

Assessing alternative proposals for a pan-European pull incentive to combat AMR: A principle-based approach

Executive Summary

Globally, there is recognition of the magnitude of the public health threat posed by antimicrobial resistance (AMR) and the need for a package of complementary policy measures to tackle this challenge. Novel pull incentives are urgently required to drive the development of a robust and sustainable R&D pipeline for innovative antimicrobials. Policies aimed at promoting innovation are necessary as they provide the foundation for an active pipeline, which is the essential first condition for ensuring access to and availability of novel antimicrobials in the future.

With the publication of the European Commission's (EC) proposals to revise the European Union's (EU) pharmaceutical legislation—including a proposal for a transferable exclusivity voucher (TEV)¹—and the publication of the EC's Health Emergency Preparedness and Response Authority (HERA) report², a period of renewed scrutiny of debate on AMR incentives is expected. As a contribution to this debate, the innovative biopharmaceutical industry has developed principles for an effective pan-European *pull* incentive drawing on the existing academic literature and policy reports. We have then applied these to different EU pull incentives proposals and considered the possibility to strengthen them.

Principles: There are five key principles that can be used to assess whether an EU pull incentive will be effective at driving the development of a robust and sustainable R&D pipeline for novel antimicrobials:

- **Incentivises innovation and appropriate use:** an incentive large enough to incentivize sustainable innovation, aligned to the EU contribution or fair share of the needed global incentive. Delinked from revenue and therefore aligned to stewardship;
- **Value for money:** represents a proportionate cost to society and an efficient approach;
- **Predictability:** provides clarity for all stakeholders, including innovators, the generic industry and payers;
- **Feasibility:** is implementable given the current context, framework and policy debate; and
- **Supports timely access:** can be implemented relatively quickly in the EU, given the urgency to address the AMR threat, and contributes to patient access through the increased supply and availability of new antimicrobials.

These principles have been used to assess different proposals for a European pull incentive namely the EC's proposal on TEV and the Revenue Guarantee Model (RGM) considered by HERA.

Application of principles to the EC's proposal on TEV: assessment of the Commission's proposal highlights some of the key *strengths* of TEV. These include: it is delinked as the reward is independent of sales volume, and thus aligned with appropriate stewardship; it could

¹ Reform of the EU pharmaceutical legislation, Available at: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

² European Commission, European Health and Digital Executive Agency (2023), *Study on bringing AMR medical countermeasures to the market : final report*, Publications Office of the European Union. Available at: <https://op.europa.eu/en/publication-detail/-/publication/51b2c82c-c21b-11ed-8912-01aa75ed71a1/language-en/format-PDF/source-282306193>. Referred to as HERA (2023) below.

provide an incentive that works for small and large companies and supports the innovation ecosystem; and it could be implemented with urgency at the EU-level within existing legal competences, without extensive coordination or upfront funding from Member States.

However, our assessment also shows some of the *weaknesses* of the Commission's proposal on TEV that could be improved. In particular, it puts in place strict conditions and obligations that significantly limit the pool of products which could benefit from the incentive, it is not likely to sufficiently incentivise innovation, limiting its ability to move the needle. Specifically, we would highlight that the TEV in the EC proposal is only linked to Regulatory Data Protection (RDP), which significantly limits the incentive's overall value. Furthermore, the proposal adopts a strict eligibility criteria that is likely to disincentivize future research. There are other elements of the proposal that could undermine its effectiveness, for example, it can only be used in relation to centrally authorised products within the first four years of RDP and is presented as a temporary scheme.

Application of principles to HERA's proposal on financial pull incentives – in the form of procurement mechanisms: Applying the same principles to HERA's RGM shows some *strengths*. It provides more certainty for payers and healthcare systems and may have greater predictability across all stakeholders under certain conditions. Additionally, it only rewards antimicrobials that are successfully commercialized (which means it is better than milestone payments for example) and it can be revised if new information emerges regarding the value of the antibiotic.

However, there are significant *weaknesses* in the RGM. There is a concern about the size of the incentive and whether it provides a meaningful pull. This is evident from the analysis in the HERA report, where the RGM made less than 25% of pre-clinical stage projects profitable at any of the magnitudes investigated. Equally, there are concerns regarding Member State acceptance and implementation which may reduce the feasibility and slow the implementation of an effective incentive for AMR.

How the proposals could be strengthened: In summary, the Commission's proposal on TEV is unlikely to sufficiently incentivise innovation due to its application to RDP and strict eligibility criteria. The same concern applies to the HERA proposal for a RGM in isolation. To strengthen the Commission's TEV and ensure that it is best placed to address the challenge of AMR, an initial assessment would suggest a range of alternatives should be considered including:

1. Most importantly, the incentive needs to be of sufficient scale. A broader application of the incentive to include Supplementary Protection Certificates (SPC) as well as RDP would address this concern.
2. Appropriately address the challenge of AMR. Broader eligibility criteria to reflect the benefits for patient, health system and societal value of novel antimicrobials, aligned to international incentive policies.
3. A predictable regime encouraging innovation. The temporary nature of the regulation should be re-thought, for example criteria for assessment of the proposal after 15 years should be articulated to provide additional predictability. The constraint on using the TEV in relation of centrally authorised products within the first four years of RDP needs to be reformulated.

The proposal regarding the RGM needs to be significantly developed, particularly with respect to the magnitude of guarantee, how it would be implemented across member states and how it can complement the use of a TEV.

By implementing these conditions, the Commission would leverage the existing advantages of TEV (such as its delinked nature, applicability to all companies, and timely implementation)

and establish an incentive scheme that truly incentivizes the development of a sustainable pipeline of new antimicrobials.

Introduction

Globally, there is recognition that antimicrobial resistance (AMR) is both a significant public health threat and that the current R&D pipeline is likely insufficient to address it.^{3,4} To tackle the challenge of AMR there is consensus that policymakers urgently need to introduce novel pull incentives that can drive the development of a robust and sustainable R&D pipeline for innovative antimicrobials. Policies targeted at innovation are the foundation of an active pipeline which is the necessary first condition for access and availability of novel antimicrobials.

In Europe, AMR was a key area for action in the Pharmaceutical Strategy for Europe, in which the European Commission (EC) committed to exploring new types of incentives for antimicrobials. The need for urgent actions has been recognised in the Commission proposal for a Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach published on the 26th of April 2023.^{5,6}

At the same time, the EC published its proposed revisions to the General Pharmaceutical Legislation (GPL) which included the European Commission's proposal to introduce a transferable exclusivity voucher (TEV).⁷ This would provide the manufacturer of a novel antimicrobial with a voucher upon receiving EU regulatory approval. The recipient could use this voucher to extend the marketing exclusivity of one of its products, or sold to another company which could then use it to extend the marketing exclusivity of one of its own products.⁸ TEV has been extensively studied in the academic literature. TEV, however, has been criticised by several non-industry stakeholders.⁹

The proposal regarding TEV needs to be considered alongside other Commission initiatives. In March, the HERA published its analyses of incentives for antimicrobial access and innovation.¹⁰ This considered “options for action in order to bring more AMR medical countermeasures to market and ensure their access across the EU Member States” focusing on Revenue Guarantee Schemes, Market Entry Rewards, and Milestone-Based Payments.

The European Commission envisages that the proposal could work together, with financial pull incentives – in the form of procurement mechanisms – in addition to the voucher scheme.¹¹ To inform this debate, EFPIA has developed a set of principles that would need to be satisfied

³ World Health Organisation (2020) “Lack of new antibiotics threatens global efforts to contain drug-resistant infections”, Available at: <https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections>.

⁴ Jacob Madden & Kevin Outterson (2023) Trends in the global antibiotics market, Biobusiness Briefs, 15 February 2023. <https://www.nature.com/articles/d41573-023-00029-5>.

⁵ https://health.ec.europa.eu/publications/commission-proposal-council-recommendation-stepping-eu-actions-combat-antimicrobial-resistance-one_en

⁶ There appears a consensus that “The EU needs both push incentives (i.e. funding for antimicrobial research and innovation, primarily via research grants and partnerships) and pull incentives (both regulatory and financial) to reward successful development and secure access to effective antimicrobials.” Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance. P.g.15

⁷ Reform of the EU pharmaceutical legislation, Available at: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

⁸ Wilsdon, T., Robson, A., & Lu, L. (2022). *A framework for assessing the potential net benefits realised through Transferable Exclusivity Extension (TEE) as an incentive for development of novel antimicrobials: FINAL REPORT*. Charles River Associates.

⁹ This includes a non-member endorsed by 14 Member States and an article in The Lancet published by some influential figures in the AMR debate.

¹⁰ European Commission, European Health and Digital Executive Agency (2023), *Study on bringing AMR medical countermeasures to the market : final report*, Publications Office of the European Union.

¹¹ Communication from the Commission, Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance. P.g.15-16

for any pull incentive to be effective. In this paper, these principles are used to assess the proposed TEV put forward in the EC's proposal and HERA's Revenue Guarantee Scheme (the most developed of the proposals within the HERA report).

Incentivising a robust and sustainable R&D pipeline for novel antimicrobials

Although the scale of the AMR crisis is now rarely disputed, the debate around an EU pull incentive has revealed that some differences in perspectives around the nature of the challenge remain. The key difference concerns what the specific focus of an EU European policy proposal should be, and how it would combat AMR.

Many stakeholders, including the industry, have focused on a pull incentive that will incentivise the innovation of *new* antimicrobials¹². This pull incentive would support the R&D pipeline for novel antimicrobials to be capable of delivering against the WHO priorities.¹³ This would mean 1-2 antimicrobials developed each year in order to address AMR.¹⁴ Similar assumptions are put forward in the recently published HERA paper.¹⁵ There is an associated academic literature on the scale of the incentive that would be required for a pull incentive to be effective (see Box 1).

Box 1: Outlining the appropriate incentive size and the required EU share

There has been substantial progress in the academic literature on understanding the size of the incentive that is needed to stimulate innovation:

- Outterson (2021) suggested that a global reward of \$2.2-4.8 billion is needed to incentivise developers to take on the risks and R&D given expected limited returns. For a de-linked subscription model the central estimate is \$4.2 billion¹⁶
- Based on this estimate and a calculated European share of 34%, this would imply €1.3 billion¹⁷
- In their recent study of AMR countermeasures, HERA noted that there is extensive variation in the literature's estimates for the required size, with the result that they tested global scenarios from \$700 million to \$3.1 billion over 10 years¹⁸

Other stakeholders put greater emphasis on European wide policies ensuring access and availability of existing antimicrobials, as prioritised by the European Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI).¹⁹ As set out below, rather than being seen as alternatives, it is possible that these approaches are complementary.

Principles for an effective EU pull incentive

Given the recent proposals on AMR incentives, EFPIA considered it timely to set out the objectives and key principles by which an EU pull incentive should be assessed. There is a clear need for a transparent set of criteria that can be used to compare how different

¹² This features prominently in the analysis of the Toulouse School of Economics. For example see, TSE (2022) *Can transferable patent extensions solve the market failure for antibiotics?*

¹³ EFPIA. A new EU pull incentive to address Antimicrobial Resistance (AMR): Recommendations from EFPIA.

¹⁴ EFPIA and BEAM Alliance (2023). "Transferable exclusivity voucher: a flawed incentive to stimulate antibiotic innovation", *The Lancet*, 9 February 2023: EFPIA-BEAM Rejoinder. Available at: <https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/efpia-rejoinder-lancet-article/>

¹⁵ HERA (2023) pg. 67

¹⁶ 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. The estimate depends on the stage of investment and the incentive structure. The incentive sizes quoted are for manufacturers who develop the antibiotic from discovery to launch. Slightly lower incentive sizes are estimated for those acquiring a Phase 2-ready antibiotic.

¹⁷ Fx rate: 1 USD = 0.92 EUR

¹⁸ HERA (2023), p. 141

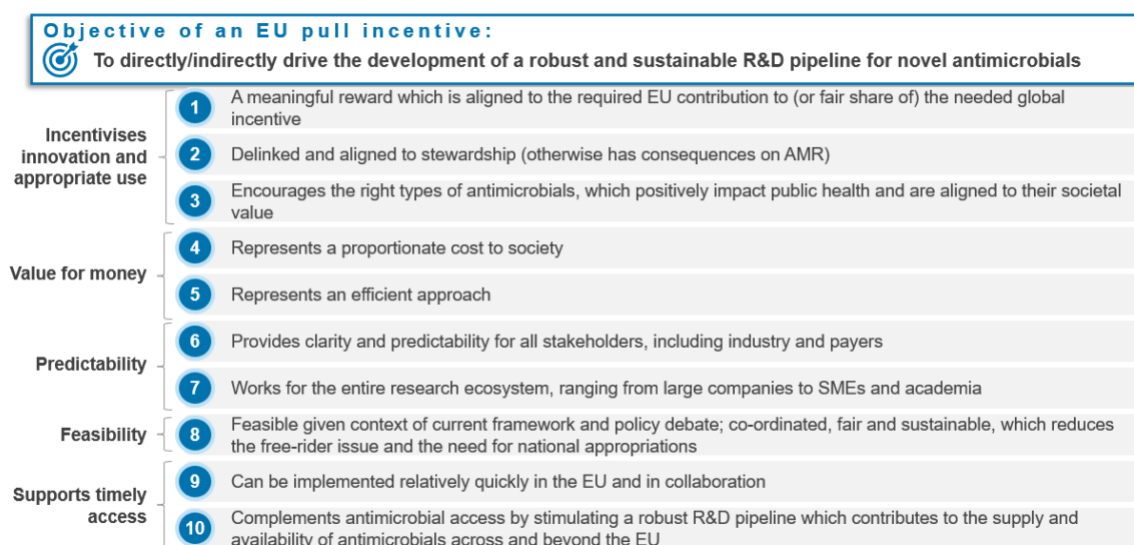
¹⁹ Årdal, C., Lacotte, Y., Edwards, S., Ploy, M. C., & European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI). (2021). National facilitators and barriers to the implementation of incentives for antibiotic access and innovation. *Antibiotics*, 10(6), 749.

approaches meet the overall objective of driving the development of a robust and sustainable R&D pipeline for novel antimicrobials.

Based on a review of the existing literature²⁰, the characteristics of an effective pull mechanism put forward by different stakeholders were consolidated into a set of principles. The principles and overall objective of an EU pull incentive are summarised in Figure 1, with the former grouped into 5 categories. These principles can be summarised as follows:

1. **Incentivises innovation and appropriate use:** an incentive large enough to incentivize sustainable innovation, aligned to the EU contribution or fair share of the needed global incentive. Aligned to the value. Delinked from revenue and therefore aligned to stewardship;
2. **Value for money:** represents a proportionate cost to society and an efficient approach;
3. **Predictability:** provides clarity for all stakeholders, including innovators, the generic industry and payers;
4. **Feasibility:** is implementable given the current context, framework and policy debate; and
5. **Supports timely access:** can be implemented relatively quickly in the EU, given the urgency to address the AMR threat, and contributes to patient access through the increased supply and availability of new antimicrobials.

Figure 1: Overview of the objective and principles of an effective EU pull incentive



Assessment of the European Commission's proposal on TEV

Using these principles, we assess the version of TEV that was published by the European Commission in its proposal to revise the European pharmaceutical legislation in April 2023. The key components of the TEV proposed are shown in Table 1 below.

²⁰ For example: Outtersen, K., & McDonnell, A. (2016). Funding antibiotic innovation with vouchers: recommendations on how to strengthen a flawed incentive policy. *Health Affairs*, 35(5), 784-790.; Årdal, C., Røttingen, J. A., Opalska, A., Van Hengel, A. J., & Larsen, J. (2017). Pull incentives for antibacterial drug development: an analysis by the transatlantic task force on antimicrobial resistance. *Clinical Infectious Diseases*, 65(8), 1378-1382.; Boluarte, T., and Schulze, U. (2022) The Case for a Subscription Model to Tackle Antimicrobial Resistance. Boston Consulting Group. Available at: <https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance>; Member State Non-Paper as report at: <https://www.politico.eu/wp-content/uploads/2022/12/01/Non-paper-Transferable-exclusivity-voucher-for-AMR-2.pdf>; HERA (2023).

Table 2: Key components of the Commission's proposal on TEV

Component	EC Proposal TEV ²¹
Approach to extending exclusivity	Application to Regulatory Data Protection
Length of extension	12-month extension
Antimicrobial eligibility	Products with a significant clinical benefit and meets additional criteria ²²
Recipient applicability	Needs to be used within the first 4 years of data exclusivity
Access	An undertaking regarding the capability to supply the medicinal product to patients across the Union in sufficient quantities
Number of vouchers	Maximum of 10 vouchers can be granted in 15 years (legislation also temporary)

The principles can be used to assess the Commission's proposal. This highlights some of the *key strengths* of TEV which include:

- It is delinked as the reward is independent of sales volume, and thus aligned with appropriate stewardship
- It provides an incentive that works for small and large companies and supports the innovation ecosystem
- It could be implemented at the EU-level without extensive coordination or upfront funding from Member States and therefore can be done in a timely fashion

However, the assessment also finds *areas of weakness* in the Commission's proposal on TEV.

- The most significant concern is whether it provides an appropriate reward that is aligned to the EU contribution and expected to be meaningful in size to move the needle. Due to its application to RDP, the size of the incentive will be reduced and is likely to be insufficient. The Commission argues that the application of RDP improves efficiency (as these products allegedly are of a smaller size). The evidence from the EC suggests that only 34.5% of products are protected by RDP (compared to 82.5% that are protected by SPC + RDP) and the average peak sale of products with RDP are 44% of those with SPCs as the final measure of protection. Our analysis suggests this does not improve the policy assessment as it would not provide a sufficient size incentive or improve efficiency: it results in an average value of €364 million²³ instead of the €1.3billion calculated as the European share of Outterson's (2021) global reward size
- Furthermore, there is a concern regarding the Commission's eligibility proposal. If it adopts a strict eligibility criteria with products needing to provide evidence of significant clinical benefit and to meet additional criteria this could mean it will only reward a select few antimicrobials and in turn will disincentivize future research. The focus should be on benefiting patients and the healthcare system rather than artificially simplistic criteria – for example, the last new class of antibiotics was developed in the 1980s.²⁴

²¹ Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency

²² Proposal for a Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, paragraph 80.

²³ Pg. 3 of draft impact assessment included in Commission proposal.

²⁴ Few antibiotics under development. Available at: <https://www.reactgroup.org/toolbox/understand/how-did-we-end-up-here/few-antibiotics-under-development/#:~:text=%E2%80%9CThe%20discovery%20void%E2%80%9D%20refers%20to,treatment%20was%20discovered%20in%201987.>

- Finally, there are concerns regarding the temporary nature of the regulation and the conditions that it is used in relation to centrally authorised products within the first four years of RDP. Developing new medicines is highly risky and takes many years, often decades. A longer time horizon or clear criteria by which the assessment would be undertaken is required. Given the proposal to adapt the length of regulatory data protection period, the four year proposal could significantly distort competition for TEV.

A summary of the assessment is set out in Table 2 below. Green indicates high conformity to the principles, whilst amber and red equal moderate and low applicability respectively.

Table 2: Assessment of the Commission's proposal on TEV

Principles	EC proposal TEV
1. Meaningful reward which is aligned to required European contribution	
2. Delinked and aligned to stewardship	
3. Encourages the right types of antimicrobial and is aligned to their value	
4. Represents a proportionate cost to society	
5. Represents an efficient approach	
6. Works for entire research ecosystem	
7. Clarity and predictability for all stakeholders	
8. Co-ordinated, fair and sustainable; reduces free-rider issue	
9. Can be implemented relatively quickly and in collaboration	
10. Complements access, contributing to supply and availability by stimulating R&D	

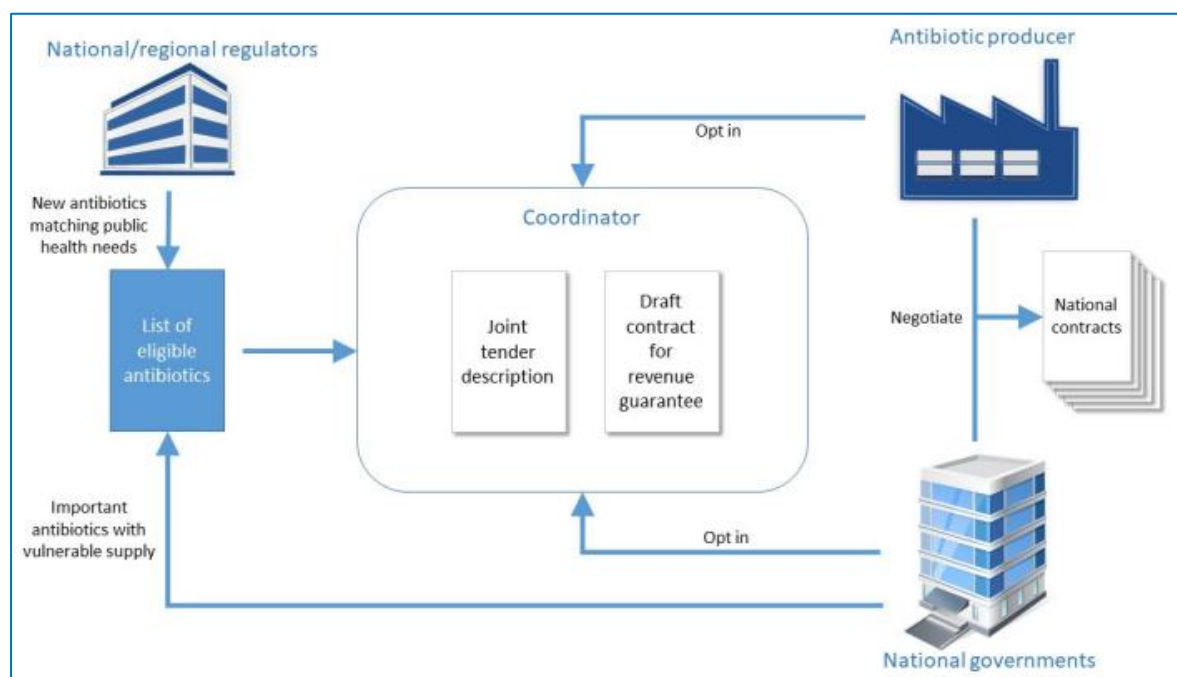
Assessment of HERA's proposal on financial pull incentives – in the form of procurement mechanisms

In addition to the European Commission's proposal to introduce pull incentives in the General Pharmaceutical Legislation, the HERA study (HERA 2023) considered different models based on procurement (revenue guarantee, market entry reward, and milestone-based payments).²⁵ The revenue guarantee model (RGM) proposed by EU-JAMRAI has perhaps received most interest.²⁶ Based on their assessment of pull incentives, EU-JAMRAI proposed a model that adapts the Swedish annual revenue guarantee pilot to the multinational level. Manufacturers of a new antimicrobial which meets certain criteria would receive a minimum annual revenue either coordinated by or through a commitment from an organisation like the EC.

²⁵ HERA (2023)

²⁶ Årdal, C., Lacotte, Y., Edwards, S., Ploy, M. C., & 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), 749.

Figure 2: Revenue guarantee model concept²⁷



We have used the same principles applied to the TEV model above to consider the Revenue Guarantee Model (in Table 3 below).

Table 3: Assessment of the HERA RGM proposal

Principles	HERA RGM proposal
1. Meaningful reward which is aligned to required European contribution	
2. Delinked and aligned to stewardship	
3. Encourages the right types of antimicrobial and is aligned to their value	
4. Represents a proportionate cost to the society	
5. Represents an efficient approach	
6. Works for entire research ecosystem	
7. Clarity and predictability for all stakeholders	
8. Co-ordinated, fair, and sustainable; reduces free-rider issue	
9. Can be implemented relatively quickly and in collaboration	
10. Complements access, contributing to supply and availability by stimulating R&D	

Looking at the revenue guarantee model it has some *strengths*:

- It provides more certainty for payers and healthcare systems and may have greater predictability across all stakeholders under some conditions

²⁷ Årdal, C., Lacotte, Y., Edwards, S., Ploy, M. C., & 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), 749.

- It only rewards antimicrobials that are ultimately commercialized (which means it is better than milestone payments for example) and can be revised if new information emerges regarding the value of the antibiotic

However, there are significant *weaknesses*:

- There is a concern about the size of the incentive and whether it provides a meaningful pull. This is evident from the analysis in the HERA report (with RGM making less than 25% of project profitable at pre-clinical stage at any of the magnitudes investigated)
- Concerns around Member State acceptance and implementation which may reduce the feasibility and slow the implementation of an effective incentive for AMR – depending on implementation it may also lead to unpredictability for developers, especially small and medium sized enterprises (SMEs) if member state participation is unpredictable
- The valuation of antibiotics becomes centrally important to ensure the model is of sufficient size. An effective RGM could require significant reform in the national value assessment process (as in the UK). However, this takes time to institute potentially delaying the proposal

Strengthening the Commission's proposals

In summary, the Commission's proposal on TEV alone is not likely to sufficiently incentivise innovation due to its application to RDP only and its strict eligibility criteria. The same concern applies to the HERA RGM proposal in isolation. To strengthen the Commission's TEV and ensure that it is best placed to address the challenge of AMR, an initial assessment would suggest a range of alternatives should be considered including:

1. Most importantly, the incentive needs to be of sufficient scale. A broader application of the incentive to include Supplementary Protection Certificates (SPC) as well as RDP would address this concern.
2. Appropriately address the challenge of AMR. Broader eligibility criteria to reflect the benefits for patient, health system and societal value of novel antimicrobials, aligned to international incentive policies.
3. A predictable regime encouraging innovation. The temporary nature of the regulation should be re-thought, for example criteria for assessment of the proposal after 15 years should be articulated to provide additional predictability. The constraint on using the TEV in relation to centrally authorised products within the first four years of RDP needs to be reformulated. For example, Clarity and predictability could be increased by applying TEV to a product with at least 2 years of protection left.

The proposal regarding the RGM needs to be significantly developed, particularly with respect to the magnitude of guarantee, how it would be implemented across member states and how it can complement the use of a TEV.

By adopting these suggestions, the Commission would build on the existing strengths of TEV i.e. it is delinked, works for all companies and can be implemented in a timely manner and ensure that it is in a strong position to incentivize a sustainable pipeline of new antimicrobial drugs.

Conclusion

Overall, while the Commission's proposal on TEV is a significant step forward, and it meets some of the articulated principles for an EU pull incentive, there are several areas where the proposal could be improved and complemented to ensure it is best placed to meet its key objective of driving the development of a robust and sustainable R&D pipeline for novel antimicrobials that deliver for patients and the healthcare system.