SYMPOSIUM ON THE ECONOMICS OF AMR R&D INCENTIVES: Cost of Inaction and Action

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Paris

Antimicrobial resistance (AMR) is one of the most pressing threats to humanity today. Its danger is exacerbated by poor market conditions that hinder investment into the development of new, critical products, such as antibiotics and diagnostic tools. To preserve their effectiveness, antimicrobials should be used as infrequently as possible. This results in limited commercial attractiveness for these products and provides a poor value proposition for developers and investors, who take their science and financing into other more viable product markets. Without a sustained innovation ecosystem, the world may forgo entirely novel antimicrobials to combat AMR.

The European Union has recognised this crisis, committing to implementing solutions to address the challenging market dynamics. Various options have been proposed, while further data continues to be generated regarding the urgency of action in the face of high societal cost due to inaction. The symposium "Economics of AMR R&D Incentives: Cost of Inaction and Action" aimed to provide a platform for dialogue on the proposed solutions and their economic factors, by gathering policymakers, developers, and economists, reviewing up-to-date literature and exploring incentive options to revitalise AMR research and development (R&D) and ensure a sustainable pipeline.

This report summarises the presentations on the issues raised by AMR and the incentive options that have been proposed. It is intended to serve as a knowledge base for decision-makers.

The cost of AMR[1]

The consumption of antimicrobials will remain high in the years to come

One of the key drivers of AMR remains the use of antibiotics. In human health, the consumption of antibiotics increased over the past two decades (Figure 1), supported in G20 countries by increased access, and in the EU, by increased reliance of modern medicine on antimicrobials. In the same period, a significant decrease has been observed in antibiotic use in animal health, where about 60% of antibiotics are consumed; but further forecasted gains appear limited. Unless we take action, consumption of antimicrobials will remain high for the years to come, and resistance to last resort drugs could more than double by 2035 compared to 2005.

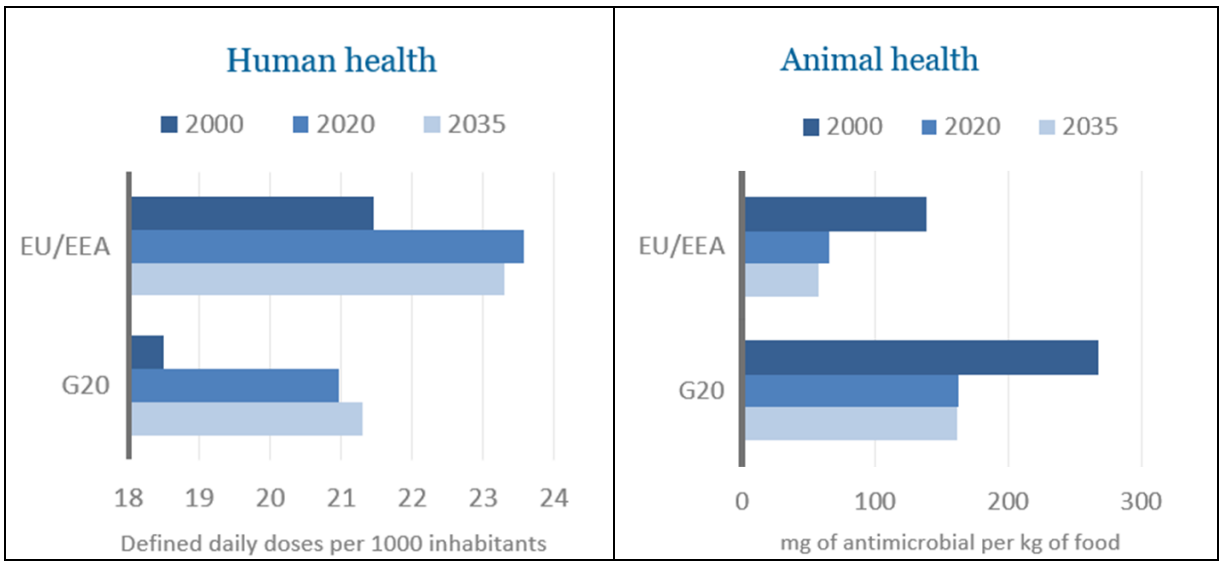

Figure 1: Evolution of antimicrobial consumption in human and animal health, in EU/EEA and G20 countries

As an example, Bulgaria ranks high for antibiotic consumption in Europe and exhibits some of the highest AMR rates among EU countries, particularly for fluoroquinolone-resistant *A. baumannii*, carbapenem-resistant *A. baumannii* and third-generation cephalosporin-resistant *K. pneumoniae*.

