

A framework for assessing the  
potential net benefits realised  
through Transferable Exclusivity  
Extension (TEE) as an incentive for  
development of novel  
antimicrobials:  
FINAL REPORT

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## Executive summary

The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates (CRA) to develop a methodology for quantifying the benefits and costs of implementing a transferable exclusivity extension (TEE) to incentivise the development of antimicrobials in Europe and, where possible, to provide high-level estimates for these.

### **Introduction**

The threat of antimicrobial resistance (AMR) is well known but bears repeating. When disease-causing bacteria, viruses, fungi and parasites no longer respond to existing medicines, this presents a major threat to global health. This has been recognised in the European Commission's Pharmaceutical Strategy.<sup>1</sup> There have been multiple calls for and commitments on 'pull' incentives to stimulate the development of antimicrobials and help fix the 'broken' economic model for incentivising antimicrobial development. The European Commission's Pharmaceutical Strategy commits to piloting pull incentives and exploring new types of incentives for antimicrobials.<sup>2</sup>

One novel proposal for a pull incentive in Europe is a TEE, whereby the manufacturer of a new antimicrobial which meets certain criteria would receive a voucher ('a TEE') upon European regulatory approval of that antimicrobial. This voucher can be used by the recipient to extend the marketing exclusivity of one of its products for a period of time, or sold to another company which can then use it to extend the marketing exclusivity of one of its own products. TEE has been put forward as an incentive that would have sufficient power to incentivise antimicrobial research and development. It is within current European Union (EU) competencies and would provide pull incentive funding in a stable manner, not dependent on appropriations from Member States (MS) and with no up-front cost, but there are also concerns about its use in Europe, particularly regarding the costs of the TEE. In the context of the ongoing debate around implementation of TEE in Europe, it is important to consider the benefits it could bring to patients and to society and compare these to what it may cost European MS.

### **The approach**

To develop a methodology for estimating the costs and benefits of TEE, we used a five-step approach, illustrated in Figure 1. First, we undertook a literature review of existing studies on TEE. This included academic articles (7), public agency publications (5), non-governmental organisation publications (3), and industry publications (3). We then developed a set of assumptions regarding the design of the TEE, drawing on previous research. Third, we collected data on the costs and benefits of TEE in six MS using two different approaches, in order to understand the current and projected future impact of AMR on patients and wider society. This led us to 13 academic articles, 18 public agency publications, and five non-governmental organisation publications focused on specific markets. In parallel, we conducted a series of nine interviews with experts to test the approach to estimating the costs and benefits of TEE, and we collected input from a multi-stakeholder event at Chatham House.

We selected six European countries as the focus for the analysis, to understand how the costs and benefits of TEE may differ between countries in Europe. In particular, given that the cost of TEE is driven to a significant extent by the policy and economic environment when a medicine faces generic

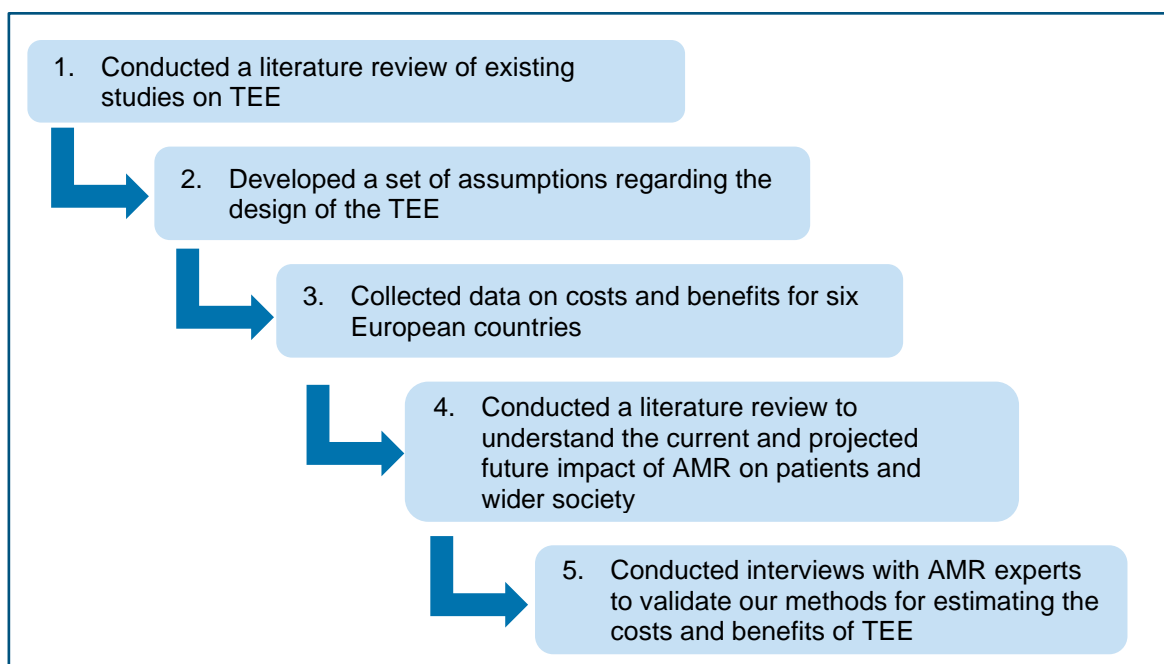
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<sup>1</sup> European Commission (2020) *Pharmaceutical Strategy for Europe*. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN> [Accessed 20 May 2022]

<sup>2</sup> Ibid.

competition, we ensured that we selected countries with different off-patent environments (particularly with regard to the speed of generic entry and the impact on prices). On this basis, we selected France, Germany, Italy, and Spain ('the EU4'), Poland, and Greece.

**Figure 1: Illustration of five-step approach**



#### ***Assumptions necessary for the cost-benefit analysis***

In order to estimate the benefits and costs of TEE to European MS, we needed to define key characteristics of the TEE policy to be assessed. We have made the following assumptions:

- that the policy would be widely applicable and affect products with different forms of protection
- that the policy would be introduced in 2024
- the pathogens for which a TEE is applicable
- the number of antibiotics awarded a TEE each year (1 or 2)
- the length of the TEE (9 or 12 months)<sup>3</sup>
- the global policy environment of pull incentives

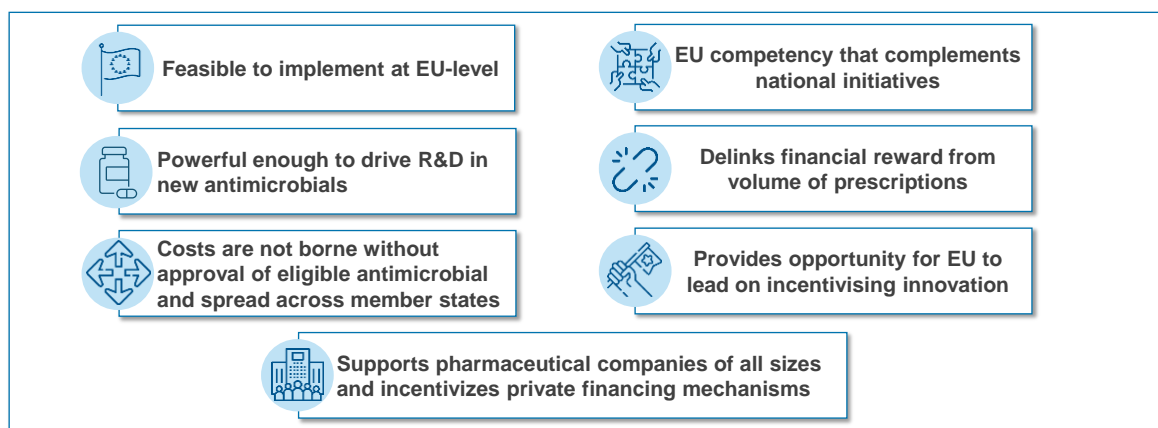
#### ***The advantages of a TEE vs the benefits***

There is a growing literature comparing the different policy proposals that could be used to incentivise antibiotics. These describe the challenges to introducing a policy to address AMR, particularly how to achieve political will, coordination across countries, and an incentive of sufficient size. Comparing TEE to other types of policy intervention, such as subscription models, TEE has a number of advantages at a European level, which have been described in previous EFPIA papers and summarised in the figure below.

**Figure 2: Advantages of implementing TEE in Europe**

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Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics.



Source: EFPIA (2021) *A new EU pull incentive to address Antimicrobial Resistance (AMR)*. Available at: <https://www.efpia.eu/media/636464/a-new-eu-pull-incentive-to-address-anti-microbial-resistance-amr.pdf> [Accessed 18 May 2022]

Equally, there are challenges to introducing a TEE. It would need to be carefully designed so that the incentive is aligned to the value of antibiotics, and there will need to be complementary policies to ensure access. These are important considerations when comparing TEE to other policy choices. This suggests feasibility is an important advantage for TEE – and there appears agreement that TEE is feasible.<sup>4</sup> However this is not the focus of this paper. This paper examines whether a TEE if implemented would deliver net benefits to society – i.e. whether the benefits outweigh the costs. To do this we first consider the benefits of TEE incentivising new antibiotics and then consider the costs.

### **Benefits of TEE**

The benefits of TEE arise primarily from the value of the antimicrobials it incentivises. We look at this from three perspectives. First, we consider the ‘society-wide perspective’. The antibiotic era revolutionised the treatment of infectious diseases worldwide. There are no detailed estimates of the value of the current portfolio of antibiotics, but based on simple estimates and expert opinion, it is reasonable to believe it is trillions of Euros.<sup>5</sup> AMR devalues this portfolio of antibiotics. The growing clinical and economic burden of AMR allows us to understand the value of having an effective arsenal of antibiotics, and the benefits of investing in maintaining it. AMR could lead to an annual decrease in European Gross Domestic Product (GDP) of \$180bn–\$680bn by 2050.<sup>6</sup> Furthermore, estimates show that by 2050, AMR will have caused approximately 1.3 million deaths in the EU / European Economic Area (EEA) region and result in an average of 1 million disability-adjusted life years (DALYs) lost each year for EU/EEA countries from 2015 to 2050.<sup>7</sup> Given the threat of AMR to the health and economy of Europe, there would be clear and substantial benefits to implementing a

<sup>4</sup> For other policy proposals there is significantly greater uncertainty regarding whether it will be possible to align Member States and hence whether an incentive of sufficient scale is possible. Feasibility is therefore a bigger consideration for other incentives.

