Assessing the costs of the EC's proposal for a transferable exclusivity voucher to address AMR

Introduction

In 2023 there have been significant European policy developments on incentives aimed at combatting antimicrobial resistance (AMR). In March, the Health Emergency Preparedness and Response Authority (HERA) published its analyses of incentives for antimicrobial access and innovation.[1] This considered "options for action in order to bring more AMR medical countermeasures to market and ensure their access across the EU Member States" and focused on several incentive types including the Revenue Guarantee Model (RGM). Shortly afterwards, the European Commission (EC) published its proposed revisions to the "general pharmaceutical legislation" (GPL), including the proposal to introduce a transferable exclusivity voucher (TEV) to stimulate antimicrobial innovation.[2]

This has resulted in extensive discussions with various stakeholders on the merits of the proposed incentives, with particular focus on both their overall cost to the EU as a whole and their likely cost to respective Member State healthcare systems.

In this paper, we seek to contribute to the debate by providing estimates of the overall and country-specific costs of the EC's proposal on TEV and comparing these to the cost of inaction. Finally, we critique existing estimates around the proposals.

The EC's proposal on TEV

In the context of the growing threat of AMR, the EC has put forward a TEV with the objective of incentivising research and development of innovative antimicrobials. The TEV would provide a 12-month extension of regulatory data protection that could later be used on other products in the portfolio of the antibiotic developer or sold to another company.

It has been shown that the benefits of TEV clearly outweigh the costs. The need for new antimicrobials is well established and is illustrated by the list of priority pathogens outlined by the World Health Organization (WHO), where there is a clear need for medicines but relatively few are in development. New antimicrobials are expected to deliver substantial benefits to European patients, healthcare systems and society as a whole, as well as cost savings for Member States.[3] Recent analysis by the Center for Global Development found that the new EU antimicrobial incentive program would save 20,000 lives and deliver $15.5bn in total benefits, with a return on investment of 4:1 over the next 10 years.[4]

However, like any effective pull incentive, there will be concerns about the costs of its introduction. This has been highlighted in the Member State non-paper and in the draft report for the European Parliament health committee submitted by MEP Tiemo Wölken, one of the two rapporteurs for the revision of the general pharmaceutical legislation.[5,6] In his report, Wölken criticized the unpredictable nature of TEV's costs for national health budgets.

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[1] 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.

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

[3] Wilsdon, T., Robson, A. and 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.

[4] Bonnifield, R. S. and Towse, A. (2022) "Estimating the EUs return on investment from an ambitious program to incentivize new antibiotics." Center for Global Development.

[5] Member State non-paper (2022) Novel stimuli for the development and keeping on the market of antimicrobials.

[6] European Parliament – Committee on the Environment, Public Health and Food Safety (2023) Draft report on the EU pharmaceutical legislation. Available at: https://www.europarl.europa.eu/doceo/document/ENVI-PR-753550_EN.pdf

The cost of the TEV will largely be met by the healthcare payers who reimburse the product that the TEV is applied to. This cost is incurred because of the extra year of regulatory protection that the product in question receives, which delays the entry of generic/biosimilar competition.

In its impact assessment accompanying the revision of the general pharmaceutical legislation, the EC seeks to quantify the costs of TEV to healthcare systems across the EU. These costs are outlined in Box 1 below.[7]

Box 1: The estimated cost of one TEV granted per year in the EU

- **For healthcare payers:** The combined additional cost calculated for national healthcare systems is €294m per year, which equates to €4.4bn over 15 years.

Setting out the costs of TEV for individual Member States

In its impact assessment, the EC does not look at the cost of TEV at the individual Member State level. However, this can be extrapolated using the overall cost of the TEV to healthcare systems and identifying each country's share of EU pharmaceutical spending. While this approach has limitations, including that the TEV-applied product might not be reimbursed in all EU countries (resulting in some countries paying more and others less), it can provide an approximation of the TEV cost across Member States.[8]

The respective share of TEV cost to Member State healthcare systems can be seen in Table 2 below.

Table 2: The healthcare system cost per TEV per Member State based on pharmaceutical spending share[9] (this equates to yearly cost given assumption of 1 TEV per year)

Member State	Estimated average cost per TEV to healthcare systems (€m)[10]
Austria	7.3
Belgium	10.3
Bulgaria	2.2
Croatia	1.5
Cyprus	0.3
Czech Republic	4.8
Denmark	4.4
Estonia	0.6
Finland	4.1

[7] European Commission (2023) Impact Assessment Report for the reform of the general pharmaceutical legislation (Annexes 1–4 and 6–9).

[8] In the EFPIA CBA undertaken by Charles River Associates, the costs were examined for eight Member States. This was based on a TEV with wider eligibility, so the costs need to be scaled to be comparable. This found Germany 81; France 70; Italy 70; Spain 44; Greece 10; Poland 9.5. This took into account the products under examination and the nature of the off-patent market; however, the results are broadly in line with the analysis above.

[9] EFPIA (2022) The Pharmaceutical Industry in Figures.

[10] This approach takes data for the EU's total pharmaceutical spending and each Member State's spending to determine each Member State's respective share. This percentage share is then applied to the average total cost per TEV to identify the cost to each Member State's healthcare system.

France	52.9
Germany	70.6
Greece	7.3
Hungary	5.9
Ireland	3.4
Italy	38.2
Latvia	0.4
Lithuania	1.3
Luxembourg	0.3
Malta	0.3
Netherlands	10.3
Poland	12.0
Portugal	6.6
Romania	7.3
Slovakia	2.9
Slovenia	1.0
Spain	29.4
Sweden	8.1

It is possible to look at these costs in a number of different ways:

- **The relative size of the costs:** These costs represent an extremely small percentage of pharmaceutical spending by Member States. For example, in the Czech Republic, pharmaceutical spending in 2020 was €3.4bn.[11] The estimated cost per TEV to the Czech Republic healthcare system is €4.85m or 0.15% of total pharmaceutical spending.
- **The relative cost compared to other approaches:** For example, in the UK there is a proposal for a subscription scheme. This would cost between £10m and £20m per year for 10 years.[12] Assuming £15m, this means the UK would pay £150m (~€170m) per product included in the subscription model compared to the cost of a TEV for France and Germany of €53m and €71m respectively.
- **The distribution of costs:** When looking at the cost of TEV to healthcare systems at the Member State level, it is evident that the bulk of the cost (around 50%) is met by the EU4 (Germany, France, Italy, and Spain). Across the majority of countries, the cost impact per TEV is relatively small, with only eight EU Member States paying above €10m per TEV.

Much of the criticism around the potential introduction of TEV centres on its costs to EU healthcare systems. This is a key argument across several pieces of the recent literature on the topic. For example, the Member State non-paper on novel stimuli for the development and keeping on the market of antimicrobials states that the only certainty of TEV is that the "costs for national health systems will be high".[13] The Medicines for Europe position paper on the revision of the general pharmaceutical legislation argues that the TEV would be "unnecessarily

[11] EFPIA (2022) The Pharmaceutical Industry in Figures.

[12] NHS England (2023) Antimicrobial Products Subscription Model.

[13] Member State non-paper (2022) Novel stimuli for the development and keeping on the market of antimicrobials.

expensive", supporting this with flawed examples of historical products that TEV could have been applied to and calculating the cost of lost savings as high as €1bn.[14,15]

Based on the EC's impact assessment, it is clear that concerns in the literature surrounding the cost of TEV to national healthcare systems have been overstated and that the costs to Member State budgets, although significant, need to be compared to the higher costs in other jurisdictions and the direct cost of inaction.

Comparing the cost of TEV with the cost of inaction

This response has so far focused on the cost of TEV, but it is also important to highlight the cost of inaction at both the broader EU and the individual Member State level.