[1] OECD Health Policy Studies (here): Embracing a One Health Framework to Fight Antimicrobial Resistance, 2023

The impact on public health systems is already significant

AMR exerts substantial pressure on healthcare resources for a variety of reasons. Patients who suffer from resistant infections tend to stay in hospitals longer and require more complicated and more expensive medical treatments. They are also delaying their return to work, and once they are back at work, they have lower productivity, which impacts economies.

Already today, the cost of AMR is substantial. Across the OECD:

- Nearly 33 million extra days are being spent at hospitals every year.
- Overall, AMR costs nearly USD 29 billion to the health systems and USD 37 billion to the economies

Innovation to help curb the AMR threat, PULL incentives to support innovation

AMR is a global, pan-sectoral issue that calls for a worldwide, One Health, multi-pronged approach. Innovation has a role to play, together with stewardship, infection prevention, and access policies. But innovation has stalled due to the lack of market viability. Market incentives (or PULL incentives) are required to revitalise the development of new antimicrobials that would keep pace with rising resistance.

What would be the value and return on investment of a PULL mechanism for governments?[2]

To identify the value and return on investment, several assumptions must be made:

- Size: A PULL mechanism with a price tag of $4.5 billion per new antimicrobial, a number derived from the literature, in the hypothesis that this mechanism would be the single source of financing to compensate for the R&D costs, risk of failure, and expected return on investment over the whole cycle.
- Number of antimicrobials needed or expected: 18[3] new antimicrobials over the next 30 years (3 drugs targeting the 6 priority pathogens from the 2017 WHO Priority Pathogen List, 6 new drugs per decade).
- Who pays: The financial burden rests with G7-EU27 countries[4] only, where EU's fair share based on GDP would be ca. $1.5 billion (34%).

Only considering the direct health gains to patients and averted hospital costs (i.e. not considering the productivity gains), the benefit-to-cost ratio for the EU would already be 4:1 after 10 years (Table 1), with 20,000 lives saved. If the model is expanded to 30 years, the benefit-to-cost ratio raises 18:1, with 385,000 lives saved.

Table 1: The cost and benefit of setting up a PULL incentive in Europe

	TOTAL COST (DISCOUNTED)	LIVES SAVED	BENEFIT: COST RATIO
10-Year	$3.99 bn	20,000	4:1
30-Year	$13.25 bn	385,000	18:1

The model uses different assumptions. The three that matter most are i) the way DALY's are valued, ii) the way the annual resistance growth is quantified, and iii) the peak efficacy of new antibiotics in reducing AMR deaths.

But even with very conservative assumptions, there are very few scenarios where the benefit-to-cost ratio in the EU goes down below 10:1 after 30 years

[2] OHE & CGD study (here): G7 Investments in New Antibiotics Would Pay Off Big—For Everyone, 2022

[3] The number is somewhat arbitrary as not every new antimicrobial will only target one pathogen from the PPL; on the other hand, antimicrobials targeting pathogens of lower priority level should also be incentivised to some extent.

[4] The model seems to include Monaco and San Marino

What size of PULL incentive is needed?[5]

Many studies have tried to evaluate the financial incentive required to support a viable business case for a new antimicrobial asset. But they embed several pitfalls: some assume increased PUSH funding, some understate manufacturing and post-approval costs, some use erroneous assumptions on preclinical success rate and global peak year sales. This demonstrates how complex the topic is and the need for careful evaluation.

An investor will start considering an antimicrobial program when the expected internal return rate would approach 10%. By modelling expected net present value (eNPV) of new antimicrobial projects, one can thus estimate the size of the incentive required.

The size of the PULL mechanism depends on the totality and timing of funding available through R&D, e.g., the amount of PUSH funding, at which stage of development funding is provided, when / if the product is acquired by a commercial entity, whether the PULL mechanism is fully delinked from volume and price, assumptions around success rates, duration of the pull mechanism, etc.

Because of uncertainties, particularly in terms of success rates in the early stages, the range of values of the total aggregated costs of development can be quite wide. To provide the most pragmatic range, the most useful model assumes:

- Sufficient (public and private) funding through phase 1
- Acquisition by a commercial entity for $500 million at the end of phase 1
- Full delinkage (e.g. via a subscription model) over 10 years.

The size of such a mechanism at global level would need to be US$2.2 Billion to US$4.8 Billion, and on average US $3.1 billion. This “best estimate” should be understood as an average: assets of high societal value should get more, while those with lower value receive less.

How does this amount compare to the revenues for other pharmaceutical products? US $3.1 billion over 10 years means US $310 million per year, less than 1/3 of a blockbuster (approximately the 400 to 500th highest selling drug in a year).