<sup>5</sup> Sertkaya, A., Eyraud, J., Birkenbach, A. et al. (2014) *Analytical Framework for Examining the Value of Antibacterial Products*. Eastern Research Group. Available at: [https://aspe.hhs.gov/sites/default/files/migrated\\_legacy\\_files/44241/rpt\\_antibacterials.pdf](https://aspe.hhs.gov/sites/default/files/migrated_legacy_files/44241/rpt_antibacterials.pdf) [Accessed 21 June 2022]

<sup>6</sup> 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> [Accessed 20 May 2022]

<sup>7</sup> Cravo Oliveira, T. & Padget, M. (2018) Trends in antimicrobial resistance in OECD countries. In: *OECD Health Policy Studies, Stemming the Superbug Tide*. OECD. <https://doi.org/10.1787/9789264307599-en> [Accessed 20 May 2022]

policy that incentivises development of the antibiotics we need to reduce its development and spread. Although it is difficult to equate this with the value of new antibiotics, this provides a guide to the magnitude.

We then consider the value from an incremental 'single antibiotic perspective'. We focus on antibiotics since that has been the focus of the existing literature, but, more broadly, a TEE can be used to incentivise any type of antimicrobial, which may be an antibiotic, antiviral, antifungal or antiparasitic. We set out the different components of value of an antibiotic, how these can be measured and tested with experts, how these can be quantified, and their applicability to different example antibiotics. We follow the approach set out by the Office of Health Economics. This distinguishes between the value of an antibiotic considered when adopting full Health Technology Assessment (HTA)<sup>8</sup> (clinical benefit, productivity), and the additional elements of value specific to antibiotics, often summarised using the acronym STEDI (spectrum value, transmission value, enablement value, diversity value, insurance value).<sup>9</sup>

We use existing estimates from the literature as 'case studies' to quantify these, with particular reference to the recent pilots in the UK. We then apply each value element described above to each of the six MS, scaling by either the size of the population or the number of infections as appropriate. Different approaches were used for enablement value (where we assumed that a new antibiotic would decrease the reduction in efficacy of prophylaxis by a certain percentage), and insurance value (where we translated the monetary value for the six MS based on population, then multiplied by an estimate of the probability of a bacterial outbreak occurrence to obtain the expected value).

The results of our analysis are set out in Table 1. There are clearly many caveats to this approach: firstly, it is comparing evidence from different antibiotics, undertaken at different points in time and covering different geographies. However, the expert interviews for this project supported that this was a reasonable approach.

**Table 1: Benefit of an antibiotic over 10 years by Member State**

Value Element	Benefits of TEE by MS (€ M Present Value)					
	France	Germany	Italy	Spain	Greece	Poland
<b>Clinical Benefit</b>	54–75	23–33	87–120	18–25	8–11	18–25
<b>Productivity</b>	69	30	111	23	10	23
<b>Transmission</b>	335–466	414–575	296–411	236–327	53–74	189–262
<b>Diversity</b>	57–79	70–97	50–69	40–55	9–13	32–44
<b>Enablement</b>	277–644	342–684	245–489	195–390	44–88	156–312
<b>Insurance</b>	43–165	54–204	38–146	30–116	7–26	24–93
<b>Spectrum value</b>	Not quantified*					

Source: CRA analysis of various sources, see text for details. Parameters used to calculate upper and lower bounds (see body text for more details): Clinical benefit, transmission value, diversity value: lower bound = €18k/QALY, upper bound = €25k/QALY. Enablement value: lower bound = 0.5% decrease in the reduction in efficacy of prophylaxis, upper bound = 1.5%

<sup>8</sup> EUnetHTA (2016) *HTA Core Model*®. Available at: <https://www.eunetha.eu/hta-core-model/> [Accessed 21 June 2022]

<sup>9</sup> Schaffer, S., West, P., Towse, A. et al. (2017) *Assessing the Value of New Antibiotics: Additional Elements of Value for Health Technology Assessment Decisions*. Office of Health Economics. Available at: <https://www.ohe.org/system/files/private/publications/OHE%20AIM%20Assessing%20The%20Value%20of%20New%20Antibiotics%20May%202017.pdf> [Accessed 20 May 2022]

*reduction in efficacy of prophylaxis. Insurance value: lower bound = 50% IV capacity, upper bound = 20% IV capacity.\* due to lack of consensus in the literature as to an appropriate methodology for estimating it*

To understand these estimates it is important to note that STEDI benefits cannot simply be added up, as there is some overlap between them – equally, they will be more important for some antibiotics than others. In light of the fact that a range of different antibiotics could receive a TEE, we contextualise the benefits in Table 1 by describing how the value elements may apply to five example antibiotics (for the following priority pathogens: carbapenem-resistant *Acinetobacter baumannii* (CRAB); *Staphylococcus aureus*; carbapenem-resistant *Enterobacteriaceae* (CRE); fluoroquinolone-resistant *Salmonella*; *Neisseria gonorrhoeae*). The value of each example antibiotic is driven by a different combination of value elements, depending on its clinical characteristics.

In addition, development of a new antibiotic will have significant value not just for patients and populations in Europe, but globally. By stimulating development of antibiotics in Europe, the European Commission and MS would be helping to provide low- and middle-income countries (LMICs) with valuable medicines; indeed, the quality-adjusted life year (QALY) benefits of antibiotics are likely to be greater in these countries than in European countries.

Finally, as noted above, the value of TEE is proxied by the value of new antibiotics. However, there are significant wider benefits from supporting the infrastructure for research and development (R&D) of antimicrobials. Antimicrobials against resistant infections are not developed ‘overnight’ but require years of investment in the overall research infrastructure for antimicrobial development to ensure the capacity for innovation (for example, from understanding the organisms that produce antibiotic substances to experience in undertaking clinical trials). Implementing TEE in Europe would stimulate R&D, which would ensure continued investment in this, supporting increased AMR innovation and ensuring antimicrobials are available when we need them in the future. We have not been able to quantify the benefit to society of continued investment in the antimicrobial innovation infrastructure, but this is a key benefit of TEE and should be considered when evaluating TEE for implementation in Europe. Only by providing a credible pull incentive will we maintain the capability, skills and expertise to respond to AMR.

### ***The cost of TEE to Member States***

To consider the merits of TEE from a policy perspective, we need to compare the magnitude of benefits to the costs of the policy. We attempt to quantify the cost of one TEE, and of the TEE policy over the first 10 years of implementation to the six selected MS. We analyse products that will lose marketing exclusivity in the future, because these are the products that will likely use a TEE. Although using historical sales data to estimate the costs would minimise the need to project sales data into the future, past originator products that have lost exclusivity are not representative of the products that will be losing exclusivity in the future (given the trend to addressing rare diseases and precision medicines, for example). In particular, focusing the cost discussion on individual high-selling products that have lost exclusivity (e.g. Humira) could paint a misleading picture. We consider three areas of cost and display the cost of each TEE in Table 2:

1. **Lost genericisation savings** resulting from the marketing exclusivity extension of a product which uses the TEE voucher. (This is not the same as the value of the TEE to the manufacturer.) To calculate this, we determine which products would likely receive a TEE each year and calculate the difference between what the MS would have paid with and without the TEE in the years after loss of exclusivity (LOE) by using sales data from Evaluate Pharma and a variety of estimates from literature for parameters outlined in Section 4.1.2. As genericisation occurs gradually over a number of years, the cost of the TEE will occur

beyond the exclusivity extension period.<sup>10</sup> We model the lost genericisation savings as the difference between what the MS pays in the year before originator LOE (when the MS only pays for originator) and what the MS pays after originator LOE (when the MS pays for originator and generics) using historical data. This difference provides us with a cost savings factor that can be applied to the sales of the originator in the three years after LOE to estimate the cost to each MS. Similarly to the benefits of TEE, we model the lost genericisation savings over the first 10 years after the TEE is applied. We assume that the cost is negligible after the first three years as the market will be fully genericised so the impact of the delayed genericisation is not seen.

2. **Administrative costs** of implementing TEE: regulatory costs of assessing potentially eligible products, assigning vouchers, and ongoing monitoring; and administrative costs associated to selling the voucher. We based this on the cost to the US Food and Drug Administration (FDA) of implementing Tropical Disease Priority Review Vouchers (PRVs) and Rare Pediatric Disease PRVs, as a proxy.
3. **Wider impacts of the marketing exclusivity extension** of a product which uses the TEE voucher – on patient access to this product and others in its class. To analyse this, we looked at IQVIA data on treatment days per capita (TD/capita) in 2021 compared with the year before biosimilar entry for a variety of biosimilars in various therapeutic areas. We find that the change in volume is relatively small across all markets, so have not quantified this impact in monetary terms.

For simplicity, Table 2 sets out the cost of a TEE if there is one per year. If there are more TEEs, the average cost of the TEE falls, as the expected cost savings from genericisation will be smaller and the fixed costs of administration are spread over more TEEs.

**Table 2: Cost of transferable exclusivity extension (TEE) per antibiotic by Member State for 1 TEE per year**

TEE Length		Average lost genericisation savings per TEE (2024–2033) (€ M Present Value)					
		France	Germany	Italy	Spain	Greece	Poland
<b>Admin</b>		1.6	2.0	1.4	1.1	0.3	0.9
12 months	Lost savings	105	121	105	66	15	14
	<b>Total</b>	<b>106.6</b>	<b>123.0</b>	<b>106.4</b>	<b>67.1</b>	<b>15.3</b>	<b>14.9</b>
9 months	Lost savings	79	91	79	50	11	10
	<b>Total</b>	<b>80.6</b>	<b>93.0</b>	<b>80.4</b>	<b>51.1</b>	<b>11.3</b>	<b>10.9</b>

Source: CRA analysis

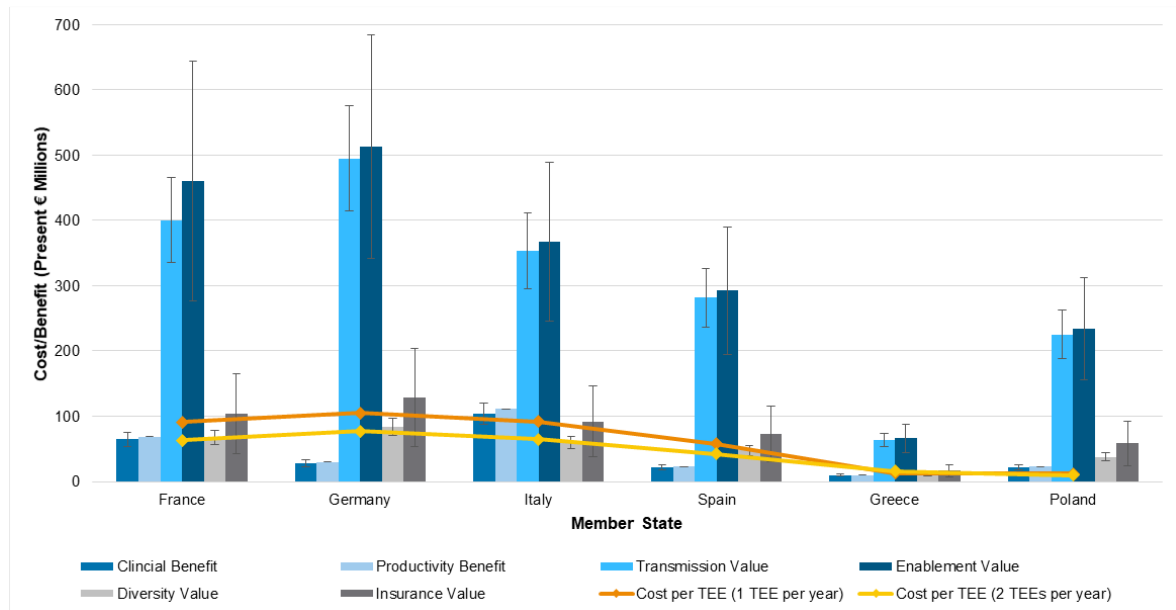
One way of contextualising the costs set out in Table 2 above is to compare them to existing models, such as those developed in the UK. This sets out a cap of £10m over 10 years. In reality, higher

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Boyer, B., Kroetsch, A. & Ridley, D. (2022) *Design of a Transferable Exclusivity Voucher Program – Incentives for drug and vaccine development for neglected diseases*. Duke Margolis Center for Health Policy. Available at: <https://healthpolicy.duke.edu/publications/design-transferable-exclusivity-voucher-program>

valuations were recognised, meaning the cap is lower bound. This would suggest a payment of €118m over 10 years. This is comparable to the estimate above. It is clear from our case studies that the benefits outweigh the costs for all the countries and case study examples.