The Organisation for Economic Co-operation and Development (OECD) and EC highlight the current high cost of AMR to Member State healthcare systems. This currently stands at €1.1bn annually and is projected to result in 35,000 deaths per year.[16] AMR could also lead to an annual decrease in European Gross Domestic Product (GDP) of $180bn – $680bn by 2050.[17] Thus there is a clear need to develop new antimicrobials to address this growing threat, but the market to do so is currently broken, with very few novel antibiotics being developed. A recent analysis by the WHO found that in 2021 there were only 27 new antimicrobials in clinical development against WHO-priority pathogens.[18] Without new antimicrobials, there will be a substantial cost to patients in many therapy areas. For example, childbirth, chemotherapy, and the performance of routine surgeries all rely on our ability to prevent and effectively treat bacterial infections.[19] **The cost of inaction in the EU will be significant.**

Table 3: The healthcare system cost per TEV and AMR per Member State based on pharmaceutical spending share and AMR cost per capita[20,21]

Member State	Estimated average cost per TEV to healthcare systems (€m)[22]	Estimated annual cost of AMR (€m)[23]
Austria	7.3	16.1
Belgium	10.3	22.0
Bulgaria	2.2	4.1
Croatia	1.5	5.5
Cyprus	0.3	2.6
Czech Republic	4.8	16.8

[14] Medicines for Europe (2023) Position paper on the revision to the general pharmaceutical legislation.
[15] For example, the cost comparisons do not take into account the cost of generics in the market.
[16] OECD (2019) *Antimicrobial Resistance: Tackling the Burden in the European Union*. Available at: https://www.oecd.org/health/health-systems/AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.pdf
[17] World Bank Group (2017) *Drug-resistant infections: a threat to our economic future*. Available at: https://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf
[18] World Health Organization (2022) *Lack of innovation set to undermine antibiotic performance and health gains.* Available at: https://www.who.int/news/item/22-06-2022-22-06-2022-lack-of-innovation-set-to-undermine-antibiotic-performance-and-health-gains#:~:text=According%20to%20WHO%20annual%20analyses,over%20the%20last%203%20years.
[19] Nanayakkara, A., Boucher, H., Fowler, V., Jezek, A., Outterson, K. and Greenberg, D. (2021) "Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward". *CA: A Cancer Journal for Clinicians*. 71(6): 488–504. https://doi.org/10.3322/caac.21697
[20] EFPIA (2022) The Pharmaceutical Industry in Figures.
[21] OECD and EU (2019). Antimicrobial resistance – tackling the burden in the European Union.
[22] This approach takes data for the EU's total pharmaceutical spending and each Member State's spending to determine each Member State's respective share. This percentage share is then applied to the total cost per TEV to identify the cost to each Member State's healthcare system.
[23] Our approach to identifying the annual cost of AMR leverages OECD data on the per capita cost of AMR and current population numbers for each Member State.

Denmark	4.4	4.10
Estonia	0.6	0.3
Finland	4.1	2.2
France	52.9	264.3
Germany	70.6	134.1
Greece	7.3	42.6
Hungary	5.9	15.5
Ireland	3.4	14.1
Italy	38.2	298.9
Latvia	0.4	0.9
Lithuania	1.3	2.0
Luxembourg	0.3	2.6
Malta	0.3	4.1
Netherlands	10.3	10.6
Poland	12.0	65.6
Portugal	6.6	47.2
Romania	7.3	23.9
Slovakia	2.9	15.6
Slovenia	1.0	3.2
Spain	29.4	76.9
Sweden	8.1	4.2
Total cost	**294**	**1,100**

While there is considerable variation in the cost of AMR at the individual Member State level, it is a burden to all EU countries. Using OECD data, we outline the cost of AMR to each Member State in Table 3 alongside the annual cost of the TEV.[24] Even if we only consider the most conservative cost estimates (excluding the cost to patients and the economy), across all but four countries the annual cost of AMR exceeds the annual cost of TEV, demonstrating that in the context of the cost of AMR, the TEV is a comparatively small investment. In many countries, the cost of AMR to the healthcare system is more than double the cost of the TEV, with this being as high as 8x in countries with a considerably high AMR burden such as Italy and Portugal.