There are some limitations of these estimates. For example, the values are calculated using 2019 US dollars and the new antimicrobials that are incentivised are mostly extensions of existing classes. Developing highly innovative approaches would be riskier, take longer and cost more (and would thus need a higher incentive).

A substantial increase of PUSH funding is also required

In addition, the model above considers that 50% of the preclinical costs are covered by PUSH funding. By way of example, to get 6 new antimicrobials per decade, 215 hit-to-lead projects are needed, which requires a significant amount of money: $560 million per year are needed annually, which is $370 million more than the current funding level.

[5] Outterson K., “Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines”, Health affairs 40(11), 2021: 1758-1765 (here); see also supplemental materials

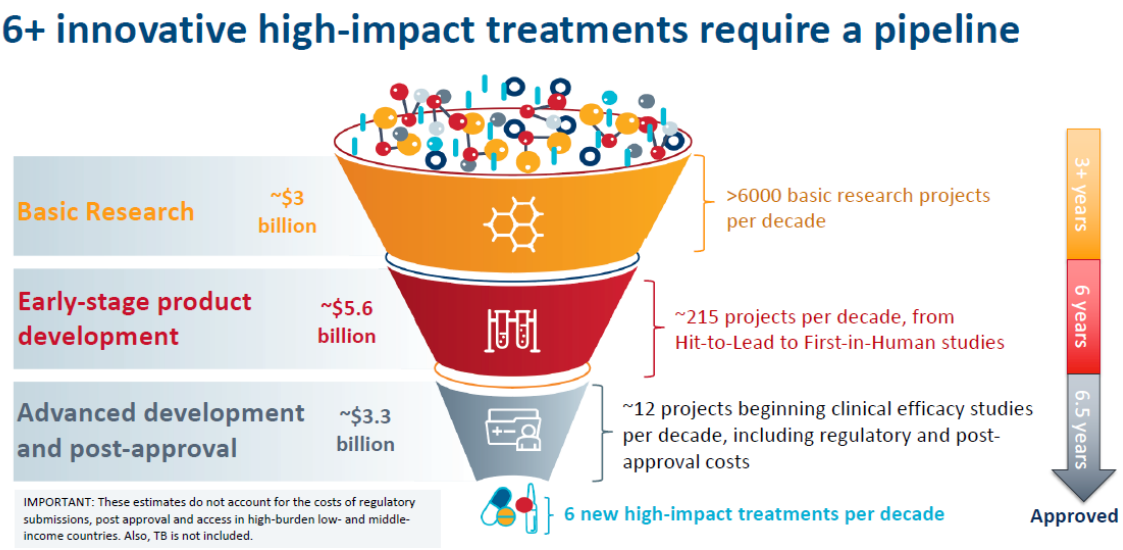

Figure 2 : The number of projects and the associated costs to deliver 6 new high-impact antimicrobials per decade

Models calculating the required size of PULL incentive are converging

A recent study, also based on an eNPV approach and commissioned by DG HERA[6], agreed on the overall size needed ($3 to 4 billion) but highlighted that only half of the projects at the preclinical stage that are eventually successful would be profitable with that amount. To circumvent the issue, the study recommends adding measures before market authorisation such as milestone prizes and pipeline coordination, as it would give more control to public payers. With such mechanisms in place, global PULL incentives at market launch may only need to be around US $1 to 1.5 billion in the form of a 10-year subscription model.

Two gaps are highlighted.

First, there is a need for a scientific panel to foster convergence in an independent way all the models that have been proposed so far and integrate them into something that is more coherent. That could lead for instance to incorporate the metrics followed by early-stage investors (e.g. return on investment, internal return rate) besides the more long-term eNPV approach. A call to this effect is expected to be made at the UN General Assembly meeting this September.

Second, though there is some coherence between the different methodology and estimates, public decision makers (e.g. HERA, CARB-X, etc.) could set a way to share their methodology and hypotheses and their updates. This would make easier any future policy discussion at an international level and would increase the transparency for potential investors. Though the point was made the metrics followed by early-stage investors (e.g. return on investment, internal return rate) could be incorporated besides the more long-term eNPV approach, it should be noted that these methods already have a lot in common and that discrepancies mainly come from different usage (design of a mechanism vs business decision making tool).

Which mechanism?: Learnings from the UK pilot and the follow-up permanent scheme

The pioneering work of NICE and NHS England, who piloted a fully delinked subscription payment model for two important antibiotics in 2022, has generated useful learnings[7].

The pilot produced the most comprehensive case study of evaluating antimicrobial products to date. Incremental net health benefits in QALYs were estimated using innovative health economic modelling analyses which captured benefits on a population level rather than an individual level (i.e. wider public health benefits,

[6] HADEA/2021/OP/0005 Study (here): Study on bringing AMR medical countermeasures to the market, 2023
[7] NICE report (here): Models for the evaluation and purchase of antimicrobials, accessed 22.04.2024

beyond the health consequences to infected patients, often described as the "STEDI[8] criteria"). There were gaps in the evidence base, leading to uncertainty in the value estimates. Nevertheless, the value of drugs in QALYs translated into a monetary value for the contracts that aligned with England's "fair share" of the global PULL incentive.

Collectively, these learnings have led to a more pragmatic approach to determining contract value for drugs that will be evaluated when the subscription model is rolled out to more antimicrobials across the UK. Instead, multi-criteria decision analysis will be implemented (Figure 3). The criteria reflect the drivers of value that were identified in the economic models and the committee deliberations in the pilot[9], and have been validated by clinical experts from the UK Government, and subjected to public consultation in 2023.

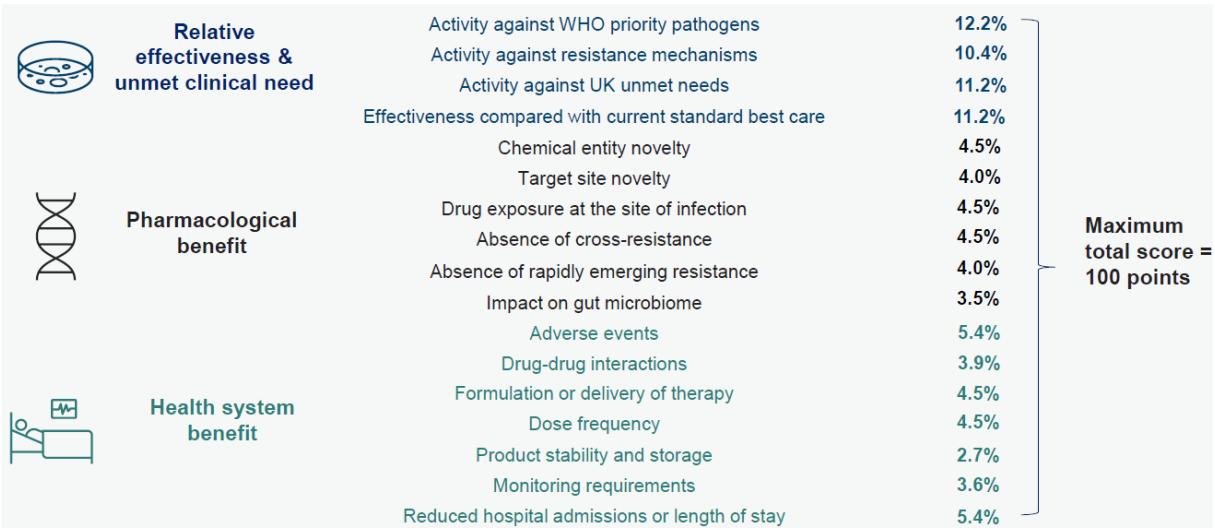

Figure 3: Award criteria to determine the value of contract payment

The permanent scheme will be run at the UK level. Such payment system over the four nations of the UK could be analogous to regional payment systems in other countries. One authority will lead and run the procurement process and product evaluations. Then, there will be nation specific contracts. But one nation can manage all four contracts once they are in place, which is obviously more efficient for both healthcare systems and for companies.

The assessment against the 17 criteria puts the product into one of four value bands, according to the percentage of maximum points achieved (Figure 4). Companies will be offered a contract of 5,10, 15 or 20 million pounds per year if they score at least 50%. The duration of the contract is a minimum of 3 years and up to 15 years or until patent expiry, whichever comes first.

Contract value band	Band 1 Breakthrough antimicrobial	Band 2 Critical antimicrobial	Band 3 Priority antimicrobial	Band 4 Important antimicrobial
Annual payment	£20m	£15m	£10m	£5m
Points scored against award criteria, % of maximum score	≥80%	70–79%	60–69%	50–59%
Values represent England's payments *Scotland, Wales and Northern Ireland will pay additional, proportionate amounts* *Each product must be worth ≥50% of available points to be offered a contract*				

Figure 4: The four contract value bands according to the points scored against the award criteria

[8] STEDI stands for Spectrum, Transmission, Enablement, Diversity and Insurance. For more information see Brassel S. et al., "Value assessment of antimicrobials using the STEDI framework – How steady is the outcome?" Health Policy, 2023, 136, 104892 (here).
[9] NHS England (here): The Antimicrobial Products Subscription Model: consultation on proposals, accessed 22.04.2024

Which mechanism(s)?: The European Commission's and Parliament's proposals

In its proposal for the revision of the General Pharmaceutical Legislation[10], the European Commission (EC) proposed a toolbox of incentives for innovation and access, including:

- Transferable Exclusivity Extension vouchers incentivising the development of new antimicrobials.
- Procurement-based incentives to improve access and innovation, that HERA has been tasked to explore.

The Transferable Exclusivity Extension vouchers as proposed by the European Commission

In the proposed Regulation[11], the EC introduced the exclusivity vouchers that can extend by 12 months the Regulatory Data Protection (RDP) of a marketed drug.

Such a voucher would be awarded to priority antimicrobials, which could be a new class, a new mechanism of action or new active substance. Conditions apply to guarantee that the marketing authorization holder has the capacity to supply in sufficient quantities for the needs of the Union markets. A maximum of 10 vouchers could be granted over a period of 15 years.

The impact assessment[12] estimated (Figure 5):

- The gain for the originator would be an additional €545 million, generated from the non-contested sales.
- From this, the manufacturing/distribution costs and the cost of capital should be subtracted, leading to a voucher value of €360m.
- If the voucher has to be sold (e.g. the antimicrobial company has no medicine to apply the voucher to), the generated income should amount €205m.
- On the other hand, the extra spending for the health system would be €283 million, increased to €441 million if including patients' unserved costs.

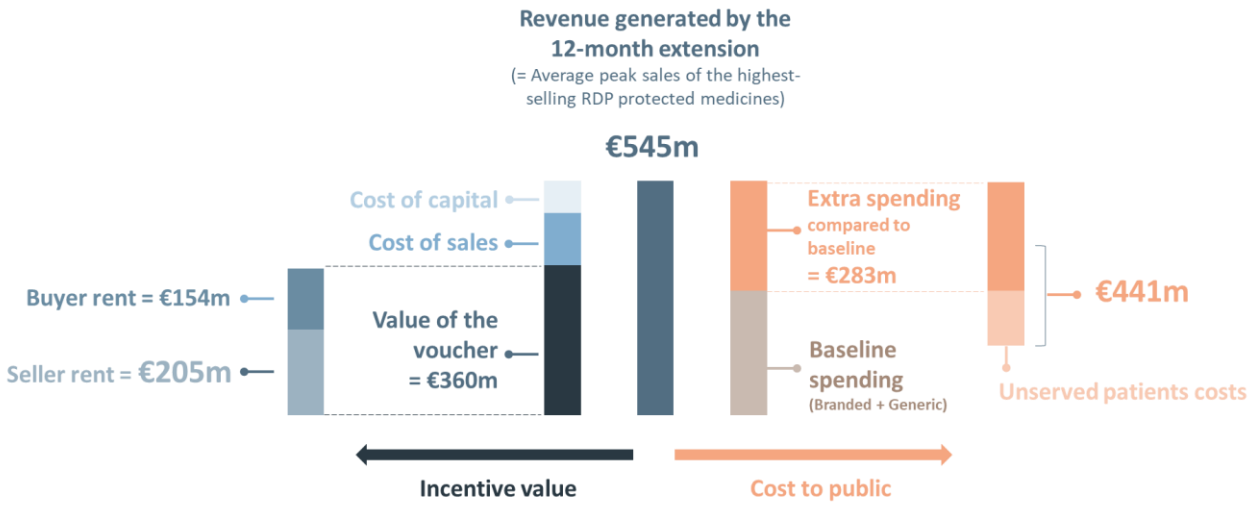

Figure 5: Incentive value and cost to public of the voucher proposed by the European Commission

[10] Reform of the EU pharmaceutical legislation (here), 2023
[11] Regulation laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency (here), 2023
[12] Directorate-General for Health and Food Safety (here): Impact assessment report and executive summary accompanying the revision of the general pharmaceutical legislation, 2023

These figures are reflecting a retrospective analysis based on the best-selling RDP drugs over the 2014-2024 period and could benefit from a sensitivity analysis, giving results in the form of a range with a confidence index.

A procurement-based incentive for access to be piloted by HERA

The procurement-based incentive was mentioned in the Council Recommendation on AMR[13], in the form of a multi-country PULL incentive where Member States could participate on a voluntary basis.

HERA is developing a pilot with the sole aim of improving access without interfering with Member States' competencies in pricing and reimbursement. The exact design and size are still a work in progress.

One of the aims of the pilot is to address potential challenges of this multi-country approach, including the possible impact from parallel import, the possible impact on price negotiations at Member States or the complexities linked to the diversity of national procedure and languages or to sales reporting.

The European Parliament's position proposes various options

The European Parliament established its own position[14], which first includes either an exclusivity voucher with additional constraints compared to the EC proposal or a milestone-based reward payment, and second, a subscription organised through a joint procurement mechanism.

For the voucher, the following features were either changed or added to its design:

- The duration of extension depends on the level of priority of the pathogen targeted by the new drug, and ranges from 6 to 12 months.
- The voucher cannot be applied to a product that already reached the maximum regulatory data protection (i.e. 8.5 years in the proposed Directive).
- The buyer of the voucher will pay the agreed amount to HERA, who will then pay the drug developer in yearly instalments.

The milestone prize will be paid out of existing financial vehicles (e.g. Horizon Europe, EIC, etc.) and it is expected that the money can be used to further develop the product and ensures the commercialisation of the product in the EU through the joint procurement mechanism.

Finally, the subscription programme is intended to gather, on a voluntary basis, Member States into a joint procurement scheme, the details of which should be described in a specific agreement.

Which mechanism(s)?: Adapting proposals

One concern about the transferable exclusivity extension voucher model is the unpredictability of the voucher value and cost to payers (which varies based on which product receives the extension). A delinked revenue guarantee is more predictable, provided the amount committed is large enough, but the multilateral contributions are classically subject to 'free riding'. With the voucher deployed through an EU regulation, the free-riding issue could be dealt with at the EU level.

[13] Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach (here), 2023

[14] European Parliament (here) : Compromise amendments to the proposal for Regulation of the General Pharmaceutical Legislation, 2024

Analysing and modifying the exclusivity vouchers[15]

The relative cost and benefit of the different proposals can be assessed through investigating the method of payment: e.g. direct payment such as through a revenue guarantee or indirect payment such as through a transferable exclusivity extension voucher. In the case of the voucher, the cost is the cost supported for delaying the entry of generics whereas the benefit is the price paid by the buyer of the voucher to the antimicrobial company.

The cost-over-reward ratio can be used to determine which of the two (direct or indirect) approaches is the most beneficial at member state level (Figure 6). The cost-over-reward ratio captures how many euros would be lost by in the reduction of social surplus[16] due to the extension of market power of the company who uses the voucher, compared to the additional benefit of rewarding the inventor of the antimicrobial.

If the cost-over-reward ratio is below 1 (*e.g.* there is less loss of social surplus compared to the benefit of the reward), the indirect payment, *e.g.* the voucher, is preferable, otherwise the direct payment is.

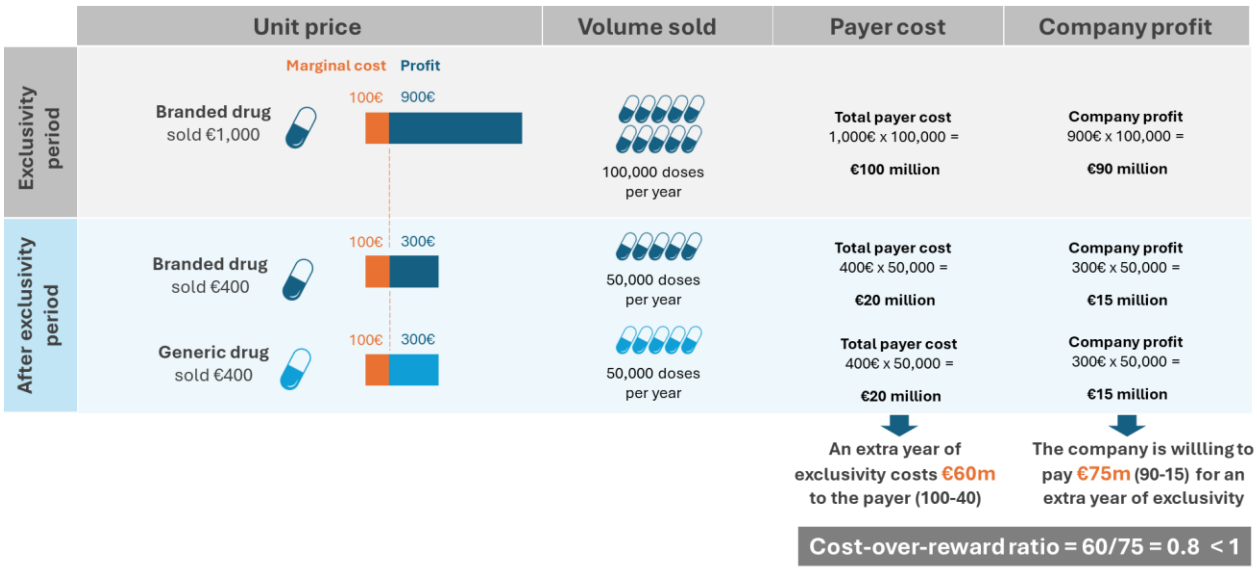

Figure 6: An example to describe the principle of cost-over-reward ratio

The calculation of cost-over-reward ratio for 15 European countries is described under Table 2, and shows values below 1 for every country.

Table 2: Value of cost-over-reward ratio for 15 countries in Europe

Country	ρ_i		
AUSTRIA	0.98	0.96	0.97
BELGIUM	0.87	0.81	0.81
FINLAND	0.90	0.94	0.94
FRANCE	0.72	0.63	0.63
GERMANY	0.73	0.74	0.83
GREECE	0.34	0.43	0.49
IRELAND	0.67	0.46	0.40
ITALY	0.91	0.77	0.89
NORWAY	0.78	0.99	0.91
POLAND	0.69	0.87	0.82
PORTUGAL	0.84	0.78	0.76
SPAIN	0.76	0.69	0.67
SWEDEN	0.89	0.94	0.94
SWITZERLAND	0.79	0.76	0.75
UK	0.73	0.69	0.69
All	0.74	0.89	0.84

[15] Dubois P, Tirole J., Moisson P.-H. (here), Can transferable patent extensions solve the market failure for antibiotics?, 2022

[16] Social surplus is the monetary gain that consumers and producers obtain due to a price that is favourable to both.

These values can be influenced by competition

- The higher the competition to buy the voucher, the higher its efficiency. Said differently, the higher the difference between the willingness-to-pay for the voucher between the highest and the second-highest selling candidate drugs for exclusivity extension, the greater the cost-over-reward ratio. In that regard, restricting the eligibility of the voucher to products protected by Regulatory Data Protection notably decreases the chances that the 2 highest bidders are close to each other
- The larger the number of vouchers available to buy, the lower the willingness-to-pay because of the given number of potential buyers in a given year, hence the greater the cost-over-reward ratio.

The value of the voucher is classically defined in length (e.g., 12-month exclusivity); the revenue that can be retrieved depends on the drug to which the voucher will be sold, bringing uncertainty for the drug developer. To increase predictability of the reward, vouchers could be offered at a specific value, and further auctioned in terms of exclusivity length: potential buyers would then bid for the shortest exclusivity extension, and the winner pays the price tag, either directly to the antimicrobial producer or to an authority that will pay the antimicrobial producer over a few years to enforce supply commitment. As a safeguard, a maximum reserve exclusivity extension could be added to the auction.

Overall, the voucher concept requires careful design. Rules constraining the profile of eligible medicines improves the predictability for the payers. On the other hand, they decrease the number of possible buyers, and lowering the competition decreases the efficiency of the voucher mechanism[17].

Which mechanism(s)?: An adapted version of the revenue guarantee

A type of revenue guarantee scaled up to also incentivise innovation can also be envisioned[18]. A multi-step process is proposed:

- First, the European Medicines Agency (EMA) ranks new antimicrobials into one of four reward tiers. Each tier is associated with predefined, non-negotiable financial commitment per country: € 120/80/15 million per year, respectively (Table 3) as well as no reward for non-differentiated antimicrobials.
- Second, Member States are given a fixed amount of time to decide whether they want to participate to the revenue guarantee scheme.
- Third, HERA negotiates the revenue guarantee contract with the antimicrobial producer.
- Finally, national pricing and reimbursement processes are implemented, and now benefit from an access guarantee.

Table 3: Criteria and annual reward of the different reward tiers proposed

Reward tier	WHO Priority Pathogens	Innovation	Clinical evidence	Suggested annual reward total (30 countries)
High	"Critical" or multiple	Yes	Yes	€ 120 m
Medium	Pathogen-specific	Yes	Yes	€ 80 m
Low	Potentially	No	Yes	€ 15 m
No reward	Potentially	No	Non-differentiated	€ 0

Only if all 30 countries participate, otherwise decreases accordingly

[17] The larger the difference between the first two bidders (bids being placed either in contract value or length of extension), the larger the difference between the price paid by the buyer to acquire the voucher and the income received using it, at the expense of the public health system.

[18] DRIVE-AB Policy Brief (here): A Pan-EU-EEA Pull Incentive for Antimicrobial Innovation and Access, 2023

The scheme could also work for generics, with an appropriate award tier.

In terms of financing, the easiest way is to provide HERA with sufficient funding to cover the part of the revenue guarantee that is not paid by Member States through national-level sales. Otherwise, more complicated mechanisms will need to be created to define how Member States will have to pay.

Finally, the scheme does not need to be part of the EU General Pharmaceutical Legislation, allowing for greater flexibility in its implementation.

Putting diagnostics into the equation

Diagnostics are critical tools to guide the appropriate use of antibiotics, but there are several roadblocks that hamper the broader use of diagnostic tests. For instance:

- The price compared to empirical treatment: even the routine C-Reactive Protein test is more expensive than a 3-day prescription of amoxicillin.
- The uncertain path to prescription and use: there is no well-defined route to reimbursement for diagnostic tests, and Health Technology Assessment (HTA) is far from being systematically used for pricing and funding decisions.
- The under-perceived value brought by the test result: in general, HTA evaluates Quality-Adjusted Life-Years (QALYs) gained, the net costs, and sometimes also the productivity and family spillovers. But diagnostic tests may bring additional elements of societal value (Figure 7).

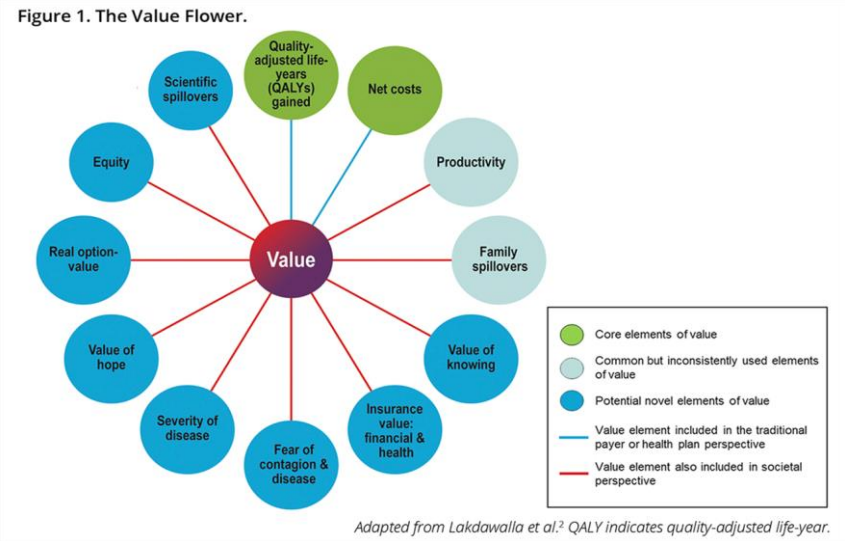

Figure 7: The value flower of the diagnostics

The clinical and public health value of a new antibiotic is partially dependent on which complementary diagnostics are also available. To be complementary, diagnostics have to affect the decisions physicians are making. But not all diagnostics are created equal. The most useful diagnostics need:

- To preserve the effectiveness of a new antibiotic for as long as possible after it is introduced, by limiting prescription to the only cases they are needed.
- To enable rapid detection of resistance to older antibiotics, as it then makes a new antibiotic more attractive and profitable.
- To provide information that can be used to specifically target the spread of resistant infections, leading to resistance targeting and transmission disruption interventions that would lower AMR prevalence to older antibiotics over time.

Policies should be designed to support the pipeline of complementary diagnostics and its coordination with the pipeline for new antibiotics[19,20]. Unfortunately, this field is still under-researched and under-explored.

The VALUE-Dx project intends to model the impact of diagnostic test use on the level of antibiotic prescriptions and use the results to extrapolate the value of using the diagnostic tests to help support future HTAs. The results are expected during the fall 2024.

Conclusion

Europe is close to a consensus on the amount of its PULL incentive's fair share that is needed[21]; and the UK work demonstrates that these figures match with public health value. Consensus also seems almost achieved on the revenue guarantee model to ensure access.

The question that seems to remain is the mechanism to incentivise innovation. The exclusivity voucher alone? With the constraints attached to the voucher proposals that have been tabled so far, it is unrealistic to believe it can reach EU fair share on its own. A combination of vouchers with complementary revenue guarantee? An upscaled revenue guarantee? Would milestone prizes have a role to play to decrease the size of the incentive needed at market entry, and how do their benefits they would also benefit to drug candidates that will never make it to the market and might generate gaming behaviours from the industry?

Finally, the question of which criteria will qualify for the incentive remains. The UK has made a valuable contribution in that regard. Criteria for EU incentives should aim to align with the UK and other G7 nations as much as possible for the global R&D targets to remain achievable for drug developers.

[19] McAdams D, Resistance Diagnosis and the Changing Epidemiology of Antibiotic Resistance, Antimicrobial Therapeutics Reviews (Annals of New York Academy of Sciences), 1388(1), 5-17, 2017

[20] McAdams, Resistance Diagnosis and the Changing Economics of Antibiotic Discovery, Antimicrobial Therapeutics Reviews (Annals of New York Academy of Sciences), 1388(1), 18-25, 2017

[21] Figures should be indexed to inflation to avoid loss of attractiveness in future years