**Figure 3: The cost versus the benefits of a TEE**



Source: CRA analysis of various sources, see text for details. Error bars represent upper and lower bounds of benefits estimates. Parameters used to calculate upper and lower bounds (see body text in Section 3.2 for more details): Clinical benefit, transmission value, diversity value: lower bound = €18k/QALY, upper bound = €25k/QALY. Enablement value: lower bound = 0.5% decrease in the reduction in efficacy of prophylaxis, upper bound = 1.5% reduction in efficacy of prophylaxis. Insurance value: lower bound = 50% IV capacity, upper bound = 20% IV capacity. Average cost per TEE of 12-month TEE duration and 9-month TEE duration are displayed for costs per TEE for 1 TEE per year and 2 TEEs per year.

## Discussion

The analysis above sets out an approach to estimating the costs and benefits of a new incentive, such as TEE, on EU MS. It attempts to address the differences across MS, and that there are different types of antibiotics needed. Although we have not been able to estimate all of the costs and benefits, and there is still uncertainty around many of the estimates, we can draw conclusions about the benefits and costs of TEEs individually and relative to one another. The results strongly support the following:

- The costs of inaction are very significant and would have important consequences for European patients, economies and healthcare systems. The risk of degrading the benefits from antibiotics demonstrates the need for action. However, it is appropriate that we consider the specific benefits of proposed policy solutions.
- The benefits to each MS, on the level of each individual TEE and of the policy as a whole, will outweigh the costs to a considerable degree. Although we have not been able to quantify the combined impact of an effective portfolio of antibiotics, and the benefit to society of continued investment in the innovation infrastructure, which are additional benefits on top of the benefits of each individual antibiotic, even if only two or three of the value elements are considered, the benefits of a TEE to each MS outweigh the costs. In addition, development of new antibiotics will have significant value not just for patients and populations in Europe, but globally. We have demonstrated that a TEE-recipient antibiotic is likely to have sufficient value to society to make a TEE a worthwhile investment in securing healthy populations in years to come.

- The cost of a TEE to MS is considerably lower than has been previously estimated. Previous studies have focused on individual products that have already lost exclusivity, and they have based their analysis on historical data. The analysis needs to be forward looking. We have also demonstrated that while the cost of an individual TEE may vary, the cost of TEE used in the debate so far is not representative of the group of products that would likely receive a TEE in the coming years. This can help to address concerns about the cost of TEE to MS.
- Our analysis helps address concerns related to the impact of TEE on patients being treated by the products using the TEE. There is a concern that patients in 'other' therapy areas (e.g. oncology) are 'paying for' anti-infectives innovation. This is seen as a problem by some commentators who say that the patients paying for the TEE are not those benefitting from the development of antibiotics. Our analysis helps address this concern in two ways: (1) we demonstrate how investment in antibiotic innovation benefits the whole population, including patients in 'other' therapy areas – enablement value is an important component of the benefits of TEE; (2) we show that the change in total treatment volume in the years immediately following LOE of a product is relatively small. Hence, we conclude that the distinction between 'AMR patients' and 'other patients' is unhelpful as this fails to recognise the benefit of reducing the development of AMR for the healthcare system and society.

This study also provides a framework which could inform the development of a methodology for a comprehensive cost-benefit analysis and impact assessment, which would be able to quantify the benefits and costs more precisely.

### **Conclusions**

We need to invest in maintaining our arsenal of effective antimicrobials. TEE has the advantage of providing a sufficiently powerful incentive to stimulate development of new antimicrobials that is feasible and relatively straightforward to implement at the joint EU level, with minimal up-front administrative costs to the European Medicines Agency (EMA) and a cost that is spread across all European MS. Our analysis suggests that the benefits of TEE to society are likely to far exceed the costs, and that the costs are lower than previously predicted.

## 1 Introduction

The European Federation of Pharmaceutical Industries and Associations (EFPIA) asked Charles River Associates (CRA) to develop a methodology for quantifying the benefits and costs of implementing a transferable exclusivity extension (TEE) in Europe and, where possible, to provide high-level estimates for these.

### 1.1 Background to transferable exclusivity extension

The threat of antimicrobial resistance (AMR) is well known but bears repeating. When disease-causing bacteria, viruses, fungi and parasites no longer respond to existing medicines, this presents a major threat to global health. It has been estimated that in Europe in 2019, there were over 400,000 deaths associated with AMR.<sup>11</sup> The number of deaths is expected to grow as resistance rates continue to increase.<sup>12</sup> By 2050, there could be up to 10 million deaths per year due to AMR globally, more than the current global number of deaths due to cancer and diabetes combined.<sup>13</sup> Increasing levels of AMR will also mean that modern medicine as we know it will not be possible. This has been recognised in the European Commission's Pharmaceutical Strategy.<sup>14</sup>

Given the severe and increasing threat of AMR, a multifaceted strategy is needed to address it. One key weapon in the arsenal in the fight against AMR is antimicrobials. The portfolio of antimicrobials we currently have available to us is an asset that saves lives now and will continue to protect us. Much like a key piece of infrastructure, our portfolio of antimicrobials requires us to invest in maintaining it to ensure that it effectively serves our needs, now and in the future. Despite this, there is broad agreement that the current economic model for incentivising development of new antimicrobials is insufficient to stimulate the development of the number and novelty of antimicrobials we need.

Proposals for changes to the model for financing development of antimicrobials have included calls for and commitments on 'pull' incentives which 'delink' the incentive for development from the sales volume of the antimicrobial.<sup>15</sup> In May 2022, the G7 Health and Finance Ministers acknowledged the need to "address antibiotic market failure" and commit to a "particular emphasis on supporting relevant pull incentives".<sup>16</sup> The European Commission's Pharmaceutical Strategy commits to piloting

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- 11 Antimicrobial Resistance Collaborators (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 339(10325): 625–655. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
- 12 Cravo Oliveira, T. & Padget, M. (2018) Trends in antimicrobial resistance in OECD countries. In: *OECD Health Policy Studies, Stemming the Superbug Tide*. OECD. <https://doi.org/10.1787/9789264307599-en> [Accessed 20 May 2022]
- 13 O'Neill, J. (2016) *Tackling drug-resistant infections globally: final report and recommendations*. Review on Antimicrobial Resistance. Available at: [https://amr-review.org/sites/default/files/160525\\_Final%20paper\\_with%20cover.pdf](https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf) [Accessed 18 May 2022]
- 14 European Commission (2020) *Pharmaceutical Strategy for Europe*. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN> [Accessed 20 May 2022]
- 15 Outterson, K. (2021) Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Affairs*. 40(11): 1758–1765. <https://doi.org/10.1377/hlthaff.2021.00688>
- 16 G7 Germany 2022 (2022) *G7 Health Ministers' Communiqué*. 20 May. Available at: <https://www.g7germany.de/resource/blob/974430/2042058/5651daa321517b089cdccaffd1e37a1/2022-05-20-g7-health-ministers-communication-data.pdf> [Accessed 23 May 2022]

pull incentives and exploring new types of incentives for antimicrobials.<sup>17</sup> Several potential pull incentives have been proposed, including subscription models, market entry rewards, and transferable vouchers.<sup>18,19</sup> There is recent research on the required size of a global pull incentive sufficient to stimulate antibiotic innovation. Outterson (2021) calculates a best estimate of \$2.2bn (range \$1.5bn–\$4.8bn) for a partially delinked global market entry reward and \$4.2bn (range \$3.3bn–\$8.9bn) for a fully delinked global subscription over 10 years.<sup>20,21</sup>

One novel proposal for a pull incentive in Europe is a TEE, whereby the manufacturer of a new antimicrobial which meets certain criteria (e.g. efficacy against pathogen(s) on the World Health Organization (WHO) priority pathogens list for R&D of new antibiotics<sup>22</sup>) would receive a voucher ('a TEE') upon European regulatory approval of that antimicrobial. The voucher would entitle the manufacturer (the 'TEE recipient') to a European marketing exclusivity extension, which the manufacturer could apply to one of their own products, or sell to another manufacturer (the 'TEE purchaser'), who could apply it to any one of their products.