The introduction of TEV would play an important role in reducing the burden and cost of AMR through the development of new antimicrobials. While the EC acknowledges that it is difficult to monetise this impact, it will have a significant impact on patients.[25] Previous analysis on the

[24] This is only a partial comparison. To compare the costs and benefits of a TEV, we would need to consider the full set of benefits including those to patients and the societal benefits, including the benefit to the economy. This was examined in Wilsdon, T., Robson, A. and 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. This shows the benefits are significantly higher than the costs.

[25] European Commission (2023) Impact Assessment Report for the reform of the general pharmaceutical legislation (Annexes 1–4 and 6–9).

cost of TEV has shown that the benefits of TEV (i.e. the development of new antimicrobials) far exceed the costs. This takes into account the actual pipeline of products that might benefit from extended exclusivity further to a TEV, the value of particular products at the point the TEV is applied, the impact of delayed genericisation on different EU member states, and that this cost is paid in the future.[26]

Overestimating costs – critiquing the EC's cost estimate

There have been many overestimates of the cost of TEV.[27] These are often based on historical blockbuster products that would not qualify for the Commission's TEV. It is common for these papers to miss out the cost of generic medicines themselves.

Even the Commission's estimates are likely to be overestimates. Notably, these cost estimates assume that one voucher will be issued each year (totalling 15 vouchers across the initial time period of the legislation). However, the EC's proposal states that a maximum of 10 vouchers can be awarded over 15 years. Furthermore, the EC's assumption centres around the TEV being applied to the eligible product with the highest revenue – and while this is a possibility, it is not guaranteed.[28]

Both of these factors suggest that the costs of the TEV to national healthcare systems put forward by the EC are likely an overestimation.

Conclusion

Overall, the costs of TEV, as designed by the Commission, to healthcare systems will be small for all EU Member States and will account for an insignificant percentage of pharmaceutical sales. In contrast, the cost of inaction would be significant to both healthcare systems (and to patients and the economy).

The TEV is an important step forward in the European policy debate on addressing AMR. For the proposal to be effective, the TEV will need to be complemented with other policies to ensure an incentive of sufficient size to incentivize the development of new antimicrobials.

[26] Wilsdon, T., Robson, A. and 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.

[27] Årdal, Christine et al. (2023) "Transferable exclusivity voucher: a flawed incentive to stimulate antibiotic innovation". *Lancet*.

[28] European Commission (2023) Impact Assessment Report for the reform of the general pharmaceutical legislation (Annexes 1–4 and 6–9).

Appendix:

What factors impact the cost of TEV?

The cost of the TEV is affected by several factors:

- Through its **approach to extending exclusivity**, i.e. application to Regulatory Data Protection (RDP) only, the TEV can only be used on a subset of products where RDP is the last measure of protection for marketing exclusivity (as opposed to those having a supplementary protection certificate (SPC) as the last measure of protection). The EC believes this reduces the cost of the TEV (and increases its efficiency) as these products tend to have lower peak sales vs those with an SPC.[29]
- The **length of extension**, i.e. 12 months, refers to the additional time period of exclusivity for the product, during which cheaper generic/biosimilar products cannot enter the market, thus leading to increased incurred costs for healthcare systems.
- Furthermore, the greater the **number of vouchers that are issued**, the more products there will be that benefit from increased exclusivity and, in turn, increase costs for healthcare systems. In the EC proposal, the number of vouchers is capped at 10, thus limiting the potential costs. However, it is also recognised that the cost of TEV will go down, on average, the larger the number of TEVs.

The cost of the TEV is also driven by the **revenue of the product to which it is applied**. For example, a product with higher revenue across the EU would lead to healthcare systems incurring greater costs through the product's extended protection period vs a product with lower revenue.

Table A1: Key components related to the cost of the Commission's proposal on TEV

Component	EC Proposal TEV[30]
Approach to extending exclusivity	Application to Regulatory Data Protection (RDP) only
Length of extension	12-month extension
Number of vouchers	A maximum of 10 vouchers can be granted in 15 years

[29] European Commission (2023) Impact Assessment Report for the reform of the general pharmaceutical legislation (Annexes 1–4 and 6–9).
[30] 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.