Study on bringing AMR Medical Countermeasures to the Market

Final Report

HADEA/2021/OP/0005

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The results of the Study on “bringing AMR MCM to market” are presented in two reports:

- An Interim report, which includes a mapping of existing AMR MCM & those in development, a gap analysis and a methodology for prioritising AMR MCM in development.

- A Final report, which includes (i) the results of a survey on needs and priorities, challenges and potential roles of HERA and (ii) an analysis of options for HERA to support development of and access to AMR MCM.

1. Abbreviations

3GCREB	Third-Generation Cephalosporin-Resistant *Enterobacteriaceae*
ADME	Absorption, Distribution, Metabolism and Excretion
AI	Artificial Intelligence
AMC	Antimicrobial consumption
AMR	Antimicrobial Resistance
APA	Advance Purchase Agreements
API	Active Pharmaceutical Ingredient
AST	Antimicrobial susceptibility testing
B2B2B	Bench to Bedside to Business and Beyond
BARDA	Biomedical Advanced Research and Development Authority (US)
BCG	The Boston Consulting Group
BEAM Alliance	Biotech companies from Europe innovating in Anti-Microbial resistance research
BIRAC	Biotechnology Industry Research Assistance Council
BMBF	German Federal Ministry of Education and Research *(Bundesministerium für Bildung und Forschung)*
BMG	German Federal Ministry of Health *(Bundesministerium für Gesundheit)*
CARB-X	The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CDC	Centres for Disease Control and Prevention (America)
CEPI	Coalition for Epidemic Preparedness Innovations
CHAI	Clinton Health Access Initiative
CJEU	Court of Justice of the European Union
COMBACTE	Combatting Bacterial Resistance in Europe
CRAB	Carbapenem-resistant *Acinetobacter baumannii*
CRE	Carbapenem-Resistant *Enterobacteriaceae*
CRPA	Carbapenem-Resistant *Pseudomonas aeruginosa*
CTIS	Clinical Trials Information System
DG HERA	Directorate-General Health Emergency Preparedness and Response Authority
DG SANTE	Directorate-General for Health and Food Safety
DHSC	Department of Health and Social Care (UK)
DNDi	Drugs for Neglected Diseases Initiative
DRG	Diagnosis-related group
DRIVE-AB	Driving re-investment in R&D and responsible antibiotic use
Dx	Differential diagnosis

DZIF	German Center for Infection Research
ECDC	European Centre for Disease Prevention and Control
ECRAID	European Clinical Research Alliance on Infectious Diseases
ECRIN	European Clinical Research Infrastructure Network
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	The European Food Safety Authority
EFSI	European Fund for Strategic Investments
EIB	European Investment Bank
EIC	European Innovation Council
EIF	European Investment Fund
EMA	European Medicines Agency
ENABLE	European Gram-negative Antibacterial Engine
ENPV	Expected Net Present Value
EOI	Expression of interest
EPHA	European Public Health Alliance
ESI funds	European Structural and Investment Funds
EU	European Union
EU27	The 27 European Union Member States
EUR	Euro
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
G20	Group of Twenty
G7	Group of Seven
GAIN Act	Generating Antibiotics Now Act
GAMRIF	The Global AMR Innovation Fund (UK)
GARDP	Global Antibiotic Research and Development Partnership
GBP	British Pound Sterling
GDP	Gross Domestic Product
Gen.	Generation
GLOPID-R	Global Research Collaboration for Infectious Disease Preparedness
HHS	United States Department of Health and Human Services
HIV	Human Deficiency Virus
HTA	Health Technology Assessment
ICMRA	International Coalition of Medicines Regulatory Authorities

IMI	Innovative Medicines Initiative
INCATE	Incubator for Antibacterial Therapies in Europe
INSERM	National Institute of Health and Medical Research (France)
IPPS	Inpatient Prospective Payment System
IPR	Intellectual Property Rights
IVD	*In-vitro* diagnostic
JAMRAI	Join Action on Antimicrobial Resistance and Healthcare-Associated Infections
JPA	Joint Procurement Agreement
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
LMIC	Low- and middle-income countries
LS	Lump-Sum
LSMER	Lump-Sum Market Entry Reward
MAH	Marketing Authorisation Holder
Max	Maximum
MBR	Milestone-Based Reward
MCM	Medical Countermeasure
MDR	Multidrug Resistance
MDR-NG	Multidrug Resistant *Neisseria gonorrhoeae*
MER	Market Entry Reward
MERino	Small Market Entry Reward (for 2 years) combined with revenue guarantee (for 4 years)
Min	Minimum
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Member States
ND4BB	New Drugs 4 Bad Bugs
NGS	Next Generation Sequencing
NHS	National Health Service
NIAID	National Institute of Allergy and Infectious Diseases (USA)
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research (UK)
NPV	Net present value
NTAP	New Technology Add-on Payment
OECD	Organisation for Economic Co-operation and Development
OH	One Health
OMV	Options Market for Vaccines

P / Ph	Phase
PASTEUR Act	Pioneering Antimicrobial Subscriptions to End Up surging Resistance Act
PCR	Polymerase Chain Reaction
PDP	Product Development Partnership
PHAS	Public Health Agency of Sweden
PrIMAVeRA	Predicting the Impact of Monoclonal Antibodies & Vaccines on Antimicrobial Resistance
QALY	Quality-Adjusted Life Year
R&D	Research and Development
REPAIR Impact Fund	The Replenishing and Enabling the Pipeline for Anti-Infective Resistance Impact Fund
RG	Revenue Guarantee
SEK	Swedish krona
SME	Small and Medium-sized Enterprises
spp.	Species
SRIA	Strategic Research and Innovation Agenda
STEDI	Spectrum, Transmission, Enablement, Diversity, Insurance
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
TEE	Transferable Exclusivity Extension
TEEV	Transferable Exclusivity Extension Voucher
TFEU	Treaty on the Functioning of the European Union
TLV	Reimbursement authority of Sweden
TPP	Target Product Profiles
TRL	Technology Readiness Level
UK	United-Kingdom
UKRI	UK Research and Innovation
UNEP	United Nations Environmental Programme
US / U.S. / USA	United States of America
USD	United States Dollar
VRE	Vancomycin-resistant *Enterococci*
WHO	The World Health Organisation
WOAH	The World Animal Health Organisation

2. Abstract

Background: This report focuses upon the prospective roles and responsibilities of the European Union (EU); specifically in supporting new developments in the pipeline and ensuring access to Antimicrobial Resistance (AMR) Medical Countermeasures (MCMs) brought to market.

Methods: Primary-data collection was carried with over 115 stakeholders actively engaged in the AMR space. The outputs of these surveys and interviews provided an understanding of the key market needs and expectations for DG HERA's action.

Findings and results: Survey respondents expect DG HERA to play an important role in the implementation of a new pull mechanism. The simulation carried out under this study suggests that this can be achieved with pull incentives including revenue guarantees.

Survey respondents also expect DG HERA to contribute or complement existing financial push incentives. An additional USD 60 to 100 million per year from the EU would help drive innovation in AMR from the early developmental stages and increase the pipeline of new vaccines, diagnostics, and treatments against key-priority pathogens.

Finally, survey respondents also noted that DG HERA could assist with the provision of non-financial support, including knowledge sharing, dissemination of best practices and capacity building for Member States for which further analysis and investigation is needed.

Extrait

Contexte : Le présent rapport analyse les responsabilités et les rôles futurs de l'Union Européenne (UE) dans ce cadre de l'accompagnement du développement de Contre-Mesures Médicales (CMM) en matière de Résistance aux AntiMicrobiens (RAM), tout en assurant leur accès au marché.

Méthodes : Une collecte de données a été réalisée auprès de 115 participants actifs dans le domaine de la RAM. Les résultats de ces enquêtes et entretiens ont permis de comprendre les principaux besoins du marché et les attentes quant-au rôle de la DG HERA.

Observations et résultats : Les participants à l'étude estiment que la DG HERA devrait jouer un rôle important dans la mise en œuvre de nouvelles interventions de type *pull*. La simulation élaborée dans le cadre de cette étude indique que ceci pourrait être atteint, par des incitants financiers de type *pull*, incluant un mécanisme de garantie des revenus.

Les participants à l'étude ont aussi suggéré que la DG HERA puisse compléter les incitations financières de type *push* existantes. 60 à 100 millions d'USD supplémentaires par an provenant de l'UE favoriseraient l'innovation dans le domaine de la RAM, ceci dès les premiers stades de développement et étofferait le portefeuille de nouveaux vaccins, diagnostics et traitements contre les pathogènes prioritaires.

Enfin, les participants à l'étude ont noté que la DG HERA pourrait aussi coordonner les actions de supports non financiers, y compris le partage de connaissances, la diffusion des meilleures pratiques et le renforcement des capacités pour les États membres, un champ d'action pour lequel une étude et une analyse complémentaire plus approfondie est requise.

3. Executive summary

3.1. The AMR threat and DG HERA's mission to address the health emergency

The coming years will be of high importance to ensure global awareness and preparedness for the fight against antimoicrobial resistance (AMR). Results from a predictive statistical model published in The Lancet in 2022[1], estimates between 3.62 to 6.57 million deaths associated with antibiotic resistant bacteria in 2019, including 1.27 million deaths directly attributable.

Despite this public health threat, the number of Medical Countermeasures (MCMs) available on the market is insufficient even for WHO's most critical pathogens (Figure 1). The R&D pipeline is still concentrated at the early stages, with approximately 68% of those treatments in the pre-clinical phase or in phase I (interim report[2]).

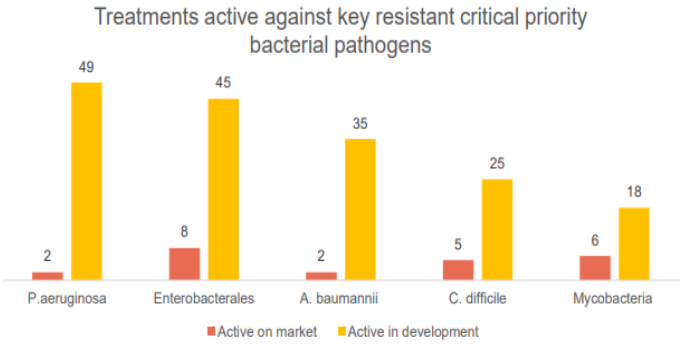


Figure 1- Comparison of treatments for bacterial pathogens considered Critical Priority according to WHO

The challenge to bring more AMR MCMs to the market is the result of a complex landscape: developers face significant scientific challenges, costly R&D processes, and low profitability due to controlled use and stewardship measures – which are an important measure to contain the spread of AMR.

In this context, the public sector has an important role to play to stimulate the development and access to market of new AMR MCMs by enabling better coordination and providing business and financial support. The Commission has established in 2021 the Directorate General Health Emergency Preparedness and Response Authority (DG HERA) with the mission to prevent, detect, and rapidly respond to health emergencies such as AMR. With its mandate, DG HERA is well positioned to address this issue, in complement and coordination with other initiatives of the Commission under the EU One Health AMR Plan against AMR.

This final report identified and analysed options for action that may be considered feasible and effective to bring more AMR MCMs to market through incentivising the R&D pipeline, and ensuring accessibility once launched with a specific focus on antimicrobial treatments for bacterial infection.

3.2. Key options of actions identified

Following a thorough literature review (interim report), complemented by surveys and interviews with 22 EU Member States and more than 90 AMR stakeholders, three recommendations were identified for the role of DG HERA:

1. Coordinate and support the implementation of pull incentives

2. Coordinate and contribute to financial push incentives

3. Ensure coordination, knowledge sharing and provision of non-financial support. This includes the dissemination of best practices and capacity building for Member States

3.3. Findings and results

Pull incentives focus on rewarding successful antimicrobials by making antibiotic R&D projects financially attractive at and after market approval. In this study, the simulation of four types of pull

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

[2] Interim Report accessible at: https://op.europa.eu/en/publication-detail/-/publication/341cf78c-bd6a-11ed-8912-01aa75ed71a1/language-en/format-PDF/source-281956123

mechanisms of different monetary sizes to incentivise antibiotic developers resulted in the shortlisting of **seven key pull options for action.** The selection was based on their ability to make projects profitable while ensuring the best allocation of public funding.

A key finding of this simulation was that only the largest incentives were able to positively impact developer profitability of projects at pre-clinical stage (at least a global payment of USD 4 billion via Market Entry Rewards). This suggests the need for reinforcing push funding for early-stage research, which reduces the size of pull incentives. Moreover, the simulation showed that strong pull effects as from phase I can be achieved through the combination of smaller pull incentives with other interventions (such as milestone-based rewards). Therefore, the selected mechanisms focused on pull models impacting developers from phase I onwards considering their effect on profitability and their funding cost. The preliminary feasibility of each pull option in an EU context was assessed both from a legal and a financial perspective. The table below, summarises the key takeaways.

Table 1: Pull mechanisms: Proposed policy actions that can boost the development and incentivise more AMR MCMs to the market

Pull mechanism	Description	Proposed interventions in USD	Rationale for selection: Impact and cost per MCMs in USD	Legal framework
Revenue Guarantee (RG)	Payments operate as complements to ensure a yearly revenue value. Consists of 10 yearly payments starting from the year of market approval.	RG at 150M/year	Makes 50% of projects profitable at the start of phase I. Public expenditure is estimated in 750M over 10 years per MCM.	Joint Procurement Agreement (JPA) / Competitive dialogue or competitive procedure with negotiations.
		RG at 100M/year	Makes almost 25% of projects profitable at the start of phase I, hence requires being combined with Milestone-Based Reward at 60M. Public expenditure is estimated in 421M over 10 years per MCM.	
Small Market Entry Reward combined with revenue guarantee (MERino)	Small market entry reward with similar sizes as the RG but paid over a shorter time frame (6 years): higher payments in the first 2 years, and smaller ones in the following 4 years.	MERino at 2x 500M + 4x 125 M	Makes more than 50% of projects profitable at the start of phase I. Public expenditure is estimated in 1321M per MCM.	JPA / Innovation Partnership or pre-commercial procurement for the market entry reward.
		MERino at 2x 330 + 4x 85M	Makes close to 50% of projects profitable at the start of phase I. Public expenditure is estimated in 821M per MCM.	
		MERino at 2x 250M + 4x 50M	Makes about 30% of projects profitable at the start of phase I. Public expenditure is estimated in 521M per MCM.	
Milestone Based Reward (MBR)	Milestone-Based Reward awarded at the successful completion of Phase I to give a financial gain (profit) to the successful developer, not simply covering a percentage of costs as grants/push incentives do.	Phase I Reward at 60M	Makes slightly more than 25% of projects profitable at phase I, and 75% of projects profitable at phase II. In addition, it can be combined with RG or MERino for generating stronger pulling effects and/or reduce the necessary size of RGs and MERinos to obtain any given effect profitability effect. Public expenditure is estimated in 169M per MCM (taking into account the need to provide more than 1 Milestone-Based Reward to get one antibiotic to the market).	EU grant in view of pre-commercial procurement on MS level or JPA[3].
LumpSum Market Entry Reward	*Large size payment received at once by the developer, fully delinking their revenue from market sales.*	*LSMER 1B*	*This intervention was excluded due to its high risk for public payers in case of a potential loss of therapeutic efficiency in the first years of launch.*	*Difficulties to justify the proportionality principle.*

The initial pre-feasibility assessment determined that all options may be implemented through existing EU regulations and/or financial frameworks – notwithstanding some notable restrictions and considerations that require further in-depth investigation. Of particular importance is the consideration that pull incentives should be considered as true procurement transactions, not grants[4].

[3] Where the legal situation is less certain due to the question of whether pre-commercial R&D constitutes a genuine procurement, a sound alternative would be for the EU to issue a grant under the Horizon Europe Regulation to research centres which would then carry out pre-commercial transactions at a national level.

As both EU and Member State contributions will probably be required, the existing Joint Procurement Agreement (JPA) mechanisms as set out in Regulation (EU) 2022/2371 of 23 November 2022 on serious cross-border threats to health may be relied upon to ensure guaranteed access to new developments.

Other considerations in relation to the implementation of a JPA include:

- The 2014 model JPA already proposes a very robust governance mechanism between the EU and the Member States that can be leveraged upon and may be adapted to cover additional points, such as the inclusion of a threshold to ensure a minimum buy-in and participation from the Member States.
- When relying on a JPA, the public procurement rules in the EU Financial Regulation apply, which is positive as the incentive should constitute procurement transactions. The most relevant types of public procurement procedures are a "competitive dialogue" a "competitive procedure with negotiation" and, if the solution does not exist on the market or as a near-to-market development activity, an "innovation partnership".
- The agreements to be concluded with the MCM suppliers following the procurement process can and must foresee the necessary stewardship and access clauses and, in some cases, the transfer of Intellectual Property Rights (IPR) and the clawback of funding if the supplier does not sustain its R&D and exploitation efforts without a sound objective reason.
- Funding coming from Member States must comply with State aid rules. If the funding is awarded after a procedure with a high degree of competition, State aid rules may become less relevant. The same is true if the Member State funding is brought under exclusive management of the EU, or the funding is not provided to the MCM supplier directly but is attributed via (a consortium of) research centres. This is relevant when the funding provided to the latter is destined exclusively for pre-commercial R&D.
- The fundamentals of proportionality and efficiency must be respected, as they are overarching principles in EU budgetary and State aid regulations. As pull measures are in principle delinked from R&D costs, the presence of a market failure justifying the measure and its budgetary envelope should be based on sound evidence, such as the model presented in this study.

There is a broad agreement that **push funding** should complement the pull models above, acting where the pull models are least efficient: in the early phases of development. Our study shows that non-dilutive financial support at this stage is the preferred option by almost 80% of respondents covering industry, academia, organisations, and associations actively engaged in the AMR space

Based on our literature review, push mechanisms for AMR MCMs require an additional global investment ranging between 250M to 400M USD per year, which would consist of an EU contribution of around 60M to 100M USD considering a 25% EU share. The Swedish Public Health Agency[5] estimates that approximately 2/3 of this value should be dedicated to non-dilutive capital for developers and the remaining 1/3 for in-kind R&D support.

According to our study, incubators and accelerators are playing an important role in improving the assertiveness of AMR drug development process globally. The survey highlights that there is a perceived lack of public-guided coordination, within which DG HERA, with other Commission services and agencies, may have a role to better connect and inform relevant stakeholders.

From a legal standpoint, funding push mechanisms could be foreseen within the EU and the Member State budgetary and aid programme frameworks. This contribution can happen directly via calls for projects and/or through existing pipeline coordinators and fund distributors.

5 E. Baraldi, F.Ciabuschi, S.Callegari, O. Lindahl, Economic incentives for the development of new antibiotics, Report commissioned by the Public Health Agency of Sweden, 2019

Combinations of contributions across EU and non-EU based transnational projects in the field of AMR are also possible subject to conditions.

Finally, some additional considerations on further actions to support diagnostics and vaccines are briefly highlighted at a high level, for further investigation consideration in potential subsequent studies.

Synthèse

3.4. La menace de la RAM et la mission de DG HERA face à l'urgence sanitaire

Les années à venir seront d'une importance cruciale pour sensibiliser et préparer, au niveau mondial, la lutte contre les bactéries résistantes aux antibiotiques. Les résultats d'un modèle statistique prédictif publiés dans The Lancet[6] en 2022, indiquent qu'en 2019, entre 3,62 millions et 6,57 millions de décès sont associés à la RAM bactérienne, dont 1,27 millions de décès qui y sont directement attribuables.

Malgré cette menace pour la santé publique, le nombre de Contre-Mesures Médicales (CMM) disponibles sur le marché est insuffisant, même pour les pathogènes prioritaires listés par l'OMS (*Figure 2*). Le portefeuille de projets R&D est encore concentré dans les premières phases de développement, avec environ 68% de ces traitements dans les phases précliniques ou en phase 1 (*cf.* rapport intermédiaire[7]).

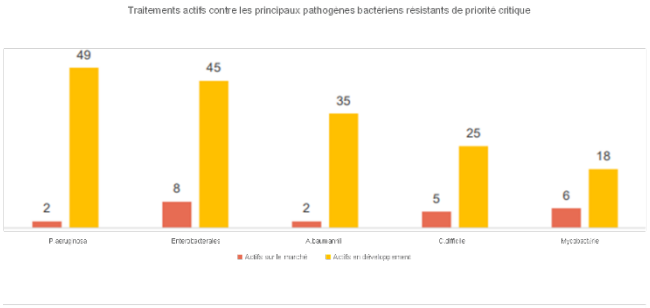


Figure 1 – Comparaison des traitements pour les pathogènes bactériens considérés comme des priorités critiques par l'OMS

Figure 2- Comparaison des traitements pour les pathogènes bactériens considérés comme des Priorités Critiques par l'OMS

La difficulté à mettre sur le marché des CMM en matière de RAM est le résultat d'un environnement complexe : l'industrie des antimicrobiens fait face à des défis scientifiques majeurs, à des processus de R&D coûteux, et à une faible rentabilité due à mesures de contrôle et de « *stewardship* », qui sont d'importance pour empêcher la propagation de la RAM.

Dans ce contexte, le secteur public a un rôle important à jouer pour stimuler le développement et la commercialisation de nouvelles CMM en matière de RAM, en assurant une meilleure coordination et en apportant une assistance commerciale et financière. La Commission a établie ne 2021 l'Autorité européenne de préparation et de réaction en cas d'urgence sanitaire (DG HERA) avec pour mission de prévenir, de détecter et de réagir rapidement aux urgences sanitaires telles que la RAM. Grâce à son mandat, la DG HERA est bien positionnée pour répondre à cette problématique, en complément et en coordination avec d'autres initiatives de la Commission dans le cadre du plan européen One Health AMR contre la RAM.

Le présent rapport a identifié et analysé des options d'intervention réalisables et efficaces pour mettre sur le marché un plus grand nombre de CMM en matière de RAM, ceci grâce au développement du portefeuille de projets R&D et en assurant l'accessibilité des traitements antimicrobiens contre les infections bactériennes après leur mise sur le marché.

3.5. Options d'action identifiées

À l'issue d'une revue détaillée de la littérature (*cf.* rapport intermédiaire), laquelle a été complétée par des enquêtes et des entretiens auprès de 22 États membres de l'UE et auprès de plus de 90 participants actifs dans le domaine de la RAM, trois types de recommandations ont été suggérées quant-au rôle de la DG HERA :

1. Coordonner et soutenir la mise en œuvre d'interventions de type *pull ;*

2. Coordonner et contribuer à des incitations financières de type *push ;*

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

[7] Rapport intermédiaire accessible par le lien: https://op.europa.eu/en/publication-detail/-/publication/341cf78c-bd6a-11ed-8912-01aa75ed71a1/language-en/format-PDF/source-281956123

3. Coordonner les actions de support non financier, le partage de connaissances, la diffusion de meilleures pratiques et le renforcement des capacités pour les États membres.

3.6. Observations et résultats

Les mesures d'incitation de type *pull* visent avant tout à supporter financièrement le développement d'antimicrobiens performants en rendant les projets de R&D financièrement soutenables jusqu'à l'approbation pour la mise sur marché. Après avoir simulé 4 types de mécanismes *pull* de différentes envergures financières, cette étude a établi une première liste de **7 principales options d'action de type *pull*.** Le choix se fonde sur la capacité à rendre les projets rentables tout en assurant la meilleure efficience d'utilisation des fonds publics.

L'une des principales conclusions de cette simulation est que, seules les mesures incitatives de grande envergure ont un impact favorable sur la rentabilité des projets depuis la phase préclinique (estimé à au moins 4 milliards d'USD de soutien financier via le mécanisme de *market entry reward*), ce qui démontre la nécessité de renforcer le mécanisme de financement *push* pour les premières phases de la recherche. En outre, il est possible de générer des effets importants de type *pull* dès la phase I, ceci en associant des mesures incitatives de type *pull* plus modestes avec d'autres interventions (par exemple, de type *milestones based rewards*). C'est pourquoi les mécanismes sélectionnés se concentrent sur les modèles de type *pull* ayant un impact sur les structures de recherche, ceci dès la phase I, en tenant compte de leur effet sur la durabilité et de leur coût de financement. L'efficacité de chaque mécanisme a été analysée parallèlement à une évaluation juridique et financière. Le tableau ci-dessous présente une synthèse des principales conclusions.

Tableau 2 : Mécanismes pull : Actions de politique proposées susceptibles de dynamiser le développement et d'encourager la commercialisation d'un plus grand nombre de CMM

Mécanisme de type *pull*	Description	Intervention proposée en USD	Motivation de la sélection : impact et coût par CMM en USD	Cadre juridique
***Revenue Guarantee* (RG)**	Les paiements interviennent en complément de manière à garantir une valeur de revenus annuelle. Consiste en 10 paiements annuels à partir de l'année d'autorisation de mise sur le marché.	RG de 150 millions/an	Rend 50 % des projets rentables en début de phase I. Les dépenses publiques sont estimées à 750 millions sur 10 ans par CMM.	Accord de passation conjointe de marché / dialogue concurrentiel ou procédure concurrentielle avec négociations.
		RG de 100 millions/an	Rend près de 25 % des projets rentables en début de phase I, ce qui nécessite une combinaison avec un prix par étape majeure à 60 millions. Les dépenses publiques sont estimées à 421 millions sur 10 ans par CMM.	
Small Market Entry Reward combined with revenue guarantee (MERino)	Support réduit à la mise sur le marché d'une envergure similaire à la RG mais versée sur une période plus courte (6 ans) : paiements plus élevés les 2 premières années et paiements plus petits les 4 années suivantes.	MERino à 2x 500 millions + 4x 125 millions	Rend plus de 50 % des projets rentables en début de phase I. Les dépenses publiques sont estimées à 1321 millions par CMM.	Accord de passation conjointe de marché / partenariat d'innovation ou passation de marché pré-commerciale pour la récompense à la mise sur le marché.
		MERino à 2x 330 + 4x 85 millions	Rend près de 50 % des projets rentables en début de phase I. Les dépenses publiques sont estimées à 821 millions par CMM.	
		MERino à 2x 250 millions + 4x 50 millions	Rend environ 30 % des projets rentables en début de phase I. Les dépenses publiques sont estimées à 521 millions par CMM.	
Milestone Based Reward (MBR)	Un prix par étape majeure sera attribué à l'issue fructueuse de la Phase I, afin d'assurer un gain financier (bénéfice) au développeur et non de couvrir simplement un pourcentage des coûts comme le font les	Prix de Phase I de 60 millions	Rend un peu plus de 25 % des projets rentables en phase I et 75 % des projets rentables en phase II. Peut également être associé à un RG ou MERino afin de produire des effets incitatifs plus forts et/ou de réduire l'enveloppe nécessaire des RG et MERino pour obtenir un niveau de rentabilité souhaitée. Les dépenses publiques sont estimées à 169 millions par CMM (compte tenu de la nécessité de	Subvention de l'UE en vue d'une passation de marché pré commerciale au niveau des Etats membres ou accord de passation

	subventions et mesures incitatives *push*.		proposer plus d'un prix par étape majeure pour assurer la commercialisation d'un antibiotique).	conjointe de marché[8]
Lump-Sum Market Entry Reward	*Paiement important reçu immédiatement par le développeur, découplant entièrement ses revenus des ventes sur le marché.*	*LSMER 1B*	*Cette intervention a été exclue en raison de son risque élevé pour les financeurs publics en cas de perte potentielle d'efficacité thérapeutique sur les premières années après le lancement.*	*Difficulté à justifier le principe de proportionnalité.*

L'évaluation initiale de préfaisabilité a confirmé que toutes les options pourraient être mises en œuvre par le biais des réglementations et/ou cadres financiers existants. Aussi, il est essentiel de tenir compte des éléments suivants : les mesures incitatives de type *pull* doivent être considérées comme des marchés publics et non comme des subventions[9].

Étant donné que des contributions de l'UE et des États membres seront probablement nécessaires, les mécanismes existants d'accords de passation conjointe de marchés, tels que définis dans le *règlement (UE) 2022/2371 du 23 novembre 2022* relatif aux menaces transfrontalières graves pour la santé, peuvent être utilisés pour garantir l'accès aux nouveaux développements.

Parmi les autres points à prendre en considération pour la mise en œuvre d'un accord conjoint de passation de marché, on peut citer notamment ce qui suit :

- Le modèle d'accord conjoint de passation de marché publié par l'UE en 2014 (*Joint Procurement Agreement*) et les Etats membres, qui pourrait être utilisé et adapté pour couvrir des points supplémentaires, tels que l'inclusion d'un seuil minimum, afin de garantir une adhésion et une participation minimales des États membres.
- Concernant les accords de passation de marché : ils sont soumis aux règles du *règlement financier de l'UE*, ce qui est positif car cela implique que la mesure envisagée doit constituer un "marché public". Les types de procédures de marchés publics concernés sont le « dialogue compétitif », la « procédure concurrentielle avec négociation » et le « partenariat d'innovation ».
- Les accords à conclure avec les fournisseurs de CMM à l'issue du processus de passation de marché, peuvent et doivent prévoir les clauses nécessaires de « stewardship » et d'accès et, dans certains cas, le transfert de propriété intellectuelle et le remboursement du financement si le fournisseur ne poursuit pas ses efforts de R&D et d'exploitation sans motif objectif valable.
- Les financements provenant des États membres doivent respecter les règles relatives aux aides d'État. Si le financement est accordé après une procédure avec un haut degré de concurrence, les règles relatives aux aides d'État peuvent devenir obsolètes. Il en va de même si le financement des Etats membres est placé sous la gestion exclusive de l'UE, ou si le financement n'est pas fourni directement au fournisseur de CMM mais est attribué au travers (d'un consortium) de centres de recherche. Ceci est pertinent lorsque le financement fourni à ce dernier est destiné exclusivement à la R&D pré commerciale.
- Il convient de respecter les principes fondamentaux de proportionnalité et d'efficience puisqu'il s'agit des principes transversaux des règlements budgétaires et en matière d'aides d'État de l'Union européenne. Étant donné que les mesures de type *pull* sont en principe dissociées des coûts de R&D, la présence d'une défaillance du marché justifiant la mesure et son enveloppe budgétaire

[8] Dans les cas où la situation juridique est moins claire quant à savoir si la R&D pré commerciale constitue réellement une passation de marché, une alternative pour l'UE serait d'octroyer une subvention au titre du règlement Horizon Europe à des centres de recherche qui réaliseraient ensuite des transactions pré commerciales au niveau national.

[9] Les subventions se fondent sur la logique des coûts éligibles, tandis que les modèles de type *pull* proposés sont entièrement dissociés des coûts estimés.

Il y a un vaste consensus sur le fait que les financements de type *push* devraient compléter les interventions de type *pull* mentionnées ci-dessus, en agissant là où les interventions de type *pull* sont le moins efficaces, dans les premières phases de développement.

Notre étude montre également qu'à ce stade, les supports financiers non dilutifs constituent l'option privilégiée pour 80% des répondants, qui couvrent l'industrie, le milieu académique, les associations et les incubateurs actifs dans le domaine de la RAM.

Sur la base de notre revue de la littérature, les mécanismes de type *push* pour les CCM dans le domaine de la RAM nécessitent un investissement additionnel global entre 250 et 400 millions d'USD par an. Cela correspondrait à une contribution de l'UE comprise entre 60 et 100 millions d'USD, s'il l'on suppose que la contribution de l'UE dans le financement mondial est de 25 %. L'Agence suédoise de santé publique[10] estime qu'environ 2/3 de ce montant devraient être alloués à du capital non dilutif pour les industriels RAM, et le tiers restant à du soutien en nature aux activités de R&D.

Selon notre étude, les incubateurs et les accélérateurs jouent globalement un rôle important pour améliorer le processus de développement de médicaments contre la RAM. L'enquête et les entretiens mettent en évidence la perception d'un manque de coordination de la part des organismes publics, là où DG HERA, avec les autres services et agences de la Commission, pourrait jouer un rôle d'information et de facilitation entre les différentes parties prenantes.

D'un point de vue juridique, le financement d'interventions de type *push* pourrait être envisagé dans le cadre budgétaire et des programmes d'aide des Etats membres et de l'UE. Cette contribution peut se faire directement via des appels à projets et/ou via les coordinateurs de portefeuille actuels et les distributeurs de fonds. Il est également possible de combiner différents financements dans le cadre de projets transnationaux au sein de l'UE et extérieurs à l'UE.

Enfin, certaines considérations supplémentaires sur les actions à mener pour soutenir les diagnostics et les vaccins sont brièvement mises en évidence, pour être ensuite approfondies dans le cadre de potentielles études ultérieures.

10 E. Baraldi, F.Ciabuschi, S.Callegari, O. Lindahl, Economic incentives for the development of new antibiotics, Rapport commandé par l'Agence suédoise de santé publique, 2019

4. Aims and objectives of this report

The purpose of this study is to deliver options for action in order to bring more AMR MCMs to market and ensure their access across the EU Member States. As previously outlined in the interim report of this study, the “on the market” and “in the pipeline” scenario of AMR MCMs (preventatives, diagnostics, and treatments) presents substantial gaps in the “in the development” products that may address “on the market” insufficiencies.

A primary data collection exercise was conducted to complement this analysis of the R&D landscape with information on the needs, priorities, and challenges of AMR stakeholders in addressing these gaps. This covered stakeholders within the field of AMR including industry, academia, fund contributors, fund distributors, product development partnerships, advocacy groups and networks.

The aim of this final report is to **select the most relevant supporting actions** based on the assessment of the current R&D pipeline and the EU Member States’ needs, in addition to providing a preliminary **analysis of their feasibility of implementation**.

In the first sections of this report, we present the following:

- Key reflections from the interim report[11] introducing the landscape of AMR treatments, diagnostics, and vaccines in development and on the market.
- Insights collected via interviews and surveys on how the different stakeholder groups prioritise their needs for support. These data were compared and validated with the available literature.

Combined, those inputs allowed outlining the potential roles of DG HERA in the form of:

- a comprehensive chapter on pull incentives for antimicrobial treatments for AMR bacteria
- recommendations in regard to push incentives
- a high-level overview of areas where DG HERA may support in coordination

As a result of feedback received by stakeholders and in consideration of the timeline associated with this study, the focus was refined to consider predominantly options for action for treatments for AMR bacteria (pull incentives). As such, separate considerations for vaccines, diagnostics, were mapped at a high level for further study and examination.

[11] Interim Report accessible at: https://op.europa.eu/en/publication-detail/-/publication/341cf78c-bd6a-11ed-8912-01aa75ed71a1/language-en/format-PDF/source-281956123

5. Survey insights and potential role of DG HERA

An assessment of the AMR MCMs currently on the market and in development, delivered within the interim report of this study[12], identified the landscape of medical countermeasures for the prevention, diagnosis and treatment of antimicrobial-resistant infections caused by the priority pathogens presented in the table below.

Table 3: Priority AMR pathogens within the scope of the study.

Bacteria	*Acinetobacter baumannii*	Carbapenem-resistant	Critical priority
	Pseudomonas aeruginosa	Carbapenem-resistant	Critical priority
	Enterobacterales	Carbapenem-resistant; 3rd gen. Cephalosporin-resistant	Critical priority
	Clostridioides difficile	Not Applicable	Critical priority
	Mycobacteria	Multidrug-resistant; Extensively drug-resistant	Critical priority
	Enterococcus faecium	Vancomycin-resistant	High priority
	Campylobacter spp.	Fluoroquinolone-resistant	High priority
	Helicobacter pylori	Clarithromycin-resistant	High priority
	Neisseria gonorrhoea	Fluoroquinolone-resistant; 3rd gen. Cephalosporin-resistant	High priority
	Salmonella	Fluoroquinolone-resistant	High priority
	Staphylococcus aureus	Methicillin-resistant; Vancomycin-resistant	High priority
	Shigella spp.	Fluoroquinolone-resistant	Medium priority
	Streptococcus pneumoniae	Penicillin-non-susceptible	Medium priority
	Haemophilus influenzae	Ampicillin-resistant	Medium priority
Fungi	*Candida auris*	Multidrug-resistant	Critical priority
	Candida spp.	Azole-resistant	Critical priority
	Aspergillus fumigatus	Azole-resistant	Critical priority
	Cryptococcus spp.	Azole-resistant	Critical priority
	Pneumocystis jirovecii	Multidrug-resistant	Critical priority
	Mucormycetes	Azole-resistant; Echinocandin-resistant	Critical priority
	Histoplasma spp.	Azole-resistant	Critical priority
Parasite	*Toxoplasma gondii*	Drug-resistant	Critical priority
Viruses	Human Immunodeficiency Virus	Drug-resistant	Critical priority

[12] Interim Report accessible at: https://op.europa.eu/en/publication-detail/-/publication/341cf78c-bd6a-11ed-8912-01aa75ed71a1/language-en/format-PDF/source-281956123

	Respiratory syncytial virus	Drug-resistant	High priority

By focusing upon a refined set of prioritised pathogens and extensive literature searches, we were able to identify the following gaps and unmet needs within the field of AMR:

- **new classes of antibiotics and antifungals** targeting priority bacteria and fungi, as well as those pathogens for which vaccines are not likely to be available in the foreseeable future (primarily critical and high priority pathogens)
- alternative treatment strategies / **non-traditional agents**
- **rapid diagnostic** devices carrying out pathogen identification and antimicrobial susceptibility testing (AST) at the point of care
- **vaccines** targeting pathogens for which candidates have a moderate to high feasibility of vaccine development (primarily high and medium priority pathogens)

The information gathered, and conclusions drawn from the interim report were complemented by primary data collected via surveys and interviews of key AMR stakeholders. Combined, this evidence served to identify: (i) the extent to which Member State needs with respect to AMR MCMs are addressed, (ii) the challenges faced by various stakeholders, and ultimately, (iii) to validate and prioritise key options for action that DG HERA could consider to address these challenges and bring more AMR MCMs to the market.

To ensure we obtained a holistic picture, seven different groups of stakeholders were mapped and surveyed through tailored questionnaires and interviews.

Table 4: Overview of the survey

Stakeholder Group		Responses received (sent)	Response rate	Approach
Member States		22 (27)	81.5%	Guided interview/survey walkthrough
Industry	SMEs	46 (320)	14.4%	Distribution of a targeted survey using the various industry networks
	Large enterprises	12 (19)	63.2%	Targeted identification of contacts via insights from Task 1 analysis – Survey sent via e-mail
Organisations & Associations	Fund contributors/ distributors	21 (36)	58.3%	Survey sent via e-mail
	Product development partnerships			
	Networks of industry			
	Advocacy			
Academia (R&D)		16 (38)	42.1%	Survey sent via e-mail

The overall response rate across all stakeholders contacted was approximately 48%.

Out of all stakeholders, Member States had the highest engagement rate, with 22 of the EU27 countries submitting their replies. The relevant contact points for each Member State were either indicated by the European Commission (13 Member States) or identified via our desk research (14 Member States).

The affiliation of the contact person for each country is shown in the following table:

Table 5: Affiliation of the contact person identified for each of the 27 EU Member States

Member State	Affiliation of contact person	Member State	Affiliation of contact person
Austria	Ministry of Health	**Italy**	Ministry of Health
Belgium	Federal Agency for Medicines and Health Products	**Latvia**	Ministry of Health
Bulgaria	National Centre of Infectious and Parasitic Diseases	**Lithuania**	Ministry of Health
Croatia	Ministry of Health	**Luxembourg**	Ministry of Health
Cyprus	Ministry of Health	**Malta**	Ministry of Health
Czechia	National Institute of Public Health	**Netherlands**	Ministry of Health
Denmark	Ministry of Health	**Poland**	Ministry of Health
Estonia	Ministry of Social Affairs	**Portugal**	Ministry of Health
Finland	Study group on AMR	**Romania**	Ministry of Health
France	Ministry of Health	**Slovakia**	Public Health Agency
Germany	National Institute of Public Health	**Slovenia**	Medicines and Medical Devices Agency
Greece	Ministry of Health	**Spain**	Ministry of Health
Hungary	National Institute of Pharmacy and Nutrition	**Sweden**	Public Health Agency of Sweden
Ireland	Department of Health		

The response rate from the remaining stakeholders was modest, particularly across the industry members. In total, 116 responses were submitted and compiled key information such as:

- **needs and priorities** in order to bring AMR MCMs to the market and ensure their access;
- **challenges faced** in bringing AMR MCMs to the market and, in turn, what **solutions and/or incentives** would help resolve these challenges;
- **DG HERA's role** in bringing more AMR MCMs to the market across Member States, as perceived by stakeholders; and
- **incentives and support actions** that could be attractive and/or potentially effective in bringing more AMR MCMs to the market and ensuring their access.

Information gaps were also identified within the primary data-collection method, mostly for Member States and industry.

In the case of Member States, certain questions remained unanswered, often due to:

- Member States' or respondent's low awareness in a specific topic
- Member States' lack of formal position / official discussion in a specific subject
- unavailability of information due to the lack of coordination between the multiple institutions involved in AMR at national level.

To mitigate this risk as much as possible, guided one-to-one interviews were conducted upon request with 20 of the 22 Member States that completed the survey. Within these interviews,

each survey question was reviewed to support the identification of relevant contact points and to clarify any queries.

In the case of the industry survey, some select questions were left unanswered primarily because the information requested was deemed to be confidential or commercially sensitive.

With the above in mind, the results summarised in the following sections also reflect upon findings from desk research, additional studies, reports, and academic publications – in order to further validate and corroborate the conclusions derived.

5.1. Member States' needs

The Member States were asked about their most pressing needs in terms of AMR MCMs' access and R&D, rating various options on a Likert scale ranging from "Not at all important" to "Extremely important". As shown below, the needs identified for access and new developments are very similar. Of the 21 Member States that responded to the specific question, approximately 70% stated a **need for last line use antimicrobials** both from an access and research and development (R&D) perspective. Approximately 60% stated the **need for rapid diagnostics for AST or differential diagnosis (Dx)** as extremely important or very important.

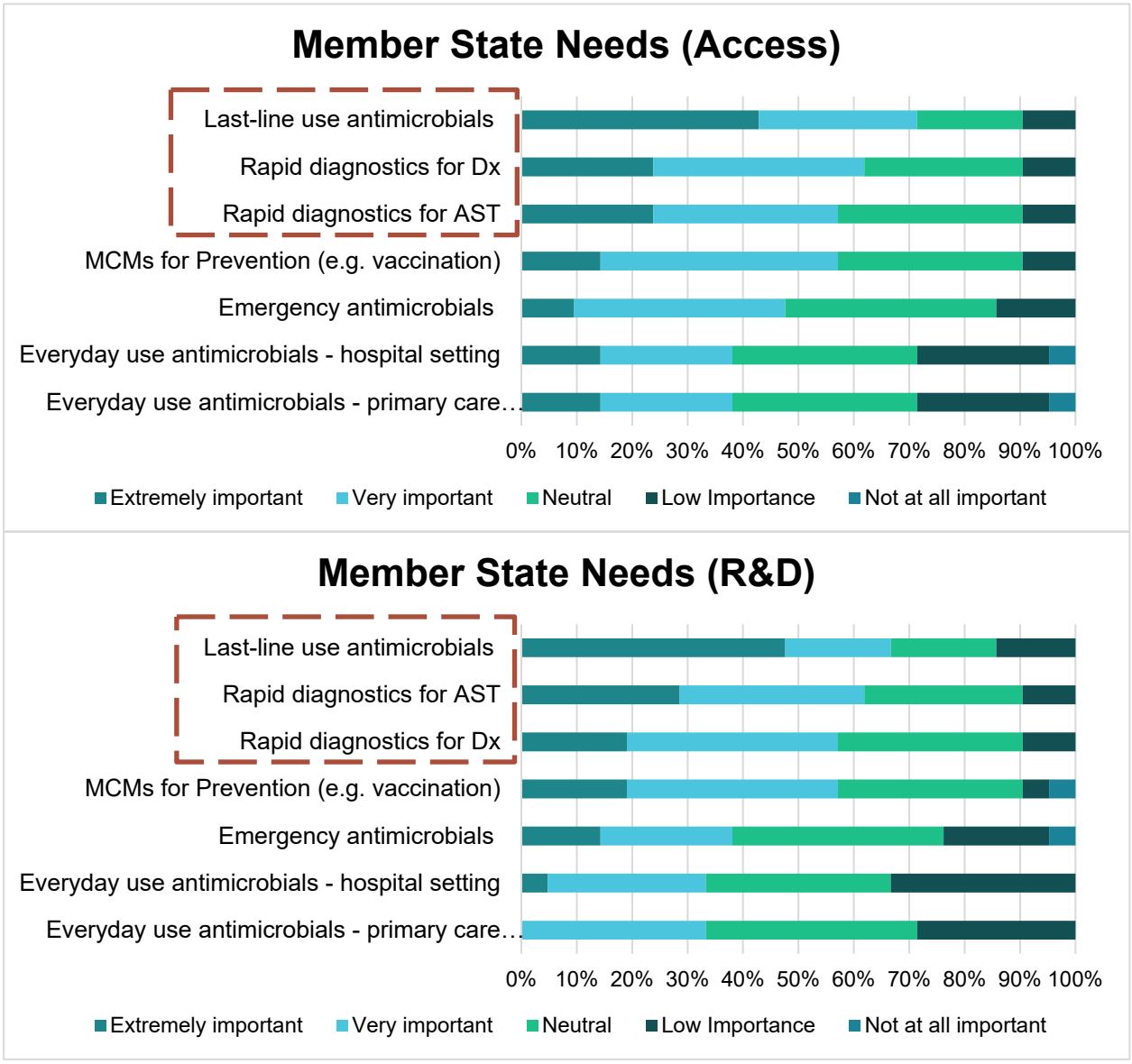
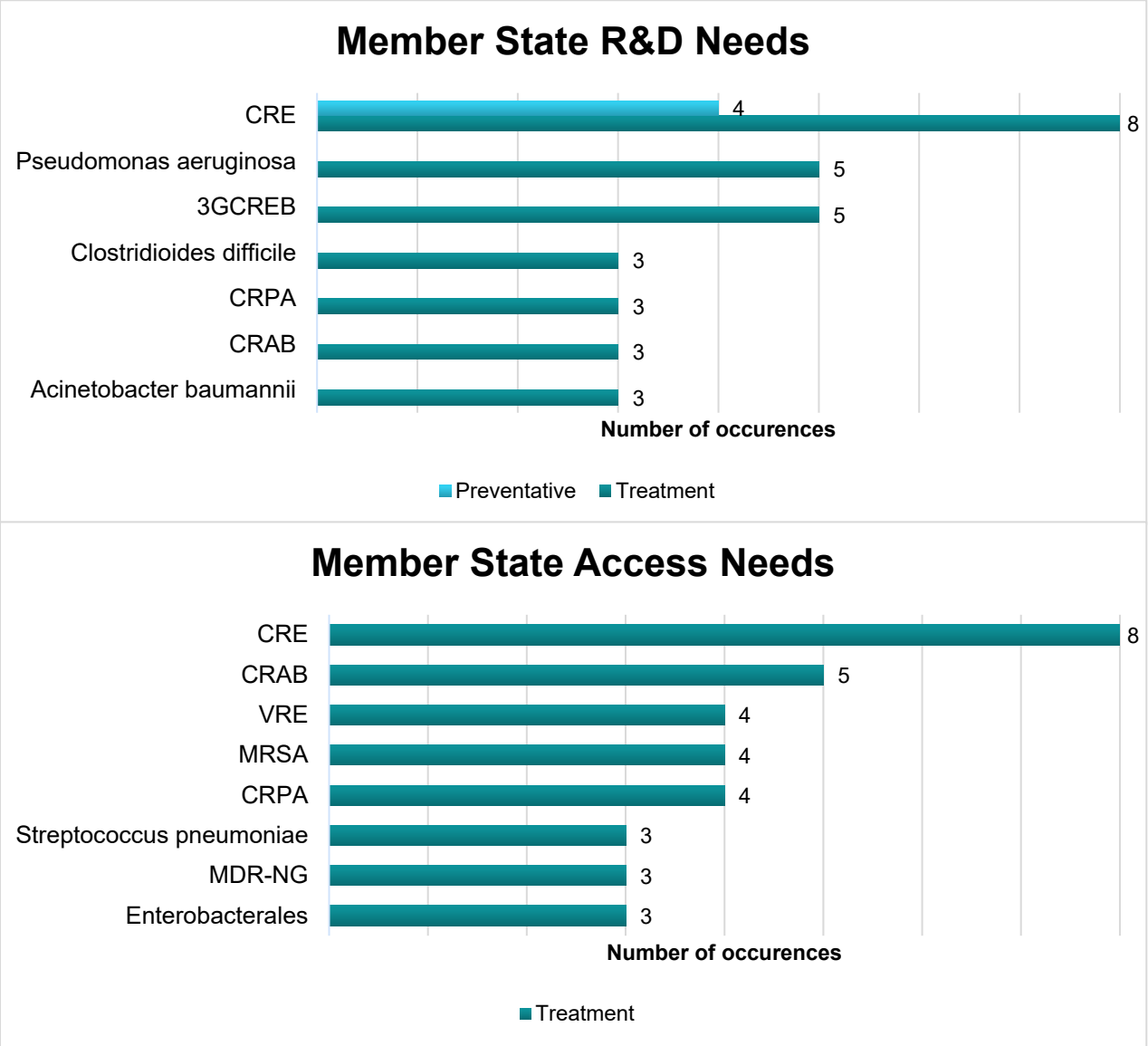


Figure 3: Most pressing needs of Member States from an R&D and access perspective. The red dotted box highlights the needs described as either extremely important or very important by at least 60% of respondents. (n=21 MS answers)

Twenty Member States marked at least one or more need as “Extremely important” or “Important”. Only one Member State reported to be satisfied with the as-is scenario, mapping no specific AMR MCMs needs from an access or R&D perspective. This was a country with medium-sized population, high Gross Domestic Product (GDP), and low level of antibiotic consumption.

The Member States were subsequently asked to list their MCM needs linked to specific pathogens. The response rate shows that 15 Member States were able to list their pathogen-specific R&D needs and 12 Member States their access needs.



For visualisation purposes, only pathogens that were listed by three or more Member States are shown below.

Figure 4: Member State needs in terms of types of MCMs required for specific pathogens from an R&D (top panel) and access (bottom panel) perspective. CRE = Carbapenem-resistant Enterobacterales, 3GCREB = 3rd generation cephalosporin-resistant Enterobacterales, CRAB = Carbapenem-resistant Acinetobacter baumannii, CRPA = Carbapenem-resistant Pseudomonas aeruginosa, MRSA = Methicillin-resistant Staphylococcus aureus, VRE = Vancomycin-resistant Enterococcus faecium, MDR-NG = multidrug-resistant Neisseria gonorrhoea. (n = 15 Member States answers for R&D/n = 12 Member States answers for access)

From an R&D perspective, there is an overall need for **treatments** targeting critical-priority bacteria as defined by the WHO. These are *Enterobacterales* – specifically carbapenem-resistant (listed 8 times) and 3rd generation cephalosporin-resistant (listed 5 times), carbapenem-resistant *Acinetobacter baumannii* (listed 3 times), and carbapenem-resistant *Pseudomonas aeruginosa* (listed 3 times). Treatments for *Acinetobacter baumannii* and *Pseudomonas aeruginosa* were stated as an R&D need by 5 Member States, with no mention of a specific drug-resistant strain of

these pathogens. In addition, 3 Member States also mentioned a need for novel treatments targeting *Clostridioides difficile*.

From an access perspective, the situation is similar. There is an overall need expressed by Member States for access to treatments targeting critical-priority and high-priority bacteria as defined by the World Health Organization (WHO). These are carbapenem-resistant *Enterobacterales* (listed 8 times), carbapenem-resistant *Acinetobacter baumannii* (listed 5 times), carbapenem-resistant *Pseudomonas aeruginosa* (listed 4 times), methicillin-resistant *Staphylococcus aureus* (listed 4 times), vancomycin-resistant *Enterococcus faecium* (listed 4 times), and multi-drug resistant *Neisseria gonorrhoea* (listed 3 times). Treatments for *Enterobacterales* and *Streptococcus pneumoniae* were also listed 3 times, with no specific mention of the drug-resistant strain.

Despite some Member States stating a need for preventatives from an R&D perspective, there was no consensus. Except for carbapenem-resistant *Enterobacterales (*mentioned 4 times), all other preventatives for specific pathogens were only listed by one or two Member States.

Diagnostic devices across a range of pathogens were listed by 12 Member States from an R&D perspective and by 6 Member States from an access perspective. This is in line with the need identified earlier for rapid **diagnostics.**

An interesting insight from this survey is that, despite an overall rise in the incidence of invasive fungal infections[13] and the emergence of antifungal resistance, Member States answers do not indicate an urgent need or awareness for access or R&D of MCMs targeting fungal infections.

Concerning Member States awareness of key threats, eight respondents indicated the need for access to treatments aligned with the list of critical priority pathogens presented at the start of this chapter. More than half highlighted R&D needs to novel treatments targeting pathogens in line with the priority list. This shows that the WHO bacterial pathogen priority list, developed in 2017 to guide and promote R&D into new antibiotics, has been effective in highlighting Member States' needs[14].

The recent publication of the fungal pathogen priority list[13] along with the landscape of diagnostics against AMR[15,] both published by the WHO, will hopefully have a similar impact in directing the development of novel antifungals and vaccines for fungal infections, as well as novel diagnostic tools to inform appropriate use and stewardship measures of antimicrobials. Such coordinated communication has proven to be effective in identifying global needs and subsequently informing and guiding R&D.

5.2. Addressing Member States' needs

The Member State needs identified must be addressed to ensure the threat posed by AMR does not continue to rise and thereby result in significant mortality and morbidity. To examine whether these needs are being addressed and how, the following sources were used:

- insights from our research and mapping of AMR MCMs on the market and in development as delivered in the interim report
- primary data collected via surveys with industry, academia, and other relevant organisations
- findings from key reports and articles.

[13] WHO fungal priority pathogens list to guide research, development and public health action. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

[14] Prioritisation of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017(WHO/EMP/IAU/2017.12). (Licence: CC BY-NC-SA 3.0 IGO..

[15] Landscape of diagnostics against antibacterial resistance, gaps and priorities. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

5.2.1. Access to AMR MCMs

Valuable insights were gathered from our mapping of AMR MCMs on the market (interim report) and can be considered from the perspective of access to AMR MCMs addressing pathogens that were identified as priority for Member States. The number of **treatments** that exist on the market today and the key resistant pathogen they target are shown in the table below.

Table 6: Number of treatments on the market targeting bacteria for which an access need was identified by Member States

Pathogen	Priority level	Number of treatments on the market
Carbapenem-resistant *Acinetobacter baumannii*	Critical	2
Carbapenem-resistant *Pseudomonas aeruginosa*	Critical	2
Carbapenem-resistant and 3rd generation cephalosporin-resistant *Enterobacterales*	Critical	8
Vancomycin-resistant *Enterococcus faecium*	High	11
Methicillin-resistant *Staphylococcus aureus*	High	38
Fluoroquinolone-resistant and 3rd generation Cephalosporin-resistant *Neisseria gonorrhoea*	High	8
Penicillin-non-susceptible *Streptococcus pneumoniae*	Medium	16

Our industry survey gathered a sample of ten treatments on the market that target the resistant pathogen strains within the table above. Given the small sample, this data was analysed only from a qualitative perspective and used to enrich the mapping above.

For critical priority pathogens (*Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacterales*), the number of treatments available on the market from our respondents is limited. Only two treatments are available for carbapenem-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Acinetobacter baumannii*, and eight treatments for carbapenem-resistant and 3rd generation cephalosporin-resistant *Enterobacterales*. The two treatments available for carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* are marketed for the treatment of complicated urinary tract infections, nosocomial pneumonia, and intra-abdominal infections, and therefore does not cover all the possible indications caused by these two critical priority pathogens. Bloodstream infections, bone and joint infections, respiratory tract infections, and skin and soft tissue infections caused by the abovementioned pathogens still remain unaddressed.

This is in line with information contained within the latest antibacterial pipeline analysis carried out by the WHO in which only five treatments targeting critical priority pathogens (four for carbapenem-resistant *Enterobacterales,* one for carbapenem-resistant *Enterobacterales, Acinetobacter baumannii* and *Pseudomonas aeruginosa*) have been approved to market by either the U.S. Food and Drug administration (FDA), the European Medicines Agency (EMA) or both since 2017[16].

The correlation between the limited number of treatment options for critical priority pathogens and the reported issue on Member States' access reinforces the need for more R&D leading to novel treatments able to reinforce the existing portfolio.

The data collected for **diagnostics** indicates that there are many commercially available devices on the market that perform differential diagnosis, species identification and/or AST/resistance testing for virtually all priority pathogens. The mapping identifies 135 diagnostic devices on the

[16] 2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

market, of which approximately 110 can perform differential diagnosis and approximately 20 can perform AST[17]. However, most of these tests are slow and rely on sophisticated infrastructure and technical expertise. It should be noted that suitability in primary and secondary care was not assessed.

The diagnostics identified within our analysis as available on the market do not meet the needs of Member States (i.e. **rapid** diagnostic devices performing Dx and AST).

5.2.2. R&D of AMR MCMs

From an R&D perspective, the mapping of AMR MCMs in development within our interim report identified a number of **treatments** that aim to address pathogens, for which Member States have identified R&D needs.

Table 7: Number of treatments in development identified targeting bacteria for which an access need was identified by Member States

Pathogen	Priority level	Number of treatments in development
Carbapenem-resistant *Acinetobacter baumannii*	Critical	35
Carbapenem-resistant *Pseudomonas aeruginosa*	Critical	49
Carbapenem-resistant and 3rd generation cephalosporin-resistant *Enterobacterales*	Critical	45
Clostridioides difficile	Critical	25

At first glance, there appear to be many treatments targeting critical-priority pathogens in the development pipeline between preclinical-stage research and phase III clinical trials (TRL5-8).

The **clinical** pipeline analysis carried out by the WHO identified 9 treatments for carbapenem-resistant *Acinetobacter baumannii,* 13 treatments for carbapenem-resistant *Pseudomonas aeruginosa*, 18 treatments for carbapenem-resistant and 3rd generation cephalosporin-resistant *Enterobacterales*, and 17 treatments for *Clostridioides difficile.* The **preclinical** pipeline analysis carried out by the WHO identified 50 treatments for *Acinetobacter baumannii*, 69 treatments for *Pseudomonas aeruginosa*, 72 treatments for *Enterobacterales*, and 20 treatments for *Clostridioides difficile* currently found in early stages of development. The stages of development covered range from clinical trial application/investigational new drug-enabling studies to the identification of preclinical candidates (TRL 3 to 5).

The mapping of AMR MCMs carried out as part of this study and described in the interim report only includes treatments with a TRL between 5 and 8, and as a result, only the relevant treatments from the WHO preclinical pipeline analysis were included. This, along with the fact that a wide range of sources were utilised to identify AMR MCMs, explains the discrepancy in the number of MCMs described in the table above and those found in the WHO **clinical and preclinical** pipeline analysis.

Through our mapping of preventative MCMs described in the interim report, we also identified 11 vaccines in the pipeline to address the R&D need of preventatives for *Enterobacterales* identified reported as priority need by 4 Member States. Out of the 11 vaccines, 8 are currently in development for *Escherichia coli* and 3 for *Klebsiella pneumoniae*.

The R&D funding captured in the Dynamic Dashboard of the Global AMR R&D Hub[18] also provides some insights as to whether the Member States' R&D needs are reflected in the

[17] Interim Report accessible at: https://op.europa.eu/en/publication-detail/-/publication/341cf78c-bd6a-11ed-8912-01aa75ed71a1/language-en/format-PDF/source-281956123

[18] Global AMR R&D Hub (2021). Annual Report 2021: The Global AMR R&D Funding Landscape. [Online] Available from: https://globalamrhub.org/annual-report-2021-the-global-amr-rd-funding-landscape/

direction of current levels of investment. Overall, 15% (USD 965 million) of the investment in the human sector captured by this dashboard is directed to R&D for critical-priority pathogens identified by Member States as critical for development. The order of investment into critical-priority bacteria, in descending order, is *Enterobacterales, Pseudomonas aeruginosa, Clostridioides difficile,* and *Acinetobacter baumannii*, which closely resembles the ranking of needs identified by Member States in the survey. However, the share of funding attributed towards critical-priority bacteria captured by the Dynamic Dashboard is insufficient to promote R&D into novel antibiotic treatments for these key bacteria.

The R&D landscape of diagnostic devices identified in the interim report partially addresses the diagnostic needs of Member States from an R&D perspective. There is a significant number (39 in total) of diagnostic devices in development which perform rapid AST with results in less than two hours[18]. Most of these diagnostic devices performing rapid AST rely on sophisticated infrastructure and cannot be performed in near-patient settings. The ability to carry out a diagnostic test at the point-of-care, although not highlighted as a need by the Member States, is of great importance as it improves the accessibility of infectious disease testing and helps address issues around antimicrobial stewardship by avoiding inappropriate use.

Primary data collected from 15 academic institutions and 33 companies (SMEs and large enterprises) highlighted AMR MCMs currently in development along with the specific pathogen they target. The survey results show that the pathogens with the most AMR MCMs in the pipeline are *Enterobacterales* (22 treatments, 5 preventatives, 4 diagnostics)*, Staphylococcus aureus* (12 treatments)*, Acinetobacter baumannii* (11 treatments) and *Pseudomonas aeruginosa* (11 treatments). However, this information is partially incomplete as the respondents did not clarify which drug-resistant strain of the pathogen is being targeted by the various treatments being developed. Based on the responses to the survey, there are 17 AMR MCMs currently in development that target the specific drug-resistant strains of the bacteria listed above. These AMR MCMs are deemed to be of critical and high priority and target methicillin-resistant *Staphylococcus aureus* (5 treatments), 3rd generation cephalosporin-resistant *Enterobacterales (*3 treatments and 3 preventatives), and carbapenem-resistant *Enterobacterales* (3 treatments and 3 preventatives).

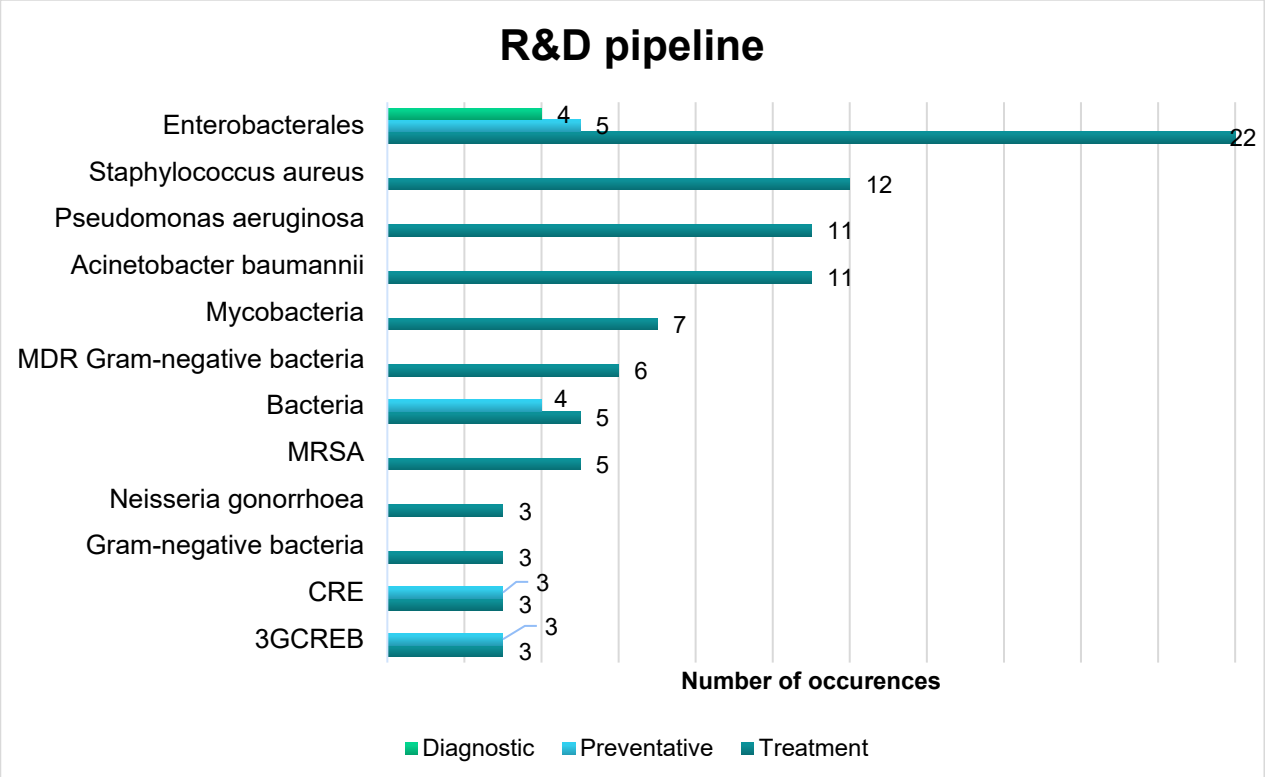


Figure 5: Types of MCMs and the pathogens targeted by R&D in academic institutions and industry. CRE = Carbapenem-resistant Enterobacterales, 3GCREB = 3rd generation cephalosporin-resistant Enterobacterales, MRSA = Methicillin-resistant Staphylococcus aureus

Amongst the responses, there are a number of AMR MCMs being developed with no mention of a specific pathogen, but rather a group of pathogens such as multidrug-resistant Gram-negative bacteria (6 treatments), bacteria (5 treatments and 4 preventatives) and Gram-negative bacteria without a specific mention of the type of resistance targeted (3 treatments). These results are summarised in the bar chart above; for visualisation purposes, only specific pathogens that were listed by 3 or more respondents are shown. The information collected from the respondents suggests that there is insufficient R&D to address the Member States' needs identified in the previous section, based on the sample size of this study. However, it should be noted that the low response rate from the industry, together with the incomplete information provided in our primary-data collection, does not allow us to draw any concrete conclusions from this primary dataset.

The vast majority of AMR MCMs identified via the academia and industry surveys are currently at the very early stages of research, as shown below. Only 17% of AMR MCMs listed by respondents are currently in clinical trials or in the marketing authorisation/approval phase, with 83% of AMR MCMs described currently in the stages of basic research, MCM discovery or pre-clinical research.

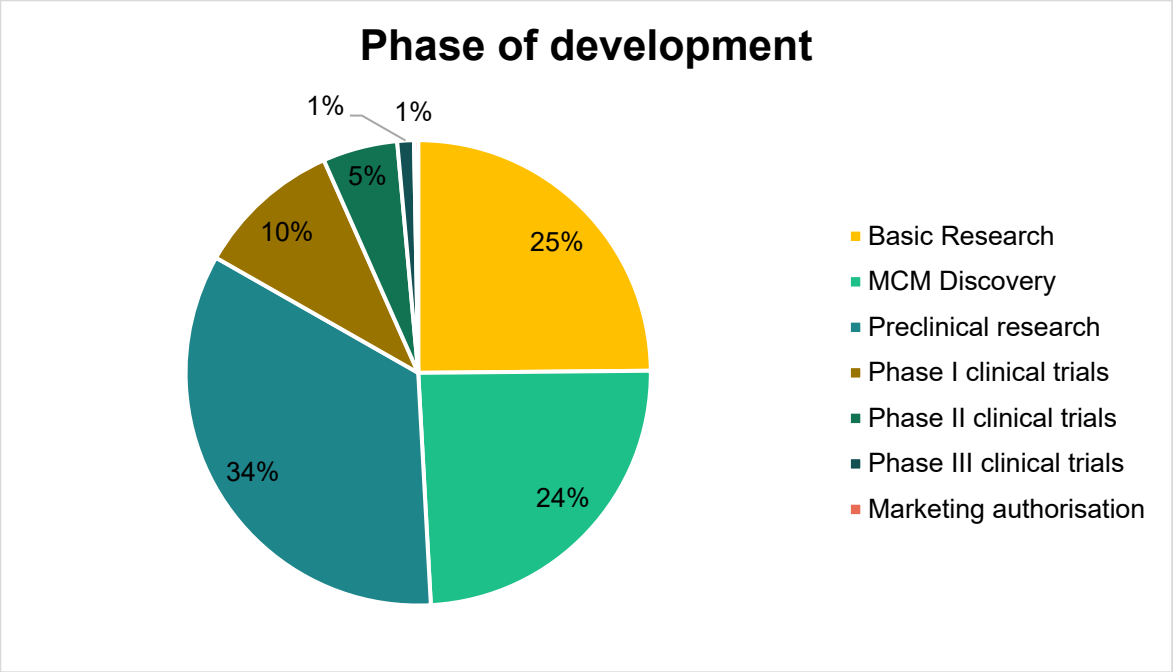


Figure 6: Phase of MCMs in development listed by industry (204 MCMs in total).

This is in line with the results of the interim report which found that a majority of AMR MCMs targeting critical priority pathogens are in the early-stages (preclinical research or phase I) of development – approximately 60% of all treatments in development identified (irrespective of pathogen) are in either preclinical research (TRL5) or phase I (TRL6) clinical trials, with less than 10% in phase III trials. The average progression rates identified by the WHO[19] (discovery and preclinical – 36.7%; phase I – 61%; phase II – 45.6%; phase III – 69.1%; registration – 87.5%) are particularly low at the early stages of development as there are a number of challenges to be overcome in progression towards the market. These challenges are described in the subsequent section. Given the average progression rates and the development duration of R&D models, the current pipeline is unlikely to generate new innovative antimicrobials in the coming years to address both the R&D and access needs of the Member States.

[19] 2020 A financial model for an impact investment fund for the development of antibacterial treatments and diagnostics. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

5.3. Challenges faced in AMR R&D and access

Stakeholders were asked to identify the key challenges present across the AMR MCM development pipeline. From the responses collected (total of 36), it is apparent that financial challenges across the entire development pipeline are burdensome, particularly during preclinical research and phase I clinical trials, indicated by 30 and 28 responses respectively. These financial challenges have been highlighted in a number of various reports and papers[20][21].

Scientific and regulatory challenges, on the other hand, follow opposite patterns, with scientific challenges prominent at the early stages of development compromising of basic research to preclinical research, while regulatory challenges appear to be absent during the early stages of development and most prevalent during phase III clinical trials and the marketing authorisation/approval phase.

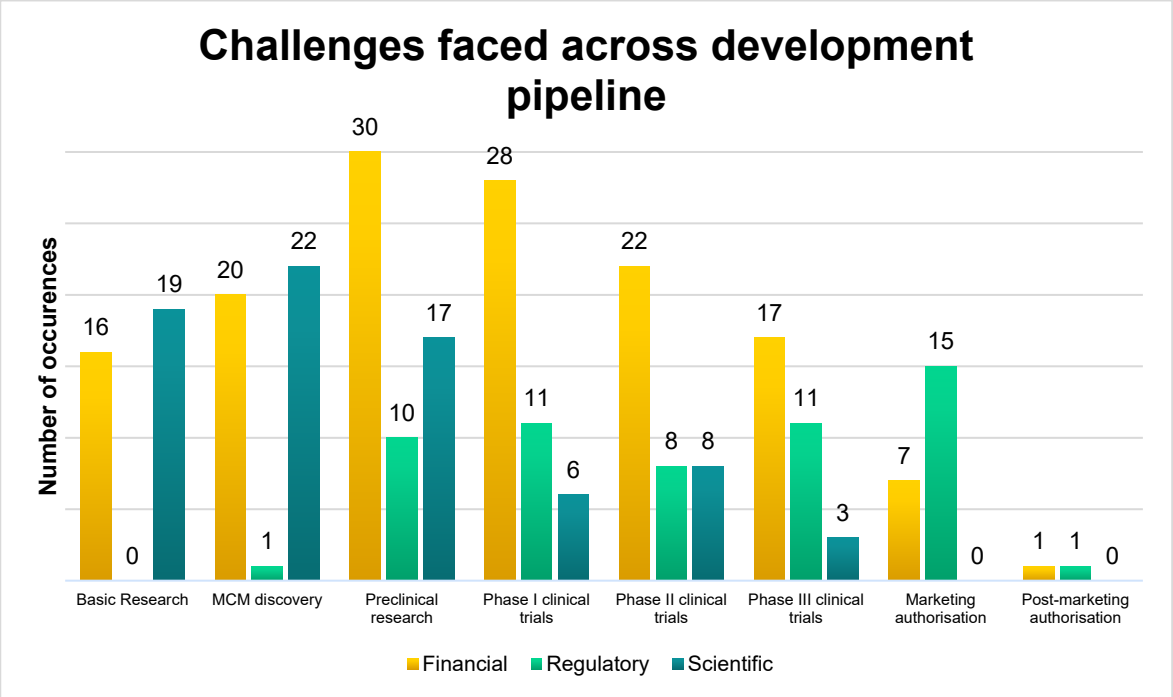


Figure 7: Types of challenges faced across the development pipeline, categorised as financial, regulatory, or scientific. 31 responses from industry, 3 responses from advocacy groups, 1 response from networks, 1 response from product development partnerships

Overall, the preclinical research stage represents the highest number of challenges, which is in line with the findings of the interim report analysis for which an extract is shown below. Of the treatments and preventatives identified in the interim report, 60% are discontinued at TRL 5, i.e. the preclinical research phase of development.

[20] Årdal, C., Balasegaram, M., Laxminarayan, R., McAdams, D., Outterson, K., Rex, J.H. and Sumpradit, N., 2020. Antibiotic development—economic, regulatory and societal challenges. *Nature Reviews Microbiology*, *18*(5), pp.267-274.

[21] World Health Organization, 2020. *Challenges to Tackling Antimicrobial Resistance Economic and Policy Responses: Economic and Policy Responses*. OECD Publishing. DOI 10.1017/9781108864121

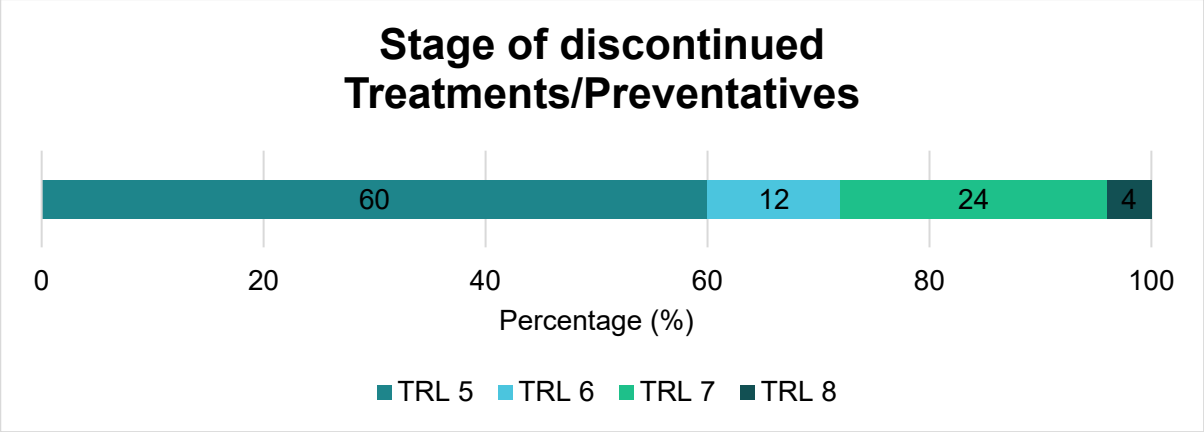


Figure 8: Percentage of trials discontinued for treatments and preventatives across the different stages of development

5.3.1. Financial challenges

The current market model for developing new AMR MCMs is not sustainable (see section: The profitability challenge 6.1.3). Companies invest considerable funds to bring new AMR MCMs to the market but cannot recover their costs or make a profit, in the event of successful market launch. This is particularly relevant to last line use antimicrobials, where a truly novel antimicrobial would likely be reserved for rare infections caused by the most highly resistant strains of pathogens to limit the development of new resistances[22]. Sales volumes are also limited by the short treatment duration inherent in antimicrobial therapy and as a result of stricter stewardship policies further restricting the use of antimicrobials. Data collected via our surveys indicate that the insufficient demand of novel antimicrobials is rated as extremely or moderately challenging by 66.7% of respondents (9 companies, 3 advocacy groups and 2 network organisations). The financial justification for developing and commercialising a novel antimicrobial, taking into consideration the low sales and low prices that limit the return on investment, does not reflect its public health value or the investments made into its R&D. The end result is that many large pharmaceutical companies leave the field, and a number of SMEs fail to achieve profitability.

With the above in mind, a scientific breakthrough does not guarantee market success for developers, as significant funding is required to see AMR MCMs through the expensive process of clinical trials, registration, and marketing authorisation/approval. Market entry does not ensure that these costs will be fully covered. Additionally, the financial challenges highlighted above are amplified by the regulatory and scientific challenges affecting the R&D and launch of AMR MCMs.

In our primary-data collection, various stakeholders were asked to rate the financial challenges associated with the R&D of AMR MCMs from “Not at all challenging” to “Extremely challenging”. From the perspective of Member States, the most critical financial challenge rated as extremely or moderately challenging by over 75% of respondents is the lack of financial incentives to market and maintain AMR MCMs on the market (as shown below). This is followed by lack of funding of clinical research and lack of return on investment for companies developing new MCMs, which are rated as extremely challenging or moderately challenging by 57% and 52% of respondents respectively.

[22] Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P T. 2015 Apr;40(4):277-83. PMID: 25859123; PMCID: PMC4378521.

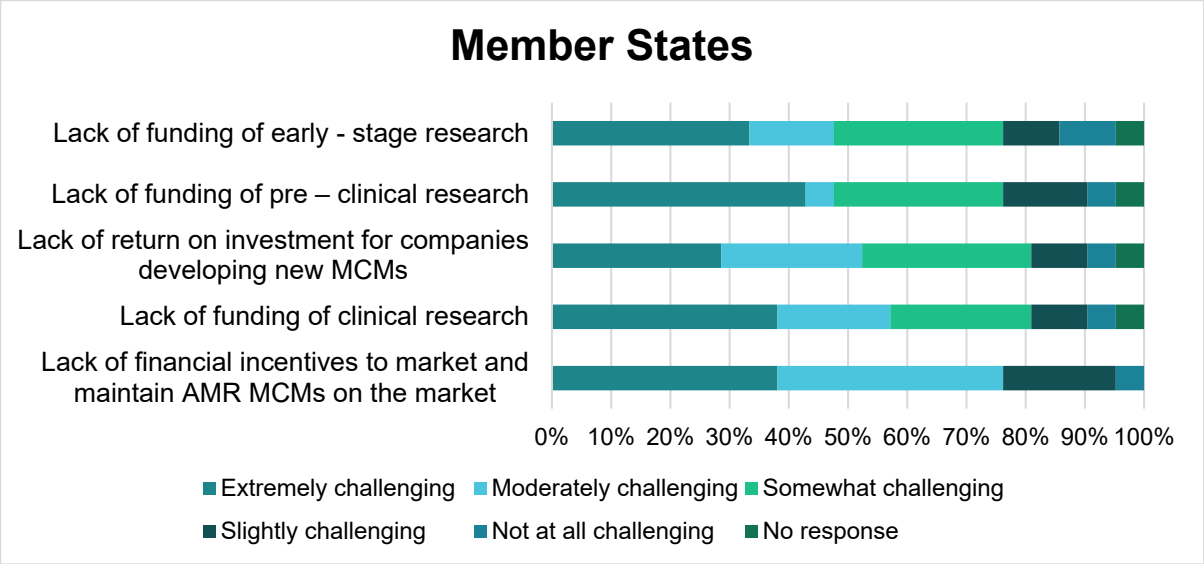


Figure 9: Financial challenges rated in order of importance by Member States (n = 21) according to their stage of development

Out of the 21 Member States that responded to the question on the types of support provided to support R&D into new and innovative AMR MCMs, only 8 Member States stated that they provide financial support (8 support basic research, 5 support pre-clinical research, 5 support clinical research, 4 support the MCM discovery phase and 1 supports the marketing authorisation/approval phase). This is in line with data reported by the Global AMR R&D Hub, where at global level, most AMR-relevant R&D funding is for basic research.

Only 4 Member States reported a monetary value for this support when responding to the question on a planned budget to fund R&D into new and innovative AMR MCMs, all of which are medium/large-sized Member States based on population size with a moderate/high GDP. Of the remaining 18 Member States, 9 stated that they have no planned national funding to support R&D, and 9 stated that they could not answer this question.

Over 80% of academics surveyed rated the lack of funding of early-stage and preclinical research and the high financial cost of R&D compared to funding as extremely challenging or moderately challenging (as shown below). This is not surprising given that academic institutions are primarily involved in the early stages of R&D. The investment required for discovery and preclinical research of a single antibiotic for example, is estimated to be USD 14.7 million[23], and is primarily funded by public-sector bodies such as research councils, health authorities and national funding agencies[24]. This is supported by the data provided by the 16 academic institutions listing 43 funding sources, of which 74.4% are public and 25.6% are private sources of funding.

[23] 2020 A financial model for an impact investment fund for the development of antibacterial treatments and diagnostics. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO

[24] Global AMR R&D Hub (2021). Annual Report 2021: The Global AMR R&D Funding Landscape.

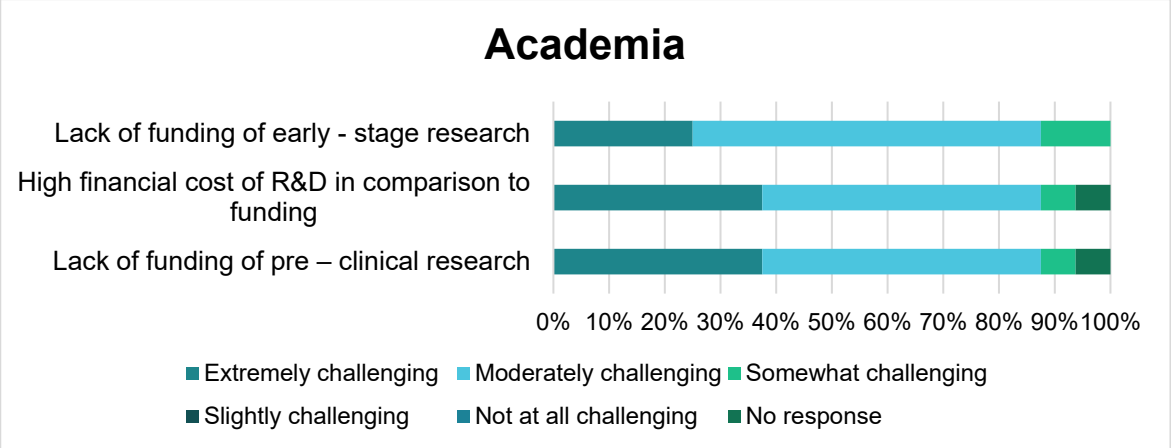


Figure 10: Financial challenges rated in order of importance by academia (n = 16) according to their stage of development

Comparatively, more advanced stages of development (clinical trials) are often funded by private-sector bodies such as independent organisations with a non-profit mandate or private pharmaceutical companies. This means that there is a break in funding and appropriate actors to transition AMR MCMs from basic science to clinical trials. This has led to the transition phase between preclinical R&D and clinical trials being termed the "valley of death"[25]. Although no data was gathered from stakeholders on the specific types of financial challenges present during clinical trials, financing clinical trials is a major hurdle that needs to be overcome. The estimated investment required to take an antibiotic from phase I to phase III clinical trials is USD 132 million[26]. The SMEs that are dominant in the AMR MCM development space are often unable to raise funds to invest in promising candidates and see a product through the development pipeline.

After an MCM has completed phase III clinical trials, it has to pass through marketing authorisation/approval, be launched on the market and manufactured. The marketing authorisation/approval and launch phase of AMR MCMs such as antibiotics, as well subsequent phase IV trials often amount to an added cost of USD 110 million. As many large pharmaceutical companies have abandoned the market, it is indicated in the literature that there is little chance that potential candidates developed by SMEs will be purchased by larger companies to get them to the market[27]. From the perspective of industry, advocacy groups and networks, over 50% of respondents rated the lack of funding for AMR MCM launch as extremely or moderately challenging. Challenges related to lack of funding to support the marketing authorisation/approval process and the high manufacturing costs were also highlighted by 46% of respondents. These challenges ultimately impact the ability of newly developed AMR MCMs to reach patients.

[25] So, A.D., Ruiz-Esparza, Q., Gupta, N. and Cars, O., 2012. 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards. *Bmj*, *344*.

[26] 2020 A financial model for an impact investment fund for the development of antibacterial treatments and diagnostics. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO

[27] Årdal, C., Balasegaram, M., Laxminarayan, R., McAdams, D., Outterson, K., Rex, J.H. and Sumpradit, N., 2020. Antibiotic development—economic, regulatory and societal challenges. *Nature Reviews Microbiology*, *18*(5), pp.267-274.

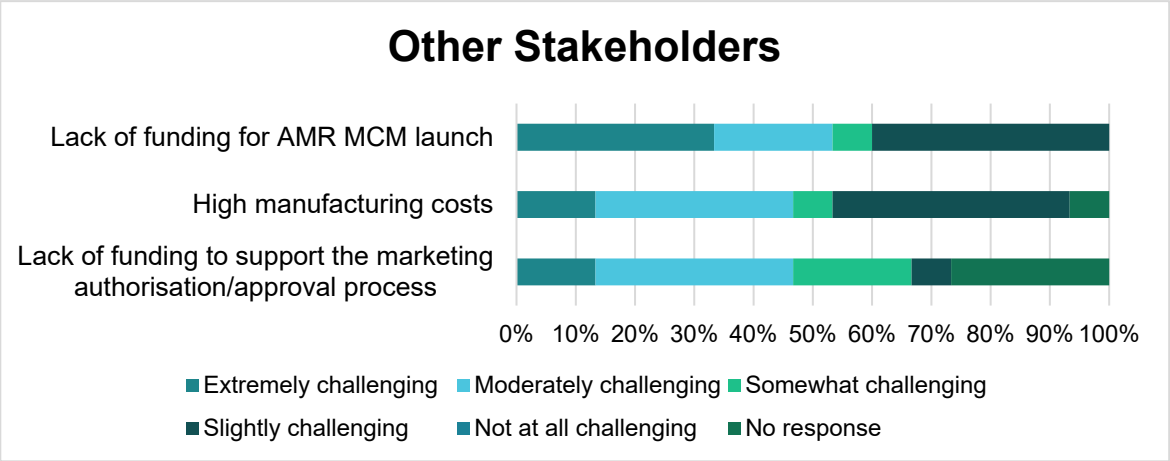


Figure 11 Financial challenges rated in order of importance by industry (n = 9), advocacy groups (n=4) and networks (n=2)

As highlighted by the responses collected from the various stakeholders and the information contained within the literature, there are financial challenges throughout the entire R&D pipeline and after a product is launched on the market. These financial challenges could be addressed by various different mechanisms (discussed in later sections) to alleviate the current market failure, bring more AMR MCMs to the market, and ensure their access.

5.3.2. Scientific challenges

The development of novel AMR MCMs, whether it be novel antibiotics, vaccines or diagnostic devices is hindered by various scientific and technical challenges. Taking the example of antibiotics, no new classes of antibiotics have been discovered since the 1980s. The antibiotics that have been brought to market in the past three decades are variations of previously discovered drugs, as the science behind discovering and developing genuinely new antibiotics is challenging. The same holds true for the development of new vaccines, where the biological feasibility of developing vaccine candidates for critical-priority pathogens is low. There is a shortage of well-defined preclinical models of drug resistant infections to guide R&D[28].

Additionally, the exit of many large pharmaceutical companies from the antimicrobial market has resulted in a smaller pool of scientific talent. There is a shortage of experts qualified to lead research programmes using promising new antimicrobial discovery methods[29] - this was highlighted as extremely or moderately challenging by 9 of the 16 academic institutions that responded to the relevant question in the survey.

Scientific challenges are most prevalent at the early stages of development, as indicated by the survey data collected from a number of stakeholders and described in an earlier section. It is essential to find ways to address these challenges in order to develop candidates that can progress through the pipeline and eventually reach the market. Out of the 21 Member States that responded to the question relating to types of support provided to industry/researchers to support R&D, only 9 Member States indicated that they provide technical/scientific support. The technical/scientific support provided is distributed across the development pipeline as shown in the table below:

Table 8: Member State Support to AMR R&D

Phase of development	Number of Member States that provide technical and scientific

[28] Hughes, D. and Karlén, A., 2014. Discovery and preclinical development of new antibiotics. *Upsala Journal of Medical Sciences*, *119*(2), pp.162-169.

[29] Renwick, M. and Mossialos, E., 2018. What are the economic barriers of antibiotic R&D and how can we overcome them?. *Expert opinion on drug discovery*, *13*(10), pp.889-892.

	support
Basic research	6
Discovery	4
Pre-clinical research	8
Clinical trials (phase I to phase III)	9
Marketing authorisation/approval	7

This indicates that more awareness is needed about the types of scientific and technical support that may help guide R&D either at a national or EU level. It should be noted that the fund distributors/contributors that responded to the survey are already actively providing this support. Out of the 9 fund distributors/contributors that responded to the survey, 8 provide ad-hoc scientific advice while 4 provide long-term scientific support.

5.3.3. Regulatory challenges

The complex regulatory ecosystem across different regulatory agencies presents a number of challenges for AMR MCMs. Different regulatory agencies such as the FDA and the EMA all have distinct procedures and requirements in terms of patient-selection criteria, clinical endpoint definitions, specification of statistical parameters, and rules on expedited approvals. When asked to rate the difficulty in determining a commercial strategy for authorisation (e.g. which regulatory agency to submit for marketing authorisation/approval first), only 27.3% of respondents rated it as extremely or moderately challenging (3 advocacy groups and 8 companies responded to the specific question). This is in line with the primary data collected from companies with AMR MCMs in development, which when asked to whom they intend to submit for initial marketing authorisation/approval, the majority of respondents (66.7% of the 93 MCMs in development) stated the FDA. The companies involved with the development of 25.8% of MCMs listed in the survey responses intend to submit for initial marketing authorisation/approval to the EMA.

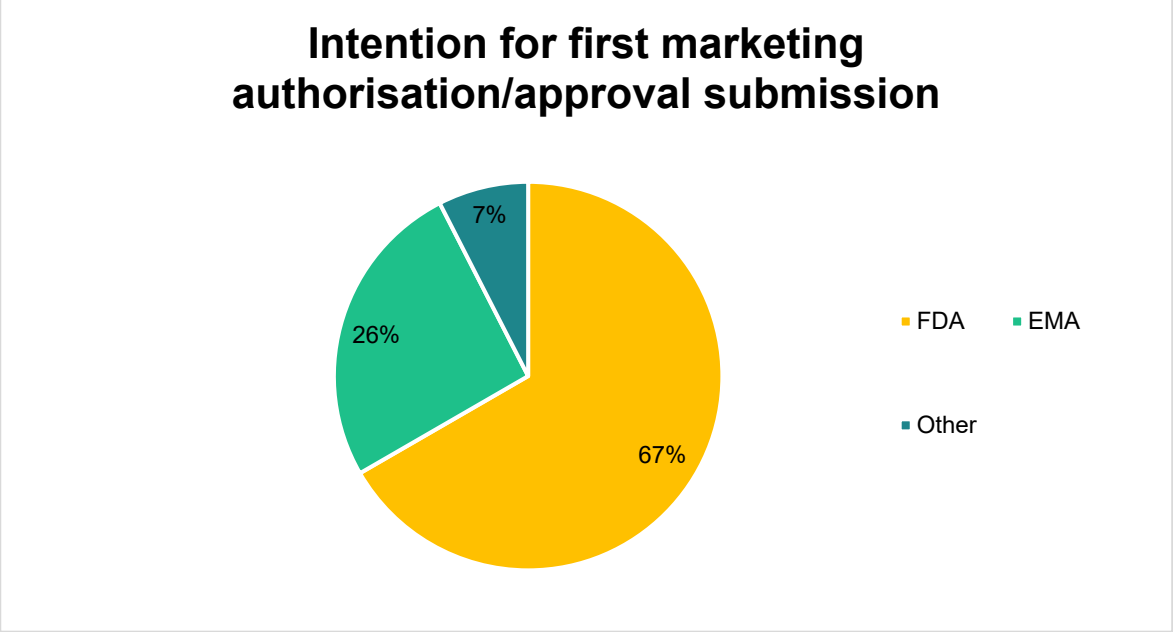


Figure 12: Intention for first marketing authorisation/approval submission by companies with MCMs in development (n = 93 MCMs)

Various reasons were provided by respondents to justify this decision:

- the United States is a large and single market and represents the highest probability of commercial success for an AMR MCM.

- despite the streamlining of the regulatory process in the Europe with a centralized procedure, pricing and access are discussed at national level, which lowers the attractiveness of initial marketing authorisation in Europe.
- in some instances, the developer is a U.S.-based company or is under U.S. governmental support/programmes.
- marketing authorisation/approval by the FDA is a fast process with a clear regulatory pathway and acts as a gateway for approval by other regulatory authorities.

Antimicrobial clinical trials usually rely on non-inferiority trials, which have high patient recruitment cut-offs despite the relatively small patient populations, particularly in Europe[30]. As a result, coordinating and recruiting patients to antimicrobial clinical trials is logistically difficult because the length of treatment is often short and there are few rapid diagnostic devices available to identify eligible patients. While it is an important challenge, the need to coordinate clinical trials was only mentioned by 2 respondents. The requirement of non-inferiority trials was highlighted as extremely or moderately challenging by 72.7% of the stakeholders that responded to the survey question (3 advocacy groups and 8 companies of the 26 respondents).

The regulatory complexity associated with pricing and reimbursement is an additional challenge identified via the primary-data collection. A total of 66.7% of Member States rated the pricing and reimbursement challenges as extremely or moderately challenging (see below). This was mirrored by 57.7% of stakeholders that responded to the relevant question (9 companies, 4 advocacy groups and 2 networks).

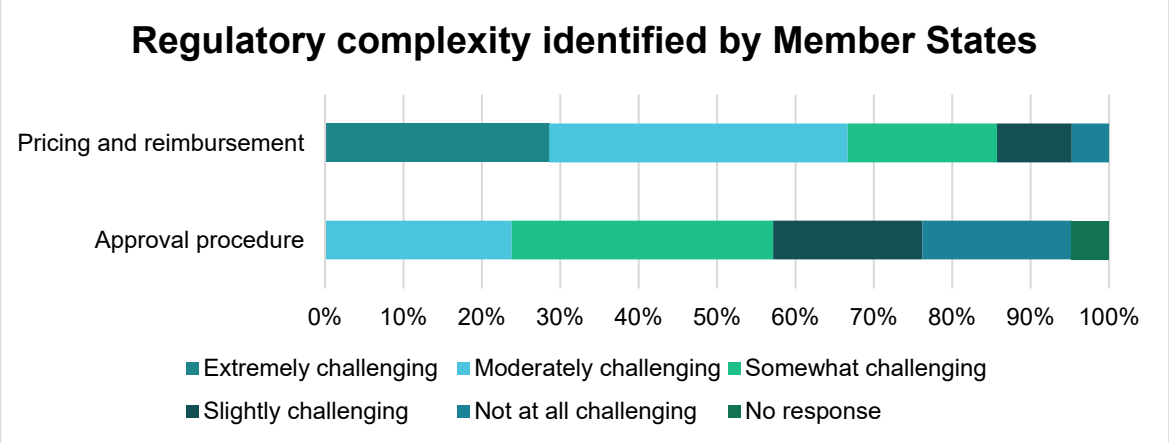


Figure 13: Regulatory complexity identified by Member States (n = 21)

Out of the 21 Member States that responded to the question on the types of support provided to support R&D into new and innovative AMR MCMs, only 8 Member States stated that they provide regulatory support. The types of support provided by Member States to ensure existing AMR MCMs are accessible and in adequate supply was quite variable. Out of the 21 Member States that responded to the question, 12 provide regulatory support, 10 provide national level stockpiling, 8 provide support in terms of hospital reporting on new AMR MCM needs and shortages, 5 provide pricing/reimbursement incentives (e.g. DRG carve-out), 4 participate in joint procurement agreements, 3 participate in multinational joint procurement and 3 provide support for manufacturing and supply.

From an access perspective, 12 Member States stated that they provide regulatory support (e.g. approach to conducting a Health Technology Assessment). Additionally, out of the 9 fund distributors that responded to the survey, 5 stated that they provide regulatory support to the projects they fund.

[30] Shlaes, D.M., 2015. Research and development of antibiotics: the next battleground. *ACS Infectious Diseases*, *1*(6), pp.232-233.

These results, when taken together, further highlight some of the key differences among different regulatory agencies and reinforces the need to streamline regulatory requirement across these agencies in order to ensure a global availability of new AMR MCMs. To overcome the aforementioned regulatory challenges, additional support needs to be provided. Not only do these challenges have a direct financial impact because they lead to increased development costs and higher expenses for the licensing company, but they also cut into the product's effective patent period.

5.4. Conclusions and the role of DG HERA

Through the primary-data collection, we asked various stakeholders the role they foresee for DG HERA. This question was answered by 21 Member States, 12 academic institutions, 5 advocacy groups, 9 fund distributors/contributors, 41 companies in the AMR industry, 3 networks and 2 product development partnerships. The answers were either described using free text or by rating a list of options based on importance. The options included:

Table 9: The role that stakeholders expect DG HERA to have

Classified Role	Total Occurrence
1. Coordinate and support, and/or implement pull incentives	68
2. Coordinate and/or contribute to funding of development and innovation of new AMR MCMs (push incentives)	54
3. Dissemination of best practices and capacity building	44
4. Provision of technical/regulatory guidance and/or streamlining of regulatory processes	33
5.Priority signalling (identify priority AMR MCM susceptible to address priority pathogens, establish target product profiles, carry-out pipeline analysis)	27
6. Pipeline coordinator	17
7. Addressing supply chain issues (forecast demand surge and supply chain vulnerabilities, targeted stockpiling actions)	13
8. Coordinate and support the development pooled procurement mechanisms	10
9. Coordinate and support the development of partnerships amongst relevant stakeholders	9

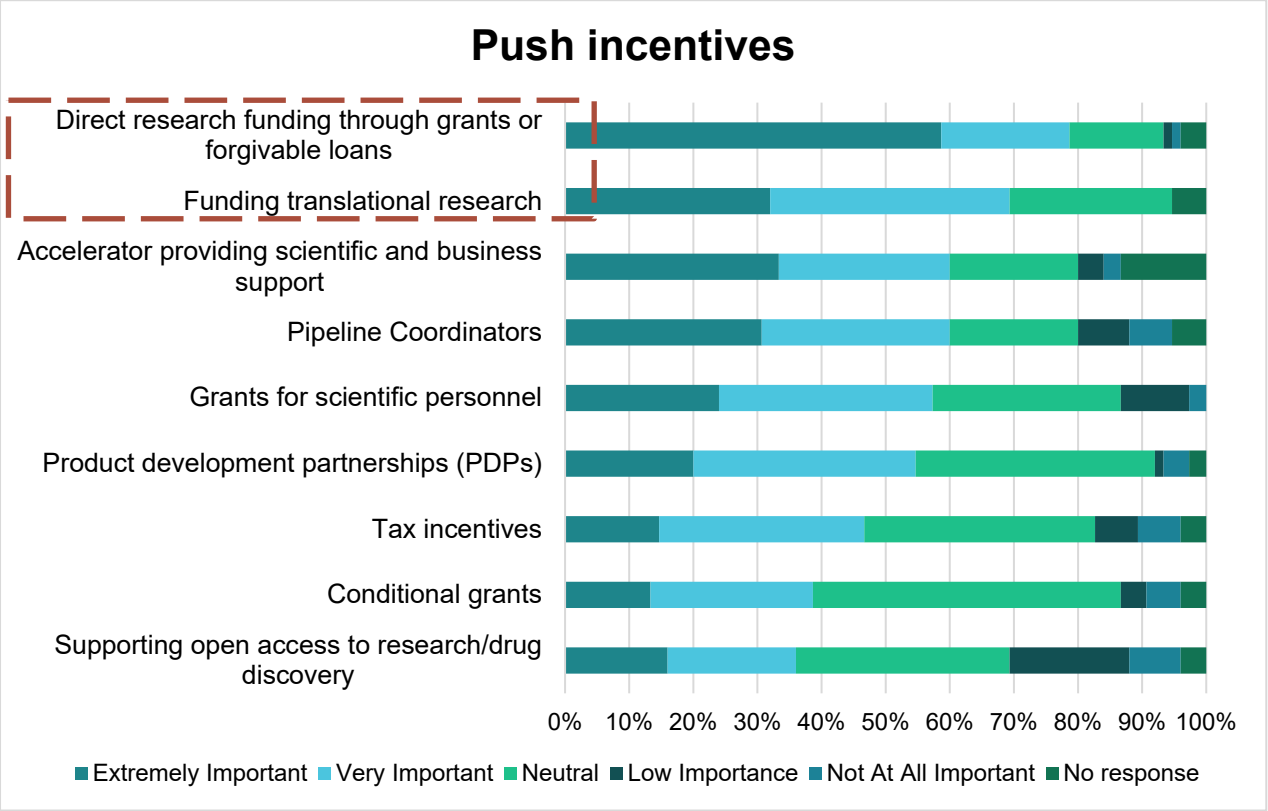
The table above shows a convergence from surveyed Member States, industry, and other relevant stakeholders on roles that DG HERA may take up to address the AMR-related financial, scientific/technical, and regulatory challenges. With this insight in mind, this study focused on developing options for action enabling DG HERA to tackle those 5 priorities.

It is clear from the table above that there is consensus across respondents that DG HERA has an important role to fulfil and is expected to take on various responsibilities. The role with the highest number of occurrences, particularly among the Member States and industry is for DG HERA to coordinate and support, and/or implement pull incentives. This is particularly relevant from the perspective of Member States to ensure access to existing AMR MCMs. When it comes to R&D, the role of coordinating and/or contributing to financial push incentives as well as pull incentives occurs almost equally among the Member States. Given the synergies amongst some of the roles, the role of dissemination of best-practices and capacity building, provision of technical/regulatory guidance (although it is rather the mandate of EMA and DG SANTE), and priority signalling were grouped together to form a broader coordination role. Across all other stakeholders, there is an almost equal occurrence of the three different roles.

In the survey, various push and pull incentives were proposed to address the challenges highlighted in the earlier section. Stakeholders were asked to rate various push and pull incentives in order of importance. From a push incentive perspective, 75 stakeholders responded to the question. As can be seen in the bar chart below, the most important **push incentive**, identified as extremely or very important by almost 80% of respondents, is “Direct research

funding through grants or forgivable loans", followed by "Funding translational research", which was deemed extremely or very important by approximately 70% of respondents. Details of the financial push incentives mentioned above will be provided in subsequent sections of this report.

Figure 14: Push incentives ranked in order of importance as identified by relevant stakeholders (n = 75; 16 academic institutions, 40 companies, 5 advocacy groups, 8 fund distributors/contributors, 3 networks, and 3 product development partnerships).



With regard to **pull incentives**, 55 stakeholders responded to the question. As shown in the bar chart below, the 5 pull incentives considered extremely or very important by over 61% of respondents in order of importance are "Fully delinked subscription models", "Fully delinked Market Entry Reward", "Partially delinked Market Entry Reward", "Transferable Exclusivity Voucher", and finally "Partially delinked Subscription Model". Details of these pull incentives will be provided in later sections of this report.

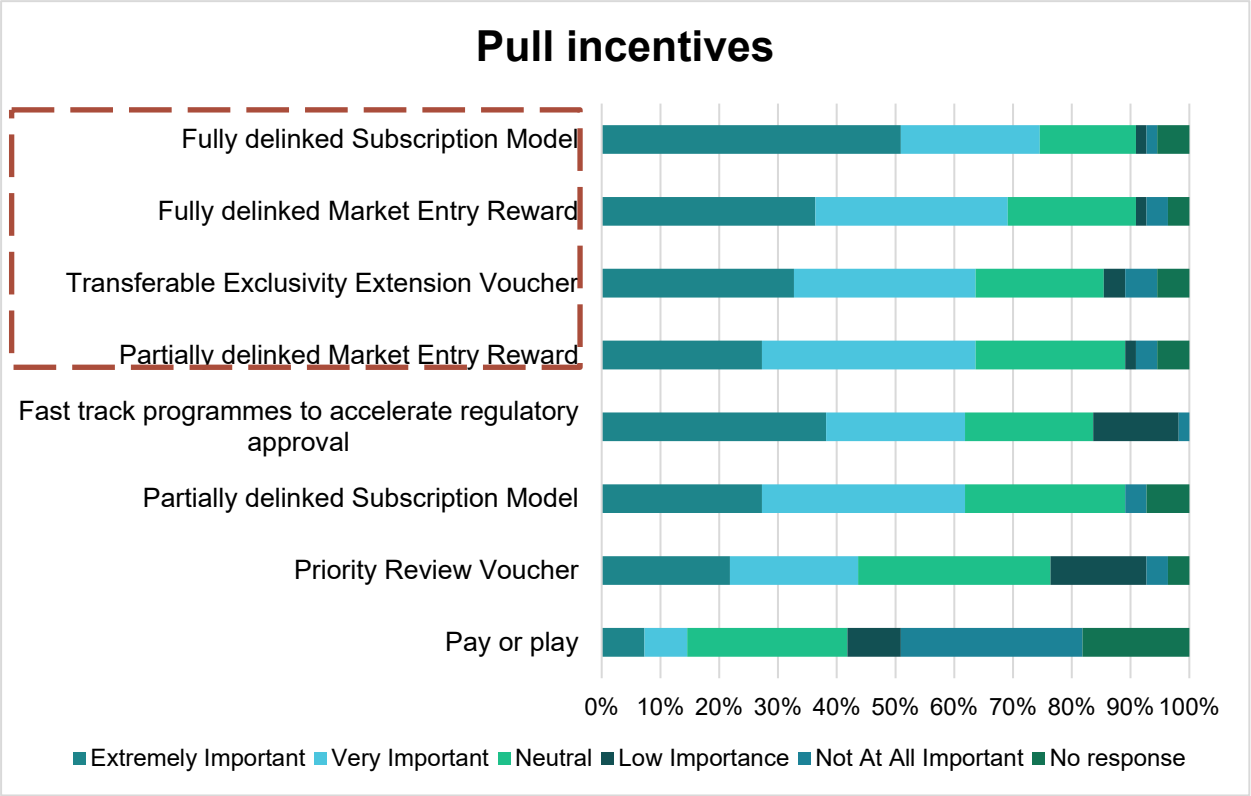


Figure 15: Pull incentives ranked in order of importance as identified by relevant stakeholders (n = 55; 38 companies, 5 advocacy groups, 8 fund distributors/contributors, 2 networks, and 2 product development partnerships)

As well as rating the various pull incentives proposed, respondents were asked to elaborate on the need for pull incentives, providing some valuable insights that feed into our subsequent proposals of options for action by DG HERA. The insights gained have to be interpreted with caution, however, as a number of responses were identical, meaning that it may not be the position of the company itself being stated, but instead that of the organisation to which they are affiliated. A total of 6 companies, all of which were SMEs, provided the following input:

Table 10: Direct quotes from the primary data collected

SME quote #1	*"Subscription models are very relevant but may be unrealistic in the short term in a EU27 context, since that would imply a financial commitment from all the Member States, with a significant risk of free-riding (i.e. a country not willing to pay its share for a new antimicrobial while benefiting from its positive "shielding" effect on the spread of a resistant pathogen in neighbouring countries). The market entry reward model suffers from the same drawback. Furthermore, a one-time payment is a significant risk to the health system if the product is ultimately unavailable for medical or commercial reasons. Such a reward (subscription or Market Entry Reward) can be fully or partially delinked. We prefer the partially delinked option since it may provide a lower disruption of the current pricing/reimbursement national systems and also solves the case of a local outbreak where the required amount of the new antimicrobial would largely exceed what is written in the contract."*
SME quote #2	*"it is of paramount importance that, regardless the model, pull incentives are sufficient in size"*
SME quote #3	*"We are in the difficult situation where a complex problem must be solved by a readily implementable solution; otherwise, there is a risk that the whole innovation ecosystem collapses, with huge consequences (loss of the portfolio, loss of professional skills to understand microbiology and develop relevant antimicrobials, etc.). We MUST ACT NOW. Some flexibility in the system should be introduced to allow for some fine-tuning in the first few years so that the mechanism is attractive enough without jeopardising the resilience of the healthcare system. Whatever the mechanism, the magnitude of the reward must be sufficient to play a true incentive role, otherwise the private investment sector would be lost forever.*

	Finally, the chosen mechanism must not only reward the first-in-class drugs, since it would prevent the discovery of sometimes very useful improvements that leads to best-in-class drugs. Nevertheless, the system must somehow avoid the multiplication of useless "me-too" drugs."
SME quote #4	*"Because of the complexity of the problem, single models alone cannot tick all boxes: they all have pros and cons. A hybrid model (i.e. a combination of PULL mechanisms) is more likely to reach the objective, especially if it both reward innovation and enable access."*

The insights gained from the comments above were taken into consideration when analysing the potential pull incentives that could be implemented within the EU.

Member States provided limited input when asked about the implementation of push and pull incentives and its potential sources of funding. When asked to describe any pull incentives to which their Member State would be interested in contributing, respondents from 19 of 22 Member States did not provide any meaningful answers. The remaining three Member States stated that they would be interested in exploring a similar model seen in the United Kingdom, fast-track programmes to accelerate regulatory approval, and a market entry reward mechanism. The lack of clarity and knowledge amongst the respondents from Member States is apparent when looking at the pie charts below. A total of 80% of Member States that responded to the question on whether their Member State would be interested in participating in the mechanism suggested by the EU-JAMRAI stated that they do not have an opinion and require more information, despite the provision of background documentation within the survey.

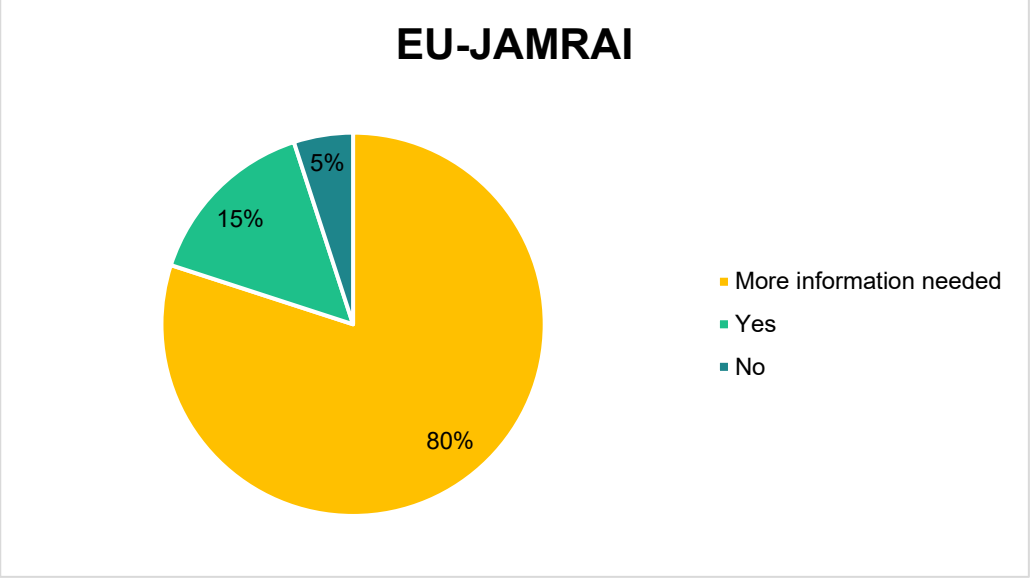


Figure 16: Interest from Member States in participating in the mechanism proposed by the EU-JAMRAI (n = 21 Member States)

The EU-JAMRAI (2017-2021) co-funded by the EU Health Programme conducted a detailed analysis and drafted corresponding recommendations in order to foster synergies among EU Member States[31]. As part of the study, interviews were conducted with human health policymakers from select EU Member States. There was consensus across all interviewed countries that new pull incentives are needed to maintain a reliable supply of both old and new essential antibiotics. However, collectively, there was uncertainty expressed by the countries taking part in this study as to which incentives may be appropriate for them, which antibiotics should be included, how to implement incentives, and the cost. This is in line with the primary data collected from Member States via both surveys and interviews. Eleven of the thirteen

[31] Årdal, C., Lacotte, Y., Edwards, S., Ploy, M.C. and European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI), 2021. National facilitators and barriers to the implementation of incentives for antibiotic access and innovation. *Antibiotics*, *10*(6), p.749.

countries interviewed preferred a multinational mechanism to provide pull incentive independent from a national Health Technology Assessment (HTA), medicine pricing, and reimbursement processes, which are complex and heterogeneous. Most EU countries opted for an independent body, potentially the EMA, to recommend new antibiotics for eligibility based upon an assessment of the value to public health. To address the expectations of the majority of the countries interviewed with regard to multinational collaboration, EU-JAMRAI recommended a revenue guarantee scheme that can be managed by the European Commission. This would provide a flexible guaranteed amount that could be adjusted based upon the public health value of the antibiotic, e.g., a first-in-class antibiotic against resistant infections could achieve a high annual revenue. This will simultaneously stimulate innovation while securing access to existing or new essential antibiotics that demonstrate a value to public health through clinical evidence.

Given that the majority of Member States do not have an opinion and require more information regarding important mechanisms proposed to address the AMR market failure, this reinforces the need for DG HERA to disseminate information and best practices, particularly among the Member States.

With the above in mind, the following chapters will provide an analysis of three options for action designed to fulfil the expected roles of DG HERA, with the aim of addressing the R&D challenges and ultimately the Member State R&D and access needs. The chapters will be divided as following:

- **Pull incentives**: a comparative simulation of delinked and partially-delinked models – a comparative analysis of the impact of revenue guarantee, MER and milestone-based rewards as incentives to the industry investing in new innovative antibiotics, as well as the strings attached to ensure access to successful products.
- **Push incentives:** funding R&D and translational research – actions, focusing on financial support, that can push new medical countermeasures to the market.
- **Coordination and capacity building:** awareness for the Member States and gain in scale and efficiency for industry and organisations – this comprises the non-financial aspects prioritised by stakeholders, including dissemination of best practices and capacity building on AMR related-topics, provision of technical and regulatory guidance, and priority signalling.

6. Pull incentives

6.1. Context and challenges

As highlighted in the aims and objectives of this report the most pressing need identified by Member States is in R&D for AMR bacterial treatments. As a result of the timeline of this study, and in order to apply focus to the most pressing needs, this section of the study specifically investigates pull incentives for antibiotics/antimicrobial treatments. As a consequence, non-traditional agents (such as phage therapy) have not been explicitly covered in this section.

Pull incentives encompass all the measures that reward R&D by increasing future revenue expectations; their primary aim is to make the completion of antibiotic R&D projects financially attractive, and thereby help tackle market failures for antimicrobials. To this end, pull mechanisms provide financial incentives to:

- ensure a level of certainty on the return on investment for product developers. As sales of antibiotics are expected to be low, pull incentives provide the financial support needed to ensure a viable market from the innovator's perspective
- guarantee sales' profitability for successful medicines. Antibiotics tend to be priced lower than drugs in other therapeutic areas, which can be compensated by pull incentives while still ensuring proper and responsible stewardship measures
- boost SMEs financial attractiveness to the private sector. As these types of reward increase the expected return on investment, SMEs investing in AMR may become more attractive to venture capitalists and private equity
- transfer the risk of failure on to the developer. As the reward is given to successful projects only, the firm bears the cost of developing the product and in the event of a failed project, the developer will lose the R&D-related costs. The opposite is true for push-incentive mechanisms[32], in which case the authorities provide the grant before the product has been developed, so the cost of failure is put on the funder.

To achieve these objectives, pull mechanisms can take different forms. In this chapter, the objective is to define the most appropriate pull mechanisms for the EU and carry out a pre-feasibility assessment. To do so, the chapter will:

- demonstrate that stakeholders have strong expectations around the role that DG HERA will have in coordinating pull incentives
- explain the current lack of financial return faced by companies when developing MCM treatments, to show in which phases of research pull incentives are most needed (6.1.3)
- present the main *theoretical* advantages and limits of the major types of pull incentives that can be provided by public authorities (6.2.1)
- derive from these two analyses a sub-set of pull incentives that should be more relevant for the EU (6.2)
- present the main findings and conclusions regarding the effect of these pull incentives selected above, especially on the profitability of R&D projects related to antibiotics (6.2.3)
- perform a pre-feasibility assessment of each recommended intervention (6.3)

[32] When a grant is provided, the funder pays for it, so if the project fails, the funder has paid for "nothing", this is what is meant by "bearing" the cost. With a reward, the developer bears the risk because if the project fails, he will not be awarded the prize.)

- conclude with guidance for the future design of options for action to incentivise R&D and bring more antimicrobial treatments for bacteria to market in the European Union (6.4)

6.1.1. Survey data

As shown by the primary data collected, stakeholders have strong expectations for DG HERA to coordinate and support pull incentives (68 out of the 81 respondents[33] mentioned that the key role of DG HERA should be to "coordinate and support, and/or implement pull incentives"). From the various options listed, this was the one with the largest number of responses.

Moreover, the survey ranked the types of pull incentives deemed most relevant by stakeholders. As presented in session 5.4, apart from the "Pay or Play" and the "Priority Review Voucher", all other models were considered extremely or very important by at least 70% of respondents.

This constitutes a strong basis for collecting further evidence on the different types of pull incentives. Furthermore, when the Member States were asked about the pull incentives that should be implemented at EU level, no consensus has been reached. Instead, a knowledge gap is evident, with a majority of them still having limited knowledge on the EU-JAMRAI proposals among other pull incentives.

6.1.2. The different types of pull incentives

There are various mechanisms to operationalise pull incentives. Important examples include awarding a higher level of reimbursement (potentially conditional to diagnosis confirmation), market entry rewards, which can be fully delinked or partially delinked, revenue guarantees, and milestone-based rewards (MBR). The advantages and disadvantages of each option, identified through a desk research and expert consultation, are summarised below[34].

[33] The respondents belong to the following categories: 21 EU Member States, 12 Academic institutions, 32 industry, 5 Advocacy Groups, 6 Funding Distributors, 3 Networks, 2 PDPs

[34] The table has been inspired by this article: Årdal C, Røttingen JA, Opalska A, Van Hengel AJ, Larsen J. Pull Incentives for Antibacterial Drug Development: An Analysis by the Transatlantic Task Force on Antimicrobial Resistance. 2017 Clin Infect Dis. Oct 15;65(8):1378-1382.

Table 11: Conceptual Advantages and disadvantages of pull incentives (results of desk research and expert consultation),

Incentive	Description	Advantage	Disadvantage
Higher reimbursement	Aims to increase the market price of a treatment to ensure profitability to the developers and distributors. In some cases, the higher reimbursement mechanism can be conditional to diagnostic confirmation to guarantee stewardship.	The price of the treatment is adjusted to better reflect its societal value Relatively straightforward to implement Does not need to collect funds upfront.	May adversely affect accessibility because the price for the treatment will increase and not all patients have full health coverage within the EU. Subject to national-level control of pricing and reimbursement. This can be of particular complexity in an EU context where reimbursement levels are decided at national level. The reward is directly linked to the number of units sold, while the objective of public health is to limit the use of antibiotics to cases where they are strictly necessary in terms of stewardship. Hence, this mechanism fails at delinking revenues and sales. Higher reimbursement in countries with low resistance rates will not represent an attractive market.
Market-entry rewards	Consists of a series of financial payments to an antibiotic developer for successfully achieving regulatory approval for an antibiotic that meets specific pre-defined criteria. In the “fully delinked” version, the mechanism’s payments are the supplier's sole source of revenue. In the “partially delinked” version, the innovator receives annual pre-defined payments in addition to revenues from unit sales.	Provides developers with a viable and predictable return on investments. In terms of effect on the pipeline, this scheme is expected to be effective in pulling more medicines to the market. Delinking the financial reward from the sales level, thus aligning public health objectives (minimising antibiotics use). However, in its partially delinked version, it may be less costly for public authorities but restores the link between profits and sales.	Complexity in determining the amount of the financial reward to be provided: excessively small prizes would not incentivise enough R&D, but excessively large rewards may be too costly. Exposes public payers to a greater risk of paying high sums for an antibiotic that may suffer a sudden loss of effectiveness. The strings attached to this mechanism can reduce this risk and are covered in more detail in the subsequent sub-section.
Annual Revenue Guarantee	With this mechanism, the public authorities “top up” revenue for developers to reach the “guaranteed” amount. If sales reach the threshold amount, no further “top up” is awarded.	This may be less costly than the fully delinked market entry reward, depending on the level of sales that determines the “top up” amounts to be paid. Payments can be conditional to a certain use and features of the drug. A model that implicitly also guarantees access on a	Complexity in determining the right threshold: an excessively low annual revenue guarantee will not provide enough incentives while excessively high thresholds may be too expensive for public authorities. The innovator may receive annual payments in addition to

		year-by-year basis and can therefore be used to secure the availability of existing antimicrobials across countries. Should allow for changing financial conditions over time, e.g. if an antibiotic loses efficacy and societal value, the guarantee could be revised downward	revenue from unit sales. This may be less costly for public authorities but restores the link between profits and sales. Smaller yearly payments may not have a sufficient "pull effect", especially for molecules in early R&D phases. Furthermore, in the event of an EU-coordinated incentive, the dependence on decisions by several countries, especially if renewed every year, would make the size of each yearly payment uncertain, reducing the pull effect even further.
Milestone-Based Reward (MBR)	Can be considered early-stage pull incentives that consist of a financial reward upon achieving certain R&D objectives prior market approval (e.g. successful completion of phase I).	Since they reward one phase of the research, the funding cost is lower than a market entry reward. There is a possibility to focus R&D on clinically relevant targets by defining clear conditions for the reward. Antibiotic SMEs have shown a clear interest in milestone-based rewards, mainly because it generates actual revenue instead of merely covering costs, as it the case with grants: such revenue can potentially raise the SME's book value, which is a key metric for venture capitalists who decide to invest in these companies. A MBR gives substantial cash directly to SMEs early in the R&D process and prior to starting the next phase, which differ from grants that are paid as ex-post reimbursements or closely linked to sustained costs.	Does not guarantee that the research will end up in a marketable treatment due to the early stage at which it can be awarded. The phase for which the MBR is awarded will be key: awarding in early phases may be less costly because prizes should be tuned to the level of costs/efforts sustained by developers but doing so will entail more risk for the public due to a higher risk of failure. A MBR at phase I and phase II may provide unreliable clinical data on which the allocation of reward is based. Such risk of fraud can be reduced by having awarding bodies such as pipeline coordinators to require full insight in clinical data and even the design and performance of the trials. Existing grant structures up to phase I clinical trials may be more effective and less costly.

It should be noted that the Transferable Exclusivity Extension Voucher (TEEV) is the topic of numerous position papers from notable organisations such as the European Federation of Pharmaceutical Industries and Associates (EFPIA)[35] and the BEAM Alliance (Biotech companies from Europe innovating in Anti-Microbial resistance)[36]. Assessment of the TEEV is within the remit of the Pharmaceutical Regulation and is not within the mandate of DG HERA, in this respect, did not fall within the scope of this study.

The key takeaway messages from this first comparative analysis of pull mechanisms can be summarised as follows:

- there are four major types of pull incentives that may help increase the expected revenue for developers: higher reimbursement, market entry rewards, an annual revenue guarantee, and a milestone-based reward.
- higher reimbursement mechanisms can be more complex to implement in an EU environment where the decisions on reimbursement levels are made at national level. Moreover, such mechanisms are unable to delink revenue and sales. This is why we reject them for further investigation.
- a market entry reward has the advantage of fully delinking the revenue of the developer from unit sales, which supports antibiotic stewardship. Thus, we pre-select this option for further investigation.
- The milestone-based reward can be less costly and the annual revenue guarantee can be less risky for public authorities, thus were pre-selected for further investigation

This assessment will be complemented, in the next session, by empirical evidence on the need for pull incentives. Combined, they create a sub-set of pull mechanisms for which a detailed analysis was performed.

6.1.3. The profitability challenge

Selecting the most appropriate options for action for DG HERA from these incentives requires understanding the profitability gap experienced by antibiotic developers in the current environment. To this end, this section aims to quantify the current antimicrobial market failure and the lack of profitability in a simulated "baseline scenario". To define this scenario, the data and assumptions were as follows:

- data used in this simulation to quantify R&D costs, the risk of failure and the duration of R&D phases are based on **factual information from large pharmaceutical companies and SMEs.** This was sourced using:
  - the DRIVE-AB (Driving re-investment in R&D and responsible antibiotic use) project consortium (DRIVE-AB report, 2018)
  - Global Antibiotic Research and Development Partnership (GARDP) online
  - Global AMR Hub
  - an industry survey performed under this study to collect additional SME costs per phase
  - other mapped data under Annex 5 - Detailed analysis of the effects of pull incentive

[35] EFPIA (2022) "A new EU pull incentive to address Antimicrobial Resistance (AMR) Recommendations from EFPIA [online] Available at: https://www.efpia.eu/media/636464/a-new-eu-pull-incentive-to-address-anti-microbial-resistance-amr.pdf [accessed 24th October 2022]

[36] BEAM Alliance (2022) "Towards a functioning AMR market: 4 pillars for a pull incentive in Europe" [online] Available at: https://beam-alliance.eu/beam-proposal-eu-incentives/ [accessed 24th October 2022]

- impact of the UK, German, French and Swedish pull programmes were not included
- developers depend on revenue that is derived only from sales after regulatory approval.
- push incentives were included in this analysis through a reduction in costs including the grants provided by CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), BARDA (Biomedical Advanced Research and Development Authority), ENABLE via the Innovative Medicines Initiative (IMI), JPIAMR and Welcome Trust.

The table below shows our input data regarding the duration, probability of success, and costs for each R&D stage. Separate cells also show how the existing push incentives reduce the R&D costs for developers in preclinical, phase I and phase II stages.

Table 12: Summary of data inputs to the simulation

	Preclinical	Phase I	Phase II	Phase III	Submission
			Probability of Success		
Min	0.09	0.33	0.46	0.55	0.75
Max	0.44	0.67	0.75	0.86	0.91
			Cost (USD Million)		
Min	2	2.2	4	30	6
Max	34	38	76	159	88
			Cost reduction (through grants)		
Min	20%	20%	20%		
Max	100%	100%	80%		
			Duration (months)		
Min	54	11	13	22	9
Max	72	33	36	35	30

Based on this input data, in the bar chart below on the left, the Y axis shows the **cashflow** (revenue minus cost in USD million over one single phase) at individual R&D phases up to 11 years after market launch. The X axis shows the timeline of a project:

- "PC" = preclinical,
- "P1 to P3" = phases I to III
- Numbers "1 to 11" = the years after market launch

The value of the cashflow[37] is represented by a rectangle. For each rectangle, the bold line is the median value, the light lines outside the rectangle are the minimum/maximum value, and the upper limit of the rectangles defines the range where 75% of the values lie, while the lower limit of the rectangles defines the range where 25% of the values lie.

[37] These results are based on a simulation of more than 100,000 projects, See Annex for further detail.

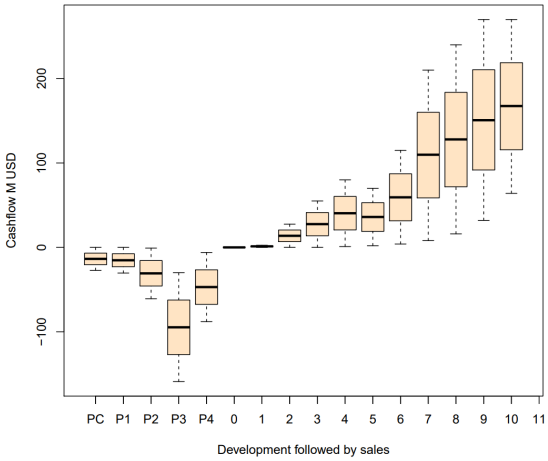


Figure 17 Cashflow per development stage

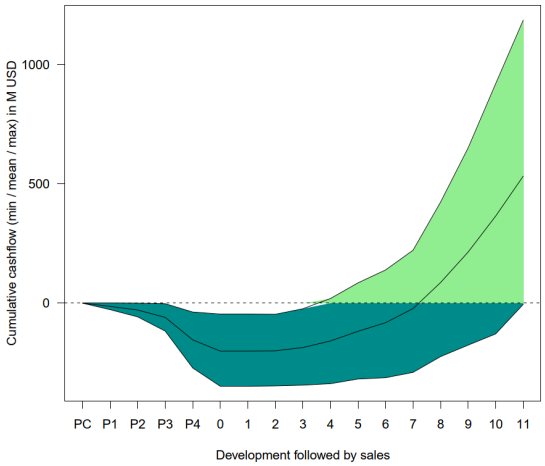


Figure 18 Cumulative cashflow

In brief, until market launch (value “0” on the X axis), antibiotic projects experience negative cashflow (due to R&D costs) in each phase, especially in phases III and IV. After market authorisation (value “0” on the Y axis), drug revenue grows slowly with low positive cashflow in years 0-2. The decline in cashflow between years 4 and 5 on the market depends on the presence of post-approval costs for conducting paediatric studies, for instance.

An improved view on profitability is offered by looking at the cumulative cashflow *over different phases* of an antibiotic’s lifecycle (and not for each phase). This is shown by the graph above on the right.

The dark green area shows negative cumulated cashflow, and the light green area shows positive cumulative cashflow, with the black line running through the middle of both areas corresponding to the median (the value reached by half of the simulated projects). The upper and lower limits correspond to the maximum and minimum value respectively, spread over 100,000 simulated projects. The large variation in the cumulated cashflow reflects the wide difference of antibiotic projects in terms of characteristics of molecules (e.g., risks of failure), preclinical assays and clinical trials performed, expected R&D duration and sales, as well as developers’ features.

In brief, cumulative cashflow remains negative until the third year after approval, and **half of projects take 7 years after launch to recuperate the investments in R&D**: the median cumulated cashflow reaches 0 at year 7. In addition, some projects continue not to offset R&D costs, even after 10 years on the market.

While cumulative cashflow shows the sum of revenue minus cost over time, drug developers decide whether to start, continue or terminate a project based on such cashflow, but also on the time-based value of money, the uncertainty of alternative investments and the risk of failure. In this respect, drug developers calculate the **Expected Net Present Value (ENPV)**, which explained in more detail in the box below. In summary, this is a more advanced measure of cumulative cashflow and can be interpreted as an **indicator of profitability**.

If the developer expects the *net present value* of their revenue to be positive, they will start or continue with the project. Instead, a negative ENPV shows that the discounted, future revenue of a project is not enough to cover upcoming costs, meaning that the developer will not start or continue the project and therefore not bring more medicines to the market. With developers making these decisions before each R&D stage, **the ENPV should be positive at each phase of development for it to pass on the next phase and have a chance to reach market launch.**

What is Expected Net Present Value?

The Expected Net Present Value is a standard economic measure. It can be defined as the expected difference between the present value of cash inflows and the present value of cash outflows over a period of time.

- "**Present** Value"

To understand this concept, it is necessary to explain a key economic concept, according to which **values that correspond to different time horizon are not directly comparable**. For instance, receiving 100 dollars today is not the same as receiving 100 dollars in one year's time - as receiving 100 dollars today provides an ability to put this amount in a saving account which will generate interest, retaining the 100 dollars plus the interest earned in one year's time. This economic reasoning implies that any value in the future is not equivalent to the same value today.

However, we often need to compare values over different periods of time: for R&D projects, developers face costs today and generate revenue tomorrow. The economic concept of "present values" consists in converting values generated over different periods of time into a same comparable unit. Applied to the ENPV, it means that the revenue generated over different time periods minus the costs generated at different phases have all been converted into present values. To do this, we need a rate that will "discount" the future values, i.e. the "discount rate"; there are many ways to estimate it, mainly thought the real interest rate, or the rate of the capital's depreciation.

- "**Expected** Value"

Last but not least, **it is called "expected" because there is uncertainty when developing the medicine**. Developers face a risk of failure, based on their knowledge, technology, chemical features, etc. As a result, they also consider the probability that the revenue will be obtained in the future. In the end, **the ENPV is the amount of expected profit (revenue minus cost), expressed in "present values" that a project can expect to generate.**

- From ENPV to the decision-making process

If a developer achieves a positive ENPV, they will decide to proceed with the project, because this means that once all revenue, costs and the risk of failure have been taken into account and converted in the same unit, their profit is expected to be positive. In contrast, if the ENPV is negative, the developer will not continue with the project. **A value of "0" sets the limit between profitable and non-profitable projects.**

ENPV can be increased by decreasing costs and increasing the probability of success or increasing their revenue – policy interventions can act on these key parameters through, for instance, grants, market entry rewards or revenue guarantees, and active support via pipeline coordination that can improve probabilities of success. All this should result an increase in the number of medicines brought to the market.

The graph below shows the ENPV at each R&D stage. The light blue shows the minimum and maximum ENPV[38], the black line the median ENPV, and the dark blue the range of value where half of the project stands.

In brief, this graph shows that **only a minority of antibiotics projects have a positive ENPV at the preclinical stage (phases I and II)**, which demonstrates the need for financial incentives to help improve the ENPV at the early stages. **When focusing on the**

[38] Of a sample of 100,000 simulated projects, previously presented

mean ENPV only (black line), it is also noticeable that ENPV reaches a minimum in phase II and remains negative until phase III.

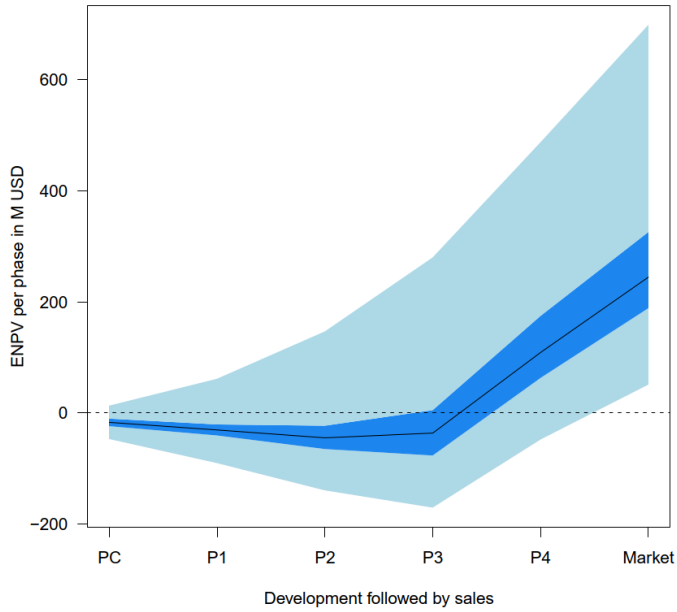


Figure 19: Antibiotic projects' Expected Net Present Value (ENPV), at various phases (baseline)

As a result, when providing options to help bring more antibiotics into the market through pull incentives, it is important to show **how these pull mechanisms can actually impact the ENPV of antibiotics, especially at each stage from preclinical to phase II** where the ENPV reaches a minimum. After phase III, most ENPV are positive values, which indicates that most developers at this stage will continue their development project, meaning that they are likely to bring their medicine to the market.

6.2. Options for action for DG HERA

6.2.1. Shortlisting four types of pull incentives for further assessment

The shortlisting of pull mechanisms was based on the following: (i) a literature review enabling an assessment of advantages and disadvantages of the pull mechanisms; (ii) the empirical arguments on the lack of profitability of antibiotic R&D projects explained above; and (iii) direct interviews and workshops with relevant stakeholders (detailed in Annex 3 – Expert workshop on pull incentives).

Based on these three criteria, we established a list of desired characteristics for the pull incentives ("interventions"):

- the pull incentives should guarantee that there is **a limited link between the revenue of the developers and the sales units** to incentivize access over consumption, thus reinforcing stewardship efforts. Therefore, the simulated interventions need to consist of either fully or partially delinked models.
- the effectiveness of the pull mechanisms is highly dependent of the **size of the financial support** that will be provided because it determines the change in ENPV achieved. Therefore, **for each type of pull mechanism investigated, a different financial amount will be considered**.
- the expected profitability of projects varies across the different R&D stages, and the lack of profitability is more severe at the early stages. Therefore, the **interventions should incorporate different timing of payments (i.e. payments distributed over a different time frame) in order to provide support in the phases that are less profitable**.

Relevant qualitative features must also be considered when designing and implementing a pull incentive, as they may equally impact profitability:

- eligibility criteria (which medical/scientific performance the antibiotic must reach to be selected for the incentive)
- moment for qualification (at which phase in the pipeline can an antibiotic be pre-qualified for eligibility to a specific intervention)
- market access/availability and stewardship requirements

These three last points were not included directly in our modelling and quantitative analysis but were instead further elaborated as part of the "strings attached" for access and stewardship. The above-mentioned method allowed for this study to focus on the following **four types of interventions**:

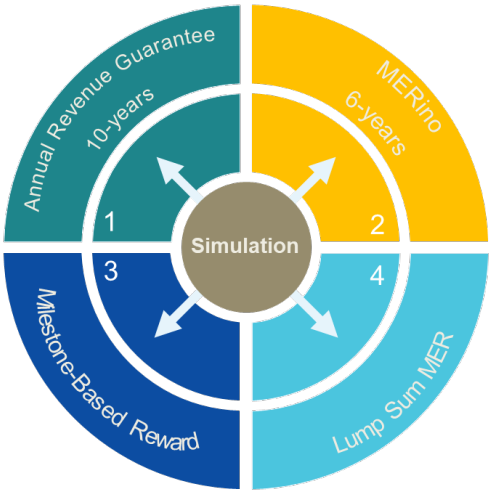


Figure 20: Pull incentives (interventions) to be simulated

It should be noted that that a recent article from the Centre of Global Development[39] mapped that several Member States have expressed their preferences for such mechanisms, especially milestone-based rewards, guarantee schemes and market entry rewards.

The table below details how each intervention will be integrated, and the following sub-section provides a quantitative assessment of the potential impact of each intervention on the profitability of projects, because, for each of them, different funding sizes will be proposed and justified.

[39]Antony Mc Dowell (2022) Centre of Global Development **The EU Wants to Transfer the Costs of New Antibiotics to its Member States—They Are Right To Revolt** [online]. Available at: https://www.cgdev.org/blog/transferring-costs-its-member-states-eus-proposed-voucher-scheme-incentivising-antibiotics [Accessed 6th December 2022].

Table 13: Descriptions of interventions

Intervention name	Description
Intervention 1 Annual Revenue Guarantee (RG) Scheme	Payments will operate as a "floor" to yearly revenues, making it a partially delinked from sales. The standard approach includes 10 yearly payments starting from the year of market approval. The annual revenue guarantee scheme is hypothesised to be the simplest pull mechanism to implement, as suggested by the EU JAMRAI report[40]. Moreover, this mechanism can be implemented for highly innovative antibiotics (through high yearly guarantee), less innovative and existing ones (through lower guarantees). Within this mechanism, single countries could opt in and contribute with different shares of a common "EU yearly guarantee", receiving in exchange access to the selected antibiotic brought to market, without affecting national level pricing and logistics. A more concrete understanding of its implementation and pre-feasibility assessment will be provided in the following section.
Intervention 2 The Market Entry Reward + small revenue guarantee (MERino)	A small market entry reward (MERino) that has the same size as the revenue guarantee spread across 10 years (Intervention 1) but is paid over a shorter time frame to account for "preference for present" payments. This intervention covers a period of six years, with two higher payments the first two years, and smaller ones in the following four years. Delimiting the revenue guarantee to six years is motivated by the fact that from the sixth year on the market, normal sales of an antibiotic are expected to be higher or comparable to the size of the yearly guaranteed payments[41]. Payments operate as a "floor" to yearly revenue, exactly like for the previous interventions, making MERino also a partially delinked incentive. A more concrete understanding of its implementation and pre-feasibility assessment will be provided in the following section.
Intervention 3 Milestone-Based Reward (MBR)	The MBR will be awarded at phase I (i.e., when safety data is known but not efficacy) and/or phase II (when some efficacy data is gathered) to give a financial gain (profit) to the successful developer, not simply covering a percentage of costs as push incentives do. This makes MBRs distinguishable from grants which are already present in the current landscape. In fact, in the specific remit of pharmaceutical R&D, MBRs are commonly utilised in interactions between big pharmaceutical companies and smaller drug developers, in addition with venture capitalists in managing, steering and motivating companies within their portfolio. A clear limit of this intervention is that it does not pull an antibiotic all the way to market launch and therefore requires to stipulate obligations for recipients to continue the R&D project through the subsequent phases until market authorisation and launch. Also, due to the high proportion of projects that fail, several MBRs will have to be awarded in order to have a sufficient number of antibiotics reaching regulatory approval. A more concrete understanding of its implementation and pre-feasibility assessment will be provided in the following section.
Intervention 4 Lump-Sum Market Entry Reward (LSMER)	Finally, we propose to model and test a LSMER. From the developer's perspective. With this intervention, we simply test if selected sizes of revenue deriving from a LSMER can function to improve the profitability of antibiotics. We model this intervention as a fully delinked LSMER, considering the large size of the payment received at once by the developer, which is able to fully substitute market sales as

[40] Christine Årdal, Marie-Cécile Ploy, Yohann Lacotte "**EU JAMRAI – D9.2 A strategy for implementation multi-country incentives in Europe to stimulate antimicrobial innovation and access"** [online] Available at: https://eu-jamrai.eu/wp-content/uploads/2021/03/EUjamrai_D9.2_Strategy-for-a-multi-country-incentive-in-Europe_INSERM-FHI.pdf [accessed 24th October 2022]

[41] Global AMR R&D Hub (2021) **Final report: Estimating Global Patient Needs & Market Potential for Priority Health Technologies Addressing Antimicrobial Resistance** [online] Available at https://globalamrhub.org/wp-content/uploads/2021/08/EAG-Report_FINAL_20082021.pdf [Accessed 26th October 2022]

	revenue sources for the developer.

6.2.2. *Defining the financial size of pull incentives*

With the selection of the interventions to be simulated, it is necessary to define in more detail the potential sizes for each of them in terms of monetary reward provided per drug in order to determine which financial support may cost effective and still have a considerable pulling effect. Based on academic research papers and on the current pilot pull programmes implemented in some countries, a robust methodological approach was used to define range of values for each type of interventions. We have used primarily the following six sources:

1. **The Swedish Pilot Revenue Guarantee Scheme** proposes a pull mechanism for mostly existing antibiotics that, if translated into global figures, would provide a revenue guarantee of SEK 70 million/year/drug over 10 years[42].
2. **The UK/NICE (National Institute for Health and Care Excellence) Subscription Model** proposes a fully delinked pull mechanism that would correspond to a global revenue guarantee of GBP 330 million/year/drug[43].
3. **The US PASTEUR (Pioneering Antimicrobial Subscriptions to End Up surging Resistance) Act.** Although the terms and conditions are not precisely defined: the pull mechanism could provide revenue schemes for companies that could vary between USD 750 million and USD 3 billion in total over 10 years, or between USD 75 million and USD 300 million/year/drug[44].
4. **The DRIVE-AB Final Report** proposes a pull mechanism based on an R&D cost and profitability approach. The report estimates that between EUR 800 million and EUR 1.5 billion (at least) in total would be necessary and could result in around 18 antibiotics reaching the market in the 30 years after implementation of this delinked model[45].
5. **The Boston Consulting Group (BCG) Study** also concludes on the need of pull incentives, in particular a revenue guarantee scheme (or subscription model) with a global amount of USD 250 million/year over ten years per antibiotic[46].
6. **An academic paper by Prof. Kevin Outterson** also focuses on innovation and recommends a delinked model. However, the size of the financial support should

[42] AMR Solutions (2020) "Sweden to test an access-focused model for new antibiotics: contracting for availability" [online] Available at: https://amr.solutions/2020/03/16/sweden-to-test-an-access-focused-model-for-new-antibiotics-contracting-for-availability/ [Accessed: 25th October 2022]

[43] National Institute for Health and Care Excellence "Models for the evaluation and purchase of antimicrobials" [online] Available at: https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials [Accessed 25th October 2022]

[44] US Congress "H.R.3932 – PASTEUR Act of 2021" [online] Available at: https://www.congress.gov/bill/117th-congress/house-bill/3932/text#:~:text=To%20establish%20a%20program%20to,pathogens%20and%20most%20threatening%20infections.&text=To%20establish%20a%20program%20to,pathogens%20and%20most%20threatening%20infections. [Accessed: 25th October 2022]

[45] Christine Årdal and David Findlay *et al.* (2018) "DRIVE-AB Report – Revitalizing the antibiotic pipeline – simulating innovation while driving sustainable use and global access" [online] Available at: http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed: 25th October 2022]

[46] Boston Consulting Group (2022) "The Case for a Subscription Model to Tackle Antimicrobial Resistance" [online] Available at: https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance [Accessed: 25th October 2022]

be higher, suggesting a global pull mechanism of USD 3.1 billion over 10 years, or USD 310 million/year and per antibiotic[47].

By using the minimum and maximum ranges suggested by the publications above and translating in global values, the final sizing for each intervention have been established and is summarised in the table below.

Table 14 Summary of the simulated interventions

Intervention	Scenario	Identifier
N/A	Baseline – no pull intervention, but includes current push incentives available as grants to antibiotic developer	Base
Intervention 1 Annual Revenue Guarantee (RG)	Low scenario – 70 million/year for 10 years	RG70
	Intermediate 1 scenario – 100 million/year for 10 years	RG100
	Intermediate 2 scenario – 150 million/year for 10 years	RG150
	High scenario – 310 million/year for 10 years	RG310
Intervention 2 The Market Entry Reward + small revenue guarantee (MERino)	Low scenario – 2 X 250 million + 4 X 50 million	MERino700
	Intermediate 1 scenario – 2 X 330 million + 4 X 85 million	MERino1000
	Intermediate 2 scenario – 2 X 500 million + 4 X 125 million	MERino1500
	High scenario – 2 X 1 billion + 4 X 275 million	MERino3100
Intervention 3 Milestone-Based Reward (MBR)	Low scenario – Phase I reward 30 million	P1Prize30
	Medium scenario – Phase I reward 40 million	P1Prize40
	High scenario – Phase I reward 60 million	P1Prize60
	Low scenario – Phase II reward 60 million	P2Prize60
	Medium scenario – Phase II reward 80 million	P2Prize80
	High scenario – Phase II reward 120 million	P2Prize120
Intervention 4 Lump Sum MER (LSMER)	Low scenario – LS MER – 1 billion	LSMER1000
	Medium scenario – LSMER – 2 billion	LSMER2000
	High scenario – LSMER – 4 billion	LSMER4000

It should be noted that the simulation assesses the pulling effect of various sizes of reward but does not consider whether this reward is provided by a single country or by a group of countries sharing the burden. Thus, once a specific intervention is considered, the question of the sharing of the burden at EU and global level must be raised.

In 2021, the Boston Consulting Group (in collaboration with the World Economic Forum, Wellcome and the Novo Nordisk Foundation) estimated the contribution of the various countries/regions under different scenarios**.** Considering a sharing of the burden based on GDP and assuming that China does not contribute, this group considers that the EU

[47] Outterson K. (2021) "Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines" Health Affairs (Millwood) doi: 10.1377/hlthaff.2021.00688.

contribution should stand between 29% and 39% of the total global initiative. Assuming that China does indeed contribute, Europe's contribution would be between 22% and 27% of the total global funding[48].

Calculating the share of the EU within a hypothetical global financial effort is challenging for the following reasons:

- what matters for a developer is not the origin of the financial support, but its amount and certainty. Therefore, from an economic perspective, it is not meaningful to calculate a specific EU support if one wants to develop the global pipeline in the field of AMR. This is why all the figures above refer to global amounts.
- the share of Europe will depend on the participation of other countries. If no other country is willing to participate, the EU could still fully support the initiative to make sure its population is correctly protected. This is why all the figures above can be interpreted as the maximum support that the EU could envisage.
- in the event of country cooperation, the participation of some key countries such as the USA or China will greatly influence Europe's remaining share. Given the current uncertain environment, it is for this reason that it is difficult to define a precise share for the EU. In the hypothesis that at least all G20 countries participate, the remaining share of the EU would be about 25%.

6.2.3. Estimating the effect of pull incentives

6.2.3.1. Methodological approach

In order to select a set of preferred pull interventions among the 17 options presented above, we applied a Monte Carlo simulation. The methodological details and complete results can be found in the Annex 5 - Detailed analysis of the effects of pull incentives Annex 5 - Detailed analysis of the effects of pull incentive.

Our modelling focus on the ENPV as the key indicator of profitability, reflecting common praxis within the industry. The simulation calculates the ENPV of all projects at six key decision points (preclinical, phase I, phase II, phase III, submission/phase IV, and at the moment of market entry). Our analysis focuses particularly on how the various interventions can improve the profitability of R&D projects (ENPV being positive) compared to the baseline scenario, where no pull interventions apply.

In turn, these simulated projects have characteristics based on real-life antibiotic R&D projects. The key advantage of this method, detailed in Annex 5 - Detailed analysis of the effects of pull incentives, is the possibility to conduct virtual "experiments" on a large sample of projects reflecting the wide variation of real-life R&D projects. As a result, a total of 1.8 million projects have been simulated for this analysis, i.e., 100,000 projects for 18 scenarios: the baseline scenario and the 17 tested interventions (four sizes for interventions 1 and 2, six sizes for intervention 3, and three sizes for intervention 4).

In particular, the simulation provides the following outputs that will be explained in more detail in the following analysis:

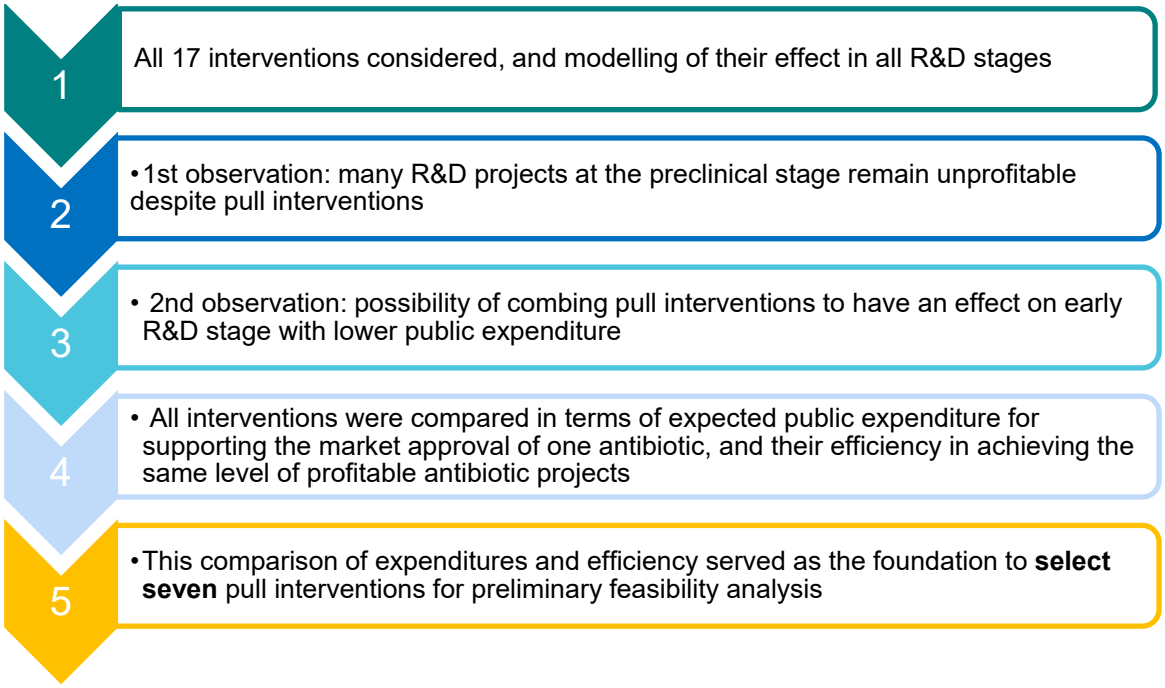
- the ENPV levels achieved with each intervention at the start of each R&D stage
- absolute and relative ENPV improvements caused by the various interventions compared to the baseline

[48] Boston Consulting Group (2022) "The Case for a Subscription Model to Tackle Antimicrobial Resistance" [online] Available at: https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance [Accessed: 25th October 2022]

- improvement rate of fully profitable antibiotic projects achieved by each intervention
- expected public cost for one launched antibiotic entailed by each intervention
- comparable public costs for doubling the ENPV improvement of all products.

Please note that the public expenditures we identify for the various pull interventions are calculated considering that the goal of the approach is to reward only one antibiotic upon approval. As we elaborate in the end of section, special considerations are needed to define total public expenditure if the goal is rewarding several antibiotics upon approval.

Against this background, we took the following approach for selecting a set of seven most prominent pull interventions from the 17 initially proposed:



6.2.3.2. Impact of the interventions at various R&D stages and explored combinations

The bar charts on the left show the impact of all 17 interventions on the ENPV at the four first stages of development. On each graph, interventions have been ranked from the least to the most effective (left to right) in terms of its ENPV improvement with respect to the baseline. It is important to look at the rectangle that indicates the value of ENPV where 50% of projects lie.

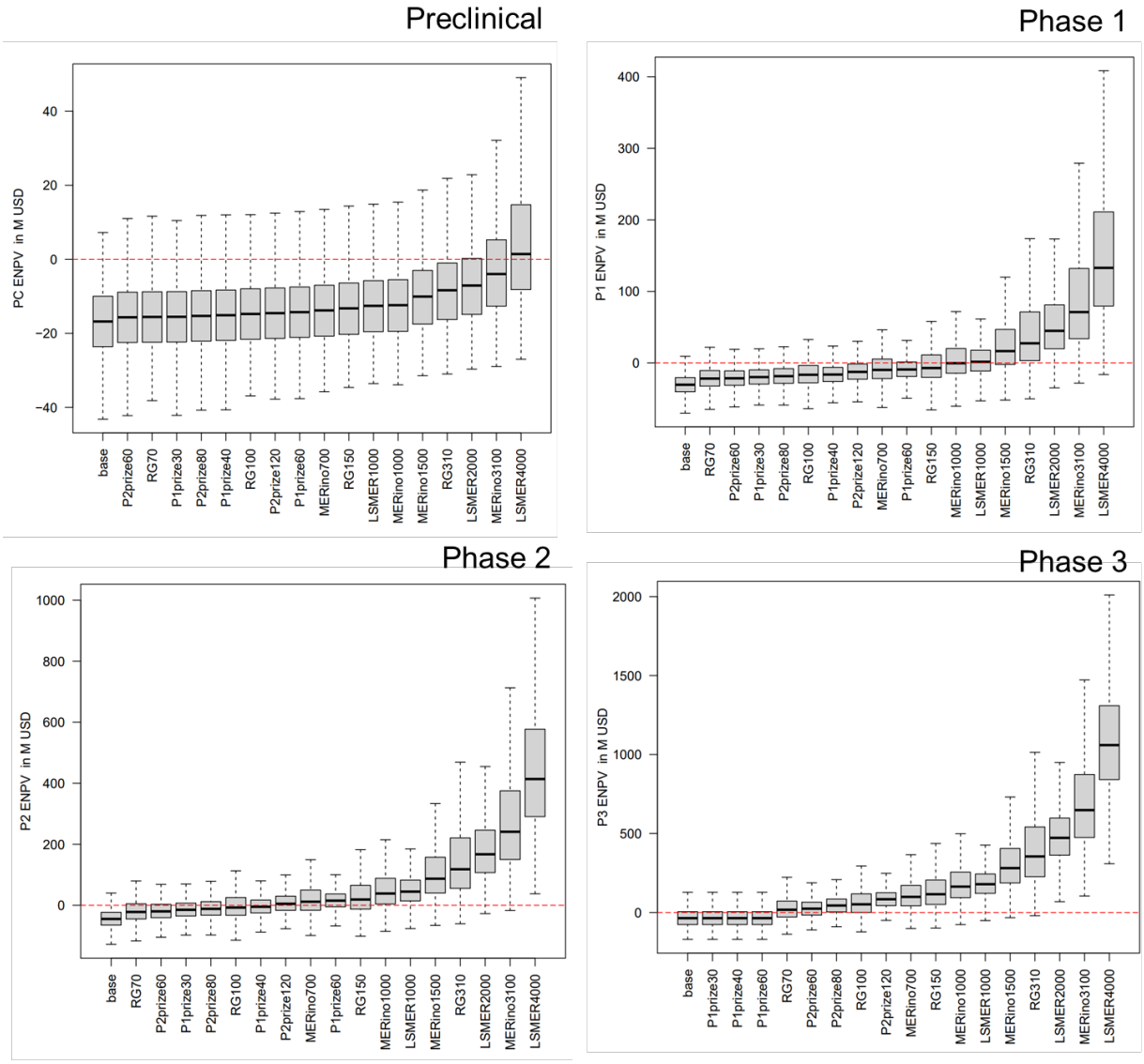


Figure 21 Impact of the 17 Interventions on ENPV across various R&D stages

From these figures, we can derive the following findings:

6.2.3.2.1. Preclinical

The “preclinical” bar chart shows that only a lump-sum MER of USD 4 billion would make at least half of the projects profitable, while a revenue guarantee of USD 3.1 billion would not achieve this (the rectangle is below zero, meaning that more than 50% of projects would have a negative ENPV). This result suggests that only a limited number of large-scale pull incentives paid upon market approval are able to sufficiently incentivise projects in the preclinical stage.

In contrast, smaller incentives such as the milestone-based reward for phase I (USD 60 million) have only a modest effect on the ENPV at the preclinical stage. Yet this rewards a candidate antibiotic with no efficacy data, only safety data. As shown in the “preclinical” bar chart, this pull mechanism makes about 25% of the simulated projects profitable, despite its limited size. In terms of effect on ENPV, this reward lies just behind all the revenue guarantee schemes and lump-sum MERs that were simulated.

6.2.3.2.2. Phase I

Regarding phase I, all the interventions located to the right of MERino1000, on the "phase I" bar chart result in at least 50% of projects profitable. It should be noted that some pull interventions may have the same impact in terms of improving profitability, for instance MERino1000 and LSMER1000. However, they are eventually not at all equally attractive if one considers other key features, such as diverging risks borne by payers (e.g. an antibiotic becomes ineffective due to rapid resistance development soon after market approval) and different levels of public expenditure. Thus, risks and expenditure are two other key dimensions that need to be considered when selecting attractive pull interventions.

6.2.3.2.3. Phase II

Regarding the ENPV at phase II, many pull incentives have a sizeable impact, which is encouraging for future policy design. Almost half of projects become profitable at the beginning of phase II when implementing the milestone-based reward phase II of USD 60 million, or the revenue guarantee of USD 150 million/year/drug over 10 years. Moreover, more than half of the projects become profitable when implementing the lump-sum MER of USD 1 billion, 2 billion or 4 billion, the MERino of USD 1 billion, 2 billion or 3.1 billion, but also the revenue guarantee of USD 1.5 billion or 3.1 billion. Among them, it could be then possible to select only the ones that would generate less public expenditure.

6.2.3.2.4. Phase III

Projects in phase III need no more than USD 700 million to be profitable. This shows that the more advanced the project is, the lower the incentive should be. This can also help explain why a global equivalent of the Swedish pilot in terms of size can be used to attract to market antibiotics that are approaching approval, and not only to guarantee access to already approved ones, which was the original aim of the Swedish model.

Based on these overall findings, two other elements have been taken into consideration to choose from among these interventions:

6.2.3.3. Complementarity of pull incentives

Given that only very large pull incentives make projects profitable at the early stage but smaller incentive such as milestone-based rewards are also quite effective at the preclinical stage, especially the one of USD 60 million for phase I, it could be promising to look for complementary interventions.

A 2019 report[49] issued by the Public Health Agency of Sweden states that pipeline coordinators[50] and milestone-based rewards can help overcome the profitability problem of projects in preclinical development. This is especially the case if pipeline coordinators such as CARB-X and the former IMI ENABLE actively engage in antibiotics projects by providing technical support and guidance. This support can increase their probability of success and shorten their duration, which would improve ENPV, especially for projects in the preclinical stage. This will be investigated further in the pre-feasibility assessment.

While we have not tested and simulated combinations of the interventions analysed in the current study due to the mathematical complexity, we have calculated the ENPV improvements at the preclinical stage of selected interventions in order to obtain a rough estimate of their combined impact (see Table 47: Heat-map showing the min./mean/max.

[49] Baraldi E., Ciabuschi F. *et al.* (2019) "Economic incentives for the development of new antibiotics" **Report Commissioned for the Public Health Agency of Sweden** [online] Available at: https://www.diva-portal.org/smash/get/diva2:1283298/FULLTEXT01.pdf [Accessed 26th October 2022]

[50] Baraldi, E., Lindahl, O., Savic, M., Findlay, D., & Årdal, C., 2018, Antibiotic Pipeline Coordinators, *Journal of Law, Medicine and Ethics*, Vol. 46 S1, pp. 25-31.

impact of 17 interventions on the ENPV in four R&D phases). In particular, by adding together the effect of P1prize60 to MERino1500, we obtain exactly the same ENPV improvement of the RG310. In other words, a combination of smaller pull interventions with milestone-based rewards can result in a similar impact as a more expensive pull intervention paid at later stages, yet milestone-based rewards will need to be awarded to some antibiotics that will never make it to market due to scientific failures.

6.2.3.4. Accounting for the efficient use of public expenditure

When selecting the pull intervention to implement, public bodies need to consider that some improvements in the number of financially profitable antibiotics may be unnecessarily high and especially very expensive to fund. In this way, the table below shows three indicators:

- **the rate of improvement of fully profitable antibiotic projects** compared to the number of profitable projects in the baseline scenario. For instance, the most "powerful" intervention (LSMER4000) makes 453 times more projects profitable (there are 453 times more projects with a positive ENPV at each decision phase) than a situation without any pull incentive. One of the interventions with the smallest impact is RG70, which makes only about 6.7 times more antibiotics profitable all the way to market.

  It could be possible to set a threshold at below 10 for instance under the basis that an intervention should have a strong enough impact on the number projects that pass all the decision points. The higher the threshold, the higher the probability to have one antibiotic finally reaching the market.

Table 15: Improvement rates of financially profitable antibiotics and public expenditures for one approved antibiotic

Intervention	Improvement rate of financially profitable antibiotics	Expected expenditure per 1 launched antibiotic (USD millions)	Expenditure per 100% improvement of financially profitable antibiotics (USD millions)
LSMER4000	453.3	4000 – Not selected if threshold < 2 billion	8.8
MERino3100	315.0	2921 – Not selected if threshold < 2 billion	9.3
LSMER2000	215.9	2000 – Not selected if threshold < 2 billion	9.3
MERino1500	127.2	1321	10.5
RG310	185.3	2366 – Not selected if threshold < 2 billion	12.8
MERino1000	60.9	821	13.7
P1prize60	12.1	169	15.3
P2prize120	13.3	205	16.6
MERino700	29.6	521	18.2
RG150	43.1	784	18.6
LSMER1000	50.0	1000	20.4
P1prize40	6.4 Not selected if threshold > 10	113	20.9
P2prize80	6.7 Not selected if threshold > 10	137	24.0
P1prize30	4.4 Not selected if threshold > 10	85	24.6
RG100	15.9	421	28.3

P2prize60	4.5 Not selected if threshold > 10	102	29.0
RG70	6.7 Not selected if threshold > 10	241	42.6 - Not selected if threshold > 30

- **the expected expenditure per one launched antibiotic**[51], i.e., the public cost that would be necessary to get one approved antibiotic to market. Here we can see that there are very expensive interventions (e.g., MERino3100 costing USD 2.9 billion per launched antibiotic), and ones that are much less expensive (e.g. P1prize30 costing only USD 85 million per launched antibiotic – taking the risk of failure into account, more than one milestone-based reward would need to be awarded to make sure that one antibiotic reaches the market). In between, we have several interventions, with a distinct improvement in the ENPV.
  Depending on the financial support that the public sector could provide, a threshold needs to be agreed upon for this variable. Here we have set the global threshold at USD 2 billion, which is a middle point between the recommendations made by Kevin Outterson and in the DRIVE-AB report.

- Finally, the third column indicates **the "efficiency" of the intervention**, which is expressed as the public expenditure needed for doubling the number of fully financially profitable antibiotics, i.e., corresponding to a 100% improvement in projects with a positive ENPV at each decision point. The higher the number, the more costly is the intervention for a given rate of improvement. Again, the most expensive interventions have the biggest impact.
  Decision makers can use this indicator to guide their decision. For example, with a threshold of 30, only one intervention would be excluded; with a smaller maximum set at 20, many interventions would be excluded, and mostly all the ones recommended in the recent academic literature (see Annex 2).

In order consider the most effective policy options for the preliminary feasibility assessment, we have taken into consideration the above-mentioned criteria, i.e. the impact on the ENPV, the size of the reward, the possibility to combine them, and the public expenditure linked to each reward. The table below presents the rationale behind the final selection of interventions.

Table 16: Recommended interventions

Interventions	Selected for further feasibility assessment	Rationale
MERino1500	Yes	This intervention makes 50% of projects profitable at the start of phase I and make 127 times more projects profitable.
MERino1000	Yes	This intervention makes almost 50% of projects profitable at the start of phase I and costs less than USD1 billion from a public expenditure perspective.
MERino700	Yes	This intervention makes 30% of projects profitable at the start of phase I

[51]Some interventions display total public expenditures per approved antibiotic that are eventually lower than the amounts allocated as nominal size for every intervention. For instance, for RGs and MERino, the yearly payments are "guaranteed revenues" considering also the levels of normal markets sales, hence when market sales are higher than the revenue guarantee, no public annual guaranteed payment will be made. On the contrary, several milestone-based rewards will be needed to guarantee the launch of one antibiotic. This is why the public expenditure is higher than the amount of one single reward.

		and sizeably less expensive than other options.
RG150	Yes	This intervention makes 50% of projects profitable at the start of phase I, and about 75% at the start of phase II and actually cost rather about USD 750 million over 10 years.
RG100	Yes	Although not effective at early stages, when combined to P1Priz60, it can achieve a sizeable effect on the profitability of projects as from phase I.
LSMER1000	Yes	This intervention makes 50% of projects profitable at the start of phase I.
P1prize60	Yes	The phase I completion MBR of USD 60 million starts being effective if we consider the ENPV at the start of phase I, but it has a strong impact at the start of phase II, where it makes as many as 75% of antibiotic projects profitable. Phase I MBR of USD 60 million performs better than all other MBRs in terms of ENPV improvement
LSMER 4000 LSMER2000	No No	These interventions do have an impact on the profitability of projects at the early stages of research. However, it is possible to achieve a comparable impact by using less expensive awards (e.g. combining MERino 1000/1500 and P1Prize 60).
RG310 MERino3100	No No	These interventions have limited impact at the preclinical stage. At later stages, these interventions can be substituted by a combination of other interventions and result in a similar impact while being less expensive (for instance combining MERino 1500 and P1Prize 60).
RG70	No	This intervention has a limited impact on the profitability of projects at the early stages and will only make an impact as from phase III, which shows that it can be used to ensure access more than innovation.
P1 Prize30 P1Prize40 P2Prize60 P2Prize80 P2Prize120	No No No No No	All the MBR, except P1Prize60, have a limited impact on the profitability of projects at the early stages, especially preclinical and phase I.

6.2.4. Key points and considerations for multiple awards

A summary of our analysis can be found below:

- It is difficult to incentivise projects at the preclinical stage only with pull interventions, unless they are extremely large and thus very expensive for public funders.
- A more feasible alternative is to introduce complementary interventions more targeted to the preclinical stage, e.g. push funding, direct technical support by pipeline coordinators and milestone-based rewards, which can reduce the necessary size of late-stage pull interventions to address the profitability problem of this early R&D stage.
- From phase I onwards, smaller pull incentives (e.g. revenue guarantees), even if applied alone, are sufficient to pull antibiotics to the subsequent R&D phases.
- As from phase II, even the smallest annual revenue guarantee of USD 70 million/year (RG70) is effective in pulling antibiotics to market launch. This suggests that a more modest revenue guarantee can be used to attract to market antibiotics which are approaching approval, and guarantee access to already approved ones.

- A pragmatic balance must be found between public expenditures and efficiency when selecting preferred interventions. In this regard, policy makers can define thresholds in terms of rate of improvement or maximum expenditures.

Finally, the public expenditure in Table 15 is estimated per antibiotic launched. According to the design of the pull incentives implemented, more than one antibiotic could reach the market during the period of implementation and be eligible for receiving the revenue guarantee or lump-sum MER or milestone-based reward, thus multiplying the public expenditure indicated in Table 15 by the number of antibiotics rewarded.

The number of rewards granted will increase the incentive to develop new products. Even though there is no certainty about the number of antibiotics that will reach the market every year due to the inherent risks of R&D, increasing the size of the pull incentive will increase the pipeline, thereby increasing the chances that more than one antibiotic will qualify for the reward.

This raises the question of whether the design of the pull incentives should include the setting of a maximum number of antibiotics to be awarded, rather than allowing all antibiotics fulfilling predefined eligibility criteria to be rewarded, and the potential race to these rewards. Below are some considerations on the matter:

6.2.4.1. Scientific uncertainty

Given the scientific uncertainty about the progression of molecules, public funders should budget for on average two antibiotics per year over the next five years, with an extension to 10 years in case some rewards were not granted. This would provide more flexibility to provide awards when antibiotics are effectively reaching the market, which is not necessarily twice a year. This also means that the figures displayed in Table 15 should be multiplied by ten at maximum over the next ten years. To avoid awarding too many antibiotics over a very short period of time, it can also be relevant to cap the number of awards to a maximum of two per year.

Setting the limit to two antibiotics is already followed by the UK/NHS (National Health Service) subscription model, which decided upfront on selecting two new antibiotics. This led to two antibiotics being awarded in 2021, cefiderocol and ceftazidime–avibactam. This pilot program has been welcomed by the industry and academics, but it requires that other countries implement similar programs in order to reinvigorate the pipeline over time[52].

It should be noted that splitting the pull incentive between several recipients would reduce the expected cash flows and ENPV from the very early stages, thereby reducing its expected impact on increasing the pipeline.

Budgeting a reward to two antibiotics has also the advantage that, in the rare case that two antibiotics would reach the approval phase in parallel, there would be no issue in providing these awards.

Depending on the requirements in terms of societal/clinical value, innovativeness and resistance development, the number of qualifiable medicines will increase/decrease accordingly. To avoid excessive uncertainty, it is advisable that any public agency involved in setting up a pull intervention decides and announces beforehand the number of antibiotics that can be awarded, as well as the requirements. By providing awards over a certain period of time (five or ten years), public authorities would be able to generate an effect on the research pipeline over several years.

[52] Financial Times (202) **How will UK's fixed-fee scheme for antibiotics help tackle the growing health crisis?** [online] Available at : https://www.ft.com/content/e191f6cd-7af3-4baa-894d-b2ccf240f891 [accessed 6th December 2022]

6.2.4.2. Race to reward

It could be possible that two developers perform a "race" to the award. Calculating this effect of multiple competing antibiotics would require advanced simulation (e.g. an agent-based model). Moreover, in the preclinical stage, the risk of wining/losing the "race" is difficult to consider for a developer because they do not know how many other projects of other developers are in each R&D stage. It would possibly only be in the later stage that companies would start considering the exact number and type of competitors to account for the risk that another product gets approved before theirs. In the event of a very close race (all competitors have the same chance of succeeding and "winning" at the same time), ENPV could steeply decrease for each developer. With a big reduction in the ENPV the pull incentive may no longer be attractive and thus developers stop their projects due to a lack of financial profitability. This is why allowing for two awards would reduce this "race" to some extent.

Given the points above, to increase the pipeline and sustain ENPV values from the developer's perspective, the option of a "race" with only one winner is better than the scenario where the reward is split between two or several winners because splitting the award would reduce the ENPV, hence the pulling effect. Lastly, if several antibiotics were to be *both* launched *and* awarded a pull incentive at market entry, the total public expenditure would double, which could be challenging from a public-finance perspective.

6.3. Preliminary feasibility assessment

The purpose of a preliminary feasibility assessment of the seven pull incentives is to provide guidelines on how DG HERA may implement these mechanisms. This encompasses guidelines for assessing the societal value of the awarded antibiotics, the legal assessment of these policy options, an assessment of the strings attached that should be included for each option, broad governance principles to keep in mind, a discussion on how to guarantee access to these medicines, and the advantages and disadvantages that should be discussed in more detail to select the final policy options.

This section is organised as follows:

- the considerations that are common to the seven interventions (societal value and legal aspects).
- analysis for each intervention: costs and benefit aspects, strings attached, governance and financial considerations, and take-away for EU-level implementation.

The interventions will be presented as follows: the revenue guarantees (RG 100 and RG 150), followed by MERinos (MERino 700, MERino 1000 and MERino 1500), lump-sum MER (LSMER1000) and finally milestone-based rewards (P1Prize 60).

6.3.1. Accounting for the societal value of antibiotics

6.3.1.1. Why accounting for the patient and societal value?

From a public-health perspective, it is necessary to provide financial support to antibiotics whose value to patients and society are higher than the financial outlays. Indeed, public resources are scarce, meaning that it is important to assign public financial support to the treatment that would bring more value than cost to society.

For instance, if "treatment A" costs USD 50 million to be developed but is rarely used, its societal benefit could be implied at USD 10 million. On the other hand, "treatment B" costs USD 50 million to be developed but will be used frequently, with an implied societal benefit of USD 100 million. If the government has USD 50 million to spend, it will allocate it to "treatment B" only.

In summary, it is necessary that the patient and societal value of a targeted antibiotic is greater than the size of the paid incentive, which in turn needs to be greater than the developer's R&D costs, and sufficient to allow profitability. We can summarise the decision process for providing pull incentives as follows:

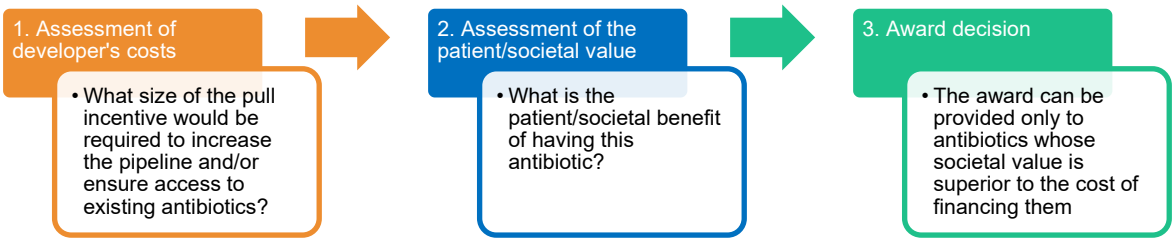


Figure 22: Private costs versus patient/societal benefits

The challenges from implementing measures that have societal value relies on:

- the need of an individual HTA per antibiotic at EU level; and
- the difficulty to assess the societal value of an antibiotic at the early stages. The societal benefit will always be antibiotic and context specific and can only be assessed once a particular medicine approaches market approval or is selected for guaranteed access. It is only at this point that data will be available on the antibiotics' effectiveness, and the particular indications. These, combined with local resistance situation and forecasted development in particular geographies, will allow the health economic impact on a patient population to be calculated.

6.3.1.2. Implementation options at EU level

From a practical implementation standpoint, the best benchmark of implementing societal value is the NICE/NHS' subscription model. In this UK intervention, the maximum size of the yearly payment was set at GBP 10 million, postponing the definition of the specific yearly payments to a selected antibiotic until the moment of approval and award of the incentive, when a specific HTA can be made. In the case of the two antibiotics selected by NICE for their model (Shionogi's cefiderocol and Pfizer's ceftazidime–avibactam) ceftazidime–avibactam was estimated in 2022 to have a societal value measured in Quality-adjusted life year (QALYs) of below GBP 10 million/year and accordingly received a lower payment. In contrast, cefiderocol was estimated to have a societal value in QALYs of about twice the maximum allowed payment but was rewarded with a GBP 10 million/year contract[53].

With the above in mind, an interesting and viable option is using societal value as a criterion for the final selection of antibiotics and the award of the selected pull interventions to be paid upon market approval[54]. Since our simulation demonstrated that the aforementioned interventions could incentivise antibiotic R&D at various stages, one could eventually award only those antibiotics with a societal value that is greater than the total size of payments of the applied pull intervention. One approach to assess the societal value of antibiotics could be to utilise the principles of the STEDI (Spectrum, Transmission, Enablement, Diversity, Insurance) framework.

[53] Not all the value components included in the "STEDI" framework by Outterson & Rex, 2020 ("Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialisation") were included due to their complexity and uncertainty. Indeed, this framework includes the following components of societal value: Spectrum (replacing broad with narrow spectrum antibiotics), Transmission (preventing infection spread), Enablement (allowing other medical treatments), Diversity (reducing selection pressure via additional therapeutic options) and Insurance (keeping the antibiotic "on the shelf" for future necessities), and some data are not always available or computable.

[54] The milestone-based reward is paid at the end of Phase 1 and would follow a different adjudication logic.

The STEDI Framework

The STEDI framework proposes to assess the societal value of antibiotics by considering 5 additional dimensions of value, moving beyond the traditional health-technology assessments based on benefits for the single patients. STEDI has been proposed among others by K. Outterson and J.H. Rex in the article "Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization", 2020[55]. In summary, it is important to broaden the set of criteria used to assess the value of antibiotics around 5 measurements:

- **Spectrum** - the ability of an antibiotic to reduce unintended impacts on the microbiome through moving from broad- to narrow-spectrum antimicrobial agents
- **Transmission** - the ability of an antibiotic to reduce spread to other individuals through effective treatment
- **Enablement** - the ability of an antibiotic to provide access to medical treatments and procedures through effective prophylaxis
- **Diversity** - a new antibiotic reduces selection pressure on pathogens by increasing the range of treatment options available
- **Insurance** - the advantage of being prepared for future increases in the prevalence of resistant infections by developing new antimicrobial agents now.

Although each value may be challenging to quantify, this new proposed metric would improve the assessment of the societal value of antibiotics.

To implement this approach at European level, decision makers would have to first address the challenge of developing a common HTA for pull incentives purpose, while HTA is a competence of EU Member States and thus performed at national level, for pricing and reimbursement purpose. A central EU entity could potentially coordinate this assessment work, possibly in collaboration with national HTA agencies. Finally, if a country opts to join the EU-level pull intervention, their agencies would be intrinsically motivated to collaborate and thus help orient the modelling of the societal value of antibiotics at EU level.

6.3.1.3. Definition of the minimum acceptable multiplier

Implementing a criterion of minimum acceptance ensures that only market-approved antibiotic(s) with a patient and societal value greater than the pull intervention will be rewarded. From an economic perspective, as long as the value is greater than the public cost (which incorporates private costs and some level of profitability), it would be justifiable to provide financial support. Nevertheless, in the event that many antibiotics meet these criteria a public-finance issue may arise.

In such a case, it could be possible to define that the value would need to be X times higher than the public cost. Determining the multiplier "X" can be only based on political positioning. This award approach would allow public bodies to ensure that their economic benefits are clearly greater than the cost of pull incentives.

[55] Outtersonn K and Rex J.H. (2020) "Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialization [online] **Translational Research** (20) pp. 182-190 Available at https://doi.org/10.1016/j.trsl.2020.02.006 [Accessed 15th October 2022]

Case Scenario
If we consider the largest MERino1500, whose public cost would be USD 1.3 billion (see Table) a two times (2X) scenario would mean rewarding only antibiotics with at least a global societal value of USD 2.6 billion spread over six years.

6.3.2. Legal assessment

The pull mechanisms are disruptive as they delink funding from sourced volumes and also from actual or estimated costs. This raises some questions from a legal perspective for each type of intervention: revenue guarantee, lump-sum MER, MERino, and milestone-based reward. Below are the main conclusions regarding the legal feasibility of these four main types of intervention.

It must be acknowledged that there is a lack of jurisprudence on these specific mechanisms due to their novelty. As a consequence, this assessment aims at clarifying what are the potential legal instruments to implement the identified mechanisms, and what can be suggested to ensure the full legal feasibility of these mechanisms.

6.3.2.1. Sources of funding

Considering the large amounts of funding that should be deployed for the pull mechanisms, especially for the revenue guarantee, lump-sum MER, and MERino models, the measures may require a co-funding by the EU and the Member States.

Regarding the EU funding mechanism*,* it is possible that a part of the funding comes from the EU and, more specifically, under Regulation (EU) 2021/522 of the European Parliament and of the Council of 24 March 2021 establishing a Programme for the Union's action in the field of health ('EU4Health Programme') and Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe.

Budgetary commitments under these regulations can extend over several years, in which case they must, in principle, take the form of annual instalments which could fit with the revenue guarantee and the MERino. Given that the lump-sum MER and Milestone-based reward models consist of one payment, this may cause complications. This being said, the regulations do not require that these instalments be equal.

The main funding tools under the EU Financial Regulation and, more particularly, Regulation (EU) 2021/522 and Regulation (EU) 2021/695 are "grants", "prizes" and "procurement". This is why these are the three primary frameworks that can be used for implementing the pull mechanisms and will be the subject of the legal assessment.

Regarding Member State funding*,* since the funding goes directly to the MCM suppliers, Member State funding is, in principle, subject to EU State aid rules, which set up considerable constraints as to the link between eligible costs and state aid). Where an "open" tender procedure can be organised (e.g., in the Swedish pilot), State aid rules will not be applicable. Also, the organisation of a "competitive procedure with negotiation" and the "competitive dialogue" will significantly mitigate State aid compliance risks.

Common principle underpinning EU & Member State funding. Both in case of EU and Member State funding, the principles of transparency, non-discrimination, equal treatment, sound financial management and, above all, proportionality are key principles that must be respected. Therefore, any model must have proper economic and other foundations in order to justify its choice, the remedied market dysfunction and the amount of funds involved.

Considering the above, the chances of legal feasibility in terms of EU/Member State funding can be explained as follows for the different models:

Table 17: Summary - EU/Member State funding

Member State	Rating	Explanation

funding		
RG		EU funding may apply due to a higher probability that the measure can be considered a classic procurement (via actual sourcing of products later on) at market conditions; access to capacity could be negotiated and there would be an element of actual sourcing of MCMs. Indeed this model has already been implemented under EU law in Sweden.
MERino		Very high budget for EU funding alone, but the potential disproportionality can be mitigated as access to capacity will be negotiated and there would be an element of actual sourcing of MCMs.
LSMER		Very high budget and, in principle, no actual sourcing or access to capacity; could be become more feasible if through strong "string attached" provisions access to capacity would be negotiated.
MBR		Delinked from costs but a much lower budget.

Legend:

- Generally feasible with less restrictions
- Feasible with restrictions
- Could be feasible but the obstacles are significant

6.3.2.1.1. Funding mechanism

EU funding can be mainly awarded via grants, prizes, or procurement. The legal assessment for each option is presented below. Other EU financial instruments, such as loans or equity provided by the European Investment Bank (EIB) or the European Investment Fund (EIF), can play a supporting role but cannot fund the pull effort as such as the funds granted for this effort is in principle not reimbursable.

6.3.2.1.2. Prize

The lump-sum MER, MERino and milestone-based reward have a clear element of rewarding one or more particular suppliers. As the reward has no link to the costs of the suppliers, it could be said that the funding should be considered a "prize" and follow the provisions laid down in Title IX of the EU Financial Regulation. However, recourse to the provisions on "prizes" would not be suitable as "prizes" are considered to be a complementary funding tool and not a funding mechanism that can be a substitute to funding via grants and public procurement (see recital (136) of Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union – the "EU Financial Regulation"). In other words, prizes are an add-on that complement other types of funding and cannot be used as a stand-alone funding mechanism.

Moreover, the set-up of a prize with a face value of more than EUR 1 million, which does not match with the size of the rewards considered in our pull incentives options,is a more burdensome procedure than other mechanisms, as the European Parliament and the Council of the European Union must be informed on beforehand.

Based on the two elements above, prizes are not deemed legally relevant for pull mechanisms assessed in our study.

6.3.2.1.3. Grants

The lump-sum MER and the milestone-based reward could also be seen as a grant given that it is a reward fully delinked to sales volumes and awarded as a one-off payment. However, grants are legally cost-oriented and also awarded on the basis of a "no profit" principle, meaning that it is not an ideal tool when there is no strict link between the grant and cost. Indeed, for the milestone-based reward of USD 60 million, the amount

corresponds to twice the cost of phase I, and the lump-sum MER takes not only costs into account but expected revenue as well.

Furthermore, even when the EU Financial Regulation in theory allow for lump-sum grants that are delinked from a logic of eligible costs, both regulations mentioned above exclusively base "grants" on eligible costs, which may not fit well with delinked pull incentive mechanisms. In this context, grants are also not deemed legally relevant for any of the pull mechanisms assessed in our study.

One potential solution involving grants for milestone-based reward (but there is no current similar legal precedent at EU level) would consist of the following: the EU could provide a grant (preferably after a competitive call), that would be proportional to the cost, to the developer who successfully passed phase I, and it would partner with private foundations to provide the same amount to the developer. This would match the required amount suggested in milestone-based reward (twice the cost), allow the use of grants by the EU commission (i.e. proportionality with eligible costs), and boost profitability from a developers' perspective (through the reward provided by the private foundation). The Longitude Prize[56] is actually an example of cooperation with the UK government and private foundations. The current collaboration with the Bill & Melinda Gates Foundation on CARB-X can be seen as promising for the development of such reward.

6.3.2.1.4. Procurements

Given the legal constraints on prize and grants, the most appropriate funding mechanism should take place under the form of "procurement", transactions whereby a public financial counterparty is foreseen for the sourcing of services or supplies, and which are subject to specific procedures assuring a competitive process. Also, the public "procurement" process should be a guarantee that the financing of the solution is in line with market conditions, meaning that there is no direct link with costs.

Both the EU4Health Programme Regulation and the Horizon Europe Regulation allow for funding under the form of "procurement".

If the model foresees a purchase of a service or products, in particular, an access to capacity or the products (which can be considered a service in itself) and/or an actual sourcing of MCMs, the qualification of "procurement" does not raise any questions. This would be the case for revenue guarantees and the revenue guarantee part of the MERinos.

However, and even when there are sound arguments to consider it a procured service as well, pre-commercial R&D on a stand-alone basis is less certain to be considered a procurement transaction, which is why the use of procurement for pure lump-sum market entry rewards and milestone-based rewards may be more difficult. Some legal clarification would be needed to ensure that the procurement procedure can also be applied for lump-sum MER and milestone-based rewards in case there would be no sourcing associated with these rewards.

The chances of legal feasibility in this respect are explained as follows for the different models:

Table 18: Summary - procurement

EU funding	Rating	Explanation
RG		Can be considered a genuine procurement.
MERino		Can be considered a genuine procurement, at least for the RG part.

[56] https://longitudeprize.org/about-the-prize/

LSMER		Qualification of a genuine procurement can be argued, but legally less certain.
MBR		Qualification of a genuine procurement can be argued, but legally less certain.

Given that procurement can be the most promising option for revenue guarantees and MERino, we provide further details on the options available under this scheme. We then propose legal options for lump-sum MER and milestone-based rewards.

Option A. Joint procurement EU & Member States

As the financing should take the form of a "procurement", and since single Member States are unlikely to be able to mobilise the entire funding required to implement the options assessed in this study, the question as to the feasibility to set up a "joint procurement", mobilising funding from both several Member States and potentially from the EU, arises. The most straightforward legal basis in the field of AMR is Regulation (EU) 2022/2371 of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU, which foresees a joint procurement procedure and a joint procurement agreement (JPA) between the EU and the Member States. This legal basis serves to conclude "advance purchase" of MCMs, which can include both products and services that are necessary for the purpose of preparedness for and response to serious cross-border threats to health, so including the right to source products. In line with DG HERA's practice, the word "advance" merely reflects the idea of preparedness and should not be an obstacle to rely on a JPA under Regulation (EU) 2022/2371.

Regarding the content of a procedure under the JPA, EU and Member States (as well as, EEA Member States and candidate countries as the case may be) are quite flexible to shape its content in terms of choice of the procurement procedure and the contract to be concluded (Art. 14 and Art. 15 of the JPA). Art. 12 3 (c) allows to restrict the parallel procurement for the same product, however, all countries participating in this JPA must agree upfront to such exclusivity on a case-by-case basis, based on the procurement assessment of the European Commission (DG HERA).

In summary, revenue guarantees may be implemented through the use of a JPA. In the case of revenue guarantee, the EU and the Member States could require access to the antibiotics, define revenue guarantees, and, hence, make reference to a right of access to the resulting products.

A priori, MERino may also be implemented using the same JPA. The legal uncertainty comes from the first two-year payments where there is no link with revenue guarantees and access to capacity or the right to source the products. Given that there is a revenue guarantee in this scheme, this could be a basis for using a JPA.

Indeed, under the revenue guarantee and the MERino, some kind of kick-back mechanism should be implemented for the concrete volumes that are sourced on Member State level and would be deducted from the revenue guarantees.

It is more difficult to legally justify the use of a JPA for lump-sum MER and milestone-based reward unless there is a reference to some access to capacity or products and/or the actual sourcing of products under the contracts that are eventually concluded with the suppliers.

Given the current legal framework, the chances of legal feasibility in this respect are explained as follows for the different models:

Table 19: Summary - Joint procurement EU & Member States

	Rating	Explanation
RG		Can be considered a genuine procurement and comes close to an Advance Purchase Agreement (APA) so that the most straightforward legal basis (Regulation (EU) 2022/2371) may be used to implement a JPA.
MERino		Can be considered a genuine procurement, at least for the RG part and includes elements that also bring it closer to an APA so that the most straightforward legal basis (Regulation (EU) 2022/2371) can be used. The non-RG part of the funding does not show these characteristics (cf. LSMER)
LSMER		Qualification of a genuine procurement can be argued, but legally is less certain. Reliance on Regulation (EU) 2022/2371 is possible but a bit less certain unless access to capacity is included. An alternative scheme for pre-commercial procurement is available under Horizon Europe Regulation (EU) 2021/695 (see option **B**.)
MBR		Qualification of a genuine procurement can be argued, but legally is less certain. Reliance on Regulation (EU) 2022/2371, is possible but a bit less certain unless access to capacity is included. An alternative scheme for pre-commercial procurement is available under Horizon Europe Regulation (EU) 2021/695 (see option **B**.)

Option B. Pre-Commercial procurement

The Horizon Europe Regulation (EU) 2021/695 foresees a specific procedure for pre-commercial procurement[57], which would provide a more solid legal basis to the lump-sum MER and milestone-based reward models which would relate to pre-commercial R&D only. Indeed, this regulation foresees a mechanism whereby a grant would be awarded to contracting authorities for the implementation of a pre-commercial procurement action. In that sense, the EU would not directly manage the relationship with the MCM suppliers but would be able to shape the process through revision of tender framework process, call for tender documents and contract notice, as well as the tender specifications for each one of the pre-commercial procurement phases.

The main advantage is that that the funding comes from the EU, and only the Member States interested in the initiative join. As in principle, the participants are organised under the form of a consortium the regular conditions of eligibility apply which means that there must be at least one participant from a Member State and two other ones from either a Member State or an associated country. As per the provisions of the Horizon Europe Regulation (EU) 2021/695 it is also possible to add Member States at later stages. In principle, only the Member States negotiate with the developer, so that when strong strings attached in terms of access for instance should be negotiated on behalf of the EU, this must be implemented via the Member States.

This solution has been foreseen in the Horizon Europe Regulation (EU) 2021/695 and, in principle, does not apply to funding available under the EU4Health Programme Regulation (EU) 2021/522

[57] 'pre-commercial procurement' means the procurement of research and development services involving risk-benefit sharing under market conditions, and competitive development in phases, where there is a clear separation of the research and development services procured from the deployment of commercial volumes of end-products.

Table 20: Summary – pre-contractual procurement

	Pre-commercial Procurement	Explanation
LSMER		Most solid legal basis for pre-commercial procurement. The negotiation around access at EU level may be difficult given that the EU is not directly involved but this may be mitigated in the EU grant agreement. A priori the solution can only be implemented under the Horizon Europe Regulation (EU) 2021/695 and, in principle, not under the EU4Health Programme Regulation (EU) 2021/522. So if the solution is too close to market and funding under the Horizon Europe Regulation (EU) 2021/695 is less likely, the mechanism may not work.
MBR		More solid legal basis for pre-commercial procurement. The negotiation around access at EU level may be difficult given that the EU is not directly involved but this may be mitigated in the EU grant agreement.

Choice of procurement

The JPA is not prescriptive on which procurement procedure to be chosen. Also, in the case of a pre-commercial procurement grant under option B., Member States will be free to choose their concrete procurement procedures.

As in the case of AMR MCMs discussions and negotiations are inevitable given their innovative character and the risks pertaining to their development and sourcing, the "open" and "restricted" procedures which require immediately a definitive offer on the basis of precise tender specifications, are not an option. This leaves *de facto* the "competitive procedure with negotiation", the "competitive dialogue" and the "innovation partnership" as sole procedures.

Considering the specific characteristics of the procurement, the "competitive procedure with negotiation" and the "competitive dialogue" can be deployed. The latter leaves more room for discussion but also has the downside that these discussions also must be continued until contracting authorities and candidates find an appropriate solution against which all offers must be benchmarked.

The procedure called "innovation partnership" is aimed at development of innovative solutions and allows to proceed in successive phases with a split between research & innovation and manufacturing & marketing phases and foresees the possibility to stop the process at the end of each successive phase.

Before engaging in an "innovation partnership" procedure a prior market consultation is required to assure that the supply or service does not exist on the market or as near-to-market development. To the extent that some pull incentives are focussed on activities that may be considered nearer to the market, this procedure, in its current form, cannot be used.

Even when it can be organised in successive phases in a flexible manner, an important feature of the "innovation partnership" is that at the outset the plan is to have not only a pre-commercial R&D service but also a subsequent procurement of the resulting supplies, which would make it less appropriate for the lump-sum MER and milestone-based reward models which only relate to pre-commercial procurement. The procedure is not used very

often but it knows some uptake. Recently, there have been +/- 10 EU-wide innovation partnership tenders ongoing in the pharmaceutical sector with contract values of up to 24 million EUR[58].

However, in the case of a pre-commercial procurement grant under option B., the participating Member States which receive an EU grant to organise one are not obliged to follow one of the specific procedures foreseen in EU public procurement law. The participating Member State contracting authorities may choose an ad hoc, simplified procedure and may provide for specific conditions such as limiting the place of performance of the procured activities to the territory of the Member State and of the associated countries, as long as the procedure complies with competition rules (incl. State aid law) and the principles of transparency, non-discrimination, equal treatment, sound financial management, proportionality as well requirement that the award of the contracts to the tenders offering best value for money while ensuring absence of conflicts of interest.

Lastly, it is also worth to be mentioned that it is also possible to enter in direct negotiations with one single economic operator in the case of absence of the competition for technical reasons and/or the necessity to protect the intellectual property rights. This procedure will not be taken up in the overview below because it will be rare that only one economic operator can be chosen. Moreover, the Swedish and the UK pilots show that more than one candidate for the development of AMR solutions have participated in the tender. Furthermore, such a single sourcing strategy also creates a State aid compliance risk.

Table 21: Summary - choice of procurement

	Competitive dialogue / procedure with negotiation	Innovation partnership	Ad flexible procedure	Explanation
RG				Competitive dialogue/procedure with negotiation is possible. Possibility of innovation partnership depends on non-existence of (near to) market product. As there are genuine procurement aspects, there is no more flexible ad hoc procedure possible.
MERino				Competitive dialogue/procedure with negotiation is possible. Possibility of innovation partnership depends on non-existence of (near to) market product. As there are genuine procurement aspects, there is no more flexible ad hoc procedure possible.
LSMER				Competitive dialogue/procedure with negotiation is possible. Innovation partnership is difficult to implement if no subsequent purchase of the resulting supplies is foreseen. Possibility of innovation partnership further depends on non-existence of (near to) market product. As the qualification as a procurement is less certain, a more flexible ad hoc

[58] See, e.g., https://ted.europa.eu/udl?uri=TED:NOTICE:155956-2017:TEXT:EN:HTML&src=0.

				procedure is possible, certainly under option B.
MBR				The early-stage character may render a competitive dialogue/procedure with negotiation more difficult. Innovation partnership is difficult to implement if no subsequent purchase of the resulting supplies is foreseen. If that drawback can be overcome, its earlier stage character is a positive point for the implementation of an innovation partnership. As the qualification as a procurement is less certain, a more flexible ad hoc procedure is possible, certainly under option B.

Conclusion

As a conclusion, and based on the legal assessment above, the following recommendations are made:

- Both in case of EU and Member State funding, the principles of transparency, non-discrimination, equal treatment, sound financial management and, above all, proportionality are key principles to be respected. Therefore, any model must have proper economic and other foundations in order to justify its choice, the remedied market dysfunction and the amount of funds involved.
- In terms of EU funding, the models must preferably include genuine procurement elements in terms of access to capacity and subsequent purchase of the resulting MCMs.
- Revenue guarantee can be implemented mainly through a JPA between EU & Member States. Moreover, the contracts set through an APA are flexible, they can include access conditions, diverse financing options for the developers, as well as diverse Member States contribution schemes. It may be a better fit for solutions that are closer to market.
- The MERino would also be implementable through JPA, given that it includes a revenue guarantee. The same reasoning applies as above with a caveat, however, to the first payments that are delinked from an actual sourcing.
- Milestone-based rewards and LSMERs are fully delinked from the number of doses to be purchased or accessible, and from MCM suppliers' costs. Hence, they are more difficult to legally assess given the lack of any case law precedents. The most legally suitable solution would be to use the EU grant mechanism for pre-commercial procurement as foreseen in the Horizon Europe Regulation (EU) 2021/695. This would allow Member States which are interested in AMRs to take the lead on the initiative and assure co-funding between EU and Member Stated without having the legal uncertainties as to whether pre-commercial R&D can constitute a genuine procurement transaction and as to whether a JPA can be implemented at all.
- Even though it has not been legally deployed yet at EU level, it could be possible to envisage milestone-based reward to be implemented through the combination of a grant delivered by the EU (if it would be possible to identify eligible costs) and prizes awarded by private foundations.

Finally, DG HERA may play a decisive role in coordinating the expertise at EU level and bringing the legal experts on this topic to make sure that the pull mechanisms that may have the greatest effect on solving the profitability challenge (revenue guarantee, MERino,

lump-sum MER, and milestone-based reward) may be implemented through the most appropriate procurements in a timely way.

6.3.3. Revenue Guarantee Schemes

The pre-feasibility analysis will be carried for the selected Revenue Guarantee below.

Table 22: Revenue guarantees included in pre-feasibility assessment

Intervention	Scenario	Identifier
Annual Revenue Guarantee	Intermediate 1 scenario – 100 million/year for 10 years	RG100
	Intermediate 2 scenario – 150 million/year for 10 years	RG150

6.3.3.1. Cost and benefit considerations

The global expenditure of this intervention will be the difference between actual yearly market sales and the set yearly guarantee over the 10-year period. This means that the total payment is variable and depends on the levels of yearly sales for the selected antibiotics.

Based on our simulation that projected the average sales levels and market revenue for numerous projects in this time period, **the expected global public cost if the revenue guarantee is awarded to a single antibiotic over 10 years would be USD 421 million for RG100 and USD 784 million for RG150.**

An important aspect to consider when selecting the required multiplier (e.g., 1 or 2 as above) as well as the size of the pull intervention (RG100 or RG150) is that choosing lower multipliers and lower pull sizes will imply selecting more antibiotics because there will be more antibiotics that "qualify" for interventions. As a result, savings in terms of payments thanks to a lower size intervention (RG100 instead of RG150) can be offset by rewarding more antibiotics.

6.3.3.2. Advantages and disadvantages of RG100 and RG150

The table below states some important advantages and disadvantages of the two annual revenue guarantees selected and adds the key point that a smaller size of this intervention can act to incentivise access to existing antibiotics.

Table 23: Operational advantages and disadvantages of RG100 and RG150

Advantages	Disadvantages
Relatively small size of yearly payments compared to the other four "market-approval" pull incentives (MERino1500, MERino1000, MERino700 and LSMER1000).	Both sizes of revenue guarantees (RG100 and RG150) make less than 25% of projects profitable since preclinical stage. At phase I, RG100 has still limited pulling effect (less than 25% of projects are profitable).
Built-in impact on access to the rewarded antibiotic, thanks to yearly payments conditional to suppliers also maintaining constant access.	In comparison to options where the reward if fully delinked from the sales, additional stewardship stipulations are required as this is not a fully delinked model.
This intervention already exists as a pilot model in Sweden and in the version of a subscription model in the UK, with a clear example on how the procurement process can be run.	

Lower sizes of RGs can support also access to existing antibiotics (e.g. the Swedish pilot, see Annex 4 – Pull incentives – defining the size of the four interventions).	
Taking into account that it is not fully delinked and actual volume sales are deducted from the RG, the qualification of a "procurement" (rather than a "grant") is less debatable. Depending on the wording used, it can be considered an advance purchase agreement for AMR MCMs so that a JPA can be actioned at EU level on a clear(er) legal basis (Regulation (EU) 2022/2371).	

6.3.3.3. *Strings attached*

Public funders should set in the contracts with antibiotic developers' requirements that the latter must fulfil to receive an annual revenue guarantee. Some of these requirements should be attached to the product itself, i.e. still be applicable in the case of a change of control, see section on milestone-based reward.

For example:

- In the grant agreement with the public funders, the Marketing Authorisation Holder (MAH) should guarantee access within predefined quantities, including possibly holding local stocks (as is the case with the Swedish pilot) in exchange for the yearly payment.
- The revenue guarantee scheme recommended in this study is a partially delinked model. Thus, the reception of revenue guarantee should be associated with stewardship requirements, especially if yearly guarantees are likely to be surpassed by market sales. Such stewardship requirements should forbid the recipient of the guarantee to advertise and provide bonuses to salespeople, incentives/discounts and other means of communication that may induce overselling or the unjustified use of the selected antibiotics. Stewardship can be promoted also by including a supplier's "commitment to stewardship" among the criteria for selecting rewarded antibiotics, as the UK/NHS subscription model does through the Access to Medicines Foundation's AMR Benchmark. Finally, continuous monitoring of the actual use of the supported antibiotic should be performed to identify potential inappropriate use of the selected antibiotic(s). These contractual obligations are easier to enforce in countries where suppliers have voluntarily joined industrial AMR alliances that already promote stewardship.
- The contract could define that the yearly annual revenue guarantee payments are reduced or cancelled if a rewarded antibiotic should lose effectiveness due to, for example, rising resistance, as is the case in the UK/NICE subscription model through yearly reviews and re-evaluation of the antibiotics societal value[59].

6.3.3.4. *Governance and Financial Considerations*

The most likely hypothesis is that Revenue Guarantee will be implemented through:

- a JPA under Regulation EU 2022/2371, which is the contract between the EU and the participating Member States amongst themselves and which lay down

[59] National Institute for Health and Care Excellence "Models for the evaluation and purchase of antimicrobials" [online] Available at https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials [Accessed 24th October 2022]

governance rules in terms of decisions to be taken in relation to this scheme, the procurement processes to be chosen and the financing;

- via an agreement with the suppliers, as the case may be, a subsequent purchase contract, which lays down the conditions to be respected by the suppliers also in terms of stewardship and access rights for the EU and the Member States. The EU can, on the basis of the mandate that normally be conferred to it by the Member States, sign that agreement.

  It is important to note that the content of the JPA and the subsequent purchase contract with the suppliers offers flexibility in terms of contractual obligations, Member States funding contribution, signatories, rules for revenue guarantee (set at national or EU level), etc.

  Hence, the final design of these contracts will be the result of negotiations, and the considerations set below can only remain general. We have pointed out some key considerations to be kept in mind in case this potential scheme is implemented:

- The contract with the developer/supplier may be signed by the European Commission, also on behalf of the Member States which have decided to take part in the program. Then, the conditions set for each Member State in terms of access, funding mechanism may be introduced in that contract as the result of the agreement reached between the European Commission and the Member States in the JPA.
- It is feasible that some Member States do not accept to join the procedure under the JPA with the EU and the APA with the supplier. This may lower the amount of public funding available for the pull mechanism, but the financial arrangements are fully flexible: it is possible that Member States finance fully the program, or that the EU co-funds the mechanism by using funds from the EU budget, under the EU4Health Programme Regulation and the Horizon Europe Regulation.
- The direct EU involvement in the contracting process may be required in order to ensure more leverage for the Member States and create a better incentive for the supplier. This contract could then cover the entire EU and extend obligations for the supplier, such as access, including for countries not directly participating in the scheme.
- The contract between the selected supplier and the EU/participating Member States would not cover the purchase of products, which is covered under normal transactions within national healthcare systems, but a guarantee of payment if a certain condition is met. Hence, the payment details may be relatively complex because the payment of a revenue guarantee at an EU level would require that yearly “open market” sales in each participating countries is carefully monitored to set the actual yearly payments[60]. A central organisation at EU level can be involved in gathering information coming from national sources in order to define the total yearly level of revenue guarantee payments to the extent that the revenue guarantee has been defined on an EU level.
- While not concerning product transactions, the contract can still cover the provision of access services about the selected product. Access may need to be contractually specified both in terms of continuous registration in participating

[60] In our modelling we calculated the yearly RG payments (and also for the last for years of all MERinos) to an awarded antibiotic by detracting from the yearly revenue guarantee the average sales level as presented in our input Table. For instance, at year 5 on the market, average sales in our distribution of projects are USD 76M (mean of 2 and 152): therefore, at year 5, the actual payments for RG100 would be USD 24M (100 – 76) and for RG150 would be USD 74M (150 – 76).

countries and service levels to be met in terms of either inventory levels at specific locations or/and delivery times to clinics/pharmacies.

6.3.3.5. Key takeaway for EU-level implementation

DG HERA could play a key role in the various governance elements above: for instance, engaging and coordinating Member States involved in the APA, help defining Member States' specific "fair shares" and activating the EU's contribution; coordinating with other relevant actors and agencies, defining selection criteria and the complex process of final selection.

Depending on the final specifications of the contract, DG HERA or other EU institutions may be involved in supervising the drafting of contracts, and potentially monitor yearly their compliance, including the definition of yearly payments.

Some national public-health agencies, regulators and payers may perceive the selected antibiotic as not matching their national needs and hence question their participation in funding this scheme.

This is a key challenge for all pull interventions reviewed and suggested in this report, namely that the EU and single Member States will need to come to an agreement as broad as possible as to which specific antibiotics will be selected for final award of any of the seven incentives.

As already mentioned, DG HERA might have a particularly relevant role in coordinating between the EU and Member States with regard to the process of agreement on target product profiles (TPPs) and evaluation criteria, as well as the final selection procedure.

6.3.4. MERinos

The following feasibility analysis will highlight relevant strengths and weaknesses from an operational and legal perspective.

Table 24 : Overview of intervention 2 – MERino

Intervention	Scenario	Identifier
Intervention 2 The MER + small revenue guarantee (MERino)	Low scenario - 2 X 250 M + 4 X 50 million*	MERino700*
	Intermediate 1 scenario - 2 X 330 million + 4 X 85 million*	MERino1000*
	Intermediate 2 scenario - 2 X 500 million + 4 X 125 million*	MERino1500*

6.3.4.1. Cost and benefit considerations

The expected public cost over six years to support one antibiotic is USD 1.321 billion for MERino1500, USD 821 million for MERino1000 and USD 521 million for MERino700. The specific EU cost share can then be calculated as being 25–50% of these three relevant global sizes, i.e., USD 330–660 million for MERino1500, USD 205-410 million for MERino1000, and USD 130–260 million for MERino700.

For the benefit aspect, we can also apply here the reasoning stated above with regard to the calculation of the societal value. The higher the multiplier, the lower the amount of antibiotics that would qualify for this scheme. Similar arguments as those made for RG100 and RG150 would apply here.

It should be noted that since MERinos generally provide more of an incentive and entail higher public costs, the corresponding minimal societal value requirements would be

higher than for RG100 and RG150 and hence result in having fewer antibiotics eligible for final reward when being approved to market.

6.3.4.2. *Advantages and disadvantages of MERino700, MERino1000 and MERino1500*

MERino is a hybrid intervention, combining some elements of revenue guarantees and of lump-sum MERs. The advantages and disadvantages are as follows:

Table 25: Operational advantages and disadvantages of MERino700, MERino1000, MERino1500

Advantages	Disadvantages
A clear pull effect possibly reaching as early as the preclinical decision point, especially for the largest size MERino1500, which depends on MERino's other main advantage of providing certainty of large revenue for suppliers in the first year immediately after an antibiotic's approval.	The total size of expected public payments is higher for MERinos than revenue guarantees with the same nominal value. Moreover, larger amounts are needed to fund in the first two years of the scheme.
MERino offers a better ENPV improvement to antibiotic developers than revenue guarantees	This model has not yet been piloted or previously tested.
Taking into account that it is not fully delinked and actual volume sales are deducted from the RG, it can be considered to be an advance purchase agreement for AMR MCMs so that a JPA can be actioned at EU level on a clear legal basis (Regulation (EU) 2022/2371). Within this JPA, a minimum threshold of participation of Member States can be foreseen (currently 4 countries).	

6.3.4.3. *Strings attached*

In terms of strings attached, it would be possible to apply the same access and stewardship provisions to MERino as for the 10-year revenue guarantee incentive (see above).

In principle, MERino is partially delinked, but for the first two years, payment sizes would be high enough to demotivate efforts to sell up, whereas from the third year on, this mechanism could require clear stewardship stipulations.

6.3.4.4. *Governance and financial considerations*

As explained in the legal assessment above, considering that MERino is not a fully delinked model, the MERino can be considered to be an advance purchase agreement for AMR MCMs so that a JPA can be actioned at EU level. As a consequence, the same applies as to revenue guarantee, and only general governance and financial considerations can apply, among other the following are:

- A central EU entity might be required to coordinate the effort of national bodies that would be in charge of determining the size of the market entry reward. Such national bodies could be the authorities currently in charge of health technology assessment.
- The cost of MERino being higher, the financial commitment of public funders needs to be higher. The share of each Member State can be agreed considering some guiding principles (cf. previous sub-section on fair share). If the EU also contributes financially, the relevant EU funding sources may be funds provided under the EU4Health Programme Regulation and the Horizon Europe Regulation.
- Apart from the market entry reward, the payment details for MERinos are as complex as the ones for revenue guarantee because it would also require that yearly sales in each participating country is carefully monitored. Hence, the same considerations as the ones explained for revenue guarantee applies.

- The same stewardship considerations and governance suggestions made for revenue guarantees apply for MERinos, but with an extra challenge that MERinos have a shorter time frame (6 vs 10 years which are in both cases long contracts that can be difficult to be managed).
- As is the case for revenue guarantees, the contract would rather concern guarantees and services related to access than the procurement of products (even when this is the ultimate goal).
- Furthermore, similar access clauses can be required for MERinos as for revenue guarantees (see the sub-section above), with the difference that MERino's payments stop after six years. At this point, "open market" sales are likely to have reached a sufficient level to motivate suppliers to keep the product on the market and ensure access. Nonetheless, additional access provisions can be added, especially for those Member States that may not be so attractive markets for suppliers. These clauses may be part of the initial MERino assignment contract or constitute new contracts which the EU may coordinate centrally so to obtain more favourable conditions for these Member States.

6.3.4.5. Key takeaway for EU-level implementation

We can expect for MERinos the same hindrances from single national public health agencies, regulators, and payors as for guaranteed revenues. Moreover, the large size of the first two years may be perceived as a strong barrier, unless the societal value of the selected antibiotic is clearly demonstrated and assessed.

6.3.5. Milestone-based reward

Several milestone-based rewards were simulated and tested in this study, however, only the ones for successful completion of phase I paying USD 60 million met the criteria we set for identifying the most attractive options. Such a reward can play an important role in complementing approval-based pull interventions of a smaller size so as to bring profitability to projects also in the preclinical stage.

Table 26: Overview of intervention 3 – milestone-based reward

Intervention	Scenario	Identifier
Intervention 3 Milestone-based reward	High scenario phase 1 prize 60 million*	P1Prize60*

6.3.5.1. Cost and benefit considerations

The total cost for bringing one antibiotic to market approval of this intervention is approximately USD 170 million. This amount corresponds to the size of a single reward, USD 60 million in our scheme, multiplied by 2.8, i.e. the number of antibiotics that need to receive it at the end of phase I to ensure that at least one of them will reach market approval, taking current attrition rates into account.

However, in practice, at least three milestone-based rewards will need to be awarded to overcome the risk of failure, which gives USD 180 million as a fair assessment of the public expenditure that is needed to have a reasonable probability that one of the supported antibiotics eventually reaches approval.

It is not possible to measure *ex-ante* the specific benefit of this intervention in terms of the target antibiotic's societal value, because at the end of phase I, it is too early to perform a HTA. Such an assessment can only be performed *ex-post*, if and when there will be any

supported antibiotic reaching market approval. However, an important and specific benefit of this milestone-based reward is its ability to support late market-entry pull (e.g. MERino1500) to reach full impact at the preclinical decision point. In this case, eligibility criteria may be more centred around conditionality of access on clinical trials at subsequent phases, etc. (see Section 6.1.2).

6.3.5.2. Advantages and disadvantages

The table below lists the main advantages and disadvantages of this intervention, including, its low cost and hence the possibility of fully controlling the milestone-based reward and, the risk of eventually not having any antibiotic finally approved, in addition to the difficulties in assessing the quality of a molecule in an early R&D stage.

Table 27: Operational advantages and disadvantages of P1prize60

Advantages	Disadvantages
Limited public cost (USD 170–180 million) in comparison to other incentives to (theoretically) bring one antibiotic to market, based on our simulated attrition rates of antibiotic R&D projects.	As funding is awarded at phase I, the antibiotic has no clinical evidence of efficacy.
Milestone-based rewards might even be a necessary complement to keep the sizes of pull incentives that can make financially viable projects at the preclinical stage within reasonable cost levels.	The qualification as "procurement" may be conceptually more difficult so that it is not excluded that the measure would be seen as a grant under the EU Financial Regulation, which should be oriented towards costs. The more remote the model is from actual procurement and costs, the harder it may be to justify the proportionality of the measure (under EU budgetary and EU State aid rules), which may be mitigated by the fact that the overall budget is much lower than the one for LSMER and MERino.
Can attract private sponsors and philanthropies due to its smaller financial requirement	Risk of fraud around selection criteria
Taking into account that the solutions are not near-to-market, they can be implemented through innovation partnership or pre-commercial procurement	Difficulty in including access and stewardship as part of the phase I award due to being far from market
	Not possible to measure ex-ante the specific benefit of this intervention in terms of the target antibiotic's societal value

6.3.5.3. Strings attached

When implementing milestone-based reward, public funders should ensure the developer's commitment to use this reward to continue its R&D on the subsequent phases to avoid fraud and drop-outs, and to ensure access to the products once it reaches the market.

Specifications of the contract with the suppliers remain flexible and unique. Nevertheless, public funders should consider the inclusion of clauses that transfer all requirements regarding the continuation of the development and access to final product to any licensee or buyer of the molecule's intellectual property rights (IPRs), including the future acquirer of the company owning the molecule[61]. This may reduce the attractiveness of the project for the future acquirer of the IPRs. Also, milestone-based rewards do not necessarily ensure access to the eventual antibiotic.

[61] It is common to have clauses that would be applicable in the case of a change of control. If the initial developer does not push through the same conditions in the molecule sale agreement, it will be contractually liable vis-à-vis the EU/Member States

Another important feature of milestone-based rewards is that their impact is bigger when combined with the latter pull incentives. In this respect, it would be key that the developers who receive a milestone-based reward remain eligible for revenue guarantees or market entry rewards.

6.3.5.4. Governance and financial considerations

The exact content of pre-commercial procurement remains flexible. Hence the following general governance and financial considerations can be made prior to the implementation of a milestone-based reward:

- As for financing, it might be difficult to have EU Member States national healthcare budgets fund milestone-based rewards, because they reward molecules that are still far away from market and clinical use. Therefore, a more relevant source of finance could be (1) national innovation and research budgets, or (2) major EU-level R&D funding programs such as Horizon Europe. Finally, milestone-based rewards can attract funding also from private sponsors and philanthropies, like the Longitude Prize for AMR diagnostics does (even though on a smaller financial scale than USD 60M).
- By implementing phase I milestone-based reward, public funders can define relevant as well as technically and scientifically demanding selection criteria during the development process, especially in terms of innovativeness. These criteria should be attuned with WHO priority lists but also be discussed and agreed upon by the EU and Member States, bearing in mind that push funders have already implemented these requirements in preclinical grants.
- The risk of fraud (i.e. developers providing unreliable clinical data for the sole purpose of being awarded the reward) is a central issue and may be addressed by involving one or more pipeline coordinators as the key technical and scientific infrastructure to manage the entire milestone-based reward scheme, which can in turn be supervised by the EU. In fact, it is only via recurrent and intensive interactions between developers and pipeline coordinators that trust can be built, including a transparent information flow about the antibiotic project under scrutiny and the technical and medical requirements it is expected to meet.
- The assignment of a milestone-based reward should signal the start of a long-term relationships between the awardee and the pipeline coordinator, and indirectly the EU represented by an entity such as DG HERA. This relationship would include both a set of mutual obligations and close collaboration and information exchange between the awardee and the intervening pipeline coordinator/DG HERA.
- The risk of funding projects “disappearing” for other reasons than technical failure (e.g. the developer goes bankrupt or there is a change in strategy) can be countered via contractual stipulations with recipients, which create clear “strings” attached to the selected antibiotic project and its molecule (see above).
- The contract signed between the awarded antibiotic developer and the EU can possibly extend to IPRs on the tested molecule. This extension can be relevant for public funders to pursue an IPR acquisition because a developer would be more willing to sell the IPRs to a molecule at such an early stage than if the same molecule proves to be very commercially attractive closer to or at market approval. DG HERA can have a key role in supervising, by interacting with the involved pipeline coordinators, a portfolio of molecules that have been awarded milestone rewards, including their IPRs. This supervising role would include contributing to the definition of selection criteria, recruiting evaluation committees, and planning how access to the future product can be achieved.
- In terms of access, it may be possible to include in the contract derived from the pre-commercial procurement that the EU and Member States will have a right to

access these products if they will be approved: in practice, this would correspond to requiring that their market authorisation holder registers and makes them available in the EU market as soon as they are approved by any trusted regulatory agency. However, a more reliable way to secure access would be to acquire, if possible, the molecule's IPRs and assign them to a non-profit developer, taking the responsibility of making the new antibiotic accessible in the EU.

6.3.5.5. Key takeaway for EU-level implementation

6.3.5.6.

Concerning hindrances from stakeholders, some developers may be unwilling to share all required information at such early stage with the body assigning the reward, which may reduce the number of attractive projects participating in the "competition". Furthermore, large pharmaceutical companies may be concerned that a milestone-based reward would increase the financial value of SMEs developers, making it more expensive for them to purchase these companies at later stages of development.

6.3.6. Lump-sum MER

For the lump-sum MER, we have selected only one size because the other two are investments that are too large and risky for public funders (see the table below).

Table 28 Overview of intervention 4 – Lump-Sum MER

Intervention	Scenario	Identifier
Intervention 4 Lump-Sum MER	Low scenario lump sum MER – USD 1 billion*	LSMER1000*

6.3.6.1. Cost and benefit considerations

The global cost of this intervention for bringing one antibiotic to approval is straightforward since it is the size of the promised lump-sum payment, i.e. USD 1 billion in the selected scheme. For this intervention, no amount is detracted from the nominal size because open market sales are not allowed in this fully delinked scheme. In the event of global coordination, the EU's cost share is expected to be 25–50% of this global size, i.e., USD 250–500 million paid as a single payment.

As for the benefits of lump-sum MER, the reasoning above for revenue guarantees and MERinos concerning a minimum accepted societal value as a requirement for receiving the reward applies here too. Only new antibiotics with a global societal value that is above the required threshold could qualify.

The same considerations concerning costs for multiple awards also apply to the lump-sum MER. However, considering the high risk taken by public investors in paying the entire incentive in one large sum, the criteria for selecting antibiotics could be more demanding in terms of innovativeness and minimal risk for cross-resistance.

6.3.6.2. Advantages and disadvantages of the lump-sum MER

Looking at the table below, this intervention seems to have more disadvantages than advantages, especially due to its high risk for funders, and the difficulty in finding funds.

Table 29 : Operational advantages and disadvantages of LSMER1000

Advantages	Disadvantages
Offers strong certainty to suppliers on the size and timing of a single large payment	It can be very difficult to find funds to cover the large-sized intervention to be awarded in one single lump-sum payment.
LSMER100 is fully delinked and hence supports stewardship	It will be legally complex to implement: the qualification as "procurement" may be conceptually more difficult so that it is not excluded that the

	measure would be seen as a grant under the EU Financial Regulation, which should be oriented towards costs. Also, the more remote the model is from actual procurement and costs, the harder it may be to justify the proportionality of the measure (under EU budgetary and EU State aid rules), certainly because the solution may be already closer to market.
	Despite full delinkage in the first year, attaining stewardship and access in the following years requires specific contracts and stipulations with the supplier. These contracts may fail if the developer goes bankrupt or closes the company.

6.3.6.3. *Strings attached*

In terms of the strings attached, a lump-sum MER requires a large amount of public funding (above USD 1 billion) to have strong pulling effects. Hence, in terms of strings attached, public authorities may decide that only extremely innovative molecules should be eligible, after monitoring their performance in several clinical trials until their eligibility can be fully assessed.

If the lump-sum MER operates as a fully delinked intervention, stewardship can be achieved without particular provisions, as the lump sum fully substitutes market sales for a certain number of years[62]. However, it is for this very reason that it will be necessary, through the contractual arrangement to stipulate clear obligations to guarantee access and availability for the years thereafter. These obligations may be complemented with a smaller annual payment after a certain number of years (e.g., from the sixth year, when actual use may have increased) to compensate the MAH for keeping a manufacturing capacity and stocks of the product. The size of these smaller annual payments should solely compensate for access/availability and no longer to achieve any “pulling effect”.

A lump-sum MER might well concern transactions and the availability of physical goods, either in predefined quantities or more likely in undefined quantities sufficient to cover the needs of all Member States. It is essential to specify these conditions for delivery and access certainly in the first year, but also for the years thereafter.

6.3.6.4. *Governance and financial assessment*

As the market entry reward is a disruptive solution with no similar precedent, the legal assessment has been more challenging. Nevertheless, the following governance and financial considerations can be anticipated:

- Payment details and procedures are simpler than for RGs and MERino because the lump-sum MER implies a single payment at market approval. Hence, it will not be necessary to track sales and detract them from any payment.
- As for stewardship, despite full delinkage in the first year, refraining suppliers from overselling in the following years requires specific contracts and stipulations. After the first year, suppliers may also be demotivated to accept and comply with stewardship requirements due to the large payment they have already received: therefore, it is necessary to include stewardship stipulations already in the contract for awarding the lump-sum MER and covering ideally the following five years.
- The role of an EU entity like DG HERA in the governance of lump sum MER is expected to be very important. Similarly to MERinos, DG HERA may also

[62] The exact number of years may be the results of negotiations. This point is further discussed in the pre-feasibility assessment

coordinate the efforts of various HTA agencies in order to achieve reliable evaluation of societal values of selected antibiotics in view of identify eligible antibiotics. Moreover, DG HERA may be the key counterpart in the contract with the supplier and then manage availability for Member States.

- The lump-sum MER is the most demanding to finance because it not only requires the largest amount of funds (USD 1 billion vs 821 USD million for MERino1500), but also because these funds need to be found directly for payment in one lump sum. Therefore, the EU's role in funding or attracting funds for these large investments needs to be more prominent.
- If set through a pre-commercial procurement or a regular procurement procedure (e.g., via an innovation partnership) rather than a traditional grant, the EU may fund the lump-sum MER through the using the financing programmes described above. Member States can also contribute and the principles governing each financial contribution will need to be specified and secured through the contract specifications, as in the example of the COVID-19 vaccines contract.

6.3.6.5. Key takeaway for EU-level implementation

Lump-sum MER presents similar hindrances to MERinos when it comes to agreeing about the selection of a specific antibiotic, with the additional problem that there will be a large payment in the first year. Moreover, due to the fully delinked nature of this lump-sum MER, large pharmaceutical companies may not be attracted by the fact that it caps any revenue accruing to the selected antibiotics at only USD 1 billion for a number of years.

6.4. Conclusions: Options for DG HERA and next steps

6.4.1. Comparing pull interventions

The interventions tested in this study are heterogeneous, as such their advantages and disadvantages can be difficult to weigh against each other. Based upon the analysis above summarise the following:

- **revenue guarantees** have lower risk and costs for public actors, but are expected to have smaller pulling effects, which may eventually boost to a lower extent the pipeline in the future. Smaller revenue guarantees can be used to ensure access to existing antibiotics.
- **MERinos** have higher risk and public costs than RGs, but they could have stronger pulling effects on antibiotics and, thanks to the payment of lower amounts for a number of years after approval, it can also secure access through the inclusion of such guarantees into the joint procurement agreement.
- **lump-sum MER** appears as the least attractive pull intervention due to its very high risk, high cost for the public sphere, and complex legal implementation.
- **the milestone-based reward** may have challenges in terms of stewardship and selection of molecules with a high societal value early in the pipeline, but it may well complement other pull incentives, and requires lower public costs.

6.4.2. Two options combining early and late stage pull interventions

If we delimit the level of public expenditure for one approved antibiotic to a **maximum of USD 1 billion** (globally), these two combinations of milestone-based reward at the end of phase I and approval-based pull interventions can be considered as attractive, both in terms of the impact on ENPVs and of feasibility:

1- **P1prize60** (costing USD 169 million for one approved antibiotic) **+ RG150** (costing USD 784M for one approved antibiotic, i.e. a total of USD 953 million). This combination can bring positive effects to ENPV starting from phase I. Moreover, in

terms of feasibility, this combination presents more advantages (e.g. the existence of already implemented models at national levels for revenue guarantee, low risk and implications for access for RGs and attractiveness for SMEs of milestone-based rewards) than disadvantages (e.g. the risk of fraud for milestone-based rewards and limited pull effect upstream in the R&D pipeline when RGs is implemented alone). This also considers the principle of proportionality required under State aid law and, more generally, under EU law whereby a choice can be made in function of the "near-to-market" character of the antibiotic or not.

2- **P1prize60** (costing USD 169 million for one approved antibiotic) + **MERino1000** (costing USD 821 million for one approved antibiotic, i.e. a total of USD 990 million). This combination can bring strong positive effects to ENPV starting from phase I and possibly also the preclinical stage. As for feasibility, although potentially more complex than a revenue guarantee, this combination also considers the principle of proportionality required under EU law whereby a choice can be made depending on the "near-to-market" character of the antibiotic or not.

It should be noted that these two options may be unable to fully stimulate antibiotic projects in the preclinical stages. Therefore, it is important to consider also complementary push measures and interventions acting across the whole R&D pipeline, as we do in the next section.

6.4.3. Push and pull interventions to support projects across the whole R&D pipeline

In order to bring new antibiotics to market, it is necessary to stimulate all stages in the R&D pipeline because the current scenario of the antibiotic field implies **negative ENPVs at all R&D stages**. Moreover, the single R&D stages present different financial challenges that can hardly be addressed by one single pull intervention.

The results of our simulation indicate that different types of interventions and different sizes of the same intervention are effective at different R&D stages and point out the need to combine them with other interventions, such as a special type of push intervention represented by pipeline coordinators. The various pull and push interventions can accordingly be used in concert and in complementary ways to simulate the entire R&D pipeline. In particular, pipeline coordinators have a key role in managing milestone-based rewards and building portfolios composed of several molecules that they support, either via milestone-based rewards or their direct technical and scientific support: creating such project portfolios would also allow for risk spreading, which is common practice among large pharmaceutical companies in their product portfolios.

Moreover, if pipeline coordinators become active in "R&D Collaboration" they can generate other positive impacts on antibiotic projects, i.e. improving the probability of success and reducing R&D times. Therefore, such pipeline coordinators can complement and greatly improve the impact of approval-based pull interventions.

Since it is necessary using multiple interventions to support an antibiotic project, ideally at several stages of R&D, it is possible that one and the same project eventually receives grants, the direct technical support of a pipeline coordinator and a pull intervention upon market approval. Summing up the monetary value of all the incentives received, such an antibiotic might have been "overcompensated". Therefore, it is important to monitor all incentives that a project receives and apply clawbacks of, for instance, grants from the substantially larger amounts of approval-based pull interventions[63]

[63] Christine Årdal and David Findlay *et al.* (2018) "DRIVE-AB Report – Revitalizing the antibiotic pipeline – simulating innovation while driving sustainable use and global access" [online] Available at: http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed: 25th October 2022]

6.4.4. Limitations and further analyses

Our analysis has tested and simulated a set of interventions in isolation from each other. However, if two interventions are implemented at the same time, it is likely that their joint impact on ENPV will be higher than the sum of their individual impact. Therefore, further modelling and simulations should analyse the combined impact of two mechanisms.

We also discussed pipeline coordinators of the type “R&D Collaboration” (and, to a lesser extent, non-profit antibiotic developers) as capable of having a positive impact on projects’ ENPVs and of increasing the impact of pull interventions if used in combination. However, in order to assess the specific impacts, it is advisable to model and simulate these complex interventions and then test their combined impact with pull incentives.

Our input and output data do not distinguish explicitly between types of antibiotic developers such as big pharmaceutical companies and SMEs, which may however apply different ranges of parameters when calculating their projects’ ENPV. Therefore, further analyses should seek specific data identifying relevant characteristics of these different antibiotic developers to assess how, for instance, SMEs as opposed to large pharmaceutical companies react to the proposed interventions.

More complex artificial intelligence models can also be used to identify the optimal size of each intervention and also of combinations of interventions. For instance, such a model would search for the optimal size of interventions for each phase given an objective in terms of ENPV as well as other variables. Alternatively, another optimisation model could be used to assess the optimal mix of pull and push incentives given a total amount of public expenditure.

Finally, prior to implementing selected interventions identified via modelling and simulations, it is necessary to conduct detailed studies and have open discussions with various stakeholders. In particular, it is necessary to assess the political will for implementation. Moreover, the interplay between the EU’s efforts and the global sphere of interventions could be further investigated in order to identify overlaps and possible areas of collaboration.

7. Push Incentives - Funding to R&D and translational research

7.1. Context and challenges

Based on the perspective of the stakeholders surveyed, the second highest priority role for DG HERA is to coordinate and/or contribute to financial push incentives for the development and innovation of new AMR MCMs.

The importance of push incentives in AMR R&D has been referenced in multiple key position papers and reports in recent years. The DRIVE-AB[64] report proposed that the broken market of antimicrobial R&D could be resolved by a balanced combination of push (grants, coordinators) and pull incentives. This is a conclusion reached by several AMR stakeholders in multiple academic articles[65,66].

DRIVE-Ab final report (2018)[67]

"There have been large increases in push incentives in the last five years, including from new initiatives such as CARB-X (The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) and GARDP (Global Antibiotic Research and Development Partnership). The OECD estimates that countries are investing approximately USD 550 million (EUR 470 million) every year in grant funding for antibiotic R&D. While significant, this level of financing and commitment is still too low."

The G7 progress report published by the Global AMR R&D hub highlights several recommendations, one of which being to support and replenish push funding for AMR R&D with a specific focus on early-stage development. This is where innovation is needed most to create novel treatments and where the chances of failure are too high to attract investors[68].

Global AMR R&D Hub & the WHO – G7 Progress Report (2022)[69].

"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, thereby ensuring a more sustainable source of funding."

[64] DRIVE-AB (2018) **DRIVE-AB REPORT Revitalizing the antibiotic pipeline Stimulating innovation while driving sustainable use and global access** [Online] Available at http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [accessed on 18 November 2022].

[65] Morel C.M and Mossialos E. **Stoking the antibiotic pipeline** (2010) British Medical Journal [Online] 340 Available at https://doi.org/10.1136/bmj.c2115 [accessed on 7 December 2022].

[66] Cooper M and Shlaes D. **Fix the antibiotics pipeline** (2011) Nature [Online] 472(32) Available at https://doi.org/10.1038/472032a [accessed on 7 December 2022].

[67] DRIVE-AB (2018) **DRIVE-AB REPORT Revitalizing the antibiotic pipeline Stimulating innovation while driving sustainable use and global access** [Online] Available at http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [accessed on 18 November 2022].

[68] Milken Institute Financial Innovations Lab ® (2022) **Models for Financing Antibiotic Development to Address Antimicrobial Resistance** [Online] Available from: https://milkeninstitute.org/sites/default/files/2022-03/FIL-AMR%20v3.22.22.pdf [Accessed: 21st November 2022].

[69] Global AMR R&D Hub & the WHO (2022) I**ncentivising the development of new antibacterial treatments – Progress Report by the Global AMR R&D Hub and WHO** [Online] Available from: https://globalamrhub.org/wp-content/uploads/2022/05/G7_ProgressReport_FINAL_16.05.2022.pdf [Accessed: 18th November 2022].

Based upon the simulation presented in section 6 – pull incentives, it is clear that the current baseline scenario presents an extremely poor situation for current pre-clinical development. In the simulation conducted by this study, only very expensive pull incentives were capable of incentivising these early stages of R&D. In order to incentivise R&D in a more cost-effective manner, other approaches may be deployed – one such approach is push incentives (or as discussed previously, milestone awards).

7.1.1. Stakeholder views of the role for DG HERA

As DG HERA was established, the call for greater push funding was reiterated with a clear role set for DG HERA in this regard. A white paper published in 2021 by The European Federation of Pharmaceutical Industries and Associations in collaboration with Vaccines Europe indicated the "gaps" which could be addressed by DG HERA. In summary, the paper states that the existing early development support is insufficient to address the unmet clinical needs.

A joint EFPIA and Vaccines Europe White Paper (2021) [70]

"While the EU invests in early-stage research, the current actions are not extensive enough. There is a 4-fold difference between the combined EU (Horizon Europe) and Member State annual funding for health research compared with that of the U.S."

The positioning of the role for DG HERA to support R&D by contributing and coordinating push incentives has been proposed by notable industry networks in the AMR market such as BEAM Alliance who stated in their 2021 position paper that early-stage support for research and development of novel antibiotics should be included within the preparedness role of DG HERAs mandate.

BEAM Alliance (2021) [71]***.***

"We urge the HERA to provide appropriate support that focuses on funding the process of innovation from preclinical R&D onward for novel antibiotics under the preparedness phase function of the mandate"… "The HERA should also prime the clinical pipeline, through the support to preclinical development and onwards, either directly, but probably more efficiently through a direct contribution to CARB-X, just like BARDA does."

It is foreseen that DG HERA will have an important role to play in funding key areas of research and development[72]. Therapeutic options to address antimicrobial resistance are clearly amongst the most pressing of the medical countermeasures where support is needed[73]. This has been highlighted by Member States and described in an earlier section of this report. A mix of push and pull mechanisms are likely to be more effective than pull

[70] EFPIA and Vaccines Europe (2021) **A joint EFPIA and Vaccines Europe White Paper – Establishment of The Health Emergency Preparedness and Response Authority** [Online] Available from: https://www.efpia.eu/media/602659/hera-white-paper_efpia_ve.pdf [Accessed: 18th November 2022].

[71] BEAM Alliance (2021) **BEAM Alliance wants HERA to effectively support R&D in antimicrobial resistance** [Online] Available at https://beam-alliance.eu/beam-alliance-wants-hera-to-effectively-support-rd-in-antimicrobial-resistance/ [Accessed: 18th November 2022].

[72] Communication from the Commission to the European Parliament, The Council, The European Economic and Social Committee and the Committee of the Regions (2020) **Building a European Health Union: Reinforcing the EU's resilience for cross-border health threats** [online] Available at: https://ec.europa.eu/info/sites/default/files/communication-european-health-union-resilience_en.pdf [accessed 7th December 2022]

[73] Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions (2020) [online] Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761 [accessed 7th December 2022]

options alone, and together help share the risk of innovation between private and public actors[74].

7.1.2. Gap in early stage to preclinical R&D

Within the WHO pipeline analysis published in 2022, a total of 76 antibacterial agents are currently in clinical development globally – approximately half of them target WHO priority pathogens. Since 2017, only 12 new antibiotics have been approved, of which only 2 can be considered "innovative". A majority of new antibacterial agents at present are undifferentiated[75], meaning that they may fail to provide physicians with meaningful treatment alternatives for resistant infections. These "me-too" compounds have the advantage of possessing similar properties as their parent compound, which can help speed up preclinical and clinical studies and reduce costs. It is frequently the case, however, that bacteria develop resistance against these "me-too" compounds in a short period of time[76].

According to the WHO, the lack of innovation is set to undermine antibiotic performance and overall health gains[77]. In order to overcome existing resistance mechanisms, we need truly novel molecules and approaches to treating infections. As such, new thinking is required at the earlier stages of the pipeline[78]. A recent publication highlighted that it is particularly in the "early discovery" stage that antibiotic developers face the major challenges because they lack experience of drug development and a whole set of medical, chemical, microbiological and project management skills[79].

Information in the literature was further validated by our survey, within which industry stakeholders were asked which stage of R&D presented the greatest challenge. There was a key focus on early-stage development, although this may also relate to the profile of the respondents. The level of "challenge" indicated by respondents increased from basic research and peaked at preclinical stages (Figure 7). When looking deeper within the "type" of challenges experienced by AMR MCM developers, early-stage development is burdened by financial and scientific challenges. A similar trend was presented within the interim report for this study, which identified that a high proportion of discontinued AMR MCMs captured by our search strategy fail prior to a phase I clinical trial – technology readiness level 5 (TRL5) (Figure 8).

When analysing active AMR R&D, a majority (41.5%) of all AMR MCMs (treatments, preventatives, and diagnostics) identified by our interim analysis were in early-stage-preclinical development (TRL5).

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[74] Anderson M., and Forman R., *et al.* (2021) "Navigating the role of the EU Health Emergency Preparedness and Response Authority (HERA) in Europe and beyond". **Lancet** [online] 9(100203) Available at: https://doi.org/10.1016/j.lanepe.2021.100203 [Accessed 5th December 2022]

[75] Butler M.S. and Gigante V. *et al.* (2022) "Analysis of the Clinical Pipeline of Treatments for Drug Resistant Bacterial Infections: Despite Progress, More Action Is Needed" **Antimicrobial Chemotherapy** [online] Available at: https://doi.org/10.1128/aac.01991-21 [Accessed 5th December 2022]

[76] Stephens L.J. and Werrett M.V. (2020) "Antimicrobial innovation: a current update and perspective on the antibiotic drug development pipeline" **Future Med Chem** [online] 12(22) pp. 2035-2065 Available at: https://doi.org/10.4155/fmc-2020-0225 [Accessed 5th December 2022]

[77] World Health Organisation **Lack of Innovation Set to Undermine Antibiotic Performance and Health Gains** (2022) [online] Available at: https://www.who.int/news/item/22-06-2022-22-06-2022-lack-of-innovation-set-to-undermine-antibiotic-performance-and-health-gains [Accessed 5th December 2022]

[78] DRIVE-AB (2018) **DRIVE-AB REPORT Revitalizing the antibiotic pipeline Stimulating innovation while driving sustainable use and global access** [Online] Available from: http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed: 18th November 2022].

[79] Theuretzbacher U, Baraldi E. *et al.* (2022) « Challenges and shortcomings of antibacterial discovery projects". **Clinical Microbiology and Infection** [Online] Available from: https://doi.org/10.1016/j.cmi.2022.11.027 [Accessed: 21st December 2022].

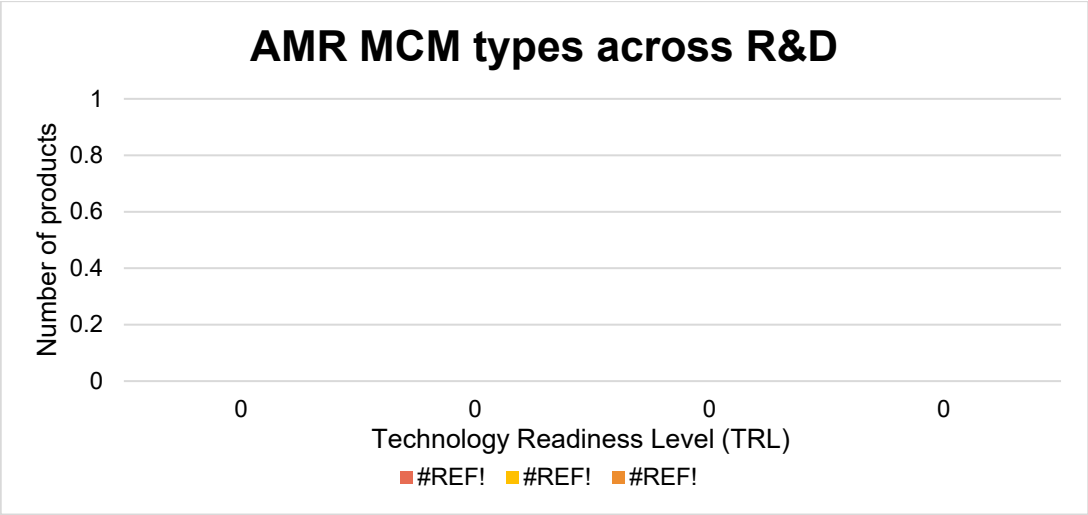

Figure 23 AMR MCM types across the research and development pipeline from TRL 5 (preclinical) to TRL 8 (phase III)

7.1.3. The needs of small-to-medium enterprises

Broadly, it is SMEs that are seen as the main drivers of innovation in AMR R&D. In the Interim report[80] of this study, we identified that SMEs made up a majority of product developers at earlier stage R&D, with large industry making up a majority of the marketed product space (seen in the figure below).

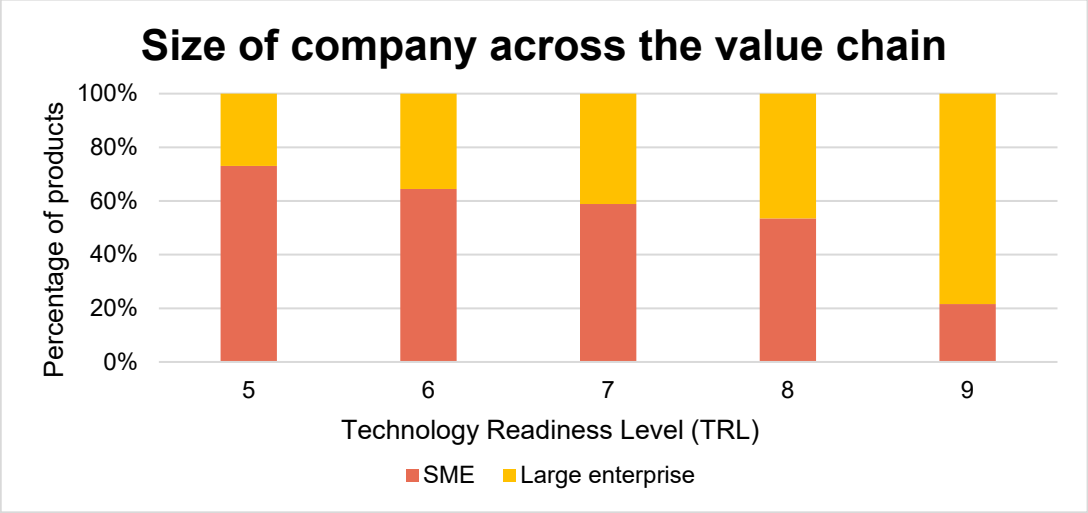

Figure 24: Percentage of SMEs and large enterprises associated with the development of AMR MCMs across the value chain – from pre-clinical research (TRL5) to market authorisation/approval (TRL9).

As in many research areas, SMEs tend to have restricted capital; in some instances, they only have enough to cover six months of activity[81]. A prior analysis of the antibiotic pipeline by the Pew Trust identified that two thirds of SMEs have never developed an antibiotic before[82] and many are single-molecule companies, meaning that there is no possibility of

[80] Interim Report accessible at: https://op.europa.eu/en/publication-detail/-/publication/341cf78c-bd6a-11ed-8912-01aa75ed71a1/language-en/format-PDF/source-281956123

[81] Mossialos E. and Morel C.M *et al.* (2010) **Policies and incentives for promoting innovation in antibiotic research** [Online] Available from: https://apps.who.int/iris/bitstream/handle/10665/326376/9789289042130-eng.pdf?sequence=1&isAllowed=y [Accessed: 7th December 2022].

[82] The PEW Trust (2021) **Tracking the Global Pipeline of Antibiotics in Development** [Online] Available from: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development. [Accessed: 7th December 2022].

cross subsidisation from marketed profitable products[83]. In early-stage R&D, there is a relative lack of evidence on the clinical effectiveness of the product under development. As a result, the developers are often not well positioned to engage strongly in dilutive, equity-related discussions with larger companies or investors[84]. As such, the optimal way of supporting these companies is through **non-dilutive funding** including support (see table below for definition), which should be inclusive to SMEs.

7.2. Landscape analysis of push incentives

There are a number of key crucial actors specifically focused on supporting the research and development of AMR MCMs both at EU level and Global level through push support. In order to provide DG HERA with a capture of this AMR-specific landscape, a high-level analysis was conducted. For each of the AMR specific push incentives below, the following information was gathered based on desk research.

Table 30: Criteria for a landscape of push mechanism features

Feature	Description
Conditions to support/funding	In a functioning market, investors support the financing of companies in promising, innovative industries in exchange for equity. Each financing round brings in additional money but releases some ownership of the company – such mechanisms are considered **dilutive**. This is in contrast to **non-dilutive** funding which provides funding without any equity considerations (such as private-debt issuance). In some instances, a contract is created that allows an organisation to provide capital to the development and launch process of an AMR MCM, thus taking financial responsibility in exchange for some licencing rights. In some cases, once the product gets to market, profits are required to be shared[85]. This is referred to as **in-licencing** **Convertible debt** is where a business is lent money with the intent to repay all or part of the loan by converting it into a number of shares. In the remit of this agreement (between the investor and the investee) the timeframe and price per share for this conversion is agreed[86]. In some cases, funding may be offered in exchange for **intellectual property rights**. **Support in kind** refers to support provided by an organisation that is not financial, e.g. donated services.
Pipeline coverage	To determine whether support is broad or focused on a specific point in development in order to resolve a specific gap.
Role as a push funding mechanism	Push funding can be offered to achieve specific goals in AMR MCM R&D. In the cases of the "push" mechanisms listed below, such financial support is often complemented with technical, scientific and/or business support in order to guide the development of the products awarded funding in a way that seeks to tackle additional challenges experienced in addition to financial ones.
Total available funding for AMR	Determine the volume of push funding available/allocated based on information available via desk research (where a specific value relates to "in-kind" support, this will

[83] Milken Institute Financial Innovations Lab ® (2022) **Models for Financing Antibiotic Development to Address Antimicrobial Resistance** [Online] Available from: https://milkeninstitute.org/sites/default/files/2022-03/FIL-AMR%20v3.22.22.pdf [Accessed: 21st November 2022].

[84] DRIVE-AB (2018) **DRIVE-AB REPORT Revitalizing the antibiotic pipeline Stimulating innovation while driving sustainable use and global access** [Online] Available from: http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed: 18th November 2022].

[85] TwoLabs Pharma Services The Basics of Licensing: In & Out, Drug & Facility [Online] Available from: https://twolabs.com/the-basics-of-licensing-in-out-drug-facility/ [Accessed: 7th December 2022].

[86] BDC **Convertible debt** [Online] Available from: https://www.bdc.ca/en/articles-tools/entrepreneur-toolkit/templates-business-guides/glossary/convertible-debt [Accessed: 7th December 2022].

R&D	be clearly highlighted).
Key contributors to the pool of funding	Identify who the "key players" are in contributing funding to these mechanisms across the spectrum of private and public entities.

In the section below we present the landscape of AMR specific push mechanisms, both current and no longer functioning, in alphabetical order.

7.2.1. Antimicrobial Action Fund – Global focus

The Antimicrobial Action Fund is a global venture capital fund that was launched in 2020 to support the development of new antibiotics in order to address unmet clinical needs as prioritised by the WHO, CDC, and other leading authorities. The support offered by the fund aims to bring up to four antibiotics to market by 2030, in addition to creating market conditions to ensure sustainable investment in the antibiotic market[87].

At the time of writing this report, the AMR Action Fund has distributed funding to two projects: Adaptive Phage Therapeutics, which is developing phage therapy, and Venatorax Pharmaceuticals, which is developing Cefepime-taniborbactam (currently in phase III clinical trials)[88]. However, the amounts invested were not disclosed.

The AMR Action Fund is described as a short-term solution. For the long-term resolution of the broken antimicrobial market, the AMR Action Fund calls for solutions to be envisioned to change the approach to buying marketed antimicrobials – where countries reimburse based on their societal value rather than volume sold (delinked pull incentive)[89].

Table 31: AMR Action Fund Overview of features

Conditions to support/funding?	The funding provided by the AMR Action Fund is dilutive in nature and structured as an investment to companies in return for an equity stake or in the form of convertible debt[90]. However, it should be noted that the AMR Action Fund is prepared to take on higher-risk projects than a "normal commercial investor"[91].
Pipeline coverage	The AMR Action Fund functions as a push incentive for phase II-III (TRL7-8), embracing the "pay or play" concept that large pharmaceutical companies who do not develop antimicrobials should contribute funding to support efforts[92].
What is their role?	The support provided by the AMR Action Fund is not only financial. In summary, the

[87] McCall B. (2020) "New fund stimulates the ailing antibiotic pipeline" [Online] **The Lancet Infectious Diseases** 20(9) Available from: https://doi.org/10.1016/S1473-3099(20)30629-0 [Accessed: 21st November 2022].

[88] AMR Action Fund (2022) **AMR Action Fund Announces First Investments in Adaptative Phage Therapeutics and Venatorx Pharmaceuticals** [Online] Available from: https://www.amractionfund.com/blog-2022/news-amr-action-fund-announces-first-investments-in-adaptive-phage-therapeutics-and-venatorx-pharmaceuticals [Accessed: 21st November 2022].

[89] Chris Dall, CIDRAP (2022) **AMR Action Fund announces its first investments** [Online] Available from: https://www.cidrap.umn.edu/news-perspective/2022/04/amr-action-fund-announces-its-first-investments [Accessed: 21st November 2022].

[90] BEAM Alliance (2020) **Reflection paper on the AMR Action Fund** [Online] Available from: https://beam-alliance.eu/wp-content/uploads/2020/09/amractionfund_reflection-paper.pdf [Accessed: 21st November 2022].

[91] Knox J (2021) **Why Wellcome is investing in the AMR Action Fund** [Online] Available from: https://www.linkedin.com/pulse/why-wellcome-investing-amr-action-fund-jeremy-knox/ [Accessed: 21st November 2022].

[92] Clancy C.J and Nguyen M.H. (2020) "Buying Time: The AMR Action Fund and the State of Antibiotic Development in the United States 2020" [Online] **Open Forum Infectious Diseases** 7(11) Available from: https://doi.org/10.1093/ofid/ofaa464 [Accessed: 21st November 2022].

(shape of partnership)	AMR Action Fund will: • invest in smaller biotech companies that are focused on addressing the highest priority public health needs; • provide technical support to portfolio companies, giving access to the deep expertise and resources of large biopharmaceutical companies; and • bring together a broad alliance of industry and non-industry stakeholders[93].
Total available funding for R&D	In total, the AMR Action Fund plans to invest approximately USD 1 billion in clinical-stage biotech companies.

Key contributors to the funding pool

A majority of the investors in the AMR Action Fund are private investors from the pharmaceutical industry, as shown below:

Industry contributors (undisclosed contribution)

Almierall	Amgen	Bayer
Boehringer Ingelheim	Boehringer Ingelheim Stiftung	Chugai
Daiichi-Sankyo	Eisai	Lilly
Pfizer	Johnson & Johnson	Lundbeck
Merck	Novartis	GlaxoSmithKline plc
Leo	Menarini	Mereck
Novo Nordisk	Novo Nordisk Fonden	Shionogi
Teva	Roche	Union Chimique Belge
Takeda		

Public contributors

European Investment Bank *EUR 24.1 million*[94]	Wellcome Trust *GBP 50 million*[95]

7.2.2. CARB-X – Global focus

CARB-X
Combating Antibiotic-Resistant Bacteria

The Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is a global non-profit public-private partnership funded by three G7 governments (USA, Germany, and the UK, and

[93] European Investment Bank (2020) **New AMR Action Fund steps in to save collapsing antibiotic pipeline with pharmaceutical industry investment of USD 1 billion** [Online] Available from: https://www.eib.org/en/press/all/2020-190-new-amr-action-fund-steps-in-to-save-collapsing-antibiotic-pipeline-with-pharmaceutical-industry-investment-of-ususd1-billion [Accessed: 21st November 2022].

[94] European Investment Bank (2021) [Online] Available from: https://www.linkedin.com/posts/european-investment-bank_amr-action-fund-activity-6768170290078863360-qEp_/?trk=public_profile_like_view&originalSubdomain=lu [Accessed: 21st November 2022].

[95] Wellcome Trust (2021) **We're backing the AMR action fund – this is what it means for antibiotic innovation** [Online] Available from: https://wellcome.org/news/were-backing-amr-action-fund-what-it-means-antibiotic-innovation [Accessed: 21st November 2022].

two foundations (Wellcome and the Bill & Melinda Gates Foundation)[96]. Specifically, CARB-X is the only global partnership that supports the development of diagnostics, preventatives and treatments for life-threating bacterial infections caused by bacteria identified by the WHO and CDC priority lists[97].

Table 32: CARB-X - Overview of features

Conditions to support/funding?	CARB-X provides non-dilutive funding (grants) with the requirement of a project-cost share. Within this model, CARB-X pays for all costs relating to R&D support. CARB-X requires that recipients have solid assets and demonstrated private investment in the specific project in question[98].
Pipeline coverage	CARB-X funds from "hit-to-lead" until the completion of phase I clinical trials and, for diagnostics, from feasibility through the verification and validation stages[99] (TRL3-6). CARB-X translates ideas from basic research in academia or biotechnology start-ups to safety data in humans.
What is their role? (shape of partnership)	CARB-X funds through public calls only – these are generally thematic in nature. Prospective projects are juried by an external advisory board that recommends projects to the CARB-X Investment Committee, which makes the final decision. Once programmes are in-portfolio, CARB-X focuses on acceleration by building tailored Company-Support Teams from internal and external experts to complement and enhance the product-developer team. Additionally, CARB-X provides scientific and business advice from a global accelerator network as well as from a large pool of subject-matter experts that cover the disciplines needed to advance a project at this stage. CARB-X also facilitates access to preclinical services (assays, chemical synthesis, etc.) offered by the US National Institute for Allergy and Infectious Diseases (NIAID)[100]. CARB-X funds a programme in stages, defined by milestones consistent with maturation towards human clinical studies. Progression to a next stage is juried by an external advisory board that makes recommendations to the CARB-X Investment Committee. When programmes reach the penultimate stage of development (before human clinical trials), CARB-X introduces a Clinical Advisory Board that helps the project shape the clinical trials to support the regulatory acceptance of the new product[101]. CARB-X also deploys "Portfolio Acceleration Tools" that are designed internally and executed within the network. Results of these efforts are shared not only with specific in-portfolio developers, but also with the greater community engaged in antibacterial discovery and development.
Total available funding for R&D	In the six years since its inception (2016-2022), CARB-X has awarded approximately USD 400 million to product developers[102]. In October 2022, renewed funding amounting to USD 370 million was announced by the U.S. Government (BARDA) and Wellcome Trust[103]. Renewals with other existing funders are expected in the coming year and CARB-X is discussing funding from other G7 countries as well as the European Commission. CARB-X is in the process of setting

[96] Milken Institute Financial Innovations Lab ® (2022) **Models for Financing Antibiotic Development to Address Antimicrobial Resistance** [Online] Available from: https://milkeninstitute.org/sites/default/files/2022-03/FIL-AMR%20v3.22.22.pdf [Accessed: 21st November 2022].

[97] CARB-X **Overview** [Online] Available from: https://carb-x.org/news/carb-x-news/ [Accessed: 23rd November 2022].

[98] CARB-X **Our Strategy** [Online] Available from: https://carb-x.org/about/our-strategy/ [Accessed: 23rd November 2022].

[99] CARB-X **Portfolio Pipeline** [Online] Available from https://carb-x.org/portfolio/portfolio-pipeline/ [Accessed: 23rd November 2022].

[100] CARB-X **Our Strategy** [Online] Available from: https://carb-x.org/about/our-strategy/ [Accessed: 23rd November 2022].

[101] CARB-X **Portfolio Acceleration Tools** [Online] Available at https://carb-x.org/portfolio/portfolio-acceleration-tools/ [Accessed: 23rd November 2022].

[102] CARB-X **Annual Report 2020-2021** [online] Available at https://carb-x.org/wp-content/uploads/2021/10/CarbX_AR_20-21.pdf [Accessed 23rd November 2022]

[103] CARB-X (2022) **News: US Government and Wellcome Commit**

	up a legal basis in Europe to facilitate these goals.
Key contributors to the funding pool[104]	
United States (BARDA) *USD 200 million 2016-2022* *USD 300 million 2022-2032*	Wellcome Trust *USD 155 million 2016-2021* *USD 70 million 2022-2024*
Germany (BMBF) *USD 46 million 2019-2022*	United States' National Institute of Allergy and Infectious Diseases (NIAID) *In-kind services (e.g. preclinical services) valued at USD 50 million*
United Kingdom (GAMRIF) *GBP 20 million 2018-2022*	Bill & Melinda Gates Foundation *USD 25 million 2018–2023*

7.2.3. IMI ENABLE 1 (2014-2021) – EU Focus

Between 2014 and 2021, the Innovative Medicine Initiative (IMI) within the New Drugs for Bad Drugs (ND4BB) programme ran the European Gram-negative Antibacterial Engine (ENABLE) in order to advance the development of potential antibiotics for Gram-negative bacteria. The specific funding for the IMI1 programme (2008-2013) within which ENABLE was funded by the Health theme of the EU's Seventh Framework Programme for Research (EUR 1 billion) and from in-kind contributions by EFPIA (EUR 1 billion)[105].

To achieve this objective over the course of the 7.5-year project, the ENABLE consortium created and managed a drug discovery and development platform that consisted of dedicated teams that pooled resources to test and optimise candidate molecules[106].

ENABLE was scheduled to complete in 2020 but was extended for 1.5 years (without a change in budget). The initial "goals" for this initiative were to:

- identify three antibacterial leads;
- select two antibacterial development candidates; and
- advance one compound into preclinical and phase I clinical study[107].

Table 33: IMI ENABLE overview

Conditions to support/funding? [108]	A value-sharing agreement, where a small percentage of future income generated from the resulting antibacterial by the programme owner would be shared between partners.

[104] CARB-X **Funding Partners** [online] Available at: https://carb-x.org/partners/funding-partners/ [Accessed 23rd November 2022]

[105] Innovative Medicines Initiative **The IMI funding model** [online] Available at: https://www.imi.europa.eu/about-imi/imi-funding-model [Accessed 3rd December 2022]

[106] ND4BB ENABLE **Welcome to ENABLE** [online] Available at: http://nd4bb-enable.eu/home [Accessed 23rd November 2022]

[107] Innovative Medicines Initiative **Press release – ENABLE goals achieved – mission continues** (2020) [online] Available at: http://files.basekit.com/a7/49/a749585d-2536-44e9-8386-fc783aea89ef.pdf [Accessed 23rd November 2022]

[108] ND4BB ENABLE **Welcome to ENABLE** Available at: http://nd4bb-enable.eu/home [Accessed 23rd November 2022]

Pipeline coverage	IMI ENABLE covered from Hit-to-Lead to phase I (TRL3-6)
What is their role? (shape of partnership)	IMI ENABLE provided: • direct molecule-tailored testing for numerous steps from early discovery until phase I clinical trials; • a financial contribution to cover work at programme owners' site. This varied on a case-specific basis but always involved support to scientific coordination and project leadership and most often direct financial support to activities (such as medicinal chemistry, crystallography, biophysical studies, biochemistry, and consumables); • access to an expert knowledge hub in the form of a Portfolio Management Committee and experts in a drug discovery and development platform; • support for everyday challenges; and • "raw diamond" support by providing pre-ENABLE funding to antibacterial-discovery programmes that did not meet eligibility thresholds (Material Transfer Agreement).
Total available funding for R&D	The total amount of funding for ENABLE over 7.5 years was EUR 100 million[109].

Key contributors to funding pool		
IMI	EFPIA in kind	Other
EUR 58 900 000	EUR 22 952 360	EUR 18 861 012

ENABLE-2 – exclusive to Swedish research groups

Following the completion of support from the Innovative Medicines Initiative (now Innovative Health Initiative), the working concept of ENABLE has continued with funding from the Swedish Research Council, which awarded SEK 25 million (approximately EUR 2.3 million) for funding in 2022 and 2023. The specific aim of ENABLE-2 is to continue supporting AMR antibiotic R&D with the same focus on Gram negative pathogens as the previous IMI ENABLE had done so. In order to develop hits up to a level of advancement where they can successfully graduate to later-stage initiatives (e.g., CARB-X, GARDP, REPAIR Impact Fund) or to out-licensing.

ENABLE-2 specifically comprises:

- **An experimental platform** with capabilities in chemistry, microbiology, ADME, safety and *in vivo* efficacy. To work with Hit owners to advance their compounds toward advanced lead status (non-dilutive experimental support)
- **Expert knowledge hub –** Mentoring provided by drug-development experts from the Portfolio Management Committee
- **Support for missing data –** If a programme does not fully meet the thresholds for entry into the ENABLE-2 Platform, there is a possibility of a Material Transfer Agreement (MTA) route[110].

The specific focus of ENABLE 2 is on "Hit-to-Lead" only (TRL3).

[109] Innovative Medicines Initiative **ENABLE** [online] Available at: https://www.imi.europa.eu/projects-results/project-factsheets/enable [Accessed 23rd November 2022]

[110] Uppsala Universitet **What ENABLE-2 can do for you** [online] Available at https://www.ilk.uu.se/enable2/for-you/ [Accessed 23rd November 2022]

7.2.4. INCATE – Global focus

The INCubator for Antibacterial Therapies in Europe (INCATE) aims to boost the AMR therapeutic and diagnostic pipeline by accelerating the translation of academic innovation into industrial research and development. INCATE is a not-for-profit organisation that was founded in 2021 by a partnership of research institutions and pharmaceutical companies. Specifically, INCATE seeks to address the early-stage pipeline to ensure that there is enough flow of innovative candidates, recognising that it is not only funding that is missing from academia and start-ups, but expert support and advice during the translational phase from academia to industry[111].

Table 34: INCATE overview

Conditions to support/funding?	The funding provided by INCATE is a combination of support in kind (stage 1) and non-dilutive funding (stage 2)
Pipeline coverage	INCATE considers projects that range from research ideas through to proof-of-concept (TRL2-4)
What is their role? (shape of partnership)[112]	INCATE provides the following elements in order to bridge the gap between academic research and the next stage of funding and support: • Advice from partners (including industry) to enable alignment at an early stage with medical needs and market demand, in addition to developing an "translational path" • Community of engaged individuals including industry, academia, entrepreneurs, policymakers, and investors. Public-health and healthcare providers to exchange ideas. • Non-dilutive funding to develop business and translational plans to convince investors at the next funding stage.
Total available funding for R&D	INCATE funding is awarded according to two stages: **Stage 1** – 6 months (coaching, sponsored services to EUR 10,000 to define milestones and refine case) **Stage 2** – 12 months (company building, up to EUR 250k to gather evidence and develop a business case for further capital. Thus far 13 projects are in receipt of INCATE support [113].

Key contributors[114]			
Boehringer Ingelheim Venture Fund	Shionogi	Roche	MSD
German Center for	The German InfectControl	Swiss National Centre of	Innovation Office of the

[111] Alt S. Haggstrom D *et al.*(2022) "INCATE: a partnership to boost the antibiotic pipeline" [online] **Comment - Nature Reviews Drug Discovery** 12 pp. 621-622. Available at: https://doi.org/10.1038/d41573-022-00138-7 [Accessed 23rd November 2022]

[112] INCATE **How we help** [online] Available at: https://www.incate.net/how-we-help/ [Accessed 23rd November 2022]

[113] INCATE **Portfolio** [online] Available at: https://www.incate.net/portfolio/ [Accessed 3rd December 2022]

[114] DZIF (2022) **INCATE selects first innovators to support in the fight against drug-resistant bacterial infections.** [online] Available at: https://www.dzif.de/en/incate-selects-first-innovators-support-fight-against-drug-resistant-bacterial-infections [Accessed 3rd December 2022]

Infection Research (DZIF)**	consortium**	Competence in Research AntiResist**	University of Basel**

* Industry partners, ** Academic founding members

7.2.5. GARDP – Global Focus

The Global Antibiotic Research and Development Partnership (GARDP) is a not-for-profit organisation that was established by the WHO in 2016 and focuses on developing treatments for drug-resistant infections that pose the greatest threat to health[115]. In the three years following its launch, GARDP was incubated by the Drugs for Neglected Diseases initiative (DNDi), becoming its own independent legal entity in 2019[116].

GARDP aims to deliver five new treatments focusing on sexually transmitted infections, sepsis in neonates and infants, and drug-resistant infections in hospitalised adults and children by 2025[117]. An important part of the GARDP business model is to find ways to improve access to antibiotics where they are needed in low- and middle-income countries (LMICs) through different forms of partnerships with developers. For example, in its partnership with Shionogi, GARDP (along with Clinton Health Access Initiative - CHAI) has the sub-license to manufacture and commercialise cefiderocol (a new antibiotic for treating Gram-negative infections) to 135 countries, most of which are LMICs[118].

Table 35: GARDP – Overview of features

Conditions to support/funding?	GARDP does not offer loans or equity, and alternatively utilises financial tools such as in-licensing, intellectual property, acquisition, and co-funding[119].
Pipeline coverage	GARDP covers all stages of the research and development pipeline, from preclinical development to the launch of the new drugs (TRL3-9). In addition, GARDP also conducts in-house discovery and exploratory research and, more recently, is conducting high-throughput screening and profiling of compounds with activity against *K. pneumoniae* and *A. baumannii* through consortium agreements/partnerships with industry and academia[120].
What is their role? (shape of partnership)	GARDP partners directly with organisations providing both technical and financial support[121].
Total available funding for R&D	In 2021, 73.4% of GARDP's funding was focused on research and development activities (approximately EUR 12.7 million), approximately half of which contributed to R&D in the field of sexually transmitted infections.

[115] The World Health Organization (2021) **Antimicrobial Resistance – Key Facts** [Online] Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance [Accessed: 18th November 2022].

[116] Drugs for Neglected Diseases Initiative – Press Releases (2019) **GARDP set up as independent legal entity** [Online] Available from: https://dndi.org/press-releases/2019/gardp-set-up-as-independent-legal-entity/ [Accessed: 18th November 2022].

[117] GARDP **Our Work** [Online] Available from: https://gardp.org/our-work/ [Accessed: 22nd November 2022].

[118] GARDP **Licence Agreement overview** [Online] Available from: https://gardp.org/wp-content/uploads/2022/06/License-Agreement-Overview-Cefiderocol-1.pdf

[119] Baraldi E. and Lindahl O *et al.* (2018) "Antibiotic Pipeline Coordinators" **Journal of Law, Medicine & Ethics** [Online] 46 (S1) pp. 25-31. Available from: https://doi.org/ 10.1177/1073110518782912 [Accessed: 21st November 2022].

[120] GARDP - **Discovery & Exploratory Research** [Online] Available from: https://gardp.org/discovery-exploratory-research/ [Accessed: 22nd November 2022].

[121] Savic M and Årdal C (2018) "A Grant Framework as a Push Incentive to Stimulate Research and Development of New Antibiotics" **Journal of Law, Medicine & Ethics** [Online] 46 (S1) pp. 9-24. Available from: https://doi.org/10.1177/1073110518782911 [Accessed: 21st November 2022].

Key contributors to funding pool			
In 2021 GARDP's total funding pool was EUR 17.3 million; over 80% of this is provided by the United Kingdom (DHSC, GAMRIF and NIHR) and Germany (BMBF & BMG), 42% and 40% respectively. When reflecting on the funding commitments and pledges to date (in total accounting for EUR 104.7 million), over half of this amount has been entirely contributed by Germany alone. Over 96% of funding received by GARDP comes from contributions from public entities[122].			
Public contributions from 2016-2025	**Amount (in EUR)**	**Private contributions from 2016-2025**	**Amount (in EUR)**
Germany	60.1 million	Bill & Melinda Gates Foundation	1.8 million
United Kingdom	21.7 million	Wellcome Trust	1.1 million
Japan	7.9 million	Others	0.8 million
Netherlands	7.5 million		
Switzerland	1.3 million		
South Africa	0.9 million		
Monaco	0.8M		
République et canton de Genève	0.5M		
Australia	0.2 million		
Luxembourg	0.1 million		

7.2.6. REPAIR Impact Fund – Global focus

The Replenishing and Enabling the Pipeline for Anti-Infective Resistance (REPAIR) Impact Fund was established in 2018 by the Novo Nordisk Foundation with the aim of delivering at least one new antimicrobial therapy to market in the next 3-5 years. Specifically, the REPAIR Impact Fund invests in start-ups, early-stage companies and corporate spinouts focusing on ambitious programmes that seek to tackle antimicrobial resistance via a broad range of approaches[123]. The REPAIR Impact Fund:

- focuses upon priority pathogens based on the WHO and CDC priority pathogen lists;
- gives priority to first-in-class therapies; and
- focuses on small molecules, biologics, and new modalities.

[122] GARDP (2022) **Financial and Performance Report 2021** [Online] Available from: https://gardp.org/news_resource/financial-report-2021/ [Accessed: 22nd November 2022].

[123] REPAIR Impact Fund **About Us** [Online] Available from: https://www.repair-impact-fund.com/about/ [Accessed: 21st November 2022].

Table 36: REPAIR Impact Fund - Overview of features

Conditions to support/funding?	The REPAIR Impact Fund operates as a hybrid investment. Specifically, this means that social impact and flexible terms are prioritised rather than financial gain or repayment. A majority of the REPAIR Impact Fund's investment is dilutive in the form of convertible debt. Non-dilutive investment is also offered in the form of a royalty-based model for larger firms, where the specific early-stage programme that requires investment is only a small part of the company's value[124].
Pipeline coverage	From early-stage drug development (lead optimisation) to the early stages of clinical development (phase I)[125] (TRL4-TRL6). It should be noted that a subsequent decision was made to reserve some capital in order to potentially support portfolio companies into phase II clinical trials[126]. The REPAIR Impact Fund invests in the early pipeline in recognition of the need for a high level of innovation in the early stages of development[127].
What is their role? (shape of partnership)	The REPAIR Impact Fund predominantly provides financing in addition to critical strategic support and connects companies to other investors in order to accelerate development[128].
Total available funding for R&D	The REPAIR Impact Fund has a budget of USD 165 million, with a range of USD 20–40 million allocated annually over a 3-to-5-year period across approximately 20 projects[129].
Key contributors to funding pool	
Novo Holdings (The Novo Nordisk Foundation)	

7.2.7. Other EU mechanisms with funding for AMR MCM R&D

7.2.7.1. Joint Programming Initiative on Antimicrobial Resistance (JPIAMR)

Launched in 2011, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) is a collaborative platform engaging 29 nations internationally and the European Commission to curb antimicrobial resistance[130].

In 2019, JPIAMR published a Strategic Research and Innovation Agenda (SRIA) updating the previous iteration that ran from 2014-2018. The 2019-2024 JPIAMR SRIA outlined the following priority topics:

- **Therapeutics**
- **Diagnostics**

[124] REPAIR Impact Fund **Investment Process FAQ** [Online] Available from: https://www.repair-impact-fund.com/wp-content/uploads/200103-REPAIR-Investment-process-FAQ.pdf [Accessed: 21st November 2022].

[125] REPAIR Impact Fund **Investment Process** [Online] Available from: https://www.repair-impact-fund.com/investment-process/ [Accessed: 21st November 2022].

[126] Engel A. (2020) "Fostering Antibiotic Development Through Impact Funding" [Online] **ACS Infectious Diseases.** 6 pp.1311-1312 Available from: https://dx.doi.org/10.1021/acsinfecdis.0c00069?ref=pdf [Accessed: 21st November 2022].

[127] Engel A. (2020) "Fostering Antibiotic Development Through Impact Funding" [Online] **ACS Infectious Diseases.** 6 pp.1311-1312 Available from: https://dx.doi.org/10.1021/acsinfecdis.0c00069?ref=pdf [Accessed: 21st November 2022].

[128] Novo Holdings (2021) **Second Global Call for New Investment Proposals to Fight AMR** [Online] Available from: https://www.novoholdings.dk/news/novo-holdings-repair-impact-fund-announces-second-global-call-for-new-investment-proposals-to-fight-amr/ Accessed: 21st November 2022].

[129] REPAIR Impact Fund **About Us** [Online] Available from: https://www.repair-impact-fund.com/about/ [Accessed: 21st November 2022].

[130] JPIAMR **About** [online] Available at https://www.jpiamr.eu/about/ [Accessed 23rd November 2022]

- **Surveillance**
- **Transmission**
- **Environment**
- **Interventions**

Between 2014 and 2024, the distribution of annual research calls according to priority area indicate that most research calls target therapeutics and diagnostics.

Table 37: JPIAMR SRIA Priority Topics and Research Calls 2014-2024

Priority area	Research call year	Priority Area	Research call year
Therapeutics	2015, 2018, 2022/23	**Diagnostics**	2019, 2023/24
Surveillance	2019, 2023/24	**Transmission**	2021/22
Environment	2016, 2020/21	**Interventions**	2017

The objectives set out by the JPIAMR SRIA in relation to therapeutics and diagnostics comprise a diverse range of aims; some are intrinsically related to research and development of some AMR MCMs, whilst some are focused more broadly on improvements to existing therapeutics and the implementation of diagnostic practice[131].

Table 38: JPIAMR SRIA objectives for therapeutics and diagnostics

Therapeutics	Diagnostics
- Find new antibiotics & targets - Develop new chemical entities and scaffolds - Improve the pharmacokinetics and pharmacodynamics of antibiotics (including those that are neglected) - Use of personalised medicine and artificial intelligence to improve therapy - Develop alternatives for antibiotics - Develop treatment protocols based on combination therapy using existing and new antibiotics - Develop policy measures and economic stimuli to minimise barriers for the development, availability and introduction of new therapies and alternatives - Assess how regulation modifies and influences the production and use of antibiotics	- Improve the efficacy of new and existing diagnostic tools to distinguish between bacterial and nonbacterial infections more effectively, and/or detect antibiotic susceptibility - Create support for the implementation of innovative technologies and linkage to data platforms promoting the use of narrow spectrum antibiotics - Improve the use of rapid diagnostics in appropriate One Health settings - Improve understanding and explore ways to overcome behavioural and socioeconomic barriers limiting the adoption and use of rapid diagnostics

Specifically, funding distributed via JPIAMR is in the form of direct research funding with a focus on very early-stage basic research. This means that stewardship and patient access to AMR MCMs that may eventually reach the market are not particularly enforced[132].

[131] JPIAMR **Activity Report 2021** [online] Available at: https://www.jpiamr.eu/app/uploads/2022/01/JPIAMR-Activity-Report-2021.pdf [Accessed 23rd November 2022]

[132] Renwick M.J., Simpkin V., Mossialos E. (2016) **Targeting innovation in antibiotic drug discovery and development: The need for a One Health – One Europe – One World Framework** [online] Available from: https://www.ncbi.nlm.nih.gov/books/NBK447334/ [Accessed 23rd November 2022]

7.2.7.2. One Health AMR Partnership

To address the emergency of AMR and its consequences on public health, the European Commission adopted the EU One Health Action Plan against AMR in June 2017 (as requested by Member States in the Council conclusions of 17 June 2016[133]). As a result, Horizon Europe requested greater streamlining amongst European AMR-related initiatives, and a broader perspective that includes stronger engagement in One Health as well as stronger engagement with funding and government agencies. The Coordination and Support Action "Design One Health AMR"[134], led by the Swedish Research Council, is currently exploring how this will be achieved. As such, the One Health (OH) AMR Partnership is under development[135].

Within the Horizon Workplan (2023-2024), the OH AMR Partnership is outlined as a mechanism that will contribute to the priorities set in the European One Health Action Plan to fight AMR, including boosting research development and innovation. More specifically, it should allow coordination and alignment of activities and funding among countries in the EU and beyond, as well as facilitating national coherence between different services/ministries with responsibility for the various aspects of AMR. The Commission estimates that an EU contribution to the OH AMR Partnership will be approximately EUR 100 million (2023-2034 Horizon Europe)

The OH AMR Partnership will build on, be complementary to and go beyond the existing initiative JPIAMR[136].

Within this workplan, three specific objectives are outlined for the OH AMR partnership:

- **Collaboration and alignment of Research and Innovation agendas on OH AMR**. Activities may include the following:
  - Joint strategic programming and global coordination of research and innovation
  - Target research and innovation efforts to the actual needs of policymakers and stakeholders
  - Create a transnational system that supports collaboration between the EU, Member States, and international initiatives
- **Boost research and innovation.** Activities may include the following:
  - Support OH AMR research and development of new preventatives, treatments, diagnostics, and interventions through annual joint transnational calls
  - Develop new tools and instruments to support research and innovation
  - Support networking, training, and mobility of researchers
  - Facilitate sharing and use of data and research infrastructure
- **Develop solutions.** Activities may include the following:

[133] European Council Press Release (2016) **Council conclusions on the next steps under a One Health approach to combat antimicrobial resistance** [online] Available from: https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-antimicrobial-resistance/ [Accessed 23rd November 2022]

[134] JPIAMR **Design OH AMR** [online] Available from: https://www.jpiamr.eu/activities/one-health-amr/design-oh-amr/ [Accessed 23rd November 2022]

[135] JPIAMR **OH AMR Partnership** [online] Available from: https://www.jpiamr.eu/activities/one-health-amr/ [Accessed 15th December 2022]

[136] Horizon Europe **Health 2023-2024 Workplan** [online] Available at https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2023-2024/wp-4-health_horizon-2023-2024_en.pdf [Accessed 15th December 2022]

- Facilitate the translation of scientific knowledge into innovative solutions
- Connect, merge, and align the dissemination of outputs with other initiatives to support evidence based OH policy
- Societal engagement by bridging science to society creating awareness of AMR

Collaborative activities set out by the OH AMR Partnership will be aligned with International Organisations such as the WHO, the World Animal Health Organisation (WOAH), the Food and Agriculture Organization (FAO), United Nations Environmental Programme (UNEP), the G7 and G20 fora, and the global AMR R&D Hub, with the aim to avoid duplication of efforts.

The OH AMR Partnership will not start its activities until 2025. In the coming years, functions of the OH AMR Partnership are focused on the "set-up phase" comprising of the following activities identified in the timeline below[137].

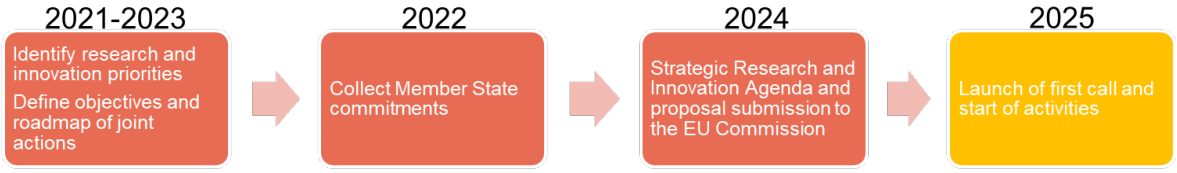

Figure 25: Timeline of the OH AMR Partnership

7.3. Summary

There are multiple mechanisms through which push funding is distributed to R&D into new AMR MCMs. A summary of the landscape mapped above is presented below, notably without the inclusion of JPIAMR (despite focusing predominantly on early research, there is no clear mention of specific TRL stages) and the OH AMR Partnership, which has not been fully established yet and has not planned to announce calls until 2025.

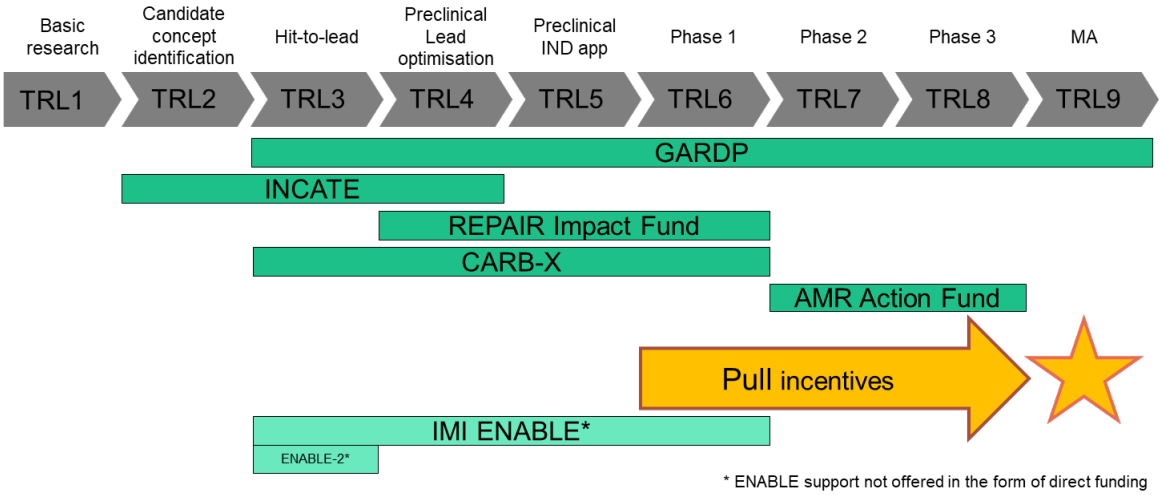

Figure 26: Overview of "push" incentives

As can be seen in the figure above, push funding is generally geared towards early and preclinical R&D between TRL3 and TRL5. The space filled by INCATE presents a novel step toward addressing an earlier part of the pipeline (TRL2) in an AMR specific manner,

[137] JPIAMR **The Horizon Europe Candidate Partnership: One Health AMR** [online] Available from: https://www.jpiamr.eu/activities/one-health-amr/ [Accessed 23rd November 2022]

however the limited magnitude of funding offered may be a key limiting factor on its ability to influence innovation at the early stages of development. As mentioned previously, the collective level of support provided to AMR R&D is insufficient.

The ability of R&D projects to gather funding is challenging due to modest public funding available and the lack of appetite for risk amongst potential private investors, who fear high levels of failure amongst AMR MCMs in the early pipeline[138]. Currently, push incentives have a clear purpose of helping de-risk investments and make them more attractive to later-stage investors. Based upon a previous study, if a larger percentage of R&D costs are supported by push mechanisms, more projects will progress to clinical trials and achieve positive ENPV projections with the suggested complementary pull incentive schemes[139] - although it should be noted that while financial failures could be resolved, scientific failures will continue. In order to support "blue skies" R&D, i.e. completely new thinking in the development of treatments accompanied by high scientific risk, it is important that there is sufficient public financing to support these projects. Additionally antifungal R&D is excluded from most of the existing funding schemes.

7.4. Assessing the public funding needs for push mechanisms

As previously stated, a combination of push and pull mechanisms are needed to properly re-activate the AMR R&D pipeline. Providing adequate preclinical push funding reduces the size of pull mechanisms needed. Hence push support is needed to help reduce R&D cost. Additionally in-kind benefits such as technical/scientific support or pipeline coordinators, may also shorten the development time and improve the probability of success of R&D projects.

The AMR Data Hub[140] has been collected on the global amount of AMR R&D derived from both public and private organisations. According to the dashboard, approximately USD 1 billion was directed to AMR globally in 2021. This includes public and private investments, all types of infectious agents, treatments, vaccines, and all types of support (from basic research to actual drug discovery and even policy). It should be noted that is not straightforward to generate an exhaustive assessment of the current level of public push funding to AMR. Specifically, push mechanisms can fund health projects in general, combine different streams of research, or rely on technical rather than financial support.

In this context, any financial assessment of the push mechanisms to be funded by public authorities needs to be taken with caution. In an attempt to assess the global needs for push public funding, we have used the reports below that have already assessed or modelled the size of such a gap.

7.4.1. DRIVE-AB report

The analysis performed in the **Drive-AB report**[141] estimated in 2018 that countries part of the Organisation for Economic Co-operation and Development (OECD), invest approximately USD 550 million every year in grant funding for antibiotic R&D. The report recommends increasing this amount to reach USD 800 million per year, which means that

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[138] Milken Institute Financial Innovations Lab ® (2022) **Models for Financing Antibiotic Development to Address Antimicrobial Resistance** [Online] Available from: https://milkeninstitute.org/sites/default/files/2022-03/FIL-AMR%20v3.22.22.pdf [Accessed: 21st November 2022].

[139] Baraldi and Ciabuschi *et al.* (2019) **Economic incentives for the development of new antibiotics** [Online] Available from: http://www.diva-portal.org/smash/get/diva2:1283298/FULLTEXT01.pdf [Accessed: 21st November 2022].

[140] Global AMR R&D Hub **Investment dashboard** [Online] Available from: https://dashboard.globalamrhub.org/reports/investments/research-area [Accessed: 21st December 2022].

[141] DRIVE-AB (2018) **DRIVE-AB REPORT Revitalizing the antibiotic pipeline Stimulating innovation while driving sustainable use and global access** [Online] Available from: http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed: 18th November 2022].

the **additional push funding would be approximately USD 250 million annually.** In addition, the report highlights the need to gather better data on preclinical projects and reflects upon the relevance of combining financial funding with in-kind support.

7.4.2. Transatlantic Taskforce on AMR

In 2015, the study for the Transatlantic Task Force[142] on Antimicrobial Resistance (TATFAR) recommended the establishment of a short-term multi-targeted **global innovation fund for antibiotic R&D** amounting to approximately **USD 2 billion over 5 years**, acknowledging that funding for push incentives is needed to effectively activate the pipeline. This means additional support of approximately USD 400 million annually.

7.4.3. Guard Report for the German Federal Ministry of Health

In 2017, the BCG prepared a follow-up report for the German GUARD Initiative "Breaking through the wall" for the German Federal Ministry of Health[143]. The report concluded that **USD 400 million in push incentives per year globally** (half in discovery and preclinical research grants and half in clinical development forgivable loans) are required to reinvigorate innovation in AMR, as a complement to pull incentives of about USD 1 billion per year. This result follows an in-depth analysis of the current public-health challenges faced in this area.

7.4.4. Public Health Agency of Sweden

The report commissioned by the Public Health Agency of Sweden[144] on the types of incentives that would help increase the development of new antibiotics simulates the impact of different push and pull mechanisms. This report demonstrated that **grants and R&D collaboration, a particular type of pipeline coordinator, are the two most effective mechanisms to improve the profitability of projects at preclinical stages**. Moreover, this report shows that, in order to bring one new antibiotic to the market, the required additional grants would amount to about USD 240 million, and funding for R&D collaboration would amount to USD 110 million per year globally. This corresponds to an additional **USD 350 million annually on a global level**.

7.4.5. Financial contribution to push mechanisms

It is important to consider that such an assessment has to be taken with caution due to the complexity of such incentives and the uncertain assessment of current public-funding support. However, appears that there is relative consensus on the need to provide additional push funding, in **a range between USD 250 and USD 400 million on an annual basis, and at a global level**. Moreover, considering the report commissioned by the Public Health Agency of Sweden, the size of investments in grants can be about twice the size of investments for in-kind technical/scientific support provided by pipeline coordinators.

This range corresponds to what is necessary for reinvigorating the pipeline in conjunction with the pull incentives. While it is not clear exactly how many new products would be brought to the market thanks to this additional funding, there is agreement that this amount would contribute significantly to improve innovation in this market.

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[142] Economic Incentives for Antimicrobial Therapy Development: Summary from the Transatlantic Task Force on Antimicrobial Resistance, 2015. Available at : https://www.cdc.gov/drugresistance/pdf/economic-incentives-for-antimicrobial-development-tatfar.pdf

[143] Stern S, Chorzelski S, Franken L, Völler S, Rentmeister H, Grosch B. Breaking through the wall: a call for concerted action on antibiotics research and development, Berlin: German Federal Ministry of Health; 2017 Available from GUARD_Follow_Up_Report_Full_Report_final.pdf (bundesgesundheitsministerium.de)

[144] Baraldi and Ciabuschi *et al.* (2019) **Economic incentives for the development of new antibiotics** [Online] Available from: http://www.diva-portal.org/smash/get/diva2:1283298/FULLTEXT01.pdf [Accessed: 21st November 2022].

Lastly, assuming that the EU could contribute to about 25% of the global effort, following the calculation of a fair share based on GDP as proposed by the BCG[145] report mentioned in the pull chapter, this would require an additional budget for push mechanisms of about **USD 60-100 million per year for the EU only**.

7.5. Role for DG HERA

As a result of the landscape analysis conducted, the potential options that DG HERA could consider within the remit of push support are the following:

- Address gaps in AMR specific funding which supports early discovery stages, i.e., TRL2-TRL3. These phases of early discovery are often carried by academia and SMEs (including university spin-outs) who require reinforced support[146]
- Bring additional funding/support to subsequent stages (TRL4-5-6) by supporting existing actors, or reinvigorating and reformatting previous mechanisms
- Support the development of clinical trial networks (further elaborated in a subsequent section)
- Expand the scope of existing funding mechanisms to include neglected areas like antifungals

The determination of an approach that ensures EU strategic autonomy by a mechanism focused on EU innovation (as the previous IMI ENABLE had functioned/ via the OH AMR Partnership) or comprises a more global focus (for example CARB-X, GARDP) is subject to political process and decision making, however there are several clear considerations for DG HERA to contemplate in this regard:

- **Ensure international alignment and avoid duplication of efforts** – There are currently a number of existing and established mechanisms of push support that would benefit from additional EU investment. Careful consideration should be taken by DG HERA not only to ensure alignment with existing initiatives (Member State level, EU level and Global level) to ensure there is no duplication of effort. As such this report sets out a variety of the key AMR specific push supports available for DG HERA to appreciate the vast number of existing mechanisms that could be further empowered.

  In the remit of AMR it is clear within the EU4Health work programme[147] that DG HERA is perceived to have a role that at its core requires interaction with its international counterparts, for example BARDA. In this respect, whether a push support is EU innovation focused or global focused, alignment and collaboration globally will be of importance.

- **Extensive stakeholder consultation/feedback** – A continuous flow of consultation/feedback should be established in regard to improvements that could be made to previous/existing/upcoming initiatives. This ensures that an eventual push support mechanism will fully meet expectations both in an EU and Global context. Additionally, DG HERA could benefit from establishing and solidifying a working relationship with organisations and related stakeholder groups (at an EU and Global level) to further its understanding of market needs and ensure that the

[145] Boston Consulting Group (2022) "The Case for a Subscription Model to Tackle Antimicrobial Resistance" [online] Available at: https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance [Accessed: 25th October 2022

[146] Theuretzbacher U, Baraldi E. *et al.* (2022) Challenges and shortcomings of antibacterial discovery projects **Clinical Microbiology and Infection** [Online] Available from: https://doi.org/10.1016/j.cmi.2022.11.027 [Accessed: 21st December 2022].

[147] European Commission (2022) **The 2023 Work Programme of EU4Health is out!** [Online] Available from: https://hadea.ec.europa.eu/news/2023-work-programme-eu4health-out-2022-11-22_en [Accessed: 7th December 2022].

push support mechanism is appropriate to meet them, with the understanding that these may change over time.

- **Long term perspective** - it will be crucial that funding mechanisms within the field of AMR take a more realistic and long-term approach as indicated by DRIVE AB[148], that include multi-year, even multi-decade financial commitments.
- **Source of funding** - From an EU perspective, the funding under the EU4Health Programme Regulation (EU) 2021/522 and the Horizon Europe Regulation (EU) 2021/695 may be a particularly relevant source of finance and their conditions must be checked carefully. Member State funding will require careful consideration in regard to State aid compliance.

[148] DRIVE-AB (2018) **DRIVE-AB REPORT Revitalizing the antibiotic pipeline Stimulating innovation while driving sustainable use and global access** [Online] Available from: http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed: 18th November 2022].

8. DG HERA as Coordination Hub

Non-financial support such as dissemination of best practices and capacity building, provision of technical/regulatory guidance and/or streamlining of regulatory processes and priority signalling ranked third to fifth according to the 93 stakeholders that responded to the survey. These roles, although distinct, are intrinsically related to improving communication across stakeholders and streamlining processes and cooperation. They can, therefore, be clustered together under one umbrella category of coordination.

This perspective is shared by several stakeholders in the field of AMR via published position papers. In a 2021 white paper published by EFPIA and Vaccines Europe the role of DG HERA in coordination was echoed throughout.

> ***EFPIA & Vaccines Europe joint white paper (2021)***[149]
>
> "In terms of its mandate, EFPIA and Vaccines Europe believe that **HERA plays a coordinating** role, linking all the activity stages in the research and development process: risk assessment, early development, late development, regulatory pathways, manufacturing, purchasing, and stockpiling. In addition to this coordinating capacity, the new authority should also provide funds to bridge the existing gaps between early-stage research and bringing a drug, vaccine, or therapeutic solution to market."

Similarly in a position paper published in 2022 by the European Public Health Alliance (EPHA) and ReAct Europe, the authors indicate that in bringing new antibiotics to market and addressing the current scarcity, DG HERA should play a key role as a coordinator of the pipeline.

> ***EPHA and ReAct Europe (2022)***[150]
>
> Scarcity of new antibiotics calls for a holistic approach combining incentives to push and pull new antibiotics to the market, and the evidence points towards more efficient solutions such as the use of push funding and milestone-based rewards and the key role of the European Health Emergency Preparedness and Response Authority (HERA) as a pipeline coordinator."

Most of the roles required to create a functioning ecosystem for antimicrobial development are already covered by existing AMR initiatives or EU/global organisations. However, there may be some gaps that require fulfilling and points of interaction that would benefit from a more seamless alignment. These could either be roles taken up directly by DG HERA, or simply facilitated by liaising with the existing actors to explore the best approach to close the missing links.

The following session will expand on the role of a **Coordination Hub** that could be led or assisted by DG HERA to fulfil these expectations.

[149] EFPIA and Vaccines Europe (2021) **A joint EFPIA and Vaccines Europe White Paper – Establishment of The Health Emergency Preparedness and Response Authority** [Online] Available from: https://www.efpia.eu/media/602659/hera-white-paper_efpia_ve.pdf [Accessed: 18th November 2022].

[150] EPHA and ReAct Europe (2022) **Joint position paper – Antibiotic Incentives in the Revision of the EU Pharmaceutical Legislation** [Online] Available from: https://epha.org/wp-content/uploads/2022/07/antibiotic-incentives-pharma-legislation-joint-paper-2022.pdf [Accessed: 18th November 2022].

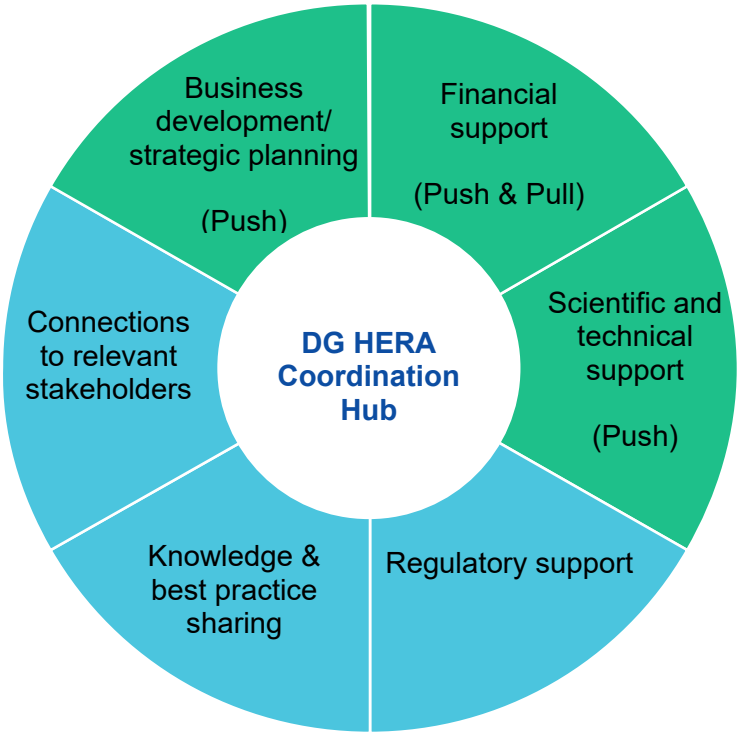

Figure 27: Areas of coordination

The figure above shows the elements of coordination within the AMR R&D pipeline. Items in green are covered in prior sections that describe push support and pull mechanisms that DG HERA may consider as feasible options for action. Items in blue are more holistic roles and are divided into two sections expanded below.

8.1. Regulatory support

Our survey respondents outlined a role for DG HERA to support regulatory processes and approval, despite such task being largely in the remit of the EMA and DG SANTE (EMA has close ties and daily contact with DG SANTE, which deals with issues concerning the regulation of medicines). This may be due to the relatively new nature of DG HERA and the limited knowledge and information of the relevant stakeholders in regard to the authority's mandate. Understanding the limited scope of DG HERA when it comes to designing and implementing regulatory process, this chapter will focus on DG HERA's capacity to foster dialogue and facilitate engagement between EMA, DG SANTE, and the relevant stakeholders.

8.1.1. Lessons learnt from COVID-19

The COVID-19 pandemic had a major impact on the development of related treatments, vaccines, and diagnostic devices.

To address the effects of this pandemic, regulators demonstrated significant agility while maintaining high standards of quality and effectiveness[151]. Regulatory agility refers to the willingness of authorities to take quick action within the accepted regulatory framework to ensure that the regulatory ecosystem quickly responds to the challenges imposed by the pandemic for the benefit of society. While many regulatory measures were introduced temporarily as a response to COVID-19, it is debateable whether some of these measures may be applicable for AMR-related MCMs.

[151] Stewart, J., Honig, P., AlJuburi, L., Autor, D., Berger, S., Brady, P., Fitton, H., Garner, C., Garvin, M., Hukkelhoven, M. and Kowalski, R., 2021. COVID-19: a catalyst to accelerate global regulatory transformation. *Clinical Pharmacology & Therapeutics*, *109*(6), pp.1390-1392.

Regulatory measures include **expedited regulatory reviews and approvals**, **streamlining of clinical trials**, and **alignment of regulatory requirements**

8.1.2. Expedited regulatory reviews and approvals

Various regulatory agencies facilitate expedited drug-development programmes where there is an unmet clinical need for a serious condition. In the case of COVID-19 this was done either via already-existing pathways or via a new COVID-19-related emergency pathway. Examples of the latter include:

- **rapid scientific advise**: provide guidance for sponsors on methods, study design, or robust data collection and generation for a medical product[152]
- **expedited reviews**: priority reviews, fast track designations, and accelerated approvals for MCMs with a major interest in public health[153]
- **rolling reviews**: procedure allowing the regulator to assess data on a particular MCM as they are made available on a rolling basis, and once complete, the sponsor can submit a formal marketing authorisation application that is reviewed under a shorter timeline[154]
- **conditional approvals**: granting of a conditional marketing authorisation for MCMs where the immediate benefit outweighs the risk of having less available data than normally available[155]
- **emergency use**: use of approved or unapproved MCMs to treat, prevent or diagnose serious conditions when there are no adequate, approved, and available alternatives[156]
- **expanded access**: use of an investigational MCMs outside clinical trials for serious, immediately life-threatening diseases and conditional when no comparable, satisfactory alternative treatment is available[157]

In 2016, the EMA launched “PRIME”, its own version of expedited reviews for drugs that have not yet been launched in the EU under any prior indication and that targets a condition where there is an unmet need. However, as of yet, no antibiotic has received a PRIME designation by the EMA. Only 4 products relevant to AMR have received such designation (a vaccine for *Mycobacterium tuberculosis*, a vaccine for Respiratory Syncytial Virus, a vaccine for Group B *Streptococcus,* and a monoclonal antibody for sepsis). The use of PRIME designation for not only antimicrobials with novel mechanisms of action, but for novel combinations/indications of approved products, could be effective in bringing more AMR MCMs to the market. DG HERA could initiate discussions with EMA

[152] European Medicines Agency COVID-19: how EMA fast-tracks development support and approval of medicines and vaccines [online] Available at: https://www.ema.europa.eu/en/documents/press-release/covid-19-how-ema-fast-tracks-development-support-approval-medicines-vaccines_en.pdf [Accessed on 13th December 2022]

[153] Food and Drug Administration US dept of health and human services. Fast track [online] Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track [Accessed on 13th December 2022]

[154] European Medicines Agency COVID-19: how EMA fast-tracks development support and approval of medicines and vaccines [online] Available at: https://www.ema.europa.eu/en/documents/press-release/covid-19-how-ema-fast-tracks-development-support-approval-medicines-vaccines_en.pdf [Accessed on 13th December 2022]

[155] European Medicines Agency Conditional marketing autorisation [online] Available at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation [Accessed on 13th December 2022]

[156] Food and Drug Administration US dept of health and human services. Emergency use authorization [online] Available at https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization [Accessed on 13th December 2022]

[157] European Medicines Agency Compassionate use [online] Available at https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use [Accessed on 13th December 2022]

and other relevant stakeholders (like clinical trial networks) to better understand how AMR MCMs may benefit from PRIME.

8.1.3. Streamlining clinical trials

There is a need for more coordination when conducting clinical trials for AMR MCMs across the EU and on a global scale. Despite coordinating clinical trial networks not described as role to be taken up by DG HERA within the primary data collected, this has been included within this report due to their importance in efficient clinical development of products. Clinical trial networks promote the collaboration of relevant stakeholders during clinical trials to facilitate their completion in a faster and more efficient manner. Conducting clinical trials is key in the process of developing new antimicrobials - there are currently a number of obstacles that justify a more coordinated approach in the EU.

Number of patients required for clinical trials - When conducting clinical trials, there is a need for a specific number of patients with the condition/disease to be treated, which is a key premise of determining non-inferiority to existing treatments. In AMR trials, it is often challenging and expensive to recruit enough patients with the specific infection, particularly since multi-drug-resistant infections are still relatively uncommon in Europe. In this respect, the ADVANCE-ID clinical trial network[158] in Asia (for example) has been established based upon the relatively high prevalence of AMR infections in these regions collaborate and conduct clinical trials in infectious diseases[159].

A clinical trials network can facilitate international collaboration and hence reduce the cost for each developer by relying on the existence of a large network of partners for recruiting patients. This is of particular importance as the companies involved in the AMR market are primarily SMEs with more financial constraints. This will subsequently result in a large clinical trial with robust results, rather than multiple small clinical trials.

Challenges related to clinical trials for antibiotics - In comparison to other diseases, antibiotic clinical trials experience unique challenges. Firstly, there is a very short window of time where a patient can be enrolled into the trial – in most cases patients need to be recruited almost immediately – and existing diagnostic tests take too long to provide results. Secondly, patients with bacterial infections cannot be moved between hospitals (in the event that it is required to transfer them to a clinical trial site) – as a result of the time-critical nature of treating a bacterial infection and the risk of spreading infections during transit[160].

Regulatory requirements - This is a key hurdle in the EU, due to the variation of national regulatory requirements. Having access to cross-region regulatory expertise can help developers understand the national level differences and adapt the methodology, data analyses and presentation of trial results accordingly. This hurdle has partly been addressed with the launch of the Clinical Trials Information System (CTIS) in January 2022[161]. The CTIS supports interactions between clinical trial sponsors (researchers or companies that run a clinical trial and collect and analyse data) and regulatory authorities

[158] Saw Swee Hock School for Public Health (2022) **ADVANcing Clinical Evidence in Infectious Diseases (ADVANCE-ID)** [online] Available at https://sph.nus.edu.sg/2022/11/advancing-clinical-evidence-in-infectious-diseases-advance-id/ [Accessed 29th November 2022]

[159] Saw Swee Hock School of Public Health (2021) **Asian Clinical Research Network established to tackle drug-resistant infections in the region** [online] Available at: https://sph.nus.edu.sg/2021/08/asian-clinical-research-network-established-to-tackle-drug-resistant-infections-in-the-region/ [Accessed 29th November 2022]

[160] Wellcome (2016) **Clinical Trial Networks for Antibiotic Development: Why they're important and how they should be developed** [online] Available at: https://wellcome.org/sites/default/files/clinical-trial-networks-for-antibiotic-development-wellcome-oct16.pdf [Accessed 29th November 2022]

[161] Clinical Trials Information System. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system [Accessed 25th January 2023]

in the EU Member States and EEA countries throughout the entire duration of the clinical trial.

Lack of standardised data – lack of alignment of common study protocols to ensure regulatory requirements are met and lack of priority criteria for planned clinical trials.

The development of a clinical trials network could help overcome most, if not all, of the challenges described above. A study by Wellcome in 2016[162] estimated that a clinical trial network involved in identifying good clinical trial sites across the world, in which a sponsor could quickly enrol their drug, could reduce the cost of phase II and phase III trials by 23%. Furthermore, the same study estimates that if clinical trials are able to share control groups, and potentially use control data from previous trials via the use of a clinical trials network, the cost of running clinical trials would be further reduced 40% and 60% respectively. The European Clinical Research Alliance for Infectious Diseases (ECRAID) seeks to address this challenge. ECRAID is the first network of its kind in Europe to offer a single point of access to a pan-EU clinical research network for infectious diseases.

8.1.4. Alignment of regulatory requirements

A number of steps towards alignment of regulatory requirements have already been made. The EMA, the Japanese Pharmaceuticals and Medical Devices Agency and the FDA are collaborating towards a single development programme for antibiotic approval which will satisfy all the requirements of the three agencies in a harmonised manner. It is hoped that this simplified and streamlined approach will further incentivise antibiotic development by providing harmonised regulatory processes across the various regions[163]. A meeting in 2019 also sought to expand this harmonisation to antifungal development in recognition of the growing problem of AMR in fungi and the limited arsenal of treatments[164].

Tackling AMR is also one of the International Coalition of Medicines Regulatory Authorities' (ICMRA) strategic priorities and has highlighted successful regulatory and non-regulatory interventions used in different countries to address the public health threat of AMR[165]. The ICMRA is a voluntary, executive-level entity of worldwide medicines regulatory authorities set up to provide strategic coordination, advocacy, and leadership, of which the EMA is a member, and has the following aims:

- identify ways to better use existing initiatives and resources
- develop strategies to address current and emerging challenges in global human medicine regulation
- provide direction for common activities and areas of work

The EMA also works with its EU and international partners (the US, Canada, Norway, and the UK) in contributing to global initiatives to combat AMR, such as the TATFAR. The aim

[162] Wellcome (2016) **Clinical Trial Networks for Antibiotic Development: Why they're important and how they should be developed** [online] Available at https://wellcome.org/sites/default/files/clinical-trial-networks-for-antibiotic-development-wellcome-oct16.pdf [Accessed 29th November 2022]

[163] Human Regulatory: Antimicrobial Resistance. European Medicines Agency. Available at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/antimicrobial-resistance [Accessed on 12th December 2022]

[164] Tripartite meeting held between the EMA, Food and Drug Administration (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA) to discuss regulatory approaches for the evaluation of antibacterial agents. European Medicines Agency. Available at: https://www.ema.europa.eu/en/events/tripartite-meeting-held-between-ema-food-drug-administration-fda-pharmaceuticals-medical-devices [Accessed on 12th December 2022]

[165] International Coalition of Medicines Regulatory Authorities: Antimicrobial Resistance Best Practices. Working Group Report and Case Studies. November 2022. Available at: https://www.icmra.info/drupal/sites/default/files/2022-11/amr_best_practices_report.pdf [Accessed on 12th December 2022]

of TATFAR is to increase levels of communication, coordination and cooperation between the EU and the US on human and veterinary antimicrobials.

The global threat of AMR has been recognised internationally by a number of regulatory authorities, resulting in a global movement towards aligning regulatory requirements to help bring more AMR MCMs to the market.

8.1.5. Role of DG HERA

Whether DG HERA should perform a role as a Coordination Hub needs to be further investigated and discussed by the Commission services and agencies to ensure alignment with existing entities. In the below table a high-level assessment is presented.

Table 39: High-level assessment of the role of DG HERA in aligning regulatory requirements

Role	Description
Coordinate with EMA/FDA	- Develop infrastructure to coordinate mid- to large-size clinical trials* - Jointly coordinate clinical trials for potential AMR MCMs - Establish whether novel AMR MCMs meet the terms and conditions of financial agreements between DG HERA and industry - Ensure that national and international regulatory pathways are streamlined and align with the demands of innovative medicines and candidate vaccines - Ensure strong coordination across EU regulators including national competent authorities and notified bodies, as well as international regulators - Expedite regulatory reviews and approaches for MCMs targeting priority pathogens given the urgent need for novel medicines (e.g., PRIME designation for novel antibiotics)
Coordinate with ECRAID (successor of COMBACTE and PREPARE) and ECRIN	- ECRAID is a not-for-profit clinical research network that will conduct clinical research for both public and private sponsors - ECRIN is a not-for-profit intergovernmental organisation that supports the conduct of multinational clinical trials in Europe - DG HERA can enhance the capacity and results of such existing networks, similarly to ADVANCE-ID
Coordinate partnerships amongst relevant stakeholders	- Form close relationships with academic institutions across the EU by leveraging pre-existing networks such as the European Global health Research Institutes Network[166] - Bring together various expertise to initiate

[166] European Global Health Research Institutes Network [online] Available at: https://eghrin.eu/ [Accessed 13th December 2022]

	conversations related to clinical trials (e.g., microbiologists, epidemiologists, experts in drug development and clinical trial design)
Leverage on existing initiatives such as Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R)[167]	- GLOPID-R facilitates coordination and information sharing among major global funding organizations through working groups, guidance, tools, and multiple resources - Clinical trials have delivered important results regarding treatment options for COVID-19 - Could be used in the context of AMR research
*DG HERA has already developed such infrastructure by launching the VACCELERATE clinical trials network involving 16 EU Member States and 5 associated countries described in an earlier section. The EMA has been given a strengthened mandate to coordinate multi-national clinical trials during public health crises by the EC through the establishment of an Emergency task Force that will provide scientific advice on clinical trial design and product development[168]	

8.2. Good practice sharing & alignment with existing stakeholders

The role of DG HERA to provide "dissemination of best practices and capacity building" was indicated as extremely/very important by 11 of 21 Member States that responded to the survey. The importance of knowledge sharing and awareness raising is corroborated when considering the low response by Member States when asked about the EU JAMRAI proposal. This indicates a lack of awareness on relevant initiatives.

The current AMR space comprises of several platforms/networks functioning within the EU that could form the basis of this knowledge sharing and dissemination of best practices. These mechanisms could be further utilised and enhanced by DG HERA, a select few at an EU level are described below:

8.2.1. Existing Networks that may be utilised/enhanced by DG HERA

8.2.1.1. AMR One Health Network

The EU AMR One-Health Network was launched in 2017 and is chaired by the European Commission. Members of the network include experts from human health, animal health and environmental health, EU scientific agencies (ECDC, EMA and EFSA) and Commission experts. The network meet on a bi-annual basis to provide members with a platform to present national AMR action plans and strategies. One of the principles of these meetings is to **share best practices, discuss policy options and determine how to enhance cooperation and coordination.**

A policy brief published by EU-JAMRAI referred to the 2019 Council Conclusions on the next steps towards making the EU a best practice region on combatting AMR. This conclusion emphasised the importance of regular meetings of this network, calling for this cooperation to be reinforced to combat AMR by multilateral/bilateral sharing of best practices in order to support Member States[169].

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[167] GloPID-R European Commission – DG Research & Innovation [online] Available at: https://www.glopid-r.org/members/european-commission-dg-research-innovation/ [Accessed 29th November 2022]

[168] Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices [online] Available at: https://ec.europa.eu/transparency/documents-register/detail?ref=COM(2020)725&lang=en [Accessed on 13th December 2022]

[169] EU-JAMRAI **Work Package 4 The need for a reinforced AMR One Health Network** [online] Available at: https://epha.org/wp-content/uploads/2021/01/eu-jamrai-pb-wp4-the-need-for-a-reinforced-amr-one-health-network.pdf [Accessed 7 December 2022]

As a recently established authority, DG HERA may investigate the potential to utilise this network to gather feedback, better understand sentiment of relevant experts and potentially further expand in order to further capitalise on the best practice sharing aspects[170]. The AMR One Health Network could also be utilised by DG HERA to form working groups in order to further discuss and elucidated Member State needs – in a previous half day session during the meeting held in January 2022 a closed session was held for Member States and EU institutions only – within which incentives were discussed and a Q&A facilitated[171].

8.2.1.2. AMR Stakeholder Network and the Member of the European Parliament AMR interest group

In 2017 the AMR Stakeholder Network was established within the remit of the EU Health Policy Platform. The network is led by the European Public Health Association (EPHA) and has several aims:

- contribute to discussions on the cross-border health threat of AMR, promoting a One Health approach
- build consensus on the key EU priorities for tackling AMR (EU One Health Action Plan)
- advocate for the EU to be a strong leader in the global fight against AMR
- campaign for increased EU support and resources for Member States to implement their national action plans for AMR

The AMR Stakeholder Network recently published a good practices report, which was the output of a "call for good practices" in order to raise the profile of AMR on the political agenda and to offer solutions that are practical to implement across the One Health spectrum. The purpose of this report was to facilitate the sharing of knowledge, innovation, new methods, and models in slowing down the spread of AMR[172].

The AMR Stakeholder Network also established the Member of the European Parliament AMR interest group[173]. This is the only AMR specific group in the European Parliament and strives to achieve the following objectives:

- ensure that AMR is high on the EU policy agenda and that the European Parliament plays a key role in boosting AMR action
- highlight the need for urgent action through a One Health multi-sectoral approach
- ensuring that the EU and its Member States deliver on their commitments and implement effective actions at EU, national and regional level.

Both groups provide useful platforms to connect key stakeholders within the AMR sphere, as well as policy experts in order to further develop the policy options for action set out in this report and align with the expectations of stakeholders and representatives of parliament.

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[170] European Commission **EU Action on Antimicrobial Resistance** [online] Available at: https://health.ec.europa.eu/antimicrobial-resistance/eu-action-antimicrobial-resistance_en [Accessed 2nd December 2022]

[171] AMR One Health Network meeting of 25th-26th January 2022 **Minutes** [online] Available at: https://health.ec.europa.eu/system/files/2022-02/amr_20220125_mi_en_1.pdf [Accessed 21st December 2022]

[172] AMR Stakeholder Network **Call for good practices report** (2022) [online] Available at: https://epha.org/wp-content/uploads/2022/03/amr-goodpracticesreport-2022.pdf [Accessed 5th December 2022]

[173] European Public Health Association **About the AMR Stakeholder Network** [online] Available at: https://epha.org/amr-stakeholder-network/ [Accessed 5 December 2022]

8.2.1.3. European Centre for Disease Prevention and Control (ECDC)

The ECDC is responsible for communicable disease surveillance, provision of scientific advice on communicable disease epidemiology, prevention and control, and training of public health professionals. The ECDC's mission is to identify, assess and communicate current and emerging threats to human health posed by infectious diseases such as AMR. The ECDC Strategy 2021-2027 defines ECDC's goals in the coming years, and has outlined the following strategic objectives:

- strengthen and apply scientific excellence in all ECDC activities and outputs to inform public health policy and practice
- support the countries to strengthen their capacities and capabilities to make evidence-based decisions on public health policies and practice
- prepare for the future through foresight and innovation assessments
- increase health security in the EU through strengthened cooperation and coordination between ECDC and partners in non-EU countries
- transform the organisation to the next generation ECDC

This will ensure that decision-makers receive the necessary advice and scientific evidence to support changes in policy and practice in the area of communicable disease prevention and control. Given the role and strategic plan of ECDC, this close collaboration with DG HERA is essential when it comes to identifying threats and updating priority areas accordingly. These priority areas should be subsequently communicated to all stakeholders in a transparent and timely manner, along with all relevant information and data used to justify these priority areas.

8.2.1.4. JPIAMR – AMR Knowledge Hub

The JPIAMR, via its AMR Knowledge Hub[174], provides access to information, data, products, and services related to AMR to increase coordination, improve visibility of the AMR research networks, research institutes, and to facilitate knowledge exchange and capacity development on a global scale. This hub is separated into 4 pillars:

- JPIAMR supported AMR research database – provides information on projects and networks supported under the various calls coordinated by the JPIAMR
- AMR data platforms – provides a collection of resources for early drug discovery, antibiotic pipeline, alternatives to antibiotics, surveillance datasets and antibiotic stewardship guidelines
- research funding datahub – provides information on investments in the AMR research and innovation landscape to determine what has already been funded across different areas and what is still required to inform strategic priorities
- research infrastructure platforms – carried in collaboration with the IMI-consortium VALUE-Dx, provides information on AMR specific collections of biological materials, databases, and research infrastructure services

The AMR knowledge hub developed by the JPIAMR provides invaluable information that could be leveraged by DG HERA.

JPIAMR through its steering committee and secretariat engage and collaborate with other AMR funding agencies, international initiatives, and relevant stakeholders with the overall aim to:

[174] JPIAMR AMR Knowledge Hub [online] Available at https://www.jpiamr.eu/resources/amr-knowledge-hub/ [Accessed 13th December 2022]

- provide the foundation from which to provide an effective response to the AMR challenge
- coordinate global AMR research funding
- set the agenda from which to inform international AMR policy and research policy

The JPIAMR collaborates with AMR international funding organisations (e.g., AMR Educational Activity-Joint Programming Committee, ICARS, Aquatic Pollutants), and international organisations (e.g., United Nations, WHO, the EC). The JPIAMR is also a member of several stakeholders' boards of different AMR international complementary initiatives such as:

- Global AMR R&D Hub
- EJP One Health
- SEDRIC Surveillance Network
- EU-JAMRAI
- ESCMID
- EU Openscreen
- IMI and its Steering Group of Infectious Diseases regarding the coordination and complementarity of funding programmes.
- MicrobiomeSupport
- European Clinical Trial Network (ECRAID) initiative
- GLOPID-R
- Transatlantic Task Force on AMR (TATFAR)
- Value DX

8.2.1.5. One Health AMR Partnership

A key insight during our survey was that Member States had to coordinate extensively amongst various national organisations in order to provide appropriate responses to the various questions on AMR. In its aim to facilitate national coherence between services and ministries the OH AMR Partnership may better facilitate this national level dialogue, which in turn could be utilised by DG HERA to disseminate best practices and facilitate discussions with clearly informed representatives in a structured way.

The activities foreseen to be carried by the OH AMR Partnership (see section 7.2.7.2) will be carried through a joint programme of activities ranging from the coordination of transnational research, networking activities, capacity building programmes, work on research infrastructures and resources including training and dissemination activities. As the OH AMR Partnership is currently being established, DG HERA may further investigate ways to align and further strengthen the activities of this partnership in order to meet the role proposed by stakeholders that participated in this study.

8.2.2. Role of DG HERA

8.2.2.1. Stakeholder connection and sharing of good practices

There are already a number of EU networks, partnerships, and agencies sharing knowledge on AMR and disseminating best practices. Given that most of the infrastructure is already in place, an open question is how DG HERA interacts or contributes to this infrastructure. One pathway may be as a Coordination Hub, a role previously proposed to be played by other actors such as CARB-X, BARDA, and GARDP acting as "pipeline

coordinators”[175]. DG HERA may be well placed to support knowledge-sharing regarding national expertise and best practices while taking into consideration the various challenges faced by Member States with regards to AMR.

8.2.2.2. Ensuring international alignment

It is foreseen within the Horizon 2023-2024 Workplan[176] that DG HERA engages cooperating with its US counterpart BARDA. In regard to all potential options for action set out within this report the need to align on a global level is of vital importance to successful and efficient implementation of AMR related incentives.

[175] Baraldi, E., Lindahl, O., Savic, M., Findlay, D. and Årdal, C., 2018. Antibiotic pipeline coordinators. The Journal of Law, Medicine & Ethics, 46(1_suppl), pp.25-31.

[176] Horizon Europe **Health 2023-2024 Workplan** [online] Available at https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2023-2024/wp-4-health_horizon-2023-2024_en.pdf [Accessed 15th December 2022]

9. Conclusion

The challenge to bring more AMR MCMs to the market is a result of a complex landscape in which developers face significant scientific challenges, costly R&D processes, and low profitability due to controlled use and stewardship measures – an important measure to contain the spread of AMR. The purpose of this study was to identify the needs of EU Member States and relevant stakeholders within the field of AMR and to deliver options for action in order to bring more AMR MCMs to market, while also ensuring their access across the EU.

Through primary and seconday data collection methods, including surveys and interviews with 22 EU Member States and more than 90 AMR stakeholders, three recommendations were identified for the role of DG HERA to help bring more AMR MCMs to market and ensure their access. These include (i) coordinate and support the implementation of pull incentives, (ii) coordinate and contribute to financial push incentives, and (iii) ensure coordination, knowledge sharing and provision of non-financial support including the dissemination of best practices and capacity building for Member States.

Pull incentives focus on rewarding successful antimicrobials at and after market approval. The main focus of the study was refined to consider predominantly options for action for treatments for AMR bacteria (pull incentives). The simulation of four types of pull mechanisms (revenue guarantee, small market entry reward combined with revenue guarantee, milestone-based reward, lump-sum market entry reward) of different monetary sizes resulted in the shortlisting of seven key pull options for action to make projects profitable while ensuring the effective and efficient allocation of public funding – each with different profiles of risk, impact and considerations. The preliminary feasibility of each pull option in an EU context was assessed both from a legal and a financial perspective and determined that in principle all options may be implemented to an extent through existing EU regulations and/or financial frameworks – notwithstanding some notable restrictions and considerations that would require further in-depth investigation.

Financial push incentives should complement the pull models above, acting where the pull models are least efficient: in the early phase of development. Push mechanisms for AMR MCMs require an additional global investment ranging between 250M to 400M USD per year, consisting of an EU contribution of around 60M to 100M USD taking into account a 25% EU share. The determination and allocation of push funding is subject to a range of considerations for DG HERA to consider, including ensuring coordination with other actors within this remit and the assurance of no duplication.

Finally, the primary data collected in this study highlights that there is a perceived lack of public-guided coordiantion within the field of AMR and R&D. Within this remit DG HERA may have a role to faciliate a better connected network of relevant stakeholders and disseminate best practices on AMR MCM R&D and access to improve awareness amongst a broad range of stakeholders including Member States.

Annex 1 - Considerations for diagnostics

Context and challenges

The current diagnostics landscape for AMR is in a paradoxical state. On the one hand, there is a reasonable number of market participants, both large companies (e.g. Becton Dickinson, BioMérieux, Bruker, Cepheid, etc.) and SMEs. On the other hand, the diagnostics available for AMR do not meet the ideal target product profiles of being able to simultaneously differentiate between bacterial from non-bacterial infections (Dx), identify the pathogen (ID) and determine its susceptibility profile, all in under two hours and at the point of care[177]. Although Dx is of particular importance in primary care settings and while ID and AST are of particular importance in hospital settings, having a single diagnostic tool available to address all three needs quickly and cheaply would minimise the need for separate uptake and training while providing enough information for antimicrobial stewardship in both settings. The recently concluded Longitude Prize in AMR[178] lends further credence to the conclusion that no available AMR diagnostic can accomplish all three goals simultaneously[179]. While the final results of this prize have yet to be announced, early signs such as the relaxing of certain criteria for the prize suggest that its targets have not been met by any of the 59 participants over its eight years. This chapter will examine some possible reasons for this and discuss potential solutions.

Phenotypic and non-phenotypic diagnostics

As shown by Craig Whiteford (Becton Dickinson) in a recent workshop on Rapid AMR Diagnostics organised by the American National Academies of Sciences, Engineering and Medicine[180], there are both phenotypic and non-phenotypic AMR diagnostic approaches (termed “AST” and “AMR” to emphasise that the former determines susceptibility or resistance while the latter can only rule in resistance, but not rule it out due to the possibility of new resistance mechanisms with unknown genetic determinants). Each approach has different strengths and weaknesses. Traditional phenotypic tests fit in well with existing clinical workflows and are cost-effective but require long waiting times (days) due to the slow bacterial growth rates, especially for bacteria such as *M. tuberculosis*[181]. Conversely, rapid phenotypic tests tend to have a limited number of pathogens they can target (while also being more expensive). This is also the case for non-phenotypic tests such as polymerase chain reaction (PCR) tests that look for specific genes or variants known to be associated with AMR.

Next Generation Sequencing technologies & machine learning

The most promising non-phenotypic technologies rely on next-generation sequencing (NGS) and consider the entire genomic landscape of pathogens found in the patient sample. Currently, NGS technologies require a rate-limiting library preparation step before being used, which in some cases is a manual process[182]. They may also include models of AMR derived directly from data using statistical or machine learning techniques; these

[177] World Health Organization, 2019. Landscape of diagnostics against antibacterial resistance, gaps, and priorities.

[178] Longitude Prize. [Online] Available from: https://longitudeprize.org/ [Accessed: 21st November 2022]

[179] Longitude prize, 2022. Final phase prize rules and challenge statement.

[180] National academies of sciences, engineering, and medicine, 2022. Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance - A Workshop (https://www.nationalacademies.org/event/10-13-2022/accelerating-the-development-of-rapid-diagnostics-to-address-antibiotic-resistance-a-workshop)

[181] National academies of sciences, engineering, and medicine, 2022. Accelerating the Development and Uptake of Rapid Diagnostics to Address Antibiotic Resistance - A Workshop (https://www.nationalacademies.org/event/10-13-2022/accelerating-the-development-of-rapid-diagnostics-to-address-antibiotic-resistance-a-workshop)

[182] Deurenberg, Ruud H., et al. "Application of next generation sequencing in clinical microbiology and infection prevention." Journal of biotechnology 243 (2017): 16-24.

models may change over time as new data is added and/or new AMR mechanisms (e.g. AMR-causing genomic variants) are discovered[183]. Regulatory requirements typically expect a consistent diagnostic process. For instance, changes in performance due to modifications in the underlying data may require a re-certification[184]. The EU requires explanations to be provided alongside decisions if diagnostic processes are made using data driven models derived from statistical or machine learning techniques. However, the regulatory hurdle is not limited to genomic-based diagnostics, as phenotypic diagnostics also change over time due to shifting boundaries between what susceptibility and resistance in specific pathogen-drug combinations[185]. Lastly, there remains the issue of the setup (capital) cost of diagnostic technologies relying on NGS, which remains high despite the per-sample (marginal) cost falling dramatically in the past two decades[186].

Challenges in reaching the ideal TPP

In summary, the following challenges can be identified on the way to realising the ideal target product profile of being able to simultaneously perform Dx, ID, and AST, all in under two hours and at the point of care[187]:

- **Resources required to cross the "valley of death" in the development of AMR diagnostics**: while they cost less than drugs to develop, they also present a smaller upside for investors due to a potentially limited uptake for reasons that include mistrust of results, risk aversion, time pressure, and cost[188]. Successfully meeting this challenge requires the provision of not only funding, which can be successfully addressed by push incentives, but also development expertise (something that is often found in public-private partnerships such as Bioaster and Hahn-Schickard, rather than in the public or private sectors alone).

- **Uncertain regulatory landscapes:** particularly the intersection of *in-vitro* diagnostic *(*IVD) regulations and artificial intelligence (AI), which are often required in combination for next-generation diagnostics[189] and the resulting barriers to market entry.

- **Integration into existing clinical workflows**: particularly acceptance by clinicians and patients, and the corresponding changes in behaviour in clinical practices[190]. It has, however, been noted that novel technological capabilities can gradually lead to changes in behaviour by simplifying existing processes.

- **Cost barriers and cost-effectiveness**: reimbursement policies only capture a fraction of the added value of diagnostics, which is not only reflected in risk reductions to individual patients, but also their community as a whole. Nevertheless, a study suggests

[183] Alcock, B.P., Huynh, W., Chalil, R., Smith, K.W., Raphenya, A.R., Wlodarski, M.A., Edalatmand, A., Petkau, A., Syed, S.A., Tsang, K.K. and Baker, S.J., 2023. CARD 2023: expanded curation, support for machine learning, and resistome prediction at the Comprehensive Antibiotic Resistance Database. Nucleic Acids Research, 51(D1), pp.D690-D699.

[184] Guidance on the regulation of In Vitro Diagnostic Medical Devices in Great Britain (2021). Available online: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/946260/IVDD_legislation_guidance_-_PDF.pdf [Accessed on 24th January 2023]

[185] European Committee on Antimicrobial Susceptibility Testing: Clinical breakpoints – breakpoints and guidance (2023). Available online: https://www.eucast.org/clinical_breakpoints [Accessed on 24th January 2023]

[186] National Human Genome Research Institute (2021). The Cost of Sequencing a Human Genome [Online]. Available from: https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost [Accessed: 24th January 2023]

[187] World Health Organization, 2019. Landscape of diagnostics against antibacterial resistance, gaps, and priorities.

[188] Wellcome (2016), Four diagnostic strategies for better-targeted antibiotic use, London: Wellcome, [Online] Available from: https://wellcome.ac.uk/sites/default/files/diagnostic-strategies-for-better-targeted-antibiotic-use-wellcome-jul15.pdf [Accessed on 19th January 2023].

[189] Artificial Intelligence in Medical Device Legislation [Online]. Available from: https://futurium.ec.europa.eu/en/european-ai-alliance/document/artificial-intelligence-medical-device-legislation [Accessed: 24th January 2023]

[190] Hall, B.H. and Khan, B. (2003). Adoption of new technology. [Online] Available from: https://www.nber.org/papers/w9730 [Accessed: 24th January 2023]

that even if only the former value is captured, this already yields an overall cost reduction to the healthcare provider[191].

- **Infrastructure requirements**: genotypic methods in particular require sequencing technologies that are integrated with clinical workflows, produce easily interpretable results, and are staffed by adequately trained personnel. The challenges for phenotypic methods are similar despite differences in technology. These are especially difficult in LMICs or other low-resource settings, although some recent work suggests that LMICs can bypass laboratories given the right technology.

The following section will describe some existing and emerging initiatives that aim to address some of these challenges as well as others faced in AMR diagnostics development and propose a number of roles that DG HERA could take on to help bring more AMR diagnostic devices to the market.

Ongoing initiatives and the potential role of DG HERA for bringing more AMR diagnostics to market

Several initiatives exist that focus (sometimes as one of several goals) on bringing more AMR diagnostics to the market. We discuss a sample of four of them that are already in place, namely, ValueDx, Foundation for Innovative New Diagnostics (FIND), CARB-X and the Longitude Prize, in addition to the Bench to Bedside to Business and Beyond (B2B2B) JPIAMR Diagnostics Network[192] which has not yet started.

Name of initiative	Role
ValueDx[193]	Group of industry and academic partners whose role it is to: • quantify the value added by diagnostics in settings such as community-acquired antibiotic-resistant respiratory tract infections; and • promote the recognition of this value by stakeholders such as clinicians, health ministries, and health payers (public or private, depending on the healthcare system).
FIND[194]	• identify the barriers to adopting AMR diagnostics in LMICs and explore ways to leverage the sequencing capabilities, vastly increased by the COVID-19 pandemic, towards this goal • a recent partnership with Curetis, a company providing sequencing-based AMR diagnostics as a subscription-based could service, is a move in this direction.
CARB-X[195]	• an accelerator programme seeking to identify and fund

[191] Patel, Twisha S., et al. "Cost analysis of implementing matrix-assisted laser desorption ionization–time of flight mass spectrometry plus real-time antimicrobial stewardship intervention for bloodstream infections." Journal of clinical microbiology 55.1 (2017): 60-67.

[192] JPIAMR. Bench, Bedside, Business, and Beyond: innovative solutions for AMR diagnostics (B2B2B AMRDx) [Online]. Available from: https://www.jpiamr.eu/projects/b2b2b-amrdx/ [Accessed: 21st November 2022]

[193] Value-Dx [Online]. Available from: https://www.value-dx.eu/ [Accessed: 21st November 2022]

[194] FIND [Online]. Available from: https://www.finddx.org/amr/ [Accessed: 21st November 2022]

[195] CARB-X [Online]. Available from: https://carb-x.org/ [Accessed: 21st November 2022]

	promising early-stage technologies in the AMR space (discussed in detail in earlier sections) • 21% of CARB-X's portfolio contains diagnostic devices, making it an important participant in this space.
Longitude Prize[196]	A mechanism funded by the UKRI[197], Innovate UK[198] and birac[199], providing approximately EUR 11.5 million (a fraction of the typical EUR 100 million required to bring a diagnostic from idea to the market[200]) to a company that produces a diagnostic with the following characteristics: • must meet an unmet need • high degree of accuracy (high sensitivity and high specificity) • affordable in LMICs • rapid (delivering results with one hour – increased from the original 30 minutes) • easy to use (minimally reliant on existing healthcare resources) • globally scalable • safe • connected to surveillance systems As of January 2023, the entries are undergoing assessment by the Prize Advisory Panel, but it seems unlikely that a single diagnostic will be able to fulfil of the aforementioned criteria[201].
B2B2B AMRDx[202]	Network funded by JPIAMR with members from almost 50 academic institutions, SMEs, hospitals, non-profit and government organisations, united by the goal of developing both technological and policy solutions to reduce the barriers to entry and enable more AMR diagnostics to enter the market. • collect a comprehensive database of AMR-diagnostics developers and make it freely available in partnership with AMR Insights' Technology pages

[196] Longitude prize on AMR [Online]. Available from: https://longitudeprize.org/ [Accessed: 21st November 2022]

[197] UK Research and Innovation [Online]. Available from: https://www.ukri.org/ [Accessed: 21st November 2022]

[198] Innovate UK [Online]. Available from: https://www.gov.uk/government/organisations/innovate-uk [Accessed: 21st November 2022]

[199] Biotechnology Industry Research Assistance Council [Online]. Available from: https://birac.nic.in/ [Accessed 21st November 2022]

[200] Global AMR R&D Hub (2021). Novel policy options for reimbursement, pricing, and procurement of AMR health technologies [Online]. Available from: https://globalamrhub.org/wp-content/uploads/2021/03/GOe_FP_AMR_Report_final.pdf [Accessed: 21st November 2022]

[201] Longitude prize (2022). Final phase prize rules and challenge statement [Online]. Available from: https://longitudeprize.org/wp-content/uploads/sites/74/2022/04/Longitude-Prize-Rules-for-the-Final-Phase.pdf [Accessed: 21st November 2022]

[202] JPIAMR. Bench, Bedside, Business, and Beyond: innovative solutions for AMR diagnostics (B2B2B AMRDx) [Online]. Available from: https://www.jpiamr.eu/projects/b2b2b-amrdx/ [Accessed: 21st November 2022]

	• develop a virtual benchmarking platform to make it easier to assess non-phenotypic diagnostics, building on past efforts by the Seq4AMR network (also funded by JPIAMR) • engage relevant stakeholders in refining policy options to address challenges faced by AMR diagnostics

The initiatives described above take on various roles to help improve the market conditions to enable the development of improved diagnostic devices in order to address the ongoing issue of AMR. There are several policy options that, based on foregoing discussion, may help to further improve the market conditions of diagnostic devices. Within this remit, DG HERA may consider the following policy approaches to bring more AMR diagnostics to the market, either through direct acting, or a supporting role.

Pay for performance

The concept of paying healthcare providers for their performance, not just for the acts they carry out, is a well-established one[203]. France has a well-established programme known as ROSP (*rémunération sur objectifs de santé publique*[204] – a remuneration system based on public health objectives), not yet specifically dedicated for diagnostics. In the context of AMR diagnostics, such a scheme could be tailored to apply at two levels: primary care (general practice), and secondary care (general hospital) or tertiary care (specialised hospital unit).

At the primary care level, an incentive to only prescribe antibiotics (or antifungals) after a (Dx-type) diagnostic test confirms that the symptoms indeed correspond to a bacterial (or a fungal) infection and not a viral one. This would be made easier by the development of rapid yet accurate diagnostics (e.g. lateral flow tests), although existing human biomarker tests such as procalcitonin or C-reactive protein may be used to accomplish the same objective[205].

At the secondary or tertiary levels, similar incentives could encourage clinicians to prescribe narrow-spectrum antibiotics if the causal pathogen and its susceptibility to antibiotics can be determined rapidly (in this case, ID and AST-type diagnostics would be needed). Existing evidence suggests that this can reduce costs due to fewer treatment complications and shorter hospital stays for the patient[206], not to mention the knock-on benefits from antimicrobial stewardship.

De-escalation (the process of either substituting a broad-spectrum antibiotic for a narrow-spectrum one or decreasing the dose of antibiotics in a patient, especially within intensive care units) is another application of AMR diagnostics where speed can improve outcomes[207]; incentivising tertiary care providers to use those diagnostics would have similar benefits.

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[203] Eijkenaar, Frank, et al. "Effects of pay for performance in health care: a systematic review of systematic reviews." Health policy 110.2-3 (2013): 115-130.

[204] Atramont, A. A., et al. "Pay for performance scheme for general practitioners in France: results in 2018." European Journal of Public Health 29.Supplement_4 (2019): ckz187-147.

[205] Li, Yang, Lanfang Min, and Xin Zhang. "Usefulness of procalcitonin (PCT), C-reactive protein (CRP), and white blood cell (WBC) levels in the differential diagnosis of acute bacterial, viral, and mycoplasmal respiratory tract infections in children." *BMC Pulmonary Medicine* 21.1 (2021): 1-8.

[206] Patel, Twisha S., et al. "Cost analysis of implementing matrix-assisted laser desorption ionization–time of flight mass spectrometry plus real-time antimicrobial stewardship intervention for bloodstream infections." *Journal of clinical microbiology* 55.1 (2017): 60-67.

[207] Patel, Twisha S., et al. "Cost analysis of implementing matrix-assisted laser desorption ionization–time of flight mass spectrometry plus real-time antimicrobial stewardship intervention for bloodstream infections." *Journal of clinical microbiology* 55.1 (2017): 60-67.

In the table below, we describe the advantages and disadvantages of implementing such a scheme across all EU Member States.

Table 40: Advantages and disadvantages of implementing a pay-for-performance programme across all EU Member States

Advantages	Disadvantages
Creates a clear expectation on the wider use of diagnostics, thereby supporting stewardship and AMR control.	If appropriate technologies are not available (e.g. rapid diagnostics), a pay-for-performance programme may lead to the use of suboptimal diagnostics and delay patient treatment.
Encourages clinicians to be rewarded based on the correct use of diagnostics.	A rise in the immediate cost of treating a patient due to the use of diagnostic test followed by the appropriate treatment.
Takes advantage of market competition and economies of scale to stimulate the development of new rapid diagnostics that will become more cost-effective over time.	A poorly implemented pay-for-performance programme may create unintended incentives, such as a use of diagnostics which does not provide comprehensive information about subsequent choice of treatment.

A pay-for-performance programme for diagnostics could be implemented at national level, with DG HERA playing a role in capacity building and best-practice sharing within this remit, as described by Member States in the primary-data collection.

Alignment of regulatory requirements

Across the EU, there is a centralised regulatory process governing IVDs under the IVDR (IVDR (EU) 2017/746). The IVDR was brought into force in 2022 to replace the old directive governing IVDs (IVDD - 98/79/EC), with one of its aims being to harmonise and centrally regulate the IVD market within the EU[208]. Despite a harmonisation of regulatory requirements within the EU, there is still a lack of alignment of these regulatory requirements across the various members of the G7 – namely those found in the EU (under the IVDR) and those found in the U.S. set out by the FDA. This leads to a situation in which, similar technologies are marketed by different companies in Europe and North America, with limited mutual awareness. It should be noted that a number of developers do try to enter both the European and the North American markets, but typically face barriers to entry due to the divergent regulatory requirements. Such differences include the post-market surveillance of marketed IVDs[209], as well as the clinical evidence required for certification of IVDs[210]. Although some of the work carried out by manufacturers of IVDs in order to get their device certified in the U.S. may be applicable to IVDR compliance in the EU, an even greater alignment in the regulation of IVDs for AMR has the potential to improve the efficient functioning of the diagnostic market.

In the table below, we describe the advantages and disadvantages of coordinating and implementing such a scheme at a global level.

[208] Regulations are applicable to all Member States

[209] The U.S. IVD regulations require device malfunctions that could lead to a serious adverse event to be reported, while the IVDR in the EU requires a much more defined and stringent plan for post-market surveillance activities

[210] In the U.S. the requirement for clinical evidence for IVDs depends on the classification of such devices with emphasis on the manufacturer's verification and validation studies to support safety and performance. Under the IVDR in the EU, the requirement is for sufficient clinical evidence for an IVD or an equivalent device, along with ongoing reporting.

Table 41: Advantages and disadvantages of aligning regulatory requirements across regulatory authorities

Advantages	Disadvantages
Avoids the duplication of technologies and/or approaches, leading to a greater efficiency in the process of bringing new innovative diagnostics to the market.	Different markets may have somewhat different needs, so the alignment of regulatory requirements might lead to the use of diagnostic tools with panels covering too many pathogens or drugs.
Lowers the barrier to enter another market once entry into the primary target market is complete.	Can potentially make the overall regulatory requirements more stringent, as diagnostic devices have to comply with multiple different requirements rolled into a single package.

Although an alignment of regulatory requirements is not within the remit of DG HERA, DG HERA could have a role in facilitating the alignment of multiple stakeholders and regulatory authorities, while also streamlining discussions and the sharing of best practices to simplify access by aligning regulatory requirements.

Establishment of TPPs for diagnostics

The establishment of clear and realistic TPPs for AMR diagnostics can facilitate the task faced by their developers. Similar to the targets set by the Longitude Prize, these TPPs can focus on cost, sensitivity, specificity, time to result and ease of use, and may be tailored to specific clinical situations or unmet medical needs. Their effectiveness and cost-effectiveness can then be estimated from epidemiological modelling exercises based on assumptions about volume of use (willingness to pay), and account for both patient-level and community-level outcomes[211]. Clear expectations from a regulatory perspective can also make a systemic difference in encouraging innovation and creating an environment that supports growth.

In the table below, we describe the advantages and disadvantages of establishing target product profiles at EU level.

Table 42: Advantages and disadvantages of establishing target product profiles for diagnostics at EU level

Advantages	Disadvantages
Simplify the go/no-go decision-making process for product developers with a better understanding of the market needs.	Other diagnostics that could be useful but do not meet the TPP might be overlooked (e.g. diagnostics that can do Dx rapidly, but struggle with pathogen ID, may get less traction).
Evidence-based approach – diagnostic tools will be developed based on surveillance data/a proactive setting of targets.	May favour the larger industry players over the smaller diagnostics developers since they typically have more resources to ensure compliance with more complex regulatory frameworks.

[211] Knight, Gwenan M., et al. "Mathematical modelling for antibiotic resistance control policy: do we know enough?." BMC infectious diseases 19.1 (2019): 1-9.

At present, TPPs for diagnostic devices are already established by organisations such as the WHO[212] and FIND[213], with the latter focusing on TPPs of diagnostic devices that are implementable in LMICs. By collaborating with such partners, DG HERA, along with other relevant EU bodies such as DG SANTE, can ensure a coordinated review and adaptation of these TPPs to make them relevant in an EU context, and possibly a national level. Specifically, TPPs that detail what is expected and needed of novel diagnostic devices and provide the Member States with the appropriate guidance as to how these TPPs should be used, will effectively steer R&D and result in more suitable diagnostic devices on the market to address AMR.

Conclusions for DG HERA and next steps

With the above in mind, it is apparent that problems exist in the current diagnostic devices market. Although these problems might not be as severe and challenging to resolve as those previously described for antimicrobial treatments, they still require solutions and interventions. The aforementioned policy approaches that may help improve the market conditions to enable the development of improved diagnostic devices may not all fall within the remit of DG HERA. However, DG HERA, if acting as a coordinator/facilitator, could support the implementation of these policy approaches by providing the necessary incentives to developers of diagnostic devices to continue investing in the AMR space.

[212] Target product profiles for antibacterial resistance diagnostics. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

[213] Target product profiles for antibacterial resistance diagnostics. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Annex 2 - Considerations for preventatives (vaccines)

From our survey analysis, the immediate needs for R&D identified by Member States were in the remit of treatment for bacterial infection rather than prevention. As a result of this, the predominant focus of this study was to address the area of highest need resulting in a focus of options for action for bacterial treatments. It is known that prevention-based strategies tend to be more cost-effective than curative treatments. Thus, where vaccine prevention is scientifically feasible it should be financially supported, in part due to its many public health benefits (including public good externalities). As a result, considerations for vaccines are discussed at a high level below for future assessment and evaluation in an evidence-based approach.

Both the analysis conducted within the interim report of this study, and the vaccine pipeline analysis conducted by the WHO indicates that the market for preventatives (vaccines) faces substantially different challenges to the market for treatments. Specifically, the development of vaccines for AMR bacteria faces obstacles in the relative feasibility of generating a vaccine against a specific pathogen. A position paper by EFPIA and Vaccines Europe recommends that DG HERA should not operate in areas where the market is functioning (or where other incentives would yield better results) – specifically stating that addressing the common vaccine challenges for communicable diseases should be excluded from DG HERA's scope[214].

In its report published in 2022, the WHO categorises pathogens into "pipeline feasibility groups". Pathogens with the lowest feasibility for developing an effective vaccine (group D) included *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., *Enterococcus faecium, Staphylococcus aureus* and *Helicobacter pylori.* For these pathogens recommendations from this report focus upon alternate methods of treatment and prevention in the form of infection prevention control rather than incentivising vaccine R&D.

In summary, the conclusions of the WHO reports on the vaccination pipeline and the antibiotic pipeline do not draw the same conclusions in regard to the "health" of the market and in turn do not draw the same recommendations (as illustrated in the table below). These are two very different product markets.

Table 43: Comparison of the WHO reports - vaccines and antibacterial agents

	The WHO Bacterial Vaccine Pipeline 2021[215]	The WHO Antibacterial agents pipeline 2021[216]
Conclusions on products in development	**Group A vaccine feasibility class** (very high) = licensed vaccines exist (*Salmonella*, *S. peneumoniae*, *Haemophilus influenzae*) **Group B vaccine feasibility class** (high)= AMR priority pathogens where a vaccine candidate is in late-stage development (*E. coli*, *S. enterica*, *N.*	New agents are mainly derivatives of existing classes The clinical "traditional" pipeline is still insufficient against priority pathogens Innovation remains a challenge for Gram-negative bacterial

[214] EFPIA and Vaccines Europe (2021) **A joint EFPIA and Vaccines Europe White Paper – Establishment of The Health Emergency Preparedness and Response Authority** [Online] Available from: https://www.efpia.eu/media/602659/hera-white-paper_efpia_ve.pdf [Accessed: 18th November 2022].

[215] The World Health Organisation (2022) **Bacterial vaccines in clinical and preclinical development 2021** [Online] Available from: https://www.who.int/publications/i/item/9789240052451 [Accessed: 18th November 2022].

[216] The World Health Organisation (2022) 2021 **Antibacterial agents in clinical and preclinical development: an overview and analysis** [Online] Available from: https://www.who.int/publications/i/item/9789240047655 [Accessed: 18th November 2022].

	gonorrhoeae, *M. tuberculosis*, and *C. difficile*.) **Group C vaccine feasibility** (moderate) = vaccine candidate has either been identified in early clinical trials or been identified as a feasible vaccine target during expert review (*E. coli*, nontyphoidal *Salmonella*, *Campylobacter* spp. and *Shigella* spp.) **Group D vaccine feasibility class** (low) = Associated with a low feasibility of vaccine development - no vaccine candidate identified. *A. baumannii, P. aeruginosa, Enterobacter* spp., *E. faecium, S. aureus* and *H. pylori*.	species There is diversity in the non-traditional approaches The preclinical pipeline is dynamic but volatile
Recommendations	Group A = increase global coverage of authorised vaccines Group B = Accelerate development of vaccines Group C = 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. Group D = Focus on other prevention and control tools to combat AMR threats linked to these priority pathogens. Incentive-based policies might be needed for some vaccines, for others alternative interventions may be more appropriate (where there is "low vaccine feasibility"	More countries need to act, ideally in a coordinated manner, to develop a favourable market dynamic and create the financial incentives that are needed to drive antibiotic R&D and innovation.

The indirect and direct role that vaccines have in AMR is clear, in that they:

- reduce the likelihood of resistance-conferring mutations in bacteria by acting prophylactically
- contain multiple immunogenic epitopes – in comparison to treatments that normally have a single target - resistance to vaccines requires more mutations and is less likely to emerge
- reduce prevalence of the resistant pathogen as well as antibiotic use
- indirectly affect AMR by preventing viral infections and hence reducing the inappropriate use of antibiotics[217]

However, one significant difference that the vaccines market has in comparison to the treatments market for antimicrobial resistance are stewardship requirements. There is a negative public health effect in overusing antibiotics, while for vaccines the greater use increases coverage across the population, which provides public health gains. For

[217] Micoli and Bagnoli *et al.* (2021) "The role of vaccines in combatting antimicrobial resistance" **Nature reviews microbiology** [Online] 19 pp.287-302. Available from: https://doi.org/10.1038/s41579-020-00506-3 [Accessed: 23rd November 2022].

treatments, the negative impact of stewardship on the return on investment (i.e. marketability) for drug developers is well known[218] - conversely for vaccines prophylactic treatment of comparatively large populations is required for effective prevention.

Considering the aforementioned, the reports focus is upon **treatments for bacterial infections**, both in terms of the pull incentives modelled and the push incentive mechanisms identified in order to align with priorities of the Member States and in turn apply focus to where substantial market failures exist. Whilst push incentives may still be applicable for the market of AMR vaccines, it should be noted that the mechanisms, timing, and type of incentives that should be proposed (in addition to the attached conditions) would vary significantly from those proposed for treatments and are dependent upon more factors such as the feasibility of vaccine development.

Reflection on the COVID-19 pandemic – emergency scenario

The Options Market for Vaccines (previously proposed)

A paper published in 2020[219] focused upon the COVID-19 crises at a time prior to an effective vaccine being brought to market and reflects upon several models that could be implemented in "extreme" circumstances such as ones similar to the COVID-19 pandemic. These include:

- Global patent pool – within which industry release their patents for medical interventions developed with no or limited conditions, enabling governments or generic manufacturers to manufacture at lower prices[220]
    - the authors of this paper consider that such an initiative would be disincentivising for further R&D and therefore likely inappropriate for the situation of AMR vaccine R&D.
- Advanced Market Commitment (AMC) – launched in collaboration with Coalition for Epidemic Preparedness Innovations (CEPI) and the WHO in 2020
    - previous studies showed that AMC in the context of pneumococcal vaccines (USD 1.5 billion from 6 donors) was effective in accelerating development of two late-stage vaccines but did not effectively stimulate early-stage research[221].
- Options Market for Vaccines (OMV) – whereby a public investor purchase options for the COVID-19 vaccine to redeem if and when a vaccine was delivered to market – as co-investors the options purchasers would be able to co-determine a market price alongside industry. Options would be cheaper at an earlier stage of development due to a high probability of failure (higher risk). Requirement could be included that once a vaccine successfully reaches the market the investor has a right to purchase at a discounted price.
    - the authors of this paper consider that such initiative may give an advantage to high-income countries

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[218] Outterson K. and Powers J.H *et al.* (2015) "Repairing The Broken Market For Antibiotic Innovation" **Health Affairs** [Online] 34 (2). Available from: https://doi.org/10.1377/hlthaff.2014.1003 [Accessed: 21st November 2022].

[219] Forman R. and Anderson M. *et al.* (2015) "Ensuring access and affordability through COVID-19 vaccine research and development investments: A proposal for the options market for vaccines" **Vaccine** [Online] 38 (39) pp. 6075-6077. Available from: https://doi.org/10.1016/j.vaccine.2020.07.068 [Accessed: 21st November 2022].

[220] Mancini D.P. - The Financial Times (2020) **Big drugmakers under pressure to share patents against coronavirus** [Online] Available from: https://www.ft.com/content/b69afd98-a8af-40d9-b520-4231d9cac68f [Accessed: 18th November 2022].

[221] GAVI The Vaccine Alliance, Boston Consulting Group (2015) "Pneumococcal AMC outcomes and impact evaluation" [Online] Available from: https://www.gavi.org/our-impact/evaluation-studies/pneumococcal-amc-outcomes-and-impact-evaluation [Accessed: 18th November 2022].

The options market for vaccines has only been theoretically investigated and only in the context of vaccines in a pandemic emergency scenario (COVID-19). Their applicability in addition to the above push incentives and other vaccine specific measures warrants further investigation and study in line with what is feasible to achieve in regard to vaccine feasibility.

The HERA Incubator (VACCELERATE)

An output recommendation from the WHO analysis of the AMR vaccine pipeline was to accelerate clinical trials for the **"Group B" vaccines** that are close to market (in late-stage development). One way of potentially accelerating vaccine development is by the use of clinical trial platforms or networks.

DG HERA established the "HERA incubator" (VACCELERATE) specifically for COVID-19 vaccine trials to act as a "pan-EU" backbone for the acceleration of phase II & III COVID-19 vaccine trials funded under the Horizon 2020 research and innovation programme[222]. Specifically, VACCELERATE combined expertise, services, resources, and solutions in order to speed up existing and future vaccine development programmes specifically for COVID-19.

It should be noted that there are additional EU based infectious disease specific clinical trial networks (see section 8.1.3. Streamlining clinical trials). However, in its specific capacity focused upon vaccines, and in its application to a crisis that required prompt acceleration of vaccine development, the VACCELERATE platform or a similar entity could be a consideration for future acceleration of vaccines for AMR pathogens[223].

IMI AMR Accelerator - PrIMAVeRa

Currently the IMI AMR Accelerator programme PrIMAVeRa (Predicting the Impact of Monoclonal Antibodies & Vaccines on Antimicrobial Resistance) is developing mathematical models to help predict the impact of vaccines and monoclonal antibodies on the reduction of AMR[224].

Together with the WHO work, these studies can support DG HERA and other decision-makers in prioritising resources for the most promising new vaccines and monoclonal antibodies.

Coalition for Epidemic Preparedness Innovations

In October 2022 a letter of intent was signed between DG HERA and the CEPI[225] in order to develop a process of cooperation and exchange of information. Specifically, CEPI is a global partnership between public, private, philanthropic, and civil society organisations. Its mission is to promote and strengthen public-private collaboration in order to develop, manufacture and stockpile vaccines and other MCMs necessary to respond to cross-border health threats. An enhanced collaboration between DG HERA and CEPI is intended to maximise their respective activities and minimise unnecessary overlap. Within the remit of this cooperation and collaborative relationship the topic of vaccines for AMR

[222] VACCELERATE [Online] Available from: https://vaccelerate.eu/ [Accessed: 23rd November 2022].

[223] Note – clinical trial networks were not indicated within our survey as a priority role for DG HERA – a high level overview has been included in recognition of their importance

[224] IMI AMR Accelerator **PriMAVeRa** [Online] Available from: https://amr-accelerator.eu/project/primavera/ [Accessed: 7th December 2022].

[225] European Commission (2022) **Letter of Intent regarding Cooperation between CEPI and HERA** [Online] Available from: https://health.ec.europa.eu/publications/letter-intent-regarding-cooperation-between-cepi-and-hera_en [Accessed: 23rd December 2022].

pathogens could form a central element and an expansion of CEPIs portfolio which is predominantly at present focused upon COVID-19[226].

[226] CEPI **Our Portfolio** [Online] Available from: https://cepi.net/research_dev/our-portfolio/ [Accessed: 23rd December 2022].

Annex 3 – Expert workshop on pull incentives

In recognition of the vast number of previous studies, reports, assessments, and academic literature within the remit of incentives for AMR R&D (push and pull), we gathered subject-matter experts in order to shortlist options for action that may form the basis of further assessment and preliminary feasibility analysis within the context of this study.

For this purpose, two workshops were carried out:

- an ideation session where initial ideas were brainstormed and captured more broadly
- a half-day "deep dive" session where these ideas were elaborated, with the advantages and disadvantages discussed and clarified.

The outputs of these workshops were presented to DG HERA and clarified in subsequent meetings, including in a meeting with DG SANTE and DG RTD in addition to DG HERA. The organisation of the workshop and meetings is presented below.

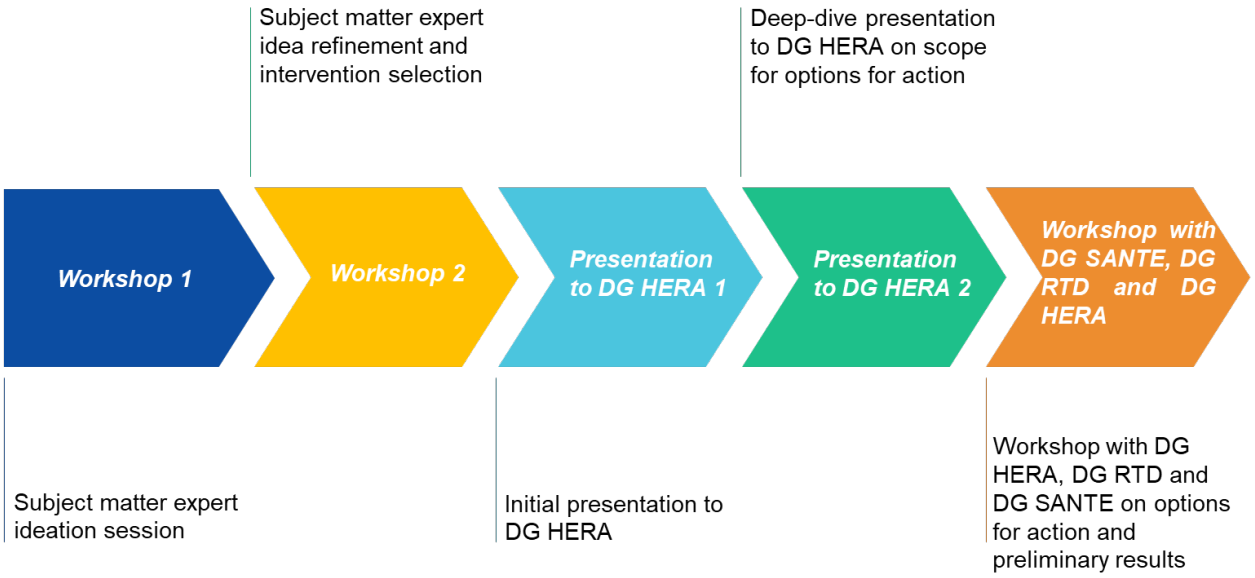

Figure 28: Timeline for the selection of options for action in order to bring more AMR MCMs to market (bacterial treatments)

Annex 4 – Pull incentives – defining the size of the four interventions

In order to define the potential sizes for each intervention in terms of financial value, we first need to distinguish interventions 1 and 2, which are similar in their objectives and design, from Intervention 3, which is an early-stage pull incentive focused on specific phases, and finally from the lump-sum payment (intervention 4). With regard to interventions 1 and intervention 2, two major considerations have been central to determine the size of the intervention from which the simulation exercise will be performed:

Considerations for the sizing of Interventions 1 and 2

We identified six major references in this field:

- the two programmes that are currently implemented in Sweden[227] and the UK[228]
- the proposed programme in the US[229]
- three research publications from the BCG[230], the Drive-AB report[231] and a publication by Prof. Kevin Outterson[232]

The programmes in France and Germany would have also been relevant under this study, however their financial amounts were not disclosed and hence could not be included in this analysis.

Source 1: Swedish Pilot Revenue Guarantee Scheme

The Swedish pilot aims to ensure the availability of medically important antibiotics from companies that receive a guaranteed annual income per product in return. It should be noted that the focus on this pilot is to guarantee the access to existing antibiotics, and not to push for further innovation. In this regard, the value of the revenue guarantee is quite low and can attract only existing antibiotics. It is set at EUR 400,000 per year and per product. This guarantee acts as a "floor on revenue", meaning that the Swedish government only pays marketing authorisation holders the difference between EUR 400,000 and actual sales. Therefore, if market sales of a selected antibiotic surpass EUR 400,000, only a small payment of EUR 40,000 will be made from this guarantee scheme that year.

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[227] AMR Solutions (2020) "Sweden to test an access-focused model for new antibiotics: contracting for availability" [online] Available at: https://amr.solutions/2020/03/16/sweden-to-test-an-access-focused-model-for-new-antibiotics-contracting-for-availability/ [Accessed: 25th October 2022]

[228] National Institute for Health and Care Excellence "Models for the evaluation and purchase of antimicrobials" [online] Available at: https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials [Accessed 25th October 2022]

[229] US Congress "H.R.3932 – PASTEUR Act of 2021" [online] Available at: https://www.congress.gov/bill/117th-congress/house-bill/3932/text#:~:text=To%20establish%20a%20program%20to,pathogens%20and%20most%20threatening%20infections.&text=To%20establish%20a%20program%20to,pathogens%20and%20most%20threatening%20infections. [Accessed: 25th October 2022]

[230] Boston Consulting Group (2022) "The Case for a Subscription Model to Tackle Antimicrobial Resistance" [online] Available at: https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance [Accessed: 25th October 2022]

[231] Christine Årdal and David Findlay *et al.* (2018) "DRIVE-AB Report – Revitalizing the antibiotic pipeline – simulating innovation while driving sustainable use and global access" [online] Available at: http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [Accessed: 25th October 2022]

[232] Outterson K. (2021) "Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines" Health Affairs (Millwood) doi: 10.1377/hlthaff.2021.00688.

By using the global share of Sweden's GDP (0.6%), we can assume that if all countries were to apply a similar approach, this would result in a global pull mechanism of approximately EUR 70 million/year per drug. This corresponds to the size of the reward per drug (including the sales of the developer for the drug), not the cost for the public authority.

Source 2: UK/NICE Subscription Model

The second pilot programme is the UK/NICE subscription model. In contrast to the Swedish pilot, which is only partially delinked, this programme is a fully delinked model where yearly payments are the only revenue allowed to suppliers, irrespective of the volume of units delivered and used in the UK market. The model sets a maximum yearly payment of GBP 10 million/year per drug. This approach aims to achieve not only access but also to have a "pulling effect" on the market, which explains why the payments are significantly higher than the ones in the Swedish pilot. In short, the UK programme proposes a pull mechanism of GBP 10 million/year over 10 years. Assuming the global share of the UK is 3%, this would correspond to a global revenue guarantee of GBP 330 million/year per drug. This corresponds to the size of the reward per drug, and also to the cost for the public authority as these are the only payments received by the developer.

Source 3: U.S. PASTEUR Act

The third programme is the U.S. PASTEUR Act, which has been proposed to the U.S. Congress but not yet approved. The purpose of this programme is to encourage both innovation and guarantee access via a revenue guarantee scheme. The terms and conditions are not precisely defined: the contracts with companies could vary between USD 750 million and USD 3 billion in total over 10 years, or between USD 75 million and USD 300 million/year per drug. Although the programme is specific to the U.S., given the size of the country's pharmaceutical market, this figure could be considered relevant for sizing a global intervention.

Source 4: The DRIVE-AB final report

The DRIVE-AB final report published in 2018 proposed a pull mechanism based on an R&D cost and profitability approach, identifying the required investment of companies to drive innovative antibiotics to market. The report estimated that between EUR 800 million and EUR 1.5 billion (at least) would be necessary annually per antibiotic and could result in about 18 antibiotics reaching the market in the 30 years after implementing this delinked model.

These figures are already global and focus mainly on boosting innovation rather than access, which can explain the divergence with the figures in the Swedish pilot and the similarity with the U.S. figures. The study recommends a reward of about EUR 1 billion in total (EUR 100 million/year over 10 years) in the partially delinked model, and a reward of EUR 1.5 billion in total (EUR 150 million/year over 10 years) in the fully delinked version. The cost for the public authorities will depend on the delinkage of the model: it will be lower if it takes the form of a revenue guarantee scheme because part of this amount is obtained through the sales of the units, while the cost for the public authority is equal to the reward in the case of a fully delinked MER.

Source 5: Boston Consulting Group study

In 2021, the BCG in collaboration with the World Economic Forum, Wellcome, and the Novo Nordisk Foundation used an R&D cost-based approach to estimate the size of the global incentives to be provided to incentivise AMR R&D. The focus of the study was on innovation and the proposal of an incentive that considers the high risk of failure[233], and

[233] The high risk of failure is also considered in the Drive-AB report, the Outterson paper, and the simulations performed in this report.

the costly process of developing innovative treatments for bacterial infections. They also conclude on the need for pull incentives, particularly a revenue guarantee scheme (or subscription model) and recommend globally USD 250 million/year over 10 years per antibiotic. This report also estimated the expected contribution of the various countries/regions under different scenarios. On the one hand, assuming that China would not contribute, the EU contribution should be between 29% and 39% of the total global initiative. If China were to contribute, Europe's contribution would be between 22% and 27% of the total global funding.

Source 6: Prof. Kevin Outterson (2021)

Finally, the paper published in 2021 by Prof. Kevin Outterson offers another estimation. This paper focuses, like the DRIVE-AB report and the BCG report, on innovation and recommends a delinked model. The conclusions on the level of incentive are higher, suggesting a **global pull mechanism of USD 3.1 billion over 10 years (USD 310 million/year and per antibiotic)**. There are several reasons that explain why this estimate is significantly higher than previous ones. Among others, this paper proposes a fully delinked model without modelling separately any additional push incentives other than the ones currently in the antibiotic field. Furthermore, Prof. Outterson has considered the post-approval costs related to manufacturing setup, paediatric studies, safety, additional phase III studies, and medical affairs, which increase the need for financial support. While other studies have assumed that sales derived from new treatments could reach USD 1 billion, Outterson has selected lower expected sales to account for the fact that, on average, sales are closer to USD 200–250 million. Finally, the R&D costs of the companies (both SMEs and large pharmaceutical companies) was corrected to account for inflation. In total, this explains why a fully delinked model of USD 3.1 billion spread over 10 annual payments is necessary to bring to the market antibiotics that are substantially more innovative than those that have been developed over the last 20 years, a period characterised by the launch of simple modifications to previous antibiotics. As a result, if the objective of public policy is to develop more highly innovative products, this is likely to be riskier and take longer, meaning that the financial support could be even more costly.

Summary

Based on these different estimates, we have elaborated four scenarios with total sizes of the interventions between the lower limit (EUR 700 million over 10 years – Swedish pilot) and the higher limit (EUR 3.1 billion over 10 years – Outterson's paper).

"LOW scenario" (USD 700 million in total)

This level of incentive scenario derives from the Swedish pilot. As explained above, Sweden is currently paying EUR 400,000 per drug per year; if rescaled at global level, this corresponds to an annual revenue guarantee scheme of approximately USD 70 million/year per drug globally for intervention 1, which we propose, similarly to the UK/NICE and the U.S. Pasteur Act to be paid for a 10-year period.

For intervention 2 (MERino), a slight variation will apply: to maintain the global contribution at USD 700 million, we will model an MER of USD 250 million for the first two years and then USD 50 million of revenue guarantees for the remaining four years. As mentioned above, the level of reward implemented by Sweden is, by design, not envisaged to have a pulling effect, but rather to stimulate access only. This level of incentive will therefore be unlikely to have a strong pulling impact.

In addition, assuming that Europe would contribute around 22–27% to a global initiative in which China would also participate (according to the BCG report), the European contribution will amount to approximately USD 700 million over ten years in which the global effort would be USD 3.1 billion (the estimate provided by Kevin Outterson). Through this scenario, we therefore also ascertain the impact of the EU's contribution,

where the global financial effort of USD 3.1 billion and Europe's share in the global contribution is 23%.

"INTERMEDIATE scenario 1" (USD 1 billion in total)

This scenario corresponds to the recommendation of the DRIVE-AB final report, and to some extent to the U.S. Pasteur Act. It corresponds to a moderate pull mechanism at global level equal to USD 100 million/year globally over 10 years for intervention 1.

For intervention 2 (MERino), a slight variation will apply: to maintain the global contribution at USD 1 billion, we will model a MER of USD 330 million for the first two years and then USD 85 million of revenue guarantees for the remaining four years.

Furthermore, assuming that the global contribution would be USD 3.1 billion, USD 1 billion can be interpreted as the stand-alone EU share if its contribution were to reach 32% of the total global effort. This corresponds to the second scenario proposed by the BCG, where China would not participate in the global pull mechanism.

"INTERMEDIATE scenario 2" (USD 1.5 billion in total)

This scenario corresponds to the upper limit of the recommendation in the DRIVE-AB final report, where a fully delinked model would be in place. It corresponds to a global pull mechanism that is equal to EUR 150 million/year over 10 years for intervention 1 (annual revenue guarantee). This remains significantly lower than what has been proposed by the BCG or Outterson but offers the advantage of simulating the impact of a moderately costly global pull mechanism.

For intervention 2 (MERino), a slight variation will apply: to maintain the global contribution at USD 1.5 billion, we will model an MER of USD 500 million for the first two years and then USD 100 million of revenue guarantees for the remaining four years.

Furthermore, assuming that the global contribution would be USD 3.1 billion, USD 1.5 billion can be interpreted as the stand-alone EU share if its contribution were to reach 48% of the total global effort. This share is significantly higher than that proposed by the BCG report. However, this may also provide some important information on the impact of a strong financial mechanism driven by Europe alone.

"HIGH scenario" (USD 3.1 billion in total)

This scenario, which corresponds to the recommendations from Prof. Outterson's model, has been welcomed by both researchers and the industry and has the merits to account for the post-approval costs of bringing treatments to the market. It corresponds to a fully delinked model in which the global pull mechanism equals to EUR 310 million/year over 10 years for intervention 1 (annual revenue guarantee).

For intervention 2 (MERino), a slight variation will apply: to maintain the global contribution at USD 3.1 billion, we will model an MER of USD 1 billion for the first two years and then USD 275 million of revenue guarantees for the remaining four years.

Through this scenario, we will analyse the impact of a sizeable global contribution. It may help show the expected improvement in innovative drugs in the AMR market and thus be used as a reference in discussions that would foster global cooperation.

Moreover, three of the four sizes that we have chosen – 700 million, 1.5 billion and 3.1 billion – are each approximately double of the preceding size, which enables to explore the impact of easily comparable sizes of the first two interventions (RGs and MERinos).

Considerations for the sizing of Intervention 3 – Milestone-Based Rewards (MBR)

Regarding intervention 3, similarly to interventions 1 and 2, we are testing multiple sizes of each of the two milestone-based rewards, therefore considering different levels of financial gain to the successful developer.

To select the appropriate sizes, we relied mostly on the observed R&D costs for antibiotics projects used as data input in our simulation, i.e. USD 20 million for phase I and USD 40 million for phase II (see the input table in the body of the report). Then, we propose testing rewards awarding a 50%, 100% and 200% financial gain. These percentages have been chosen following a preliminary analysis of the likely impact these rewards could have on the ENPV at different phases of the project.

Table 44: Level of incentive scenarios for Intervention 3

Scenario	Intervention 3 – Phase I completion reward	Intervention 3 – Phase II completion reward
Low Scenario	P1 prize 30 = 1.5 x USD 20 million (50% gain)	P2 prize 60 = 1.5 x USD 40 million (50% gain)
Medium Scenario	P1 prize 40 = 2 x USD 20 million (100% gain)	P2 prize 80 = 2 x USD 40 million (100% gain)
High Scenario	P1 prize 60 = 3 x USD 20 million (200% gain)	P2 prize 120 = 3 x USD 40 million (200% gain)

One can clearly anticipate that the profitability improvement (ENPV increase) will be greater with the highest percentage gains for each reward. It should be noted that we also compare the impact of a phase I or a phase II completion reward on profitability with its cost for public funders, drawing conclusions about the efficiency of such an intervention.

Considerations for the sizing of Intervention 4 – Lump-sum Market Entry Reward

Regarding intervention 4, we tested different sizes, and the final selected sizes were based on the following logic:

- the size of the lump-sum transfer should be large enough to significantly impact the ENPV
- the overall size should be comparable to the other pull interventions that have been simulated, so as to enable a comparison of the efficiency of this lump-sum versus the annual revenue guarantees and MERinos.

Within this context, we eventually chose three sizes for the lump-sum MER: USD 1 billion, USD 2 billion, and USD 4 billion, paid as one lump sum at regulatory approval. As each size is double the preceding one, taken together, they offer the possibility to compare the impact of broadly different alternatives, following the same logic as RGs and MERinos, which were also nearly double from one size to the next – 700 million to 1.5 billion to 3.1 billion.

Table 45: Level of incentive scenarios for Intervention 4

Scenario	Intervention 4(Lump-sum MER)
Low scenario	USD 1 billion
Medium scenario	USD 2 billion
High scenario	USD 4 billion

Finally, the three programmes that have been used for sizing the simulated interventions given their features and available data are explained in further detail below:

The Swedish Exceptional Procurement Pilot with Partial Delinkage – Swedish Revenue Guarantee

Primary Goals

Antibiotics are used in a relatively restrictive way in Sweden compared to many other countries. Consequently, some products face such low demand that there is a risk that pharmaceutical companies choose not to make them available on the Swedish market. To keep approved antibiotics available on the Swedish market, the government commissioned the PHAS in June 2018 to propose and pilot a new reimbursement and procurement model for ensuring good accessibility in Sweden against the lowest guaranteed income. It should be noted that this model is focused upon ensuring access, not upon incentivising the research and development of new and innovative medical countermeasures.

The ongoing new reimbursement pilot (developed by the PHAS and the Swedish Dental and Pharmaceutical Benefits Agency, TLV) led by the PHAS aims to ensure access to new antibiotics that are of special medical value to the country. The starting point for the level of guaranteed annual compensation is to ensure availability from a medical need based on the current state of resistance and a possible national need during the contract years.

In early 2020, the PHAS launched an open procurement call and invited Marketing Authorisation Holders (MAHs) to submit candidate medicines for the pilot. The selected companies that were able to guarantee a rapid and timely supply of recently approved antibiotics with special medical value will receive a guaranteed minimum annual income while the regions continue to pay as usual for their consumption.

Eligibility criteria

The antibiotic product should meet defined requirements for special medical value to be determined by the following criteria:

- demonstratable lack of availability on the Swedish market, or a risk of shortage
- low annual sales value for the product
- an antibacterial spectrum with demonstrated good activity against multidrug-resistant *Enterobacterales*
- approved for treatment on the WHO's critical priority pathogens list (2017), for at least two of the following indications:
    - Complicated intra-abdominal infection
    - Complicated urinary tract infection including acute pyelonephritis
    - Hospital acquired pneumonia

- Infections caused by aerobic gram-negative organisms in patients with limited treatment options

- must have a bactericidal effect, i.e., killing effect leading to bacterial cell death at therapeutic concentrations with a good safety profile

Selected beneficiaries

Following the closure of the public procurement procedure in June 2020, four companies (MSD i.e., Merck & Co, Shionogi, Pharmaprim and Unimedic Pharma) and five products (ceftolozan-tazobactam, imipenem-cilastatin-relebactam, cefiderocol, meropenem-vaborbactam and fosfomycin) were selected for a period of two years for the annual revenue guarantee according to the following requirements.

Requirements of the selected companies

Stock: The supplier must ensure that the stock of the current product per quarter corresponds to double the amount of previous quarter's sales stored in a warehouse located in Sweden. The inventory must also correspond to at least two weeks' worth of treatment at each emergency hospital in Sweden. The supplier has three months from the start of the contract to build up the stock volume, unless otherwise agreed. Compensation for availability will be paid only when the supplier can demonstrate that the stock meets the said volumes.

Delivery: Regions and hospitals shall order the product according to regular routines. To ensure availability, distribution of the agreed product must take place no later than the next day from order (weekdays) if the order is made no later than 4 p.m. by the hospitals.

Reports: The supplier must submit documentation once the warehouse is established; distribution channels are in place and the supplier is ready to fulfil its obligations in accordance with the agreement. The supplier must also provide quarterly reports, including sales and deliveries of the antibiotic product with a specification of the time for receiving the orders and delivery time.

Funding model

The PHAS set a minimum 'guaranteed annual revenue' for each selected antibacterial, based on the cost of a 'security stock' (an estimated safe reserve amount) at 50% above the average European list price. If the guaranteed annual revenue is exceeded through unexpectedly large volumes of sales, the relevant companies would be paid a bonus equal to the price of buying 10% of the 'security stock' amount, to keep the PHAS model attractive to companies as an alternative to normal volume-based sales.

For older medicines without market protections, where there is a danger of shortages due to low revenue causing manufacturers to exit the Swedish market, manufacturers can apply to the reimbursement authority (TLV) for permission to increase prices. PHAS has developed an algorithm for assessing which antibacterials are of 'special medical value', based on local resistance patterns, and has recommended that TLV takes this assessment into consideration when it comes to granting price increases.

Impact and implications

The procurement volumes will likely not be large enough in the PHAS model to represent a substantial incentive for antibacterial R&D, which was not the intention of the pilot project. In the PHAS pilot study, medicines are reimbursed at prices 50% above the European average list price. If the antibacterials would have been marketed in Sweden regardless, the PHAS model will have resulted in higher per-unit expenditure than the status quo[363].

This pilot's primary aim to ensure access is explicitly not an innovation incentive, meaning it is not attempting to provide a return on investment for the R&D costs of new antibacterials. It guarantees annual revenues of approximately USD 475,000 per drug to enhance patient access in Sweden. The program's design is elegant in its simplicity and could be scaled up to also provide an innovation incentive proportional to Sweden's economic stature, or indeed any other country so inclined[234].

Planned evaluation

The pilot will determine whether the model is efficient and effective enough to be considered to be implemented permanently in Sweden. Meanwhile, the PHAS intends to conduct follow-up research continuously during the pilot period in order to obtain relevant timely information for continuous improvement of the model, such as:

"**availability before and after the implementation of new compensation model**" to investigate whether the pilot model has improved the availability in Swedish healthcare for the antibiotic included in the pilot study and whether it has affected sales of similar drugs;

"**economic impact of the pilot model**" to describe the costs of the financing model and the possible impact on sales of alternative competing products, from different perspectives; and

"**the procurement process**" to evaluate the procurement procedure in terms of, inter alia, the definition of which antibiotics are to be procured, the advantages and disadvantages of the selected procurement model compared to alternative models, and the experience gained from the pilot project regarding collaboration between different authorities.

The evaluation report, including a cost-benefit analysis, is expected to be available by the end of December 2022.

Current evaluative insights

The preliminary interviews conducted with the industry were presented by Jenny Hellman from the PHAS during the Scientific Symposium (Research and innovation to reduce the burden of antibiotic resistance: strengthening the European action) organised by the INSERM on 7th June 2022. Specifically, the primary findings indicate a:

- generally positive picture of the pilot model as a first step in the right direction
    - predictable volumes for completely new products, which facilitates planning and decision making.
    - could be used for other antibiotics, both old and new
    - scaled up by other countries
- challenges were predominantly related to:
    - the level of the guaranteed income
    - the requirements on the stock affecting access in other countries and waste large quantities of products
    - products with a higher level of use may receive less extra money than products with a low level of use

[234] Outterson, K.; Orubu, E. S. F.; Rex, J.; Årdal, C.; Zaman, M. H. Patient Access in 14 High-Income Countries to New Antibacterials Approved by the US Food and Drug Administration, European Medicines Agency, Japanese Pharmaceuticals and Medical Devices Agency, or Health Canada, 2010–2020. Clinical Infectious Diseases 2022, 74 (7), 1183–1190. https://doi.org/10.1093/cid/ciab612.

- preference of industry to have longer contract time

The UK Antibiotic Subscription Pilot

Primary goals

This pilot model is the first that switches from procurement of antibacterials by volume to procurement of antibacterials as a service or 'subscription'. The pilot aims to incentivise pharmaceutical manufacturers to develop novel antibiotic classes and products. The mechanism is planned to select two products targeting serious bloodstream infections, sepsis, or hospital-acquired pneumonia for the initial trial. The selected candidates passed through an antimicrobial-adapted NICE HTA designed to recognise the full value of antimicrobials. The assessment results produced by this new and innovative value based HTA model will form the basis for commercial discussions to achieve payments to companies by a fixed annual fee. It will employ a subscription-based approach where the contract value is fully delinked from the volumes sold, to meet England's demand over a period of at least three years, with the possibility of a further 10-year extension.

The project milestones are indicated below. Based on information publicly available at the time of writing this report, the pilot is at stage five, with payments expected to start imminently (2022−2025).

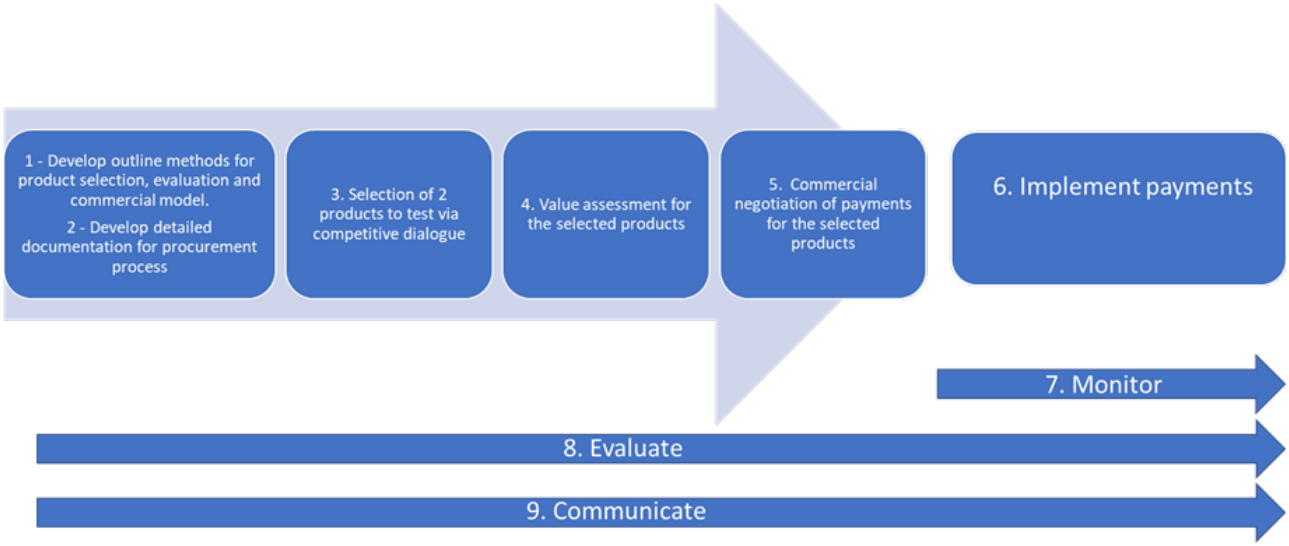

Figure **29***:* **Milestones of the UK pilot**

Eligibility criteria[235]

The eligibility criteria have been designed specifically for the purchase of new antimicrobials. The societal value of the selected medicines has been assessed using the new HTA allowing for the assessment of clinical value to the patient as well as population-level values based on STEDI principles (Spectrum, Transmission, Enablement, Diversity, Insurance).

The pool of candidate products was made up of submissions by originator pharmaceutical companies in which any company was free to submit a candidate. Based on the eligibility criteria set, these candidates must either:

- be an existing antimicrobial that achieved marketing authorisation in the last 1.5−3 years; or

be a new-to-market antimicrobial (at a late-stage of development expected to be approved by the end of 2020 and with plans to launch in the UK).

Any company considered for the model must have demonstrated a commitment to relevant environmental standards, and performance on the AMR Benchmark, an index published by the Access To Medicine Foundation[236]. The candidate drugs selected will only be used to treat patients with severe drug-resistant infections who would otherwise have limited or no other treatment options.

Selected beneficiaries

The two products chosen competitively via the procurement process, that complies with the Public Contracts Regulation (PCR15), to receive subscriptions are indicated QALY based value:

- Cefiderocol, Shionogi (FDA approval: September 2020): 970 QALYs/year x 10 years[237]
- Ceftazidime/avibactam, Pfizer (FDA approval: February 2018): 530 QALYs/year x 10 years[238]

Funding model

The actual award of the model is capped annually at GBP 10 million (based on GBP 20,000 and GBP 30,000 per QALY, as a threshold is used by the NICE) over 10 years (GBP 100 million / ~USD 128 million in total) to each pharmaceutical manufacturer. The exact amount of payment for each antibacterial will be based on the NICE's assessment to be followed by commercial negotiations with the proprietors of the two selected products in order to agree on payments, which will be an annual fixed fee of up to GBP 10 million per product[239,240]. Initial contracts will be for 3 years, with an option to extend to 10 years.

In April 2022, NICE announced the draft guidance for the first two pilot drugs. Estimating the full value of new antimicrobials, and therefore what the annual fee should be, is complex since it requires a different economic modelling approach. NICE's current evaluation methodology focuses on the health benefits for people that receive the drug, along with their carers. NICE is the first HTA organisation in the world that is attempting to estimate the full value of an antimicrobial by taking public-health benefits into consideration. The NICE draft guidance on cefiderocol and ceftazidime–avibactam provides an estimate of their benefits to the health of the overall population in England, measured in QALYs.

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[236] Access to Medicine Foundation (2021) AMR Benchmark [online] Available athttps://accesstomedicinefoundation.org/amr-benchmark#:~:text=The%20AMR%20Benchmark%3A%20tracking%20pharma's,responsible%20manufacturing%2C%20access%20and%20stewardship [accessed: 25th October 2022]

[237] *Cefiderocol for treating severe drug-resistant Gram-negative bacterial infections*. NICE National Institute for Health and Care Excellence. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol (accessed 2022-06-15).

[238] *Ceftazidime with avibactam for treating severe drug-resistant Gram-negative bacterial infections*. NICE National Institute for Health and Care Excellence. https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam (accessed 2022-06-14).

[239] Mahase, E. UK Launches Subscription Style Model for Antibiotics to Encourage New Development. BMJ 2020, m2468. https://doi.org/10.1136/bmj.m2468.

[240] Mullard, A. UK Outlines Its Antibiotic Pull Incentive Plan. Nat Rev Drug Discov 2020, 19 (5), 298–298. https://doi.org/10.1038/d41573-020-00070-8.

NICE will issue final guidance once the commercial discussions between NHS England, NHS Improvement, and the drug manufacturers have concluded. NICE and its partners will work with stakeholders to review the approach taken in this project and develop routine arrangements for the evaluation and purchase of antimicrobials for the NHS[241].

Impact and implications

The model is expected to yield valuable lessons both for the future approaches to tackle AMR and for the broader policy debates on incentives in pharmaceutical R&D. The use of an innovative and tailored HTA methodology specific to the context of the antimicrobials, with the aim of ensuring cost-effectiveness from a societal perspective, is considered an advantage over many other mechanisms. In the long term, and if converted into a permanent or semi-permanent mechanism, the model could provide a novel type of market incentive for drug developers.

It is highly important, and also challenging, to ensure that only new antibacterials with true added clinical value are procured through this model, to avoid incentivising the development of drugs that offer marginal or no benefits over existing therapies. Its success is also contingent upon a sufficient pool of new products that relies on buy-in from pharmaceutical companies.

Evaluation

The pilot just entered a three-year (2022-2025) payment implementation phase that may be extended up to 10 years. Over this period, monitoring and evaluation will be conducted and communicated accordingly.

Based on the interviews conducted under the Global AMR R&D Hub's study[371,326], the following stakeholder perceptions were reported:

- it is unclear how value to society will be addressed via HTA.
- perceived low risk for government due to the late stages considered (i.e. close to approval/approved recently as criteria for candidate selection)
- full delinkage − use can be guided by clinical need alone
- capped value at the upper range of a 'fair share' for England – as measured by global pharma sales or GDP among the G20
- insufficient recognition of the true value of antibiotics (industry representatives)
- likely result in greater overall costs than 'normal' procurement based on the negotiated unit price

The US Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act

The PASTEUR Act[242,243] aims to establish a new federal funding stream for new antimicrobials, which would apply to federal payers in the USA (e.g. Medicare, Medicaid) in order to increase public-health preparedness by keeping novel antibiotics on the market

[241] Gotham, D.; Moja, L.; van der Heijden, M.; Paulin, S.; Smith, I.; Beyer, P. Reimbursement Models to Tackle Market Failures for Antimicrobials: Approaches Taken in France, Germany, Sweden, the United Kingdom, and the United States. Health Policy 2021, 125 (3), 296–306. https://doi.org/10.1016/j.healthpol.2020.11.015.

[242] Dynamic Dashboard - Incentives for antibacterial R&D. Global AMR R&D Hub Dashboard. https://dashboard.globalamrhub.org/reports/incentives/incentives (accessed 2022-06-15).

[243] Bennet, M.; Young, T.; Doyle, M.; Ferguson, D. The Pioneering Antimicrobial Subscriptions to End Up Surging Resistance (PASTEUR) Act of 2021.

and improving appropriate use across the healthcare system. This policy would establish a subscription model to pay for critically needed novel antimicrobial drugs. The United States Department of Health and Human Services (HHS) would provide companies with a federal payment delinked from the sales or use of those newly developed antibiotics. This payment will ensure a predictable return on investment and improve the appropriate use of the drug. The policy contains investment in programmes to address antimicrobial resistance, which is critical for patient care and public health.

To date, the USA has passed the following three pieces of legislation that collectively aim to improve developer returns for products used within the Medicare & Medicaid systems:

- New Technology Add-on Payment (NTAP) in 2001
- Generating Antibiotics Now (GAIN) Act in 2012
- The Inpatient Prospective Payment System (IPPS) Rule in October 2019 − recognising the overall cost of managing drug-resistant infections.

The PASTEUR Act would establish a 'Committee on Critical Need Antimicrobials' to grant subscription contracts to pharmaceutical companies that have developed a new antimicrobial meeting the specific conditions outlined. The Committee would solicit applications and develop more detailed criteria for assessing the eligibility for a contract. Subscription contracts would then be granted to successful applicants, ranging in value from USD 750 million to USD 3 billion paid over a period of 5−10 years or until patent expiry.

The exact methods for deciding the value of contracts within this range would be determined by the Committee. The PASTEUR Act would provide a budget of USD 11 billion over 10 years for implementation of the model to issue between 3 and 14 contracts. These contracts would include requirements regarding availability, resistance surveillance and ensuring appropriate use. Any revenue from sales of the antimicrobial to federal insurance programmes (e.g., Medicare) would be subtracted from the value of the contract. In other words, the value of the contract would provide minimum guaranteed revenue. The PASTEUR Act does not specify an unlimited supply of the antimicrobial, but a set amount. This is a key difference between this model and the UK model or other 'subscription' models that have been used for Hepatitis C medicines, where an annual fee is paid in exchange for an unlimited volume of the product.

Full details on the PASTEUR model are not yet available, as key elements would be left for the Committee established by the Act to design, such as eligibility criteria and methods for determining contract value. The value of contracts foreseen in the PASTEUR Act are substantial and would represent a significant incentive to antimicrobial developers as it would guarantee minimum sales/revenue. Under the PASTEUR Act, individual hospitals may still pay the full price for the treatment, even if this is 'recouped' at federal level, meaning hospitals would still be discouraged from overuse.

The ability of the model to effectively incentivise true therapeutic advances in a cost-effective manner will largely depend on the methodology developed by the Committee. Additionally, the PASTEUR model does not offer a mechanism for ensuring affordable pricing for patients under private insurance.

Annex 5 - Detailed analysis of the effects of pull incentives

Introduction to the simulation

Selecting relevant pull interventions requires a comparison of their effects on the profitability of R&D projects for new antibiotics, in terms of improvements from the baseline scenario. To assess how various pull interventions impact this profitability (expressed as expected net present value – ENPV), we use a **Monte Carlo simulation method**, which is a standard approach in this field[244]. This method uses recurring random sampling to account for considerable uncertainty in the inputs that characterise R&D projects, e.g. costs and revenue that can vary from project to project and from one year to another. As a result, this simulation allows a large number of "simulated R&D projects" to be investigated, with costs and revenue presenting different probability distributions with values based on data about real antibiotic R&D projects.

In summary, we can analyse the effects of each intervention on a very large number of alternatives, all grounded on reality-based scenarios. To do so, we take the input parameters (e.g., costs, probability of success) of real antibiotic projects published in previous reports and scientific publications, as well as proprietary data from this project's survey conducted with companies. All this input data is then recombined using Monte Carlo sampling methods to create thousands of simulated projects that possess combinations of reality-based inputs falling between predefined intervals.

This very large sample of projects constitutes the baseline scenario of this report, i.e. a situation where there is no pull intervention and only the current push incentives in the form of grants. For each of the projects in this sample, the simulator calculates the expected net present value based on key parameters such as the development costs, future revenue, risks of failure (i.e. probability of success) as well as costs of capital (discount rate). The distribution of values of these factors is based on the ranges of real data shown in the full body of the report. Combining values from these ranges makes the simulated projects differ in a random manner and, after calculating the ENPV of each project, one obtains a full distribution of ENPVs. The simulator computes ENPV as follows:

$$\mathrm{ENPV}_{r}^{N} = \sum_{n \in N} \frac{C_n \, P_0}{(1+r)^{T_n} \, P_n}$$

Figure 30: Computation formula for ENPV

Where:

N represents all R&D steps and all years during which an antibiotic creates revenue in the market,

r represents the discounting rate of the owner who is running a particular antibiotic project,

$\mathbf{C_n}$ represents the cashflow (revenue minus costs) of step **n**

[244] Previous studies that have used this method include the DRIVE-AB report (2018), which applies agent-based and Monte Carlo simulation of Market Entry Rewards and grants to study optimal size and impact of these interventions; a report for the Public Health Agency of Sweden (2019) which simulates and compares several push, pull and coordination-based incentives with Monte Carlo methods; and the article published in the Journal of Business Research by Ciabuschi et al. (2020) "Supporting innovation against the threat of antibiotic resistance: exploring the impact of public incentives on firm performance and entrepreneurial orientation", which also relies on Monte Carlo simulations of push and pull interventions and identifies different impacts for small as opposed to large firms.

P_0 is the probability of the project surviving all the way to market launch, as calculated from the point at which ENPV is computed

P_n is the probability of surviving all the way to market launch from the entrance into stage n.

The ENPV of antibiotics projects is appraised at multiple decision points, specifically before entering a new stage of development. Based on common praxis in the pharmaceutical industry, we assume that project owners decide whether to continue or terminate their projects on the basis of the ENPV. Specifically, the assessment of the ENPV is conducted at six different decision points in time (**before starting the corresponding R&D stage**):

- Preclinical
- Phase I Clinical Trials (Phase1)
- Phase II Clinical Trials (Phase2)
- Phase III Clinical Trials (Phase3)
- Submission (to regulatory agencies for approval)
- Market Launch

The various R&D steps vary according to how long they are (duration), how expensive they are (costs), and how likely it is that the projects are able to complete the particular development step (probability of success).

Next to the baseline scenario with a large sample of projects (100,000), we performed **additional simulations to assess the impact (i.e. potential improvements) of each intervention on projects' ENPVs**. The various distributions of ENPVs (100,000 projects simulated for each intervention) differ clearly from each other depending on the types and sizes of interventions and can accordingly be compared in terms of percentage of financially profitable antibiotics and the number of consecutive decisions to continue development (from preclinical to market).

The data inputs to the simulation

The calculation of the ENPV for the simulated projects uses data for each of the following phases: Preclinical, phase I Clinical Trials (Phase1), phase II Clinical Trials (Phase2), phase III Clinical Trials (Phase3), Submission, and Market Launch. This data has been collected as follows:

Probability of Success (PoS). This indicates the probability that a project succeeds scientifically to the next phase; its value is between zero and one. The specific minimum and maximum values in our sample of projects are derived from previous studies (see box below)

Cost for performing the phase, measured in USD. Costs are also compiled in ranges: the minimum is taken from a survey sent by PwC to antibiotic developers during 2022, and the maximum taken from previous studies.

Duration of the phase, measured in months, using ranges taken from previous studies.

The discount rate applied in the ENPV for single projects varies from a minimum of 8% to a maximum of 30%. This data was obtained from experts and panels composed of representatives from academia, health authorities, and large and small pharmaceutical companies between 2016 and 2018 (in collaboration with the DRIVE-AB project consortium – see the DRIVE-AB report, 2018).

After market launch phase, the data consists of the sales revenue spread over a 10-year period. This input is also expressed in ranges of US dollars taken from a report by the Global AMR R&D Hub but is increased by 50% per year to account for additional indications of a drug, since said report considered a single-indication drug. Moreover, yearly revenues are reduced by post approval costs in the first 6 years after launch according to input data provided by a GARDP webinar.

The ranges used in the modelling for R&D costs, duration and discount rates include also data provided by R&D companies under the condition of not being associated with the individual company. Hence descriptive data statistics are provided to the largest extent possible, bearing in mind that these data exclude individual firms' information. An overview of the data input to our simulation is provided in Table 12: Summary of data inputs to the simulation. It shows, for each R&D phase, the duration, PoS, costs as well as the percentage of cost reduction thanks to the grants already present in the antibiotic field. These grants represent push incentives, which accordingly reduce costs for firms, and since they already exist, are also included in the baseline scenario shown in The profitability challenge.

Minimum and maximum data values to build the ranges in the simulation are derived from the following sources:

-Stephens PIH. (2015). Stimulating Antibiotic R&D London: Review on AMR. https://amr-review.org/sites/default/files/IMS%20HEALTH.pdf.

-Czaplewski, L., Bax, R., Clokie, M., Dawson, M., Fairhead, H., Fischetti, V. A., ... & Rex, J. H. (2016). Alternatives to antibiotics—a pipeline portfolio review. *The Lancet infectious diseases*, *16*(2), 239-251.

-Outterson, K. (2021). Estimating The Appropriate Size of Global Pull Incentives for Antibacterial Medicines: Study examines global antibacterial pull incentives. *Health Affairs*, *40*(11), 1758-1765.

-Sertkaya, A., Eyraud, J. T., Birkenbach, A., Franz, C., Ackerley, N., Overton, V., & Outterson, K. (2014). Analytical framework for examining the value of antibacterial products. https://aspe.hhs.gov/system/files/pdf/76891/rpt_antibacterials.pdf

-Ardal C, Findlay D, Savic M, Carmeli Y, Gyssens I, Laxminarayan R, et al. (2018) DRIVE-AB Report: Revitalizing the antibiotic pipeline: stimulating innovation while driving sustainable use and global access. http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf

-The Review on Antimicrobial Resistance (AMR Review), *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, (2016). https://amr-review.org/

-WHO. A financial model for an impact investment fund for the development of antibacterial treatments and diagnostics Geneva, Switzerland: World Health Organization; (2020) https://www.who.int/publications/i/item/a-financial-model-for-an-impact-investment-fund-for-the-development-of-antibacterial-treatments-and-diagnostics-a-user-guide

-Stern S, Chorzelski S, Franken L, Voller S, Rentmeister H, Grosch B. (2017) "follow-up report for the German GUARD INITIATIVE. Breaking through the wall: A call for concerted action on antibiotics research and development Berlin: German Federal Ministry of Health & Boston Consulting Group https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf

-FoHM - Baraldi, E., Ciabuschi, F., Callegari, S. Lindahl, O. (2019) Report for the Swedish Health Agency, *Economic incentives for the development of new antibiotics: Report commissioned by the Public Health Agency of Sweden.* DIVA Uppsala University

Next to the revenue from market sales (first column), from which post-approval costs are detracted (second column), this table also shows the revenue paid to a project by each intervention, which also includes the revenue of milestone-based rewards paid at the start of phase I and at the start of phase II. A total of 1.8 million projects have been simulated for this Monte Carlo simulation, i.e. 100,000 projects for 18 scenarios: one scenario for each of the 17 tested interventions (four sizes for interventions 1 and 2, six sizes for interventions 3, and three sizes for intervention 4) and a baseline scenario.

Table 46 Data inputs to the simulation for market revenue and revenue from interventions (all data in USD million)

	Revenues (baseline)	Post Approval Costs	RG 70	RG 100	RG 150	RG 310	MERino 700	MERino 1000	MERino 1500	MERino 3100	LS-MER 1000	LS-MER 2000	LS-MER 4000	P1 award 30	P1 award 40	P1 award 60	P2 award 60	P2 award 80	P2 award 120
Market Year 1	0–7.5	-5	70	100	150	310	250	330	500	1000	1000	2000	4000	0–7.5	0–7.5	0–7.5	0–7.5	0-7.5	0-7.5
Market Year 2	0–37.5	-10	70	100	150	310	250	330	500	1000	0	0	0	0–37.5	0–37.5	0–37.5	0–37.5	0–37.5	0–37.5
Market Year 3	0–75	-20	70	100	150	310	50	85	125	275	0	0	0	0–75	0–75	0–75	0–75	0–75	0–75
Market Year 4	1–120	-40	70	100	150	310	50	85	125	275	0	0	0	1–120	1–120	1–120	1–120	1–120	1–120
Market Year 5	2–150	-80	70	100	150	310	50	85	125	275	0	0	0	2–150	2–150	2–150	2–150	2–150	2–150
Market Year 6	4–180	-65	70–115	100–115	150	310	50	85	125	275	0	0	0	4–180	4–180	4–180	4–180	4–180	4–180
Market Year 7	8–210	0	70–210	100–210	150-210	310	8–210	8–210	8–210	8–210	0	0	0	8–210	8–210	8–210	8–210	8–210	8–210
Market Year 8	16–240	0	70–240	100–240	150-240	310	16–240	16–240	16–240	16–240	0	0	0	16–240	16–240	16–240	16–240	16–240	16–240
Market Year 9	32–270	0	70–270	100–270	150-270	310	32–270	32–270	32–270	32–270	0	0	0	32–270	32–270	32–270	32–270	32–270	32–270
Market Year 10	64–270	0	70–270	100–270	150-270	310	64–270	64–270	64–270	64–270	0	0	0	64–270	64–270	64–270	64–270	64-270	64-270
Phase 2 Year 1	0	0	0	0	0	0	0	0	0	0	0	0	0	30	40	60	0	0	
Phase 3 Year 1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	60	80	120

Considerations for the interpretation of results

Some general considerations should be kept in mind in interpretation of the results of the simulation:

- the figures and graphs will show the effect on projects' ENPV of each single intervention, compared to the baseline (without any pull incentive, but with current push/grants) and with each other.
- the effects on a projects' ENPV is calculated at the start of the six aforementioned decision points, meaning that the various figures and graphs included here will show the impact of each intervention at individual R&D stages. This makes it possible to see how far back in the R&D pipeline the impact of each intervention can reach (e.g. as early as the preclinical stage).
- the aggregate results will show that there are major challenges in project profitability for the earliest R&D phase (preclinical), for which sizeable pull interventions are needed to be effective, i.e. to get ENPVs sufficiently close to zero; instead, projects in later R&D phases can be effectively incentivised to reach profitability with smaller pull incentives. Therefore, it is important to avoid over-incentivising projects in later stages with excessively large pull interventions.
- the public expenditure entailed by the various pull interventions concerns one antibiotic approved for market sales. Special considerations are needed to assess the total public expenditure if the goal is to reward several antibiotics upon market approval based on, for example, eligibility criteria, the number of antibiotics fulfilling them as well as the possibility of either splitting payments over multiple recipients or depending on the sequence of approvals and each antibiotic's therapeutic features.

Results at a glance: all 17 interventions and their impacts in all R&D stages

The figures below show the profitability of antibiotic projects (ENPV) associated with the baseline scenario (Y axis) and the 17 tested interventions (X axis). The six graphs in the figure below indicate this profitability at six key decision points, from preclinical through to regulatory submission. The level of profitability, measured by the ENPV, is displayed as boxplots showing the variety of projects' profitability, with +/- 25% intervals around averages (medians). The level zero of ENPV, a minimal requirement for profitability and for deciding to continue a project, is marked with a red dotted line to allow tracing whether an intervention contributes to bringing a certain percentage of antibiotics over this minimal profitability benchmark. Average lines (see the bold black lines in the middle of each boxplot) intersecting or placed above the red line indicate that at least 50% of projects associated with a specific intervention are profitable and will receive a decision to continue to the next R&D stage.

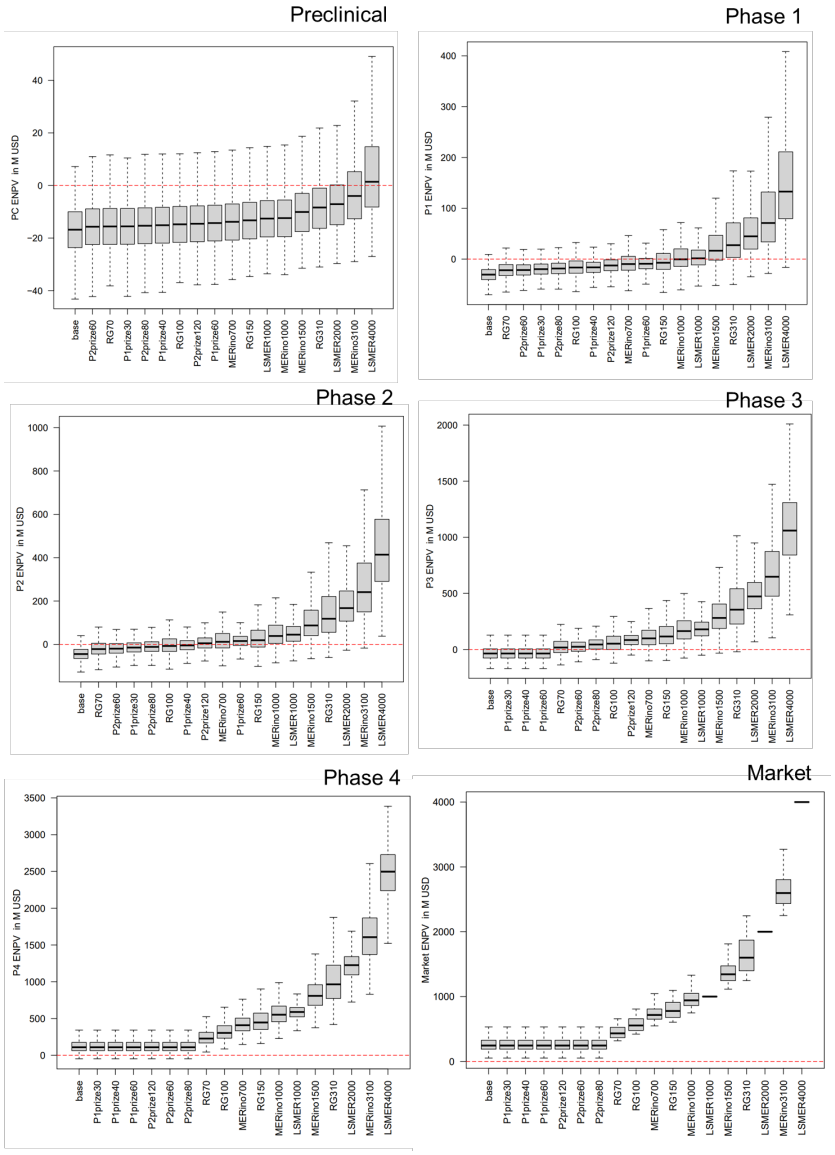

Figure 31: ENPV at six decision points, baseline and with 17 interventions – Preclinical to Market

The figure shows that at the preclinical and the phase I decision points, almost no interventions can bring the majority of projects to profitability at early decision points (the 50% solid lines in most boxplots remain under the red line). In fact, only large pull incentives can bring the ENPV into positive territory, especially at the preclinical stage.

After phase II, no large pull interventions are needed to improve profitability of antibiotic projects: the smallest MERino700 succeeds in pulling more than 50% of all projects into profitability (see the solid average lines above the red line) and a relatively small 10-year revenue guarantee (RG100) can do the same for almost 50% of the projects. The situation improves even more at the phase III decision point, where even the smallest 10-year revenue guarantee (RG70) makes more than 50% of antibiotic projects profitable.

A key problem is that, in the current "as-is" baseline scenario, the ENPV from preclinical to phase II decreases, reaching a minimum at phase II. This means that some of those very few projects that are started at preclinical and complete that stage will likely be terminated due to worsening profitability in subsequent clinical development, thereby further reducing an already very small number of projects in the pipeline.

We can conclude our overview of the impacts of interventions in the six R&D stages by stressing that:

- reaching profitability for around half of projects in early stages, especially preclinical, would need very large pull interventions of over USD 3.1 billion globally (i.e. the high-level MERino);
- projects in phase II need public global expenditure of between USD 700 million (low size MERino) and USD 1 billion (an annual revenue guarantee of USD 100 million for 10 years – intermediate revenue guarantee size); and
- projects in phase III need no more than USD 700 million (low-size annual revenue guarantee), which corresponds to the global equivalent of the Swedish pilot model for access.

Since there seems to be such a large difference between the size of pull interventions, which can be sufficient at later stages (phases II and III), as opposed to those needed in the earlier stages – phase I and especially preclinical – we can now delve into the situation at these two specific decision points. We are particularly interested in understanding if and how smaller interventions can become relevant for preclinical projects.

The impacts of 17 interventions in preclinical and phase I

Preclinical stage decision point

The figure below focuses on the preclinical decision point. Only the largest pull interventions can bring antibiotics to profitability by substantially improving ENPVs compared to the baseline; this is achieved by the largest intervention (LSMER4000). The incentivising impact of this award makes at least 50% of antibiotic projects profitable at the preclinical decision point. The improvement impact of LSMER4000 is closely followed by the MERino3100, which makes approximately 30% of projects in the preclinical stage profitable, and then by LSMER2000, which makes about 25% of projects profitable.

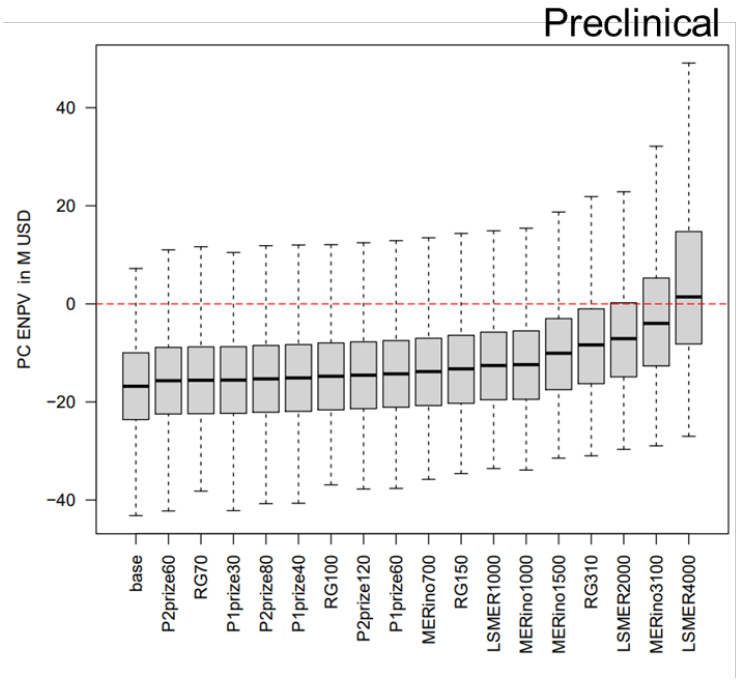

Figure 32: ENPV at the start of the preclinical stage (baseline and 17 interventions)

It is interesting to note that the RG310, corresponding to a 10-year revenue guarantee of USD 310 million/year, is able to make only approximately 25% of projects profitable at the preclinical decision point. This situation indicates a major challenge in "rescuing" the preclinical pipeline through pull incentives, as even the largest pull interventions have limited effectiveness.

Finally, the baseline situation clearly shows that the profitability of projects at preclinical development in the current "as is" scenario is very limited. Moreover, based upon the probability of success in our data inputs, up to 99% of these preclinical projects will fail due to scientific or technical reasons before reaching approval. This situation further motivates the need to find solutions that can complement market approval-based pull interventions: since existing grants together with very large pull mechanisms (e.g. RG310), are not enough to substantially improve the profitability of preclinical projects, we will consider the possibility of combining various types of interventions, especially with earlier pull mechanisms such as milestone-based rewards.

Phase I decision point

The figure below indicates that much smaller pull incentives can be effective at this stage. Even the smallest MERino (MERino700) makes slightly more than 25% of projects profitable (see the intercepts of the red line with the 25% limit in the boxplot), and the relatively small revenue guarantee (RG100) is near to pulling 25% of projects into a positive ENPV.

MERino1000 and LSMER1000 have about the same impact on profitability at the start of phase I, as they both pull at least 50% of projects into profitability. However, as we will see later, MERino1000 has a lower public spending profile and entails a lower risk than LSMER1000 for public actors of paying a large lump-sum for an antibiotic which may lose therapeutic efficacy. As a result, based on this criterion of risk as well as public expenditure, MERino1000 is clearly a better option than LSMER1000, as it brings about the same pull effect with lower risks and costs for public actors.

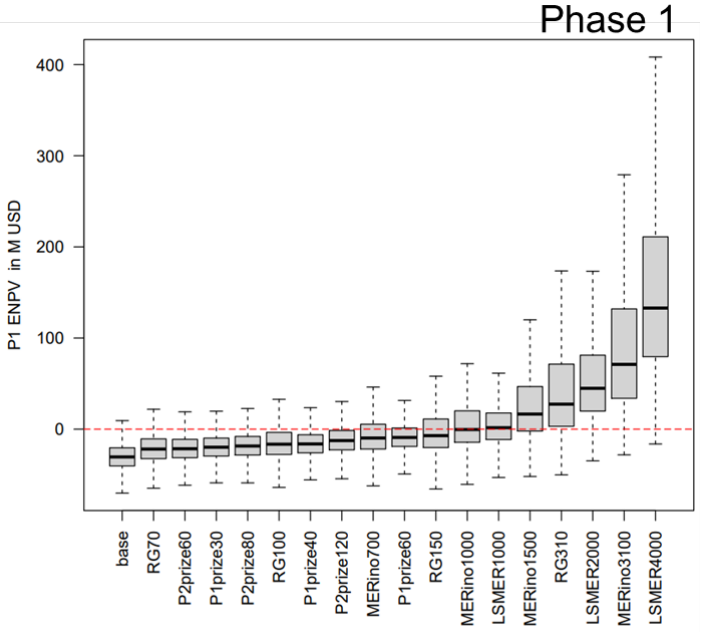

Figure 33: ENPV at the start of phase I (baseline and 17 interventions)

Finally, Figure 33 shows that milestone-based reward of USD 60 million can make 25% of projects profitable at the start of phase I. However, it is important to stress that while this milestone-based reward has a clear pull effect in financial terms, the incentivised projects may be terminated due to scientific and technical reasons in the subsequent stages. Therefore, to be sure that at least one of the antibiotics receiving milestone-based reward will reach the market, several antibiotics will need to be awarded to offset the attrition rate[245].

The potential to combine smaller interventions

Our analysis has so far established that antibiotic projects suffer from a very serious lack of profitability at the preclinical stage decision point. Moreover, only the following very large-sized pull interventions can pull them to market launch. However, there are other interventions that may improve projects' ENPV at the earliest development stages. These interventions are not the classical push mechanism of current grants, which are already included in the baseline scenario. Even if we have not tested any combinations of interventions in this simulation, there are good reasons to assume that the combination[246] of non-profit developers, pipeline coordinators and milestone-based rewards can help overcome part of the profitability issues faced by projects in preclinical development. This assumption is based on the following reasons:

Pipeline coordinators[247] such as the former ENABLE, and CARB-X can improve the quality of projects in preclinical development if they move from simply providing grants to actively engaging in the provision of technical support and guidance. In this way, active pipeline

[245] In particular, based on the PoS input data of our simulation, three antibiotics will need to receive a Phase 1 completion reward and two antibiotics will need to receive a Phase 2 completion reward, due to the attrition rates from these two phases to regulatory approval.

[246] Baraldi E., Ciabuschi F. *et al.* (2019) "Economic incentives for the development of new antibiotics" **Report Commissioned for the Public Health Agency of Sweden** [online] Available at: https://www.diva-portal.org/smash/get/diva2:1283298/FULLTEXT01.pdf [Accessed 26th October 2022]

[247] Baraldi, E., Lindahl, O., Savic, M., Findlay, D., & Årdal, C., 2018, Antibiotic Pipeline Coordinators, *Journal of Law, Medicine and Ethics*, Vol. 46 S1, pp. 25-31.

coordinators can increase the probability of success (PoS), one of the key ENPV parameters, which when very low, adversely affects project profitability at this early stage. Moreover, as confirmed by managers of pipeline coordinators that are very active in steering antibiotic projects under their responsibility, they can also reduce the duration of a particularly long R&D stage like preclinical (indeed the longest of all, between 54 and 72 months according to our input parameters) and reducing the duration of an antibiotic project can further improve ENPV.

Non-profit developers, i.e. organisations that develop antibiotics without the aim of achieving any profit (e.g. GARDP), can be empowered to control and manage a certain number of projects in the preclinical stage: such an arrangement would basically "insulate" these projects from profitability requirements and hence the application of the ENPV rule.

Finally, the combination of milestone-based rewards and smaller approval-based pull incentives adds an earlier revenue stream (e.g. upon completion of phase I) to the pull incentive's revenue awarded much later, i.e. upon market approval. This corresponds to a new scenario where the impact on the profitability of projects (ENPV) is expected to be higher than for the scenario with only the late-stage pull incentives (i.e. interventions 1, 2 or 4).

Public Health Agency of Sweden – 2019 report

A 2019 report[3] commissioned by the Public Health Agency of Sweden provides advice on which incentives for antibiotic R&D should be taken into consideration for potential national-level public investment. Late stage pull interventions such as Market Entry Rewards were not considered viable for Sweden acting alone due to the demanding financial engagement required, but they would be relevant only in cooperation with other countries (e.g. the EU27). The overall recommendations for Sweden included grants, **milestone-based rewards**, **pipeline coordinators** and **non-profit developers**, based upon a simulation that was used to determine not only the impact of these incentives on their own, but also the **impact of combining them**.

Pipeline coordinators were modelled according to two basic types, performing specific roles ("R&D Collaboration" and "Non-Profit Developer"). The difference is that the R&D Collaboration Pipeline Coordinator performs early R&D steps on behalf of molecule owners, whereas Non-Profit Developers directly own molecules and aim to bring them to market without an interest in making a profit. The specific recommendation was not for Sweden to establish its own pipeline coordinator, but to **combine its resources with other countries and within existing international structures that could be further developed at EU level.**

The simulation within the remit of this study showed that an **R&D Collaboration Pipeline Coordinator was the strongest and most effective of all simulated incentives:** investing around USD 18 million per project it manages in the preclinical stage and phase I (for costs such as multiple assay performance and continuous evaluations). This type of highly active pipeline coordinator would result in **10 times more profitable projects compared to the baseline** in that simulation, and **cost around USD 110 million per antibiotic approved**. The public expenditure to double the number of profitable R&D projects would be only around USD 12 million, making the R&D Collaboration Pipeline Coordinator the most efficient of all simulated interventions in thi study.

The 2019 study also investigated the **impact of combining different interventions**, including a combination of an R&D Collaboration Pipeline Coordinator with a MER, and of "R&D Collaboration" with milestone-based rewards – two combinations which are both relevant for the current report for DG HERA. Combining "R&D Collaboration" with milestone-based rewards (upon completion of phase I) yielded a 1.150% increase in profitable antibiotic projects compared to a 960% increase if we add together the separate impacts of these two interventions; combining "R&D Collaboration" with an MER (partially

delinked) resulted in a 3.600% increase in profitable projects, compared to only around a 1.800% increase if these two interventions are applied separately.

Combinations of the interventions in question seems to have stronger impacts on projects' profitability than if applied separately (i.e. than the sum of their separate impacts).

In conclusion, the 2019 report[3] issued by the Public Health Agency of Sweden indicates that combining the pull interventions with an R&D Collaboration Pipeline Coordinator is likely to increase their impact, possibly to the point of overcoming the limitations of late stage pull interventions in stimulating projects in the preclinical stage.

However, a separate study and simulation with the same input parameters as those applied in this report would be needed to fully confirm this statement.

As a simplified example to capture the combined impact of milestone-based rewards and smaller pull incentives on preclinical projects, we can look at the table below and consider the mean improvement of the ENPV given by each of the 17 interventions in the preclinical stage. By adding up the ENPV improvements of two interventions, we can obtain a rough estimate of their combined impact. This improvement is calculated as the difference between the mean ENPV of each intervention and the mean ENPV in the baseline.

Table 47: Heat-map showing the min./mean/max. impact of 17 interventions on the ENPV in four R&D phases

	Preclinical eNPV			Phase1 eNPV			Phase2 eNPV			Phase3 eNPV		
group	min	mean	max	min	mean	max	min	mean	max	min	mean	max
base	-47	-17	13	-90	-30	62	-139	-42	147	-170	-32	280
P2prize60	-42	-16	18	-74	-21	84	-108	-17	185	-110	28	340
RG70	-38	-16	16	-77	-21	90	-122	-17	187	-138	25	319
P1prize30	-42	-16	17	-75	-19	79	-109	-12	177	-170	-32	280
P2prize80	-41	-15	20	-70	-17	92	-97	-8	198	-90	48	360
P1prize40	-41	-15	19	-70	-15	85	-99	-2	187	-170	-32	280
RG100	-37	-15	24	-73	-14	121	-114	0	241	-122	63	403
P2prize120	-38	-15	24	-62	-11	107	-77	9	224	-50	88	400
P1prize60	-38	-14	21	-60	-8	97	-79	18	207	-170	-32	280
MERino700	-36	-14	32	-67	-6	144	-99	21	301	-101	112	519
RG150	-35	-13	40	-66	-2	180	-101	31	343	-99	134	571
LSMER1000	-34	-13	35	-56	5	162	-76	51	314	-52	185	530
MERino1000	-34	-12	47	-61	6	198	-85	51	395	-77	181	666
MERino1500	-31	-10	71	-52	26	291	-66	106	556	-33	305	932
RG310	-31	-7	102	-50	43	418	-60	149	753	-20	399	1243
LSMER2000	-30	-6	90	-35	55	369	-27	184	674	68	487	1114
MERino3100	-29	-1	149	-28	91	586	-17	276	1081	104	691	1795
LSMER4000	-27	6	199	-16	156	785	38	448	1476	308	1090	2323

The box below identifies the average ENPV improvements at the preclinical stage of selected interventions (see red rectangles), which can be added together in order reach the same ENPV improvement of RG310.

Comparing ENPV improvements of incentives at the preclinical stage – P1prize60, MERino700-1500 and RG310

Mean ENPV improvement of P1prize60 = USD +3 million (baseline mean is USD -17 million, improves to USD -14 million)

Mean ENPV improvement of MERino700 = USD +3 million (baseline mean is USD -17 million, improves to USD -14 million)

Mean ENPV improvement of MERino1000 = USD +4 million *(baseline mean is USD -17 million, improves to USD -12 million)*

Mean ENPV improvement of MERino1500 = USD +7 million*(baseline mean is USD -17 million, improves to USD -10 million)*

Mean ENPV improvement of RG310 = USD +10 million *(baseline mean is USD -17 million, improves to USD -7 million)*

As a simplified analysis to gain some insight into how a milestone-based reward can help reduce the necessary size of later-stage pull interventions, we can add together the mean ENPV improvement of P1prize60, which is the milestone-based reward giving the highest mean ENPV improvement (USD +3 million as calculated above), and the ENPV improvements of "smaller" pull incentives. We can then verify if this sum can reach a comparable ENPV improvement of "bigger" pull interventions. For instance:

the ENPV improvement from adding the impact of P1prize60 (USD 3 million) to that of MERino700 (USD 3 million) almost matches that of MERino1500 (USD 7 million); and more importantly;

adding together the impact of P1prize60 (USD 3 million) and MERino1500 (USD 7 million) gives exactly the same ENPV improvement as the RG310 (USD 10 million).

Comparing efficiency and public expenditures of the 17 interventions

The discussion so far has considered the effects on profitability of the various interventions in specific R&D stages, but it is also important to consider the effect of each intervention across all R&D stages, until antibiotics are pulled all the way to market approval. Achieving such a result means that a "go decision" has been made at all six key decision points (from preclinical to market launch).

The table below here shows that the 17 interventions perform very differently in reaching this result. The first column shows the rate of improvement of fully profitable antibiotic projects compared to the number of profitable projects in the baseline scenario. For instance, the most "powerful" intervention LSMER4000 makes profitable 453 times more projects than a situation without any pull incentive, whereas MERino1000 makes fully profitable until launch 60 times more projects than the baseline scenario. This column also shows that RG70 has a much smaller effect, as it makes profitable all the way to market only about 7 times more antibiotics.

Table 48: Improvement rates of financially profitable antibiotics and public expenditures for one approved antibiotic

Intervention	Improvement rate of financially profitable antibiotics	Expected expenditure per 1 launched antibiotic (USD million)	Expenditure per 100% improvement of financially profitable antibiotics (USD million)
LSMER4000	453.3	4000	8.8
MERino3100	315.0	2921	9.3
LSMER2000	215.9	2000	9.3
MERino1500	127.2	1321	10.5
RG310	185.3	2366	12.8
MERino1000	60.9	821	13.7
P1prize60	12.1	169	15.3
P2prize120	13.3	205	16.6
MERino700	29.6	521	18.2
RG150	43.1	784	18.6
LSMER1000	50.0	1000	20.4
P1prize40	6.4	113	20.9
P2prize80	6.7	137	24.0
P1prize30	4.4	85	24.6
RG100	15.9	421	28.3
P2prize60	4.5	102	29.0
RG70	6.7	241	42.6

Next to the impact in terms of improvement of fully financially profitable antibiotics, public expenditure associated with every intervention should be considered, which is shown in the second column. It is important to note here that some interventions display total public expenditure per approved antibiotic that is eventually lower than the amounts allocated as nominal size for every intervention. This depends on the fact that in both RGs and MERino, the yearly payments are “guaranteed revenue” also considering the levels of normal markets sales: in particular, every year that normal market sales are higher than the revenue guarantee, no public annual guaranteed payment will be made.

The table above also shows that there are very expensive but powerful interventions (e.g. MERino3100 has 315 times more profitable antibiotics, but costs USD 2.9 billion per launched antibiotic), and much less expensive but not so powerful ones (e.g. P1prize30 has 4.4 times more profitable antibiotics, but costs only USD 85 million per launched antibiotic). Between these two extremes, we have several interventions characterised by a substantial impact and moderate public expenditure: for instance, MERino1000 (about 60 more profitable antibiotics and costing USD 821 million per launched antibiotic), RG150 (43 times more profitable antibiotics and costing USD 784 million per launched antibiotic) or LSMER100 (50 times more profitable antibiotics and costing USD 1 billion per launched antibiotic).

Finally, we calculated a measure of efficiency expressed as the public expenditure needed for doubling the number of antibiotics that are fully financially profitable (corresponding to a 100% improvement), shown in the third column of the table. The most expensive interventions have the biggest impact, but this impact comes at a very high cost per launched antibiotic. Moreover, as previously mentioned, improving 200 or 300 times the number of profitable antibiotics may not be necessary. Therefore, we can propose a more “pragmatic” way of using the table for comparing and selecting pull interventions.

This pragmatic approach would start by defining an acceptable limit in terms of improvement rate of fully profitable antibiotics (first column) and then a maximum acceptable expenditure per launched antibiotic (second column). If for instance, one sets the minimum accepted improvement rate to 10 times and the cost limit to USD 1.5 billion, then the following interventions would be selected: RG100 and RG150, MERino 700, MERino1000, MERino1500, LSMER1000, P1prize60 and P2prize120. Within this short list, one may then apply the efficiency measure of the third column for final selection: here,

MERino1500 would be the top performer, i.e. the one resulting in the highest level of efficiency, with USD 10.5 million for doubling the rate of fully profitable antibiotics.

An important point in this analysis is that we have considered the cost for one launched antibiotic to define the public expenditure of each intervention. If several antibiotics were to be launched and awarded a pull incentive at market entry, the total public expenditure would increase. This cost will depend on several factors such as the number of antibiotics in the R&D pipeline, the eligibility criteria (the tougher the requirements in terms of societal/clinical value, innovativeness and resistance development, the fewer the awards), rules for adjudication (such as implementing the pull intervention as a “race” whereby only the first or the second antibiotics to market receive it), ranking criteria (implying partial adjudication whereby smaller payments are given to antibiotics reaching market later or to antibiotics with less attractive clinical features). However, it is advisable that any public agency involved in setting up a pull intervention awarded upon market approval decides the number of antibiotics that can be awarded by this incentive before announcing the intervention. This is the approach followed by the UK/NHS subscription model, which decided upfront that two innovative antibiotics would be selected.

Conclusions about the effects of the tested interventions

A general conclusion from our analysis is that it is pivotal to consider where in the R&D pipeline an intervention is expected to have an impact. Against this background, we have demonstrated that, if applied alone, very high pull incentives are needed to address the serious profitability problems in the preclinical stage. Indeed, no pull interventions alone can solve the problem of preclinical decision points, except for LSMERs (intervention 4) between USD 2 billion and USD 4 billion.

Therefore, it may be necessary to intervene in another way in the preclinical stage, such as supporting it with pipeline coordinators, which can improve the underlying quality of projects and improve their PoS and/or duration. Another option, which should also involve pipeline coordinators, is to combine milestone-based rewards with smaller late-stage pull interventions (annual revenue guarantees or MERino). However, the specific impact in terms of profitability improvement resulting from any combination of different interventions should be tested and simulated in a subsequent study.

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