The concept of a TEE has been discussed, and it has been put forward as an incentive that would have sufficient high value and therefore power to incentivise antimicrobial research and development (R&D).<sup>23,24,25,26</sup> TEE can be implemented at the European Union (EU) level as an EU competency to complement Member State (MS) initiatives. TEE can also provide pull incentive funding in a stable manner with no up-front government funding: it is not dependent on appropriations from MS but baked into health budgets,<sup>27</sup> spread across MS, and allows governments flexibility to plan for future

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- 17 European Commission (2020) *Pharmaceutical Strategy for Europe*. Available at: <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0761&from=EN> [Accessed 20 May 2022]
- 18 Outterson, K., Samora, J. B. & Keller-Cuda, K. (2007) Will longer antimicrobial patents improve global public health? *Lancet Infect Dis.* 7(8):559–66. doi: 10.1016/S1473-3099(07)70188-3
- 19 Outterson, K. & McDonnell, A. (2016) Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy. *Health Affairs.* 35(5): 784–790. doi: 10.1377/hlthaff.2015.1139
- 20 Outterson, K. (2021) Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Affairs.* 40(11): 1758–1765. <https://doi.org/10.1377/hlthaff.2021.00688>
- 21 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.
- 22 World Health Organization (2017) *WHO publishes list of bacteria for which new antibiotics are urgently needed*. 27 February. Available at: <https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed> [Accessed 20 May 2022]
- 23 McDonnell, A., Klemperer, K., Pincombe, M. & Guzman, J. (2022) Leveraging Purchasing Systems to Ensure Access, Stewardship, and Innovation. Center for Global Development Working Paper. Available at: <https://www.cgdev.org/sites/default/files/leveraging-purchasing-systems-ensure-access-stewardship-and-innovation-landscape-review.pdf> [Accessed 1 July 2022]
- 24 Rome, B. N. & Kesselheim, A.S. (2020) Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. *Clin Infect Dis.* 71(7): 1671–1675. <https://doi.org/10.1093/cid/ciz1039>
- 25 Boyer, B., Kroetsch, A. & Ridley, D. (2022) *Design of a Transferable Exclusivity Voucher Program*. Duke Margolis Center for Health Policy. Available at: <https://healthpolicy.duke.edu/sites/default/files/2022-01/Transferable%20Exclusivity%20Voucher%20Program.pdf> [Accessed 20 May 2022]
- 26 BEAM Alliance (2022) *Reflection paper on the Pull Incentive Mechanisms Suitable For SMEs Developing AMR Products In Europe*. 31 Jan. Available at: <https://beam-alliance.eu/wp-content/uploads/2022/01/beam-proposal-eu-incentives.pdf> [Accessed 21 Jun 2022]
- 27 Outterson, K. & McDonnell, A. (2016) Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy. *Health Affairs.* 35(5): 784–790. doi: 10.1377/hlthaff.2015.1139

expenses that can be calculated. In addition, TEE is pro-stewardship as it delinks the financial reward for antimicrobial development from the volume of prescriptions.

The Office of Health Economics (OHE), on behalf of EFPIA, has set out the length and other parameters of a European TEE to ensure it is a sufficient incentive to kick-start antimicrobial development.<sup>28</sup> EFPIA has subsequently published a set of recommendations for the design and implementation of TEE in Europe, taking into account proposals from academia.<sup>29</sup> These include modulating the length of the TEE based on the characteristics of the recipient antimicrobial, and measures to support predictability for the generic industry, including ensuring there is a reasonable remaining exclusivity period when a TEE is purchased, and only allowing one TEE to be applied to each product.

There are also concerns about the use of TEE as a pull incentive for AMR. These include perceptions that the cost of TEE would be undefined or would outweigh the benefits, that TEE would delay patient access to generics and biosimilars, and that the patients benefitting from a TEE are not those assumed to be ‘paying’ for it.<sup>30,31</sup> These concerns are addressed in the following chapters.

In the context of the ongoing debate on the potential feasibility and appropriateness of TEE as a pull incentive for antimicrobial development, it is important to consider the clinical and economic benefits it could bring to patients and to society, and compare these to what it may cost European MS.

## 1.2 The approach

To document the benefits and costs of TEE, a five-step methodology was adopted. This is illustrated in Figure 4.

### Figure 4: Illustration of five-step approach

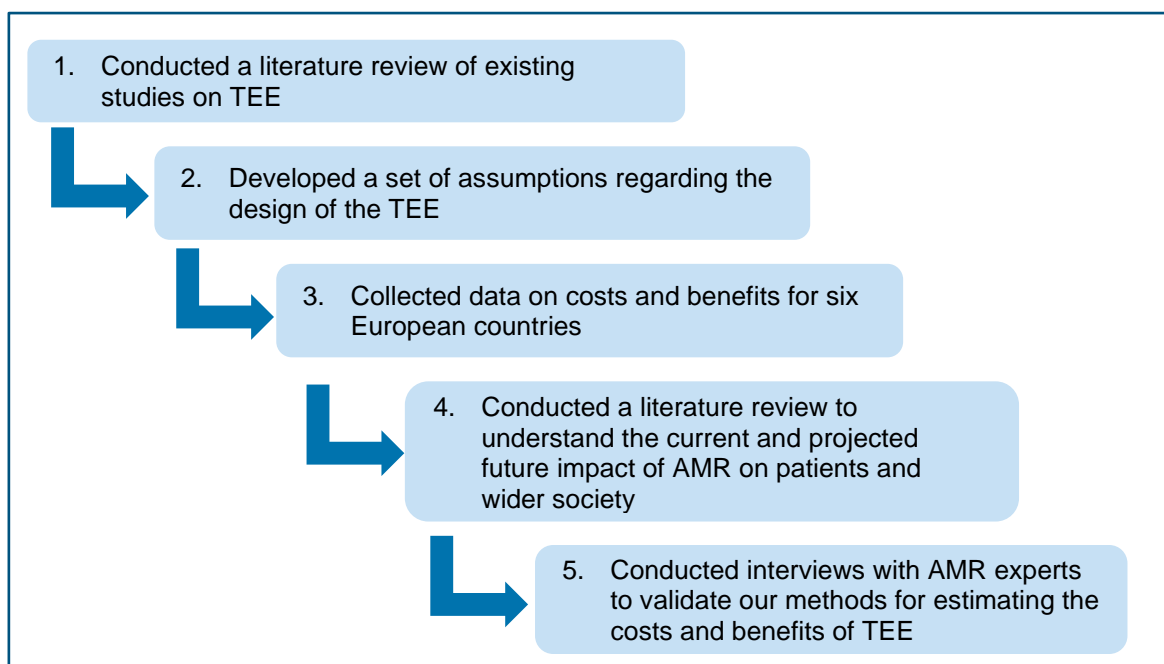
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28 Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics.

29 EFPIA (2021) *A new EU pull incentive to address Antimicrobial Resistance (AMR)*. Available at: <https://www.efpia.eu/media/636464/a-new-eu-pull-incentive-to-address-anti-microbial-resistance-amr.pdf> [Accessed 18 May 2022]

30 Årdal, C., Lacotte, Y. & Ploy, M.-C. (2020) Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clin Infect Dis*. 71(8): 1994–9. <https://doi.org/10.1093/cid/ciaa153>

31 Medicines for Europe (2022) *Note on Transferable Vouchers*. Available at: <https://www.medicinesforeurope.com/wp-content/uploads/2022/03/Medicines-for-Europe-Note-on-Transferable-Vouchers-March-2022.pdf> [Accessed 20 May 2022]



First, we undertook a literature review of existing studies on pull incentives and TEE. This was based on academic articles (7), public agency publications (5), non-governmental organisation publications (3), and industry publications (3). The academic literature included peer-reviewed articles available in academic and open-source databases (including PubMed, Springer, Embase and Google Scholar). We used a keyword search to identify relevant literature, using combinations of the terms ‘transferable exclusivity extension’, ‘TEE’, ‘transferable exclusivity voucher’, ‘antimicrobial resistance’, ‘AMR’, ‘incentive’ and ‘pull incentive’. The review focused on literature published from 2005 to 2022. Identified relevant studies focusing on TEE are listed in [Table 3](#) below.

**Table 3: Selected identified studies focusing on TEE for antibiotics**

Author	Year	Title
Outterson, K., Samora, J. B. & Keller-Cuda, K.	2007	Will longer antimicrobial patents improve global public health? <sup>32</sup>
Outterson, K. & McDonnell, A.	2016	Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy <sup>33</sup>
Seabury, S. & Sood, N.	2017	Toward A New Model For Promoting The Development Of Antimicrobial Drugs <sup>34</sup>

<sup>32</sup> Outterson, K., Samora, J. B. & Keller-Cuda, K. (2007) Will longer antimicrobial patents improve global public health? *Lancet Infect Dis.* 7(8): 559–66. doi: 10.1016/S1473-3099(07)70188-3

<sup>33</sup> Outterson, K. & McDonnell, A. (2016) Funding Antibiotic Innovation With Vouchers: Recommendations On How To Strengthen A Flawed Incentive Policy. *Health Affairs.* 35(5): 784–790. doi: 10.1377/hlthaff.2015.1139

<sup>34</sup> Seabury, S. & Sood, N. (2017) Toward A New Model For Promoting The Development Of Antimicrobial Drugs. *Health Affairs Blog.* May 18. doi: 10.1377/forefront.20170518.060144

Årdal, C., Lacotte, Y., Ploy, M.-C. (on behalf of EU-JAMRAI)	2020	Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe <sup>35</sup>
Rome, B. N. & Kesselheim, A. S.	2020	Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis <sup>36</sup>
Boyer, B., Kroetsch, A. & Ridley, D. (Duke Margolis Center for Health Policy)	2022	Design of a Transferable Exclusivity Voucher Program: Incentives for drug and vaccine development for neglected diseases <sup>37</sup>

Source: CRA research

Second, we developed a set of assumptions (see Chapter 2) regarding the design of the TEE, drawing on previous research commissioned by EFPIA and recent academic studies. We ensured that our assumptions of the required length of a TEE, to be used throughout the analysis, reflected new data published over the last few years. This involved identifying new estimates from the literature on the required magnitude of pull incentives for antibiotic development and reviewing the willingness to pay of potential TEE purchasers. We used these inputs to ensure the required length of TEE estimated by the OHE in 2019 was still the best estimate of the required length of TEE.<sup>38</sup> The results of this analysis are described in Chapter **¡Error! No se encuentra el origen de la referencia.** below.

Third, we started to collect data on the costs and benefits of TEE. We selected six European countries as the focus for the analysis, to understand how the costs and benefits of TEE may differ between countries in Europe. Since our study aims to document the benefits and costs of TEE to MS, we selected countries which represented a range of policy environments to represent the make-up of the EU. In particular, given that the cost of TEE is driven to a significant extent by the policy and economic environment for genericisation in a country, we ensured the countries we selected represented a range of genericisation environments. Given their economic and policy significance in Europe, we selected France, Germany, Italy, and Spain ('the EU4'). We then selected two countries which differed to a large extent from the EU4 on two indicators (spending on innovative medicines, impact of genericisation):

- Poland was identified as a country which differed from the EU4 on the first indicator, market share of innovative products, with the data showing low spending on innovative medicines.<sup>39</sup> It was selected for inclusion in the analysis to understand how TEE may impact countries with lower innovative medicines spending.

<sup>35</sup> Årdal, C., Lacotte, Y. & Ploy, M.-C. (2020) Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clin Infect Dis.* 71(8):1994–9. <https://doi.org/10.1093/cid/ciaa153>

<sup>36</sup> Rome, B. N. & Kesselheim, A. S. (2020) Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis. *Clin Infect Dis.* 71(7):1671–1675. <https://doi.org/10.1093/cid/ciz1039>

<sup>37</sup> Boyer, B., Kroetsch, A. & Ridley, D. (2022) *Design of a Transferable Exclusivity Voucher Program*. Duke Margolis Center for Health Policy. Available at: <https://healthpolicy.duke.edu/sites/default/files/2022-01/Transferable%20Exclusivity%20Voucher%20Program.pdf> [Accessed 20 May 2022]

<sup>38</sup> Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics.

<sup>39</sup> IQVIA Patients W.A.I.T Indicator 2021 Survey

- Greece was identified as a country with lower impact of generic/biosimilar entry, with smaller price decreases and lower biosimilar savings than the EU4 countries.<sup>40</sup> It was selected to understand how TEE may impact countries with a lower impact of generic/biosimilar entry.

Regarding the benefits of TEE to MS, we conducted a second literature review to understand the current and projected future impact of AMR on patients and wider society. The literature review aimed to inform the 'baseline' or 'benchmark' against which the benefits of implementing TEE can be assessed, and development of methodology. A keyword search identified relevant literature, using combinations of the terms 'antibiotic resistance', 'antimicrobial resistance', 'AMR', 'impact', 'cost', 'deaths', 'burden', 'development', 'future', 'Europe'. The review focused on literature published in the last 10 years (2013–2022). This led to 13 academic articles, 18 public agency publications, and five non-governmental organisation publications.

Finally, we conducted a series of nine interviews with experts to validate our methods and results for estimating the costs and benefits of TEE (Table 4). Interviews were structured thirty-minute or one-hour discussions, conducted in May/June 2022. We also conducted a Chatham House Roundtable in June 2022, with industry, government, academic and non-governmental organisation representatives. The objective of the Roundtable was to discuss the role of the TEE as a pull incentive for antimicrobials in Europe and how to overcome barriers and concerns. Preliminary results were presented and feedback collected. The discussion was used to inform the development of this report. The draft report was also shared with the interviewees and comments provided.

**Table 4: Overview of interviewees**

Name	Role
<b>Dr Christine Årdal</b>	Senior Advisor, Institute of Public Health, Norway Co-lead of EU-JAMRAI
<b>Dr Nick Crabb</b>	Programme Director, Scientific Affairs, NICE
<b>Prof. Kevin Outterson</b>	Director of the Social Innovation on Drug Resistance (SIDR) programme Professor of Law, Boston University
<b>Dr John Rex</b>	Chief Medical Officer, F2G Ltd. Operating Partner, Advent Life Sciences Adjunct Professor of Medicine, McGovern Medical School
<b>Dr David Ridley</b>	Faculty Director for Health Sector Management, Duke-Margolis Center for Health Policy Professor of the Practice of Business and Economics, Duke University's Fuqua School of Business
<b>Dr Lotte Steuten</b>	Head of Consulting and Vice President, Office of Health Economics
<b>Dr Ferenc Marofka</b>	European Commission Representative, Policy Officer for Health (Medicines)
<b>European Member State representatives</b>	Health Attaché from European Member State

40

IQVIA (2021) *Impact of Biosimilar Competition in Europe*. <https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf> [Accessed 18 May 2022]

<b>Industry representative</b>	Health Economics and Outcomes Research (HEOR) Director at biopharmaceutical company involved in R&D of novel antimicrobials
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### 1.3 Structure of this report

The structure of this report is as follows:

- Chapter 2 sets out key assumptions necessary for a cost-benefit analysis of TEE in Europe, taking into account the recent literature.
- Chapter 3 sets out an approach for estimating the benefits of implementing TEE in Europe and provides quantitative estimates for the six MS of interest.
- Chapter 4 sets out an approach for estimating the cost of TEE to MS and a quantitative estimate for this for the six MS.
- Chapter 5 presents a discussion and policy conclusions based on the analysis.

## 2 Assumptions necessary for the cost-benefit analysis

In order to estimate the benefits and costs of TEE to European MS, we need to define some characteristics of the TEE policy to be assessed. In particular:

- The mechanism for extending exclusivity
- The year when the policy is introduced
- The pathogens for which a TEE is applicable
- The number of antibiotics that would be awarded a TEE each year
- The length of the TEE in months (i.e. the number of months of additional exclusivity the user of a TEE would gain for the product the TEE was applied to)
- The global policy environment

EFPIA has previously commissioned research on the value of TEEs, although looking at a different issue; this included assumptions about the structure and number of TEEs. We reviewed the existing literature and assessed whether there is new relevant data, in order to update prior assumptions made by Berdud, et al. (2019). This is described below.

### 2.1 The mechanism for extending exclusivity

There are different ways that the exclusivity of a product could be extended with a TEE. This could be through extending the supplementary protection certificate (SPC) or through extending regulatory data protection (RDP). We do not consider the legal issues with this choice, but in terms of the economic impact this is important as it determines the number of products eligible for the TEE. We have assumed that the extension to exclusivity is applied in a way that could impact a wide range of products (i.e. products protected by SPC or RDP). There are a number of reasons to make this assumption:

- The efficiency of the policy depends on competition between purchasers for the TEE. The greater the intensity of competition, the smaller the difference between the valuation of the first and second purchaser and the better the negotiation position of the seller of the TEE. Restricting the application of TEE to only one type of product, such as those with RDP, will reduce the efficiency of the policy and reduce the incentive.
- The impact of the incentive depends on the predictability of the sale price. The more potential purchasers of the TEE, the greater the level of certainty and the bigger the impact on financing of antibiotic innovation.
- The length of the extension has been estimated based on affecting a wide selection of products. If a narrower definition were used then the extension would need to be longer.

### 2.2 The year when the policy is introduced

In order to develop costs and benefits, we need to have a baseline of what would happen in the absence of the TEE. Different approaches can be taken, assuming it occurred in the past, modelling from today or some hypothetical date in the future. Each of these has pros and cons. Applying TEE to historic data has the advantage that we know the sales of the products, and we can observe actual genericisation. However, if the distribution of products changes in terms of size (as appears to be the case), this makes these comparisons unrepresentative. Modelling too far in the future, means that we do not have actual sales data on the products. We have chosen to apply this to actual future

products in the near future, reflecting the current distribution of sales, as if the TEE policy were already in place.

For the purposes of the model, we assume the first TEEs are issued in 2024, 'as if' the policy started to have an effect in that year.

### 2.3 The pathogens for which a TEE is applicable

The purpose of the TEE is to incentivise the development of novel antimicrobials. The benefits of TEE arise partly from the value of the antibiotics it incentivises (see Section 3.4 on other benefits). However, in practice there are different types of antibiotics and therefore it is difficult to consider an 'average' antibiotic when assessing the benefits of TEE. To address this, we have considered the characteristics that TEE recipient antibiotics could have, and the implications of these for their value. Since each antibiotic launching in the future will have different characteristics (e.g. target pathogens, indications, route of administration, etc.), the value of each antibiotic will vary and arise from different attributes. To understand this, and the implications for evaluating the benefits of TEE, we created example antibiotic profiles of products which could receive a TEE, drawing from several sources:

- **WHO list of priority pathogens for antibiotic development.**<sup>41</sup> This categorises various bacteria as critical, high, and medium priority. We selected a range of critical and high priority pathogens for inclusion in our example antibiotic profiles.
- **WHO target product profiles (TPPs) of needed antibacterial agents** for typhoid fever, gonorrhoea, neonatal sepsis and urinary tract infections.<sup>42</sup> We used these TPPs to inform development of our example antibiotic profiles.
- **The pipeline of global antibiotic development tracked by the WHO.**<sup>43</sup> Since current late-stage pipeline antibiotics will likely be unaffected by the introduction of TEE, we focus on the early pipeline antibiotics (Phases 1 and 2) to understand the potential indications, microbiology and settings of care of potential TEE-recipient antibiotics.

We created five example profiles of hypothetical antibiotics to illustrate how value would be realised for antibiotics that could receive a TEE (Table 5). We chose these antibiotic profiles because these antibiotics treat a variety of gram-positive and gram-negative bacterial infections relevant for Europe, involve various settings of care (e.g. ICU, hospital, community) and have different routes of administration (ROA) (e.g. oral, intravenous). In Section 3.3.4, we use these profiles to discuss the potential benefits of implementing TEE in Europe, by setting out how these example antibiotics would bring value to patients and society.

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41 World Health Organization (2017) *Antibacterial Agents in Clinical Development: an analysis of the antibacterial clinical development pipeline, including tuberculosis*. Available at: <https://apps.who.int/iris/bitstream/handle/10665/258965/WHO-EMP-IAU-2017.11-eng.pdf?sequence=1> [Accessed 18 May 2022]

42 World Health Organization (2020) *Target product profiles for needed antibacterial agents: enteric fever, gonorrhoea, neonatal sepsis, urinary tract infections and meeting report*. Available at: <https://www.who.int/publications/i/item/9789240003897> [Accessed 25 May 2022]

43 World Health Organization (2021) *Antibacterial products in clinical development for priority pathogens*. Available at: <https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens> [Accessed 21 Jun 2022]

**Table 5: Hypothetical profiles of antibiotics which could receive a TEE in the future**

	Microbiology	WHO priority level	Potential indications	Setting of care	Route of administration
<b>Antibiotic profile #1</b>	Carbapenem-resistant <i>Acinetobacter baumannii</i> (CRAB)	Critical	Bloodstream infections (BSI); hospital-acquired bacterial pneumonia /ventilator-associated bacterial pneumonia (HAP/VAP)	Hospital intensive care units (ICUs)	Intravenous
<b>Antibiotic profile #2</b>	<i>Staphylococcus aureus</i>	High	Acute bacterial skin and skin structure infections (ABSSSI)	Hospital and potentially community	Intravenous
<b>Antibiotic profile #3</b>	Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE)	Critical	Uncomplicated/complicated urinary tract infection (uUTI/cUTI)	Community and hospital	Oral
<b>Antibiotic profile #4</b>	Fluoroquinolone (FQ)-resistant <i>Salmonella</i>	High	BSI; gastroenteritis; typhoid fever	Community and hospital	Oral
<b>Antibiotic profile #5</b>	<i>Neisseria gonorrhoeae</i>	High	Uncomplicated gonorrhoea	Community and hospital	Oral

Source: CRA analysis of various sources.

## 2.4 The number of antibiotics awarded a TEE each year

The structure of the TEE policy will affect the number of antibiotics developed. Equally, the number of antibiotics developed and the number of TEEs issued will affect the value of the TEE and the cost of the TEE on the MS. Berdud et al. (2019) assumed two or three TEEs per year based on the assumption that three new antibiotics are required for each WHO critical or high priority pathogen, and that these will all receive a TEE.<sup>44</sup> However, given the sparse antibiotic pipeline and the fact that 18 antibiotics have been approved in the past decade, we model scenarios of one or two TEEs to be awarded per year (i.e. 10 or 20 over the next decade). This was validated in interviews. Årdal et al. (2020) stated that possibly two antibiotics would be eligible for a TEE within approximately the next five years.<sup>45</sup>

## 2.5 The length of a TEE

The length of a TEE is an important consideration for estimating the costs of TEE. This is because it determines the additional number of months of originator sales before loss of exclusivity of a TEE user vs. without TEE. This directly impacts the cost to MS of a TEE (see **Error! No se encuentra el origen de la referencia.** below).

<sup>44</sup> Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics.

<sup>45</sup> Årdal, C., Lacotte, Y., Ploy, M.-C. (2020) Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clinical Infectious Diseases*. 71(8): 1994–9. <https://doi.org/10.1093/cid/ciaa153>

To calculate an assumption for the length of TEE in Europe, we started with a 2019 estimate from Berdud et al. (2019). They determined the length of a TEE in Europe in two steps:

1. Calculating the required value of a TEE in Europe by multiplying the global required incentive size by a European share percentage
2. Determining the length of TEE that would have this required value by using pharmaceutical sales data to assess companies' willingness to pay (WTP) for a TEE

For an antibiotic in a novel class, they estimated that a TEE of between 9 and 12 months would be appropriate. We sought to update this estimate based on two data points published since 2019:

- A new estimate by Kevin Outterson of the global size of pull incentives required to incentivise development of new antibiotics.<sup>46</sup> The best estimates for required sizes of a partially delinked global market entry reward (MER) and fully delinked 10-year subscription model are \$2.2bn (with a range from \$1.5bn to \$4.8bn) and \$4.2bn (with a range from \$3.3bn to \$8.9bn) respectively, for an antibiotic which was developed from discovery to approval by the same company. We use the MER estimate as the basis for our analysis since this is the incentive more closely aligned with TEE in structure and partial delinkage.<sup>47</sup>
- Updated sales data of the pharmaceutical products that could be expected to receive a TEE, directly impacting the WTP and therefore the required length of TEE

The method for using each of these data points to update the length of TEE assumption is described below.

### 2.5.1 Required value of TEE

First, the \$2.2bn (€2.0bn) required value of a partially delinked global MER was substituted for the €1.8bn total R&D cost of a new antibiotic used by Berdud et al. (2019), as a new benchmark for the total global required value of a TEE.<sup>48</sup> The administrative cost to the TEE recipient of selling the voucher has been estimated to be \$1m (€0.9m) per TEE.<sup>49,50</sup> This cost is small relative to the value of the TEE, less than 0.3%, but was added to the global incentive size.

We then sought to ensure the European share of the incentive was up to date. Berdud et al. (2019) calculated a European share of 28.8%. There are a number of more recent analyses. In analysis of the contribution levels of different countries to a global subscription model, BCG estimated the EU fair share to be 29%–39% out of a total including the G7 and EU, and 22%–27% when considering

<sup>46</sup> Outterson, K. (2021) Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines. *Health Affairs*. 40(11): 1758–1765. <https://doi.org/10.1377/hlthaff.2021.00688>

<sup>47</sup> For the purposes of our analysis, we use the global market entry reward required for an antibiotic which was developed from discovery to approval by the same company. This assumes partial delinkage, as it continues to benefit from revenues from reimbursement in the Member States. Outterson (2021) also calculates that the best estimate of a market entry reward required for an antibiotic which was acquired as a Phase 2-ready asset is \$1.6bn. For comparison, if the incentive was structured as a fully delinked subscription model, the incentive required over the course of 10 years would need to be \$3.1bn for an antibiotic which was acquired as a Phase 2-ready asset and \$4.2bn for an antibiotic which was developed from discovery to approval by the same company.

<sup>48</sup> Fx rate: 1 USD = 0.93 EUR.

<sup>49</sup> Ibid.

<sup>50</sup> Årdal, C., Lacotte, Y. & Ploy, M.-C. (2020) Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clinical Infectious Diseases*. 71(8): 1994–1999. <https://doi.org/10.1093/cid/ciaa153>

the total of the G7, EU and China.<sup>51</sup> Taking this into account, we use a European share of TEE of 30% to estimate the required value of a European TEE. We therefore multiply the total global incentive size required (€2.0bn) by 30% to produce a European share of total incentive size of €614m.<sup>52</sup>

### 2.5.2 Updating the length of a TEE

To determine whether an update is needed to the TEE length of 9–12 months proposed by Berdud et al. (2019), we compared the increase in required value of a TEE in Europe (see above) with the change in WTP from 2018 to 2021:

- Our updated required value of €614m is a 39% increase from the Berdud et al. (2019) estimate of €441m.
- To compare the WTP for TEE in 2021 with that in 2018 (the year analysed by the OHE), we calculated the percentage differences in the mean sales of the top 10 selling on-patent pharmaceutical products in Europe (excluding vaccines) between 2018 and 2021. This was calculated to be an 18% increase.

Considering the above, we proceeded with the cost-benefit analysis based on the existing durations of 9 months and 12 months respectively.

## 2.6 The global policy environment

AMR is a global issue that requires a joined-up effort to address. The impact on future antimicrobials will depend on global incentives. In addition to the UK pilot payment models for cefiderocol and ceftazidime-avibactam, there have been proposals for pull incentives in a range of countries designed to reflect local healthcare systems and regulations. For example:

- In the US, the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act was introduced in 2021 and seeks to establish a delinked subscription programme to incentivise development of innovative antibiotics.<sup>53</sup> The US Department of Health and Human Services (HHS) would develop terms of the subscription contract between the manufacturer and HHS. A drug developer may apply to HHS for a subscription contract at or within five years following approval by the US Food and Drug Administration (FDA). Contracts would be paid out over a period of up to 10 years or through the length of marketing exclusivity. Contract value would be based on drug characteristics, and contracts would be fully delinked. In return, patients covered by federal insurance programs would receive these drugs at no cost.
- Another proposal, by the AMR Alliance Japan, recommends implementing an antibiotic pull incentive in Japan. Three types of pull incentives were proposed, including market entry

51 Boluarte, T. & 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> [Accessed 18 May 2022]

52 Berdud et al. (2019) subtracted the net present value of an antibiotic from the required European incentive. However, this is already accounted for in the Outterson (2021) estimate of the required value of a market entry reward.

53 US Senators Michael F. Bennet (D-Colo.) and Todd Young (R-Ind.) (n.d.) The PASTEUR Act: One Pager. Available at: [https://www.bennet.senate.gov/public/\\_cache/files/c/2/c2068e9f-8440-4960-86f4-acdd13145430/513C16806B1E8526E9F919EA7A72A004.pasteur-act---one-pager-1-.pdf](https://www.bennet.senate.gov/public/_cache/files/c/2/c2068e9f-8440-4960-86f4-acdd13145430/513C16806B1E8526E9F919EA7A72A004.pasteur-act---one-pager-1-.pdf) [Accessed 25 May 2022]

rewards, delinked subscription model, and profit guarantee scheme.<sup>54</sup> The Japan Agency for Medical Research and Development (AMED) Industry-Academia-Government Liaison Committee for Infectious Disease Drug Discovery developed a Japanese priority pathogens list, which could serve as the starting point for selecting antibiotics that should be eligible for a pull incentive.

In order to assess the impact of TEE, we assume that a European TEE would be implemented alongside other national/regional incentives such as these to provide a sufficient global incentive to stimulate antibiotic development.

## 2.7 Summary of TEE characteristics used in this analysis

In Table 6 we set out the characteristics of a TEE described above.

**Table 6: Summary of assumptions of TEE characteristics**

	Assumptions
<b>Types of product eligible for TEE</b>	We assume that this could be applied widely including products protected by SPCs and RDP
<b>Introduction of the policy</b>	2024
<b>Number of TEEs per year</b>	1 or 2 TEEs per year
<b>Length of a TEE</b>	9 or 12 months
<b>Global policy environment</b>	European TEE would be implemented alongside other national/regional incentives to provide a sufficient global incentive

Source: CRA analysis

54

AMR Alliance Japan (2021) *Strengthening AMR Countermeasures to Respond to Health Crises: Recommendations to the Japanese Government on Establishing a Pull Incentive System for the Antimicrobial Market: Creating an Ecosystem for Sustainable Antimicrobial Development to Protect the Lives of the Public*. Nikkei FT Communicable Diseases Conference. Available at: <https://hgpi.org/en/research/amr-21.html> [Accessed 20 May 2022]

### 3 Benefits of TEE

It is important to distinguish between the advantages of TEE as a policy to incentivise antibiotics and the economic benefits of TEE. In our approach the economic benefits of TEE arise primarily from the value of the antibiotics it incentivises. We look at this from three perspectives:

First, we consider the ‘society-wide perspective’ by considering the current and future cost of AMR to society and therefore the value of having an effective arsenal of antibiotics to minimise its development and impact – a top-down approach.

Second, we consider the value from an incremental ‘single antibiotic perspective’. The value of a TEE to health systems can be estimated from the value to the health system of the antibiotic it incentivises. We set out the different components of value of an antibiotic and how these can be measured – a bottom-up approach.

We then consider the broader benefits of supporting the infrastructure for the development of antimicrobials.

#### 3.1 The difference between the advantages and the benefits of TEE

There is a growing literature comparing the different policy proposals that could be used to incentivise antibiotics. This considers the challenges of introducing a policy to address AMR, with a focus on how to achieve political will, coordination across countries, and an incentive of sufficient size. This compares TEE to other types of policy intervention, such as subscription models.

TEE has a number of advantages, which have been described in previous EFPIA papers:

1. It can be implemented via EU-level legislation.
2. It does not require up-front government funding and is not dependent on a Member State's economic situation or changes in the political situation.
3. It would address the failure of the current incentive framework by offering a potential incentive at the scale that is required to drive greater R&D in new antimicrobials and that recognises their broader societal value.
4. It would support all pharmaceutical companies. For example, this would be beneficial for small- and medium-sized enterprises (SMEs) as they would be rewarded as early as regulatory approval for a new antimicrobial. It would also increase the attractiveness of the antimicrobial field for private financing mechanisms, such as venture capital.
5. It is pro-stewardship and respects prudent use, leading to improved medical outcomes for patients by delinking financial reward from the volume of prescriptions
6. It would be complementary with other EU and national initiatives, such as Health Emergency Preparedness and Response Authority (HERA) and country-level health technology assessment (HTA) and reimbursement reform.
7. It provides an opportunity for the EU to lead, in the development of a new form of incentive that could be replicated in other regions.

Equally, there are challenges to introducing a TEE. It would need to be carefully designed so that the incentive is aligned to the value of antibiotics, and there will need to be complementary policies to ensure access.

These are important considerations when comparing TEE to other policy choices. This suggests feasibility is an important advantage for TEE – and there appears agreement that TEE is feasible.<sup>55</sup> However this is not the focus of this paper. This paper considers whether a TEE, if implemented, would deliver net benefits to society – i.e. whether the benefits outweigh the costs. To consider this we first look at the benefits of TEE incentivising new antibiotics and in the next chapter look at the costs.

### 3.2 The importance of antibiotics to society

First, we look at the benefits of TEE by considering the value of the portfolio of antibiotics we have – to society as a whole, and to MS. This facilitates an understanding of the value of maintaining it. To do this, it is helpful to consider what a world without effective antibiotics would look like for patients, health systems and the wider European and global economy.

This would include the value of all of today's antibiotics. Today there are hundreds of different antibiotics that may be prescribed based upon the type of infection and suspected bacteria. For serious or severe infections, a broad-spectrum antibiotic (i.e. one that is effective against many different bacteria) is used initially. A narrow-spectrum antibiotic (i.e. one that is effective against a few specific types of bacteria) may then be used, once the infecting bacterium has been identified. The antibiotic era revolutionised the treatment of infectious diseases worldwide.<sup>56</sup> There are no detailed estimates of the value of this for Europe, but it is reasonable to believe it is trillions of Euros. A US study estimated the social value of antibiotics in a number of indications, with mean estimates ranging from \$486.6m to \$12.1bn.<sup>57</sup>

Another way to look at this is by considering the cost of increasing resistance; this has a number of components.

#### 3.2.1 Direct clinical burden of AMR

The global disease burden associated with AMR is significant. In 2019, there were ~4.95 million deaths associated with AMR, of which ~1.27 million were directly attributable to resistance.<sup>58</sup> The Organisation for Economic Co-operation and Development (OECD) forecasted the health and economic impact of AMR across 33 OECD and EU/EEA member countries from 2015 to 2050.<sup>59</sup> With the current trends of resistance, the direct costs to the patient and to health systems are significant. With an average of 18 deaths per 100,000 persons due to AMR each year, Italy has the highest mortality rate among included countries, followed by Greece, France, Poland, Spain and Germany (Figure 5). In addition to morbidity and mortality, the OECD model also predicts a large

55 For other policy proposals there is significantly greater uncertainty regarding whether it will be possible to align Member States and hence whether an incentive of sufficient scale is possible. Feasibility is therefore a bigger consideration for other incentives.

56 Adedeji, W. A. (2016) The Treasure Called Antibiotics. *Ann Ib Postgrad Med.* 14(2): 56–57. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5354621/>

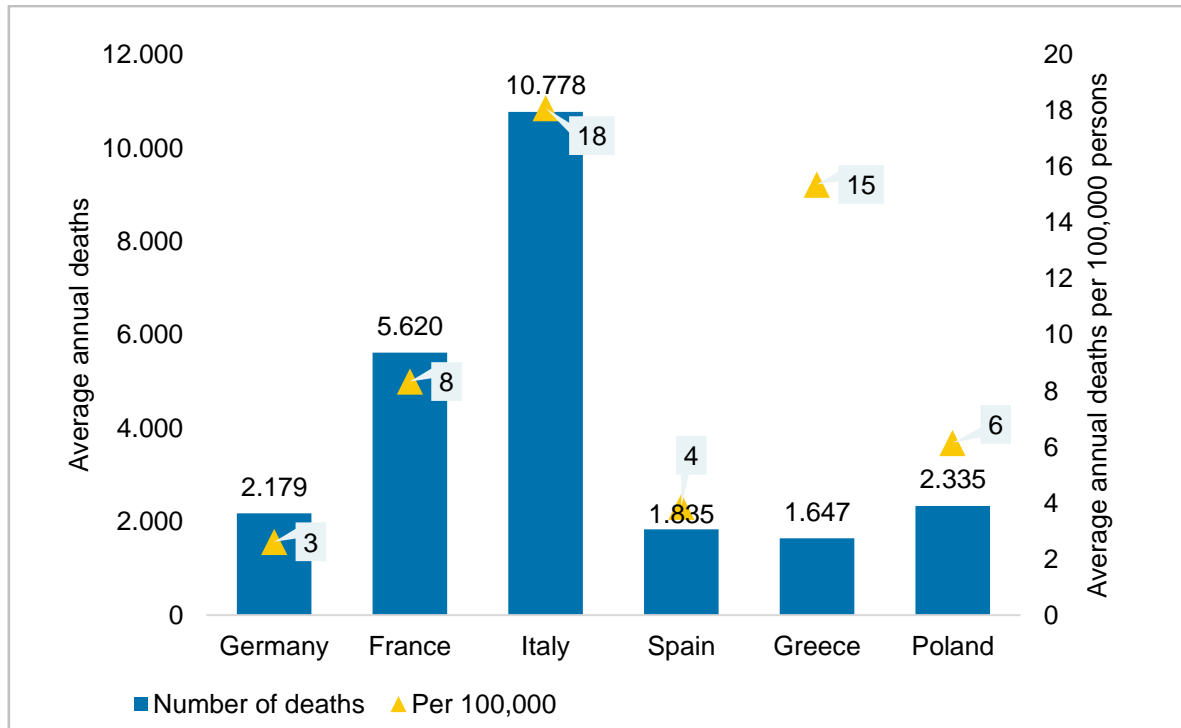
57 Sertkaya, A., Eyraud, J., Birkenbach, A. et al. (2014) *Analytical Framework for Examining the Value of Antibacterial Products*. Eastern Research Group. Available at: [https://aspe.hhs.gov/sites/default/files/migrated\\_legacy\\_files/44241/rpt\\_antibacterials.pdf](https://aspe.hhs.gov/sites/default/files/migrated_legacy_files/44241/rpt_antibacterials.pdf) [Accessed 21 June 2022]

58 Global Research on Antimicrobial Resistance (2019) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet.* 399 (10325): 629–655. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)

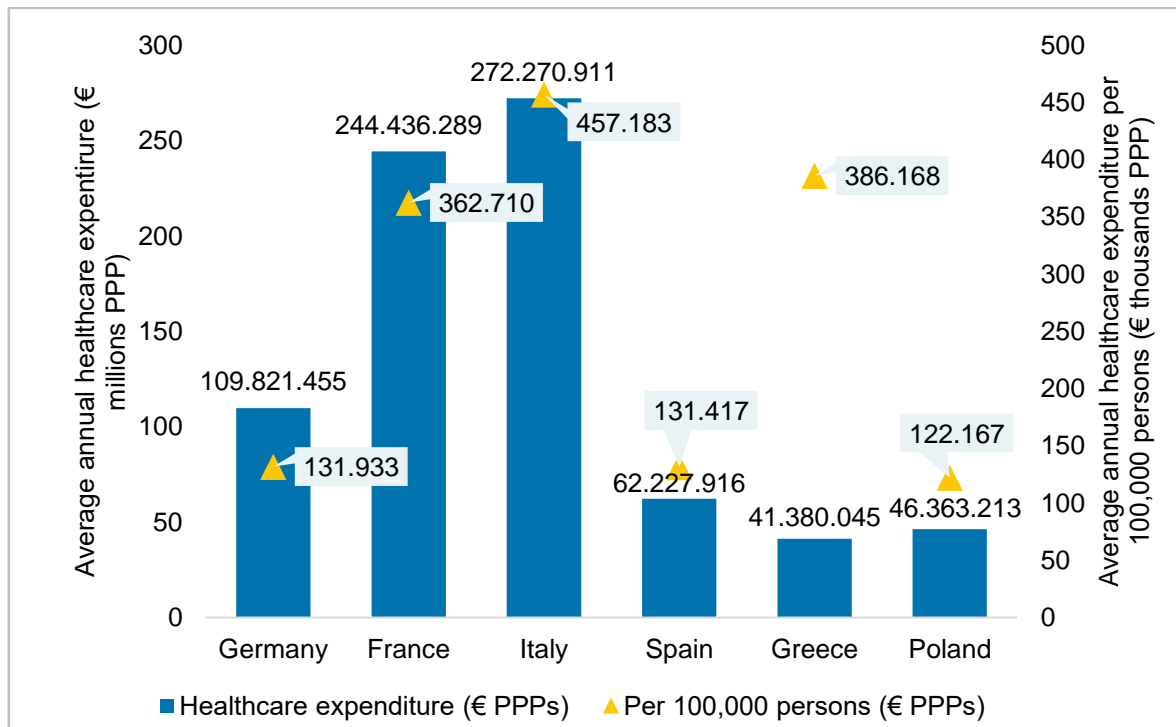
59 OECD (2018) *Stemming the Superbug Tide: Just a Few Dollars More*. OECD Health Policy Studies. Available at: <https://www.oecd-ilibrary.org/sites/9789264307599-7-en/index.html?itemId=/content/component/9789264307599-7-en> [Accessed 18 May 2022]

average annual number of extra hospital days due to AMR infections, and increased average annual healthcare expenditure. The OECD estimates the healthcare expenditure associated with AMR to be highest in Italy, with an average of €457 at purchasing power parity (PPP) per 100,000 persons each year, followed by Greece, France, Germany, Spain and Poland (Figure 6).

**Figure 5: Average annual number of deaths attributable to AMR across six European Member States (2015–2050)**



Source: OECD (2018) [here](#). Note: OECD source is used because it provides country-level data and forecasts up to 2050. Global Research on Antimicrobial Resistance (GRAM) (2019) ([here](#)) provides the number of deaths attributable to AMR across European regions in 2019: 19,000 deaths (Central Europe), 41,800 (Eastern Europe), 51,100 (Western Europe). Region-level GRAM data suggests that the OECD model provides conservative estimates of average annual number of deaths attributable to AMR

**Figure 6:** Average annual healthcare expenditure associated with AMR across six European Member States (2015–2050)

Source: OECD (2018) [here](#).

### 3.2.2 Wider impact on healthcare

Safe performance of routine surgeries, chemotherapy for cancer and transplants relies on our ability to prevent and effectively treat bacterial infections. What are currently minor and treatable infections and injuries will become fatal.<sup>60</sup> Nanayakkara et al. (2021) highlight that antibiotic resistance leads to detrimental effects in cancer patients since a patient with cancer has a three times greater risk of dying from a fatal infection than a patient without cancer.<sup>61</sup> Teillant et al. (2015) investigated the potential health consequences of increases in antibiotic resistance on the 10 most common surgical procedures and immunosuppressing cancer chemotherapies that rely on antibiotic prophylaxis in the United States.<sup>62</sup> The results showed that a 30% reduction in the efficacy of antibiotic prophylaxis for these procedures would result in 120,000 additional surgical site infections and infections after chemotherapy per year in the US (ranging from 40,000 for a 10% reduction in efficacy to 280,000 for a 70% reduction in efficacy), and 6,300 infection-related deaths (range: 2,100 for a 10% reduction in efficacy to 15,000 for a 70% reduction). Similar effects can be expected in Europe. The OECD

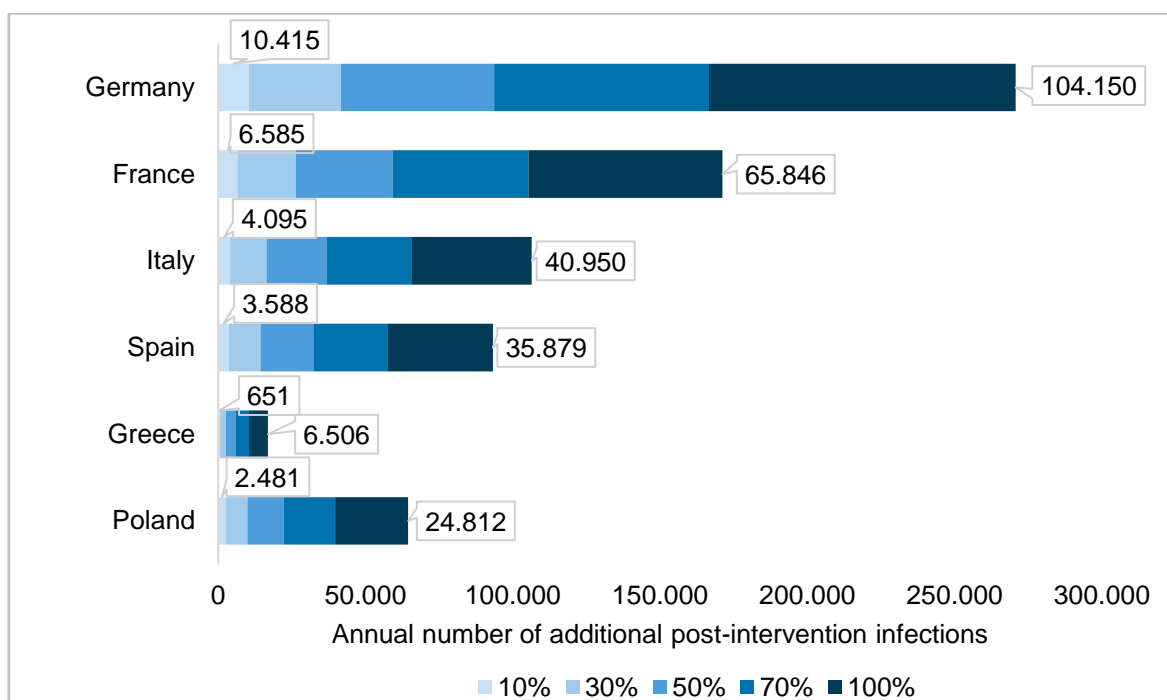
60 World Health Organization (2020) *Antibiotic Resistance*. 31 July. Available at: <https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance> [Accessed 18 May 2022]

61 Nanayakkara, A., Boucher, H., Fowler, V., Jezek, A., Outtersson, K. & 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>

62 Teillant, A., Gandra, S., Barter, D., Morgan, D. & Laxminarayan, R. (2015) Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *The Lancet*. 15(12): 1529–1437. [https://doi.org/10.1016/S1473-3099\(15\)00270-4](https://doi.org/10.1016/S1473-3099(15)00270-4)

demonstrated that the potential adverse impact of AMR on the outcomes of some of the most commonly performed surgical procedures in Europe is severe (Figure 7).<sup>63</sup>

**Figure 7: Annual number of additional post-intervention infections associated with different scenarios of reduced effectiveness of prophylactic antimicrobial therapy**



Source: OECD (2018) [here](#). Note: OECD used the Eurostat and EUCAN databases to identify the 10 most common surgical and blood cancer chemotherapies procedures performed in Europe for which antibiotic prophylaxis is recommended by current guidelines. The included procedures are: cataract surgery, caesarean section, hip replacement, appendectomy, knee replacement, hysterectomy, spinal surgery, transurethral prostatectomy, colorectal surgery, cholecystectomy, chemotherapy for blood cancers.

### 3.2.3 Economic impact of AMR

AMR's impact on health is having a growing negative impact on the global economy. Current rates of resistance could lead to an annual loss of 0.14% world Gross Domestic Product (GDP) by 2040, equivalent to \$188bn.<sup>64</sup> If resistance rates increase, this cost could be up to \$9.8 trillion. The World Bank quantifies the losses that AMR may inflict on the global economy between now and 2050.<sup>65</sup> In the optimistic case of low AMR impact, the simulations found that by 2050, annual global GDP would likely fall by 1.1% relative to a base-case scenario with no AMR effects. This is equivalent to a GDP decrease exceeding \$1tn annually after 2030. In the high AMR-impact scenario, the world would lose 3.8% of its annual GDP by 2050, an annual decrease of \$3.4tn by 2030. Since the EU contributes approximately 18% of global GDP, this annual decrease after 2030 is equivalent to \$180bn–\$613bn

<sup>63</sup> OECD (2018) *Stemming the Superbug Tide: Just a Few Dollars More*. OECD Health Policy Studies. Available at: <https://www.oecd-ilibrary.org/sites/9789264307599-7-en/index.html?itemId=/content/component/9789264307599-7-en> [Accessed 18 May 2022]

<sup>64</sup> Taylor, J., Hafner, M., Yerushalmi, E. et al. (2014) *Estimating the economic costs of antimicrobial resistance: Model and Results*. RAND Corporation. <https://doi.org/10.7249/RR911>

<sup>65</sup> 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> [Accessed 20 May 2022]

of EU GDP.<sup>66</sup> Furthermore, KPMG's (2014) model shows that if there is an absolute increase in current rates of resistance of 40%, reduction in GDP in 2050 in Europe is estimated at 1.01%.<sup>67</sup>

### 3.2.4 Summary of the importance of antibiotics to society

As resistance increases, this diminishes the value of existing antibiotics.<sup>68</sup> Even the new antibiotics that are now in development have been described by the WHO as not "expected to be effective against the most dangerous forms of antibiotic-resistant bacteria".<sup>69</sup> Given the threat of AMR to the health and economy of Europe, there would be clear and substantial benefits to implementing a policy that incentivises development of the antibiotics we need to reduce its development and spread.

If new antibiotics are developed to address increased resistance, and we expect around two new antibiotics a year, the lower estimates of European GDP loss above would suggest a conservative value of €90 billion per antibiotic.<sup>70</sup> However, although a useful upper bound, this does not provide an estimate of the incremental benefits of encouraging additional antibiotics.

### 3.3 The 'case study' method for estimating the benefits of TEE

An alternative approach is to consider the benefits of a typical TEE. Given that the benefits (and costs, since these are not borne if an eligible antibiotic is not approved) of TEE primarily materialise from the antibiotics it incentivises, the benefit of an individual TEE can be proxied by calculating the value of such an antibiotic.<sup>71</sup>

There is a large literature on how to estimate the benefits of a new antibiotic. The benefits of an antibiotic can be separated into value elements, some of which are, in principle, included in HTA of new medicines, and others which are not:

- There is clearly direct value to patients and their contribution to the economy. These elements of value are, in principle, included when adopting full HTA<sup>72</sup> of antibiotics (although we note that productivity benefits are rarely included in practice).
- This does not capture the full extent of antibiotics' value to health systems, populations and society as a whole.<sup>73</sup> Several studies have set out the additional value elements that need to be considered when evaluating an antibiotic, including additional value elements that are important for quantifying the value that arises from externalities associated with antibiotic

<sup>66</sup> World Bank (2022) Indicators: GDP (current US\$). Available at: <https://data.worldbank.org/indicator/NY.GDP.MKTP.CD>

<sup>67</sup> KPMG (2014) *The global economic impact of anti-microbial resistance*. Available at: <https://assets.kpmg/content/dam/kpmg/pdf/2014/12/amr-report-final.pdf> [Accessed 18 May 2022]

<sup>68</sup> World Health Organization (2020) *Lack of new antibiotics threatens global efforts to contain drug-resistant infections*. 17 January. Available at: <https://www.who.int/news/item/17-01-2020-lack-of-new-antibiotics-threatens-global-efforts-to-contain-drug-resistant-infections> [Accessed 18 May 2022]

<sup>69</sup> World Health Organization (2020) *Antibiotic Resistance*. 31 July. Available at: <https://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance> [Accessed 18 May 2022]

<sup>70</sup> This is assuming two novel antibiotics per year which together alleviate the €180bn GDP loss per year described in Section 3.2.3.

<sup>71</sup> It is worth noting that the benefits of an antibiotic are not solely attributable to the TEE; additional push and other funding will have been invested in the antibiotic.

<sup>72</sup> EUnetHTA (2016) *HTA Core Model*®. Available at: <https://www.eunetha.eu/hta-core-model/> [Accessed 21 June 2022]

<sup>73</sup> Simoens, S. & Spriet, I. (2021) Guidance for Demonstrating the Societal Value of New Antibiotics. *Frontiers in Pharmacology*. 11:618238. <https://doi.org/10.3389/fphar.2020.618238>

use.<sup>74</sup> These are listed and defined in Table 7. They are sometimes summarised using the acronym STEDI (spectrum, transmission, enablement, diversity, insurance). We tested with experts how these can be quantified and their applicability to different example antibiotics.

**Table 7: Definition of additional value elements for antibiotics**

Value element	Description
<b>Spectrum value</b>	Benefits of replacing broad-spectrum with narrow-spectrum antibiotics that target specific pathogens to prevent 'collateral damage' to the microbiome and reduce AMR build-up
<b>Transmission value</b>	Benefits of avoiding the spread of infection to other individuals in the population
<b>Enablement value</b>	Benefits of enabling surgical and medical procedures to take place
<b>Diversity value</b>	Benefits of having a range of treatments available to reduce selection pressure and preserve the efficacy of existing antibiotics
<b>Insurance value</b>	Benefits of having treatments available in case of sudden, or major, increase in incidence of a certain bacterial infection
<b>Novel action value*</b>	Benefits of having a new mechanism of action (MOA) that helps prevent cross-resistance developing among classes of antibiotics and paves the way for 'follow-on' products with the same MOA

Source: CRA analysis of various sources. \*Novel action value has been proposed as an important element of antibiotic value but is not included in the STEDI framework.

A recent attempt to quantify the value of antibiotics has been made by the UK National Institute for Health and Care Excellence (NICE), which published an estimate of the quality-adjusted life years (QALYs) two antibiotics selected for NICE's pilot subscription model programme would provide to the National Health Service (NHS) when used within the restrictions they set out.<sup>75,76</sup> These antibiotics are cefiderocol and ceftazidime with avibactam (CAZ-AVI). NICE estimated that cefiderocol and CAZ-AVI would provide 16,200 and 8,880 QALYs to the NHS over 20 years, respectively, and the value assigned for each year of the 10-year subscription contract should be at least 970 and 530 QALYs respectively. As recognised in the analysis, it was not possible to estimate all the elements of the STEDI framework. (Spectrum, transmission and diversity value were not quantified; enablement and insurