Implementing an EU pull incentive for antimicrobial innovation and access: blueprint for action

Michael Anderson, Adrian Towse, Kevin Outterson, Elias Mossialos

In June, 2023, the Council of the EU published a recommendation that the European Commission should contribute to the design and governance of an EU cross-country pull incentive to stimulate antimicrobial innovation and access. In this Personal View, we discuss six key considerations to support the implementation of the new pull incentive—ie, the size of the potential pull incentive and possible contributions of the member states, design of the incentive model, interplay of the new pull incentive with the proposed revisions of the EU pharmaceutical legislation, roles and responsibilities of both the EU and member states, balance between pull and push incentives, and global cooperation and responsibility. As the involvement of the member states with the EU pull incentive will be voluntary, member states should have confidence that the processes used to identify eligible antimicrobials, negotiate terms and conditions, and oversee access agreements are transparent, inclusive, and methodologically robust.

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Health Organisation, Policy, Economics (HOPE), Centre for Primary Care & Health Services Research, The University of Manchester, Manchester, UK (M Anderson PhD); **LSE Health, Department of Health Policy, The London School of Economics and Political Science, London, UK** (M Anderson, Prof E Mossialos PhD, Prof A Towse MPhil); **Office of Health Economics, London, UK** (Prof A Towse); **School of Law, Boston University, Boston, MA, USA** (Prof K Outterson PhD); **Combating Antibiotic- Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), Boston, MA, USA** (Prof K Outterson); **Institute of Global Health Innovation, Imperial College London, London, UK** (Prof E Mossialos)

Correspondence to:
Dr Michael Anderson, Health Organisation, Policy, Economics (HOPE), Centre for Primary Care & Health Services Research, The University of Manchester, Manchester M13 9PL, UK
michael.anderson-3@manchester.ac.uk

Introduction

WHO has described the existing pipeline for research and development on antimicrobials as insufficient to tackle the challenge of rapid emergence and spread of antimicrobial resistance (AMR).[1] Research and development on antimicrobials remains challenging because of a complex mix of economic, scientific, and regulatory factors.[2] The high failure rate of antimicrobials under development makes investments in antimicrobial research and development financially risky and many antimicrobial candidates are abandoned because the developers cannot source investment. Even under the condition that an antimicrobial reaches the market successfully, many developers have subsequently experienced substantial financial losses or filed for bankruptcy,[3–6] because new antimicrobials have low sales volumes as they are often used as last-line options to treat infections. In addition, new antimicrobials are often sold for low prices owing to competition with pre-existing generics, as their regulatory approval is based on data from non-inferiority clinical trials.[7]

The prioritised action of the EU to incentivise research and development on antimicrobials in recent months is promising. In June, 2023, the Council of the EU published a recommendation on accelerating EU actions to combat AMR, including a commitment from the European Commission to contribute to the design and governance of a cross-country pull incentive for antimicrobials, to stimulate research and development on new antimicrobials and secure sustainable access to new and existing antimicrobials.[8] Several options have been proposed within the recommendations of the Council of the EU that can be used independently or in combination, including annual revenue guarantees, market entry rewards (MERs), and milestone payments. In March 2024, the European Parliament's Environment, Public Health and Food Safety Committee approved amendments to the EU pharmaceutical legislation that included the use of these potential options for pull incentives.[9] Concurrently, the European Commission's Health Emergency Preparedness and Response Authority (HERA) is also working on a pilot programme for an EU cross-country pull incentive to improve access to antibiotics.[10]

Among the benefits of developing an EU-level incentive rather than one at the member state-level are creation of an incentive of substantial size by combining the resources of many member states and ensuring consistent messaging to the industry. Crucially, the participation of EU member states in such initiatives would be entirely voluntary. Moreover, successful pull incentives presume the existence of effective push incentives through initiatives such as Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X),[11] and the Global Antibiotic Research and Development Partnership (GARDP).[12] Without sufficient push funding, pull incentives will have little material to work with.

