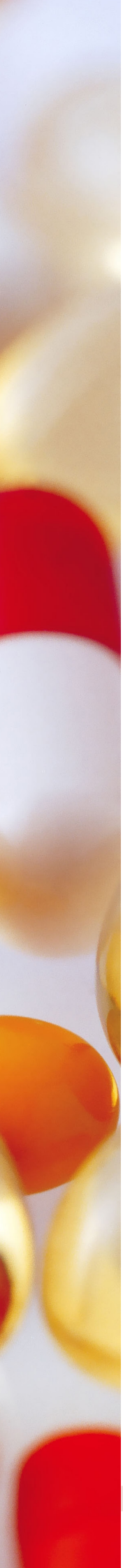
One important prerequisite to involve LMICs in the REMAAP initiative is to understand and address the issue of equity, both in terms of burden of AMR and access to antibiotics. A first step could be to investigate the manufacturing capacity (for medicines and vaccines) of the targeted LMIC, and rapidly build on the existing initiatives to create additional capacity at country- and regional levels. For example, as there are increasingly clinical trial sites in LMICs, it will likely increase both the access to more patient populations as well as the buy-in from such countries. Notwithstanding that if the clinical trials are conducted by an external entity, it is paramount that the tested country/population has shared ownership. Currently there are a few actors working to build coalitions and partnerships in LMICs, such as the Fleming fund, Wellcome Trust, ReAct and GARDP. However, to better understand the needs of LMICs, their diverse voices should be part of the policy processes and debates. Partnerships must be built and policy makers need to realise and be convinced that they need to build efficient management to improve the overall health system and help setting priorities.

Key highlights and takeaways with proposed messages to be taken forward

The workshop brought together leading experts in the field of antibiotic R&D, with a particular focus on the early stages. Through participants' individual contributions and ideas generated in group discussions and exercises, a wide and rich landscape of challenges and potential solutions emerged, particularly concerning antibiotic discovery. Overall, it was clear from the discussions, that the underlying causes and effects of the different challenges are often intertwined.

The complexity and scope of various types of challenges in the early stages (not least those characterised as structural are not always well understood, whether in the AMR community or among policy makers. Understanding these challenges is not only essential for the experts and stakeholders directly involved in the research, but it is also a prerequisite for identifying appropriate solutions from a policy perspective.

As reflected by the workshop discussions, some of these solutions will involve alternative models (in the form of revised structures and financing) to improve the progress and outcomes also in the later stages of



R&D, and to ultimately improve the overall success of innovation and access to new antibiotics.

While time was not sufficient during this workshop to more fully flesh out such models or solutions, it is nevertheless important to identify the common traits and core elements of messages that can be conveyed in a simple manner to policy makers, in order to move the needle and more effectively advance early-stage research.

For the sake of policy messages to take forward, among the recurrent themes discussed during the workshop, a few key problem areas as well as emerging elements important for developing solutions to persistent problems in the early R&D stages can be identified.

These areas are here presented together with **a set of proposed policy recommendations as follows:**

1. Increased governmental ownership of the issue & political leadership required to address the R&D challenges

Political leadership to address the challenges in early antibiotic R&D is currently insufficient. Governments and policy makers often lack insight into the required funding needs, and how to target funding to the different needs within this phase. Additionally, it is a challenge that the multinational and long-term nature of drug development and the long-term funding predictability that it requires, is poorly understood.

Suggested ways forward:

- Governments and policy makers should seek to deepen their understanding of the complexity of the antibiotic R&D process, the constraints of the current market model and the consequences for public health, as well as the key role that public funders can play. This should enable governments to increasingly own the processes and problems, and thereby also more effectively contribute to the solutions.
- Global alliances and ensuring representation of LMICs when developing solutions is paramount for sustainability in access to and stewardship of new antibiotics.

2. Strengthened global coordination and exchange of knowledge & expertise

The antibiotic discovery field suffers from fragmentation and lack of coordination, collaboration and knowledge-sharing between research groups. This leads to repetition of mistakes, a waste of resources and time, and fewer molecules likely to move forward.

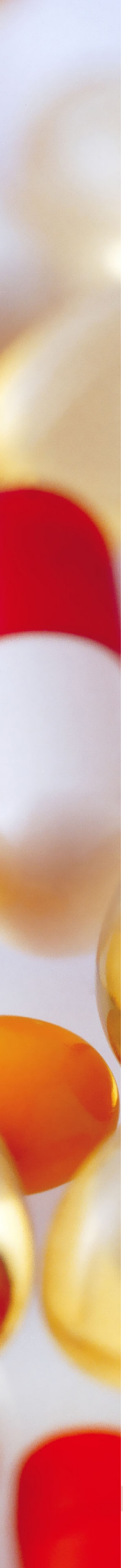
Few research entities (especially academic) engaged in discovery and early R&D stages have a full 'end-to-end' understanding of the entire R&D process - from early discovery to drug development and patient access. Furthermore, academic research incentives (e.g. to publish work in prestigious journals) are not well-aligned with drug discovery and public health-driven research agendas.

Suggested ways forward:

- New and existing early-stage research funding and structures should demand and enable knowledge- and data sharing (including of negative data) between experts, as well as providing support and incentives for researchers to take their research to the next phase.
- Existing actors in the field such as ENABLE2 (preclinical research), CARB-X (funder of pre-clinical and some phase 1 R&D) and GARDP (focus is clinical R&D with Discovery and Access programmes) operating in different R&D stages should be better and more sustainably supported. Alignment and collaboration between their respective mandates should be strengthened.
- To overcome the fragmentation problems, one should consider establishing a sustainably funded centralised coordination entity or hub (for example a network of R&D centres or a consortium of existing actors to coordinate research and discovery) to maintain expertise, equipment, and potentially funding. LMICs partners should be part of such an entity to ensure global health needs are met and access to the end product is planned for.

3. Provide longer-term, sustainable, targeted and coordinated funding

Contrary to the dominating narrative, funding for early antibiotic R&D is still limited, unpredictable, and often not sufficiently long-term Only few R&D funders still focus on antibiotics and AMR. This creates uncertainties that have a discouraging effect on attracting and maintaining researchers in the field. Highly valuable expertise, structures and access to equipment risk being lost when funding ends prematurely. The lack of coordination among funding agencies also creates inefficiencies in the application processes. The lack of more targeted funding and funding conditions (e.g. to enable equitable access, knowledge and data-sharing) also hinder progress.



Suggested ways forward:

- To yield better results funding must be made long-term and predictable to maintain expertise, structures and institutional memory in the field incl. by funding entities rather than short-term projects.

- Acting as "honest brokers", a consortium of funders (governments and organisations) can coordinate funding efforts to identify gaps, and require more collaboration and information exchange between research groups.

- Following the lead of the few R&D funders still focusing on AMR, more funders should include conditions to ensure global access to end products and data sharing, also covering early-stage funding. Further exploring is needed of where such conditions are best placed to require public health friendly IP management such as licensing (e.g. through a licence and access pool) and use of open knowledge systems.

- Alternative academic incentives to that of publication in scientific journals should also be introduced via a new coordination entity, designed to promote knowledge- and data-sharing (inclusive of failed projects and negative data), with the aim to solve the most critical scientific problems.

4. Expand the use of public and not-for-profit models in discovery and early stages of R&D

The commercial prospects of new antibiotics are uncertain. New antibiotics will likely have small markets and/or low or uncertain profit margins. This commercial problem is even more pronounced in poorer countries where prices will have to be lower, and for formulations for smaller patient groups like children. Public and not-for-profit funders and developers have been shown to have comparative advantages in advancing antibiotic R&D, especially for areas with lower commercial interest, and for countries that face problems with limited access to new antibiotics. They offer an alternative pathway to the traditional approach where the drug is first developed and marketed in HICs only to "trickle down" to low- and middle-income countries many years later.

Suggested ways forward:

- The role of public and non-for-profit entities should be expanded into the discovery and preclinical phases of antibiotic R&D, and should be supported by pooled funding from philanthropists and governments including from LMICs to broaden ownership.

- A cost and efficiency comparison between non-profit pathways and other ways to finance drug development (e.g. through incentives to the private pharmaceutical sector) would be beneficial.

5. Build stronger regional institutions and networks

Exploring models that can more appropriately address the diverse sets of challenges related to antibiotic R&D and access should take into account variations across different geographical regions. A key benefit of regional approaches is to build local ownership, initiatives, leadership, and sustainability, hence moving away from HICs "giving access" to LMICs, and instead shifting the power balance, to build local ownership and encourage initiatives and partnerships.

Suggested ways forward:

- Strengthen collaboration and support for new and existing regional institutions and networks such as regional CDCs (Africa CDC, the emergent ASEAN CDC, etc.) involved in antibiotic R&D and responsible for identifying local needs, coordinating clinical trials, networks of manufacturers, regulatory procedures, procurement, production, as well as integrated stewardship policy guidance.
- Additionally, production, with proper conditions, could be out-licensed to middle income countries with production capacity to create ownership.

- Multiple regions can operate in parallel and in collaboration in a "trans-regional" global model and regional coordination bodies can be expanded for building capacity to create an end-to-end knowledge for antibiotic R&D.

The overarching goal of antibiotic R&D should be that **effective antibiotics become affordably, sustainably, and equitably accessible to everyone in need.** Whether this will succeed will depend on whether and how drug development is financed and coordinated. To overcome current fragmentation and misaligned incentives in antibiotic R&D policy makers at global, regional, and national level should make use of all relevant platforms and processes to accelerate progress towards ensuring a more coherent response.

Considerations for the next steps of the REMAAP initiative

The first workshop in the REMAAP initiative has contributed to a comprehensive landscaping analysis of roadblocks and potential solutions by a diverse group of experts towards building evidence for alternative R&D models and generating interest and commitment amongst policymakers and funders to support such models. In consultation with participants of the first workshop, the intention is to share a brief summary of the key findings amongst influential opinion leaders, media, civil society, and policymakers.

While the first workshop has focused on important aspects in the early R&D stages, forthcoming meetings will include a deep-dive on the later stages of R&D and access. The collaborative analysis and dialogue-based process of the REMAAP initiative is expected to continue to be rolled out in a phased manner, with the outcomes of each step informing the following activity.

To inform the next steps, the participants of the first workshop were asked to provide input on **areas that have not been sufficiently discussed or addressed that could be taken forward in the next workshop**. Key points highlighted in this discussion were:

- **Clinical trials:** Clinical trials phases, clinical trial networks, capacity building in LMICs and financing. The participants briefly touched upon the need to have better estimates of clinical trial costs.
- **Diagnostics:** The role of diagnostics (e.g. when it comes to using narrow spectrum antibiotics), access and availability of diagnostic tools (especially in LMICs), as well as diagnostics for clinical studies, those used post-approval routinely on the ground to guide stewardship.
- **Access:** How can access to antibiotics and diagnostic tools be further secured? Some organisations are already working on that (e.g. CARB-X, GARDP (Shionogi), MSF, SECURE) but what are the very real challenges, for example in terms of cost of goods and the establishment of appropriate manufacturing capacity?
- **Wider engagement:** REMAAP can represent a platform that engages, at different stages, multi-sectoral stakeholders, including policy makers (government, parliamentarians) and the private sector (SMEs and big pharma), from multiple geographical regions, especially from those countries where the burden is higher. Thus, organising one of REMAAPs workshops in critical regions could facilitate wider participation from highly AMR-affected regions. Additionally, it would be valuable to involve actors, such as product development partnerships, e.g. DNDi, which although operating in other areas than antibiotics could share their valuable experiences.

ReAct highly appreciates the input and recommendations and will take these recommendations into consideration in the planning of the next steps of the REMAAP initiative. Forthcoming planning will also be informed by resources available for a continuation of the REMAAP initiative.

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