Key considerations

Within this context, we present six key considerations aimed at facilitating the implementation of an EU-level pull incentive for antimicrobial innovation and access—the size of the potential pull incentive and possible contributions of the member states, design of the incentive model, interplay of the new pull incentive with the proposed revisions of the EU pharmaceutical legislation, roles and responsibilities of both the EU and its member states, balance between pull and push incentives, and global cooperation and responsibility. When we refer to antimicrobials in this Personal View, we are primarily concerned with antibacterial agents. Our analysis would also be applicable to antifungal agents, which face similar economic and regulatory challenges in research and development, but would be less applicable to antiviral agents, which are not subject to these challenges to the same extent as antibacterial and antifungal agents.

Optimal magnitude of pull incentives

Member states would need to reach a consensus on the optimal magnitude of pull incentives to stimulate research and development on antimicrobials, while acknowledging and considering the EU's commitment to providing its fair share of these incentives on the global stage. In 2021,

Outterson[13] reviewed the expected costs and transition probabilities at each stage of research and development on antibacterials and concluded that an international pull incentive amounting to revenues of US$3·1 billion (€2·9 billion) per antibacterial candidate would be required to incentivise its development from phase 2 clinical trials onwards.[13]

Although other estimates also exist on the appropriate size of a global pull incentive for research and development on antibacterials,[14] the estimates of Outterson[13] are regarded as the most up to date and involve reviewing cost estimates used in previous studies as well. This model assumes robust push incentives, equal to half of the cost of preclinical product development. Assuming that an international pull incentive of this size was funded by the EU and select G7 countries (USA, UK, Canada, and Japan), estimation of the fair share of each country based on their total gross domestic product would present an average joint contribution of $1·2 billion (€1·1 billion) in revenues per antibacterial candidate from the EU27 member states. These numbers are taken from the report by Outterson,[13] and reflect US$ and exchange rates as of April, 2021.

For the corresponding calculations, included in the supplementary material of the study, see https://open.bu.edu/handle/2144/42568.

Would investments at this level return positive social value for Europe? Estimates of positive economic impact and potential return on investment with access to effective antimicrobials will be key to securing political engagement among member states. The Centre for Global Development has estimated the health and economic impact of AMR and the potential return on investment for the EU27, USA, UK, Canada, and Japan, upon contribution to an international pull incentive for research and development on antimicrobials.[15] The required contribution of each EU member state to a G7+EU27 pull incentive of the size recommended by Outterson[13] are presented in the table, under the assumption that six new antimicrobials reach the market each decade over the next three decades and all member states agree to contribute and fully fund the pull incentive without contributions from the European Commission. The contributions of the member states were calculated proportionally to align with the mechanism used to calculate the contributions from member states to the EU budget, which is based on the gross national income. Estimates on the health burden of AMR were taken from the latest publication of the Global Research on AntiMicrobial (GRAM) Resistance Project,[17] and the expected return on investment was calculated using modelled savings in healthcare costs and the value of disability-adjusted life-years averted by using effective antimicrobials.

Importantly, this analysis has some limitations, drawing on estimates in the literature—especially, the GRAM Project[17]—and making assumptions to calculate health and economic impacts, including the increase in the deaths from AMR. Further modelling is needed to consider alternative scenarios, for example, of the number of novel antimicrobials coming to the market and the assumptions about their expected health benefits and positive effects on the economy. Moreover, these health and economic benefits might not be realised if the other pull incentives being developed in G7 countries, such as the PASTEUR Act in the USA,[18] are not implemented. However, as the second-biggest pharmaceutical market globally,[19] the EU cannot wait for pull incentives to be implemented by all the other G7 countries before acting, as even an EU incentive in its own right sends a strong signal to the pharmaceutical industry to prioritise research and development on antimicrobials.

Nonetheless, this analysis is useful for illustrative purposes and for informed discussions on the potential return on investment from a global pull incentive for antimicrobials. Although the health and economic burden of AMR and consequent return on investment vary considerably across EU member states, all of them will have high positive return on investment. The observation that the return on investment is highest in southern and eastern Europe is not surprising as the health burden of AMR is considerably higher in these regions than in northern and central Europe.[17] EU-level policy makers have the opportunity to emphasise the advantages of collective action in addressing AMR. Resistant infections do not adhere to national boundaries, and evidence of AMR transmission is seen across Europe, linked to tourism,[20] migration,[21] and conflict.[22–24] Additionally, the solidarity clause in the Treaty on the Functioning of the European Union includes a commitment by all member states to act jointly in response to natural or man-made disasters.[25]

Incentives suited to the circumstances

There needs to be consensus and clarity regarding which pull incentive or combination of incentives would be adopted and under what circumstances. A study commissioned by HERA has reviewed annual revenue guarantees and MERs.[26] Another study commissioned by the European Parliament's Panel for the Future of Science and Technology recommended the use of annual revenue guarantees to incentivise research and development on antimicrobials.[27] Annual revenue guarantees ensure that the antimicrobial market authorisation holders (MAHs) garner specified revenues annually in return for commitments to supply relevant antimicrobials to specific markets. Payments are delinked from sales volumes, thereby incentivising both the development of new antimicrobials and their continued availability in the market and removing the incentives for MAHs to oversell antimicrobials.[28] MERs are financial rewards granted to antimicrobial MAHs once the antimicrobials in development achieve regulatory approval.[29] MERs can provide the initial resources to fund the commercialisation and launch of new antimicrobials, and payments can be split over several years conditional on access commitments.

We know from the experience of Sweden that a revenue guarantee can achieve the access objective for which the revenue guarantee was designed and funded.[30] However, a revenue guarantee can only fulfil both the objectives of ensuring sustainable access and incentivising research and

Member state	Reduced disease burden		Financial benefits and cost			Return on investment‡
	Deaths averted	DALYs averted	Value of DALYs averted (€ million)	Savings in health care (€ million)	Total proportional payment (€ million over 30 years)†	(ratio of benefit to cost)
Austria	4320	72 578	2512	69	240	10·8
Belgium	9431	158 435	5483	151	300	18·8
Bulgaria	10 166	170 794	5911	163	37	162·0
Croatia	3897	65 478	2266	62	30	77·6
Cyprus	947	15 909	551	15	15	37·7
Czech Republic	7208	121 094	4191	115	135	31·9
Denmark	3091	51 935	1797	50	202	9·1
Estonia	759	12 754	441	12	15	30·2
Finland	2199	36 946	1279	35	157	8·3
France	48 327	811 898	28 097	774	1522	19·0
Germany	65 130	1 094 189	37 867	1044	2220	17·5
Greece	13 547	227 594	7876	217	105	77·1
Hungary	10 292	172 898	5983	165	90	68·3
Ireland	2520	42 337	1465	40	180	8·4
Italy	59 488	999 391	34 586	953	1087	32·7
Latvia	1769	29 715	1028	28	22	47·0
Lithuania	2684	45 098	1561	43	30	53·5
Luxembourg	297	4996	173	5	30	5·9
Malta	352	5917	205	6	7	28·1
Netherlands	9212	154 754	5356	148	510	10·8
Poland	34 827	585 093	20 248	558	322	64·5
Portugal	15 058	252 970	8755	241	127	70·6
Romania	27 768	466 496	16 144	445	142	116·4
Slovakia	5463	91 774	3176	88	60	54·4
Slovenia	1377	23 141	801	22	30	27·4
Spain	40 931	687 648	23 797	656	742	32·9
Sweden	3788	63 637	2202	61	330	6·9
Total	384 850	6 465 471	223 750	6166	8691	26·5

These numbers are taken from an earlier report.[16] DALYs=disability-adjusted life-years. *All numbers for health and economic benefits from novel antimicrobials coming to market are taken from an earlier report.[15] The calculations assume that six eligible antimicrobials successfully reach the market every decade over the next three decades. We have adopted pro-rated payments for new antibiotics considering that the revenues for each new antibiotic should amount to US$3·1 billion (€2·9 billion), aligning with the estimate provided by Outterson[13] for a pull incentive required for a phase 2-ready asset. This estimate contrasts with the figure of $4·5 billion (€4·3 billion), estimated using the CGD model, which represented an inflation-adjusted figure based on the central-best estimate within the range modelled by Outterson, originally at $4·2 billion when all R&D costs are covered by pull incentives. †We have allocated EU costs taken from the CGD model across member states using the relative size of the contributions based on the gross national income of each member state to the EU budget.[16] ‡Return on investment=(Value of DALYs averted+Savings in health care)/Total proportional payment.

Table: **Return on investment and proportional payments to a G7+EU27 pull incentive for research and development on antimicrobials over a 30-year period***

development of new antimicrobials under the condition that the guarantee amount is priced to reflect the fair share of each country to an international pull incentive and risks of investment in research and development on antimicrobials, as outlined above.[13] Another option is to combine a revenue guarantee with a one-off MER. This combination of pull incentives could also create an opportunity for the European Commission to share the financial burden of the combined pull incentives, by agreeing to fund the MER (while member states would fund the revenue guarantee pool, with their contributions reduced to reflect the funding allocated by the European Commission to the MER). Sharing the financial burden with the European Commission could further encourage and sustain high levels of member state participation. However, the aggregate value of these incentives should also align with the EU's equitable contribution to international pull incentives, as mentioned previously.

Potential effects of revisions to pharmaceutical legislation

Any decisions regarding the size or combination of pull incentives need to consider the potential effects of revisions to pharmaceutical legislation proposed by the European Commission.[31] The current version of these revisions includes plans to grant transferable exclusivity extensions (TEEs) to MAHs successfully bringing new antimicrobials to the market, which could be used by the same pharmaceutical company or sold to another pharmaceutical company to extend the data protection for any drug in any therapeutic area by an additional 12 months.[32] In either case,

the TEE would increase revenues for antimicrobial developers, and the size of other co-existing pull incentives could be reduced by an equivalent amount to reflect this increase in revenue.

Amendments to these revisions have been proposed in the ongoing legislative process, which specify that antimicrobial developers are not eligible for a TEE under the conditions that they have received a MER or milestone payment and that they cannot be used for drugs that have already benefited from the maximum regulatory data protection period.[9] However, what will be included in the final legislation following inter-institutional negotiations is not yet clear, and the Council of the EU might require further clarification on how multiple incentives can be combined and operationalised.

The implementation of TEEs has been opposed by some EU member states and some civil society organisations, owing to the uncertainty regarding the financial effect of TEEs on national health-care budgets and the implications associated with increasing costs in other therapeutic areas.[33–35] Moreover, the proposed amendments could mean that the pharmaceutical industry will no longer perceive TEEs as an attractive incentive and instead opt for other pull incentives such as MERs, milestone payments, and annual revenue guarantees. The legislative process will extend into the next legislative period following European elections in June, 2024, and the appointment of the next European Commission later in 2024.

Roles and responsibilities of EU institutions and member states

A pull mechanism needs clarity regarding the roles and responsibilities of EU institutions and member states. Of note, the European Commission does not have a mandate to implement a pull incentive without the consent of member states, as it should respect the responsibility of each member state to manage their own health systems, as stipulated by the Treaty of the European Union.[36] The Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (JAMRAI) and alumni from Driving

Panel: **Process for establishing an EU-level cross-country pull incentive for antimicrobial access and innovation**

First, a steering committee to oversee the governance and implementation of the pull incentive could be established by the Directorate-General for Health and Food Safety, with representation from all member states. This committee would facilitate transparent and inclusive decision making. Following this, European Medicines Agency (EMA) could delineate the EU-level priorities for new antimicrobials, drawing from the broader WHO priority pathogen lists for antibacterials[39] and antifungals.[40] EMA should also consider whether the new antimicrobial would be classified by WHO as a reserve antimicrobial,[41] as this classification would mean that the new antimicrobial would have small sales volumes and depend on pull incentives for its commercial viability.

In this set-up, EMA would also inform the steering committee about potential antimicrobial candidates in the development pipeline that could be eligible for pull incentives once they have completed phase 1 clinical trials. Member states could then nominate an antimicrobial as eligible for a pull incentive once the market authorisation holder (MAH) has made an application to EMA for regulatory approval, upon which the steering committee could initiate a request for Health Emergency Preparedness and Response Authority (HERA) to commission a technical report from a health technology assessment (HTA) authority in the EU that is recognised by the member state Coordination Group on HTA as having adequate technical expertise for conducting joint clinical assessments.[42] This report would include information on the potential efficacy, utilisation, and value of the new antimicrobial in clinical development and consider its implications for all EU member states. Joint assessment would offer advantages over each member state undertaking separate HTA, in terms of both expedience and best use of the available capacities and expertise, aligned with the intention of the HTA Regulation.[43] Following a review of the technical report, member states would vote on whether the antimicrobial candidate proceeds to the negotiation phase. If a qualified majority of member states agree that the antimicrobial candidate is eligible for a pull incentive agreement, then HERA would be given a mandate to collectively negotiate the terms and conditions of the pull incentive agreement, including the size of the incentive, access agreements based on clinical need, and manufacturing terms and conditions.

This strategy fits within the mandate of HERA, which includes funding research and development, supporting manufacturing capacity, and adopting medical countermeasures.[44] The concept of a qualified majority is the most commonly used voting mechanism by the Council of the EU and consists of 15 (55%) of 27 member states, representing at least 65% of the EU population, voting in favour of a policy or legislation.[45] If a new antimicrobial addresses an urgent public health need, then this process could be expedited by a request from the steering committee that HERA initiate negotiations with the MAH before completion of the technical report, with reimbursement agreements conditional on the potential efficacy, utilisation, and value of the new antimicrobial.

Once there is a provisionally agreed contract between HERA and the MAH, the steering committee would vote on whether the terms and conditions are acceptable. If a qualified majority is achieved, then the contract would be approved by the steering committee but member states would still be able to opt out of the contract. However, in doing so, national policy makers would be required to provide a justification to their electorate. Therefore, this opt-out model can be expected to secure greater participation of member states than the opt-in models suggested by the Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections and alumni from Driving reinvestment in research and development and responsible antibiotic use. Additionally, member states that opt out could encounter delays in gaining access to new antimicrobials that are considered eligible for pull incentives under the condition that the MAH decides not to prioritise launching in their market. After EMA grants the new antimicrobial regulatory approval and the pull incentive is operationalised, Directorate-General for Health and Food Safety would be tasked with overseeing and ensuring compliance with access and manufacturing agreements.

Please note that this process was designed to be applicable with current arrangements for pharmaceutical legislation in EU27. The proposed revisions to the EU pharmaceutical legislation include granting two additional years of market exclusivity to MAHs that launch new medicines in all member states.[46] These revisions would create an additional incentive for MAHs to improve access to new antimicrobials in the EU but would also need to be combined with an appropriately sized pull incentive with high levels of engagement from the member states, as described above, to promote both innovation in and access to new antimicrobials.

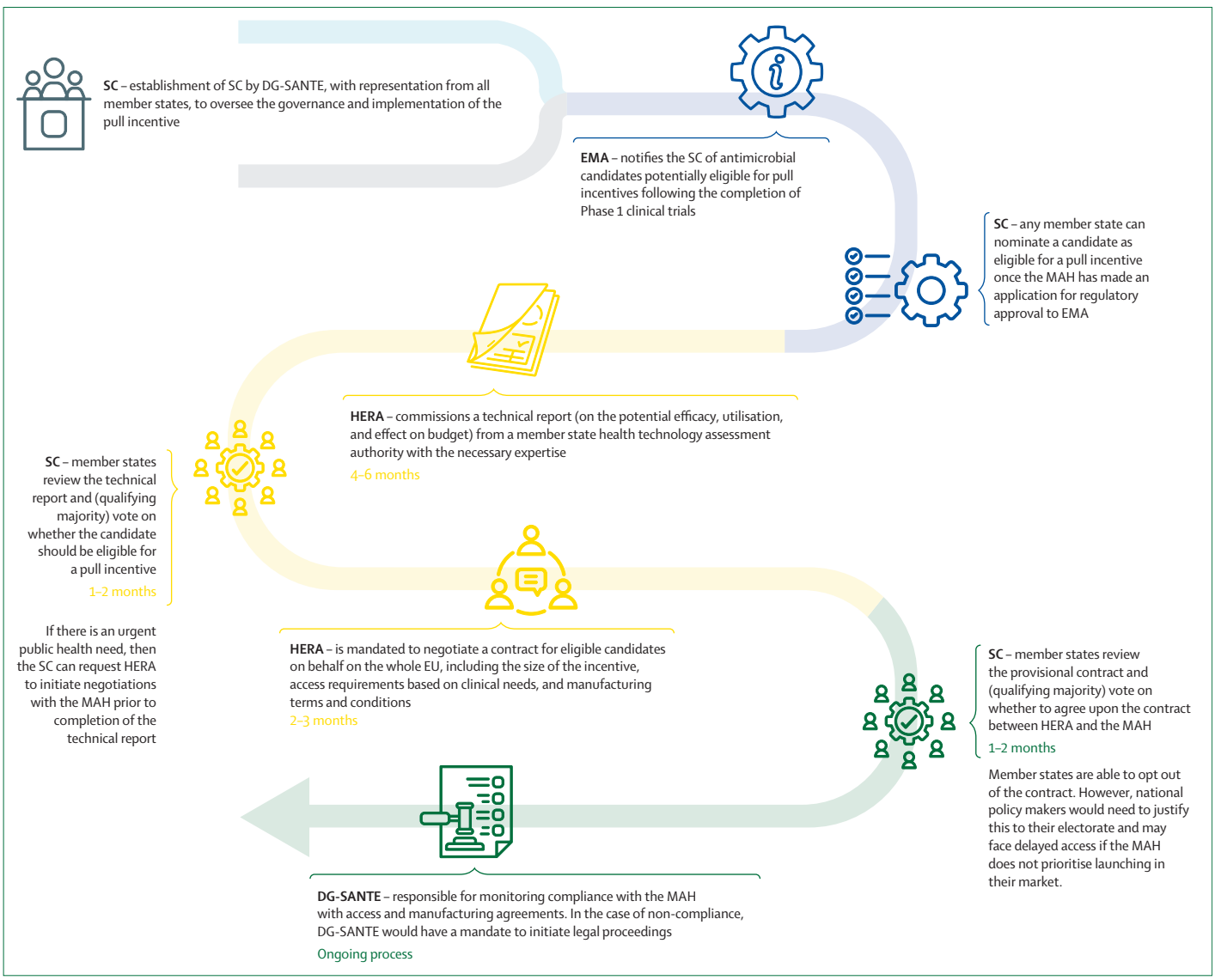

***Figure*: Flowchart for EU-level multicountry pull incentive for antimicrobial access and innovation**
DG-SANTE=Directorate-General for Health and Food Safety. EMA=European Medicines Agency. HERA=Health Emergency Response Authority. MAH=market authorisation holder. SC=steering committee. Please note that we have included provisional timescales that account to approximately 12 months between regulatory approval and implementation of the pull incentive. These timescales could be accelerated in situations of great and urgent public health need.

reinvestment in research and development and responsible antibiotic use (DRIVE-AB) have proposed similar models for an annual revenue guarantee mechanism, whereby the European Medicines Agency would identify new antimicrobials eligible for annual revenue guarantees and member states opt in to a joint tender for eligible antimicrobials.[37,38] At the end of each financial year, member states would pay any difference between the actual revenues of the pharmaceutical companies and the revenue guarantee.

Although the exact number of member states required for participation is not specified, the JAMRAI proposal mentions that for the model to succeed, a minimum number of member states would need to express interest to be included in the joint tender for a given antimicrobial. This condition presents a potential challenge, as there are variations in the degree to which AMR is prioritised as a national political issue across the EU. Consequently, participation of only some member states is a valid concern, which could then either render joint tenders unfeasible or create free rider problems.

To maximise participation, member states would need to have a high level of confidence in the processes used for the identification of eligible antimicrobials, determination of suitable incentive magnitudes, negotiation of contractual terms and conditions, and oversight of access agreements. These processes should be characterised by transparency, inclusivity, and methodological rigour.

With these principles in mind, the processes outlined by the JAMRAI and the alumni of DRIVE-AB could be adapted, as set out in the panel and illustrated in the figure, considering the insights drawn from the EU's joint procurement efforts during the COVID-19 pandemic.[47] The process could be incorporated as a further amendment to the proposed revisions to the EU pharmaceutical legislation,[9] or could leverage pre-existing legislation used for joint procurement of medical countermeasures by member states.[48]

Trade-offs between incentives

The EU, alongside global policy makers, needs to consider the appropriate trade-off between investment in push incentives, including public–private partnerships, and pull incentives. Although a large enough pull incentive could in theory incentivise increased investment in preclinical research and early clinical development, antimicrobial developers could still struggle to find investment from the private sector during these development stages, because of high failure rates. Outterson[13] reviewed evidence on transition probabilities and estimated that since 82·7% of antimicrobial candidates do not proceed from the hit-to-lead stage to phase 1 clinical trials, 6·2 projects should begin first-in-human phase 1 clinical trials to secure one regulatory approval. Moreover, most antimicrobial developers are small and medium-sized enterprises that do not have the capital reserves to fund their own research independently without additional support. Thus, push incentives during the earlier stages of antimicrobial development to directly fund research are more efficient than increasing the size of pull incentives to reassure private sector investors that their investments are worth the financial risks during the initial stages of research and development on antimicrobials. For our proposed model, we suggest that push incentives should be used from initial drug discovery until at least the completion of phase 1 clinical trials.

This model considers a recent analysis of global push incentive funding for research and development on antimicrobials that highlighted substantial gaps in public and private funding during these stages, currently exceeding $370 million per year.[29] Without additional investment in push incentives for these earlier stages of research and development on antimicrobials, the antimicrobial development pipeline will be insufficient, and few clinically effective drugs will be available for pull incentives to select from.

Need for a global perspective

In developing a cross-country pull incentive for new and pre-existing antimicrobials, the EU would need to incorporate a global perspective that requires coordinating with current and future global initiatives,[49] including revenue guarantees that have already been implemented in the UK,[50] and Sweden,[30] and to consult with teams involved in developing pull incentives in the USA,[18] Canada,[51] and Japan.[52] This step is crucial as the current and emerging pull incentives will have low effect under the condition that they are implemented in isolation without coordinated aims and objectives, or do not collectively represent an optimal size of incentive. Ideally, the EU could use platforms such as G7 or G20, building on the work of WHO, to send consistent messages to the research ecosystem regarding target drug profiles, clinical indications, and priority pathogens. The international community should also collectively consider mechanisms to ensure access to new and existing antimicrobials in low-income and middle-income countries.

The analysis described above on the appropriate size of a global antimicrobial pull incentive assumes that only the EU and G7 countries (USA, UK, Canada, and Japan) contribute financially. This global pull incentive programme could include requirements that antimicrobial developers supply new antimicrobials to low-income and middle-income countries at the marginal cost of production or provide a licence similar to Shionogi's voluntarily signed agreement with GARDP for cefiderocol.[53] Non-G7 high-income countries (such as South Korea, Australia, Switzerland, Saudi Arabia, United Arab Emirates, Qatar, and Singapore) could then fund either additional pull incentives or access to low-income and middle-income countries for both new and existing antimicrobials, as a way to offset their benefits from G7/EU investments. This step would be of mutual benefit for all countries, as without comprehensive access to pre-existing and new antimicrobials in low-income and middle-income countries, some countries could become reservoirs for multidrug-resistant infections. Most importantly, global access is necessary to substantially reduce the global burden of mortality from bacterial infections.

Conclusion

This Personal View outlines a structure for a pull incentive for antimicrobials that could be deployed in the EU with the aim of securing maximal participation of member states. We also outline contextual considerations to ensure complementarity with other ongoing related initiatives in the EU and internationally. Pull incentives would need to be combined with push incentives to sustain innovation in antibacterials and global access and stewardship. Delaying action risks the growth of AMR and the EU forgoing an opportunity to play a leading role in the global development of these incentives.

Contributors

MA drafted the manuscript. All other authors provided comments and edits to iterative versions of the manuscript.

Declaration of interests

MA declares consultancy fees from the European Observatory on Health Systems and Policies. AT declares consultancy fees from the Centre for Global Development. KO is the principal investigator and executive director of Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and also declares honoraria for academic lectures at Tufts University, Memorial Sloan Kettering, and the Sanger Institute. EM declares no competing interests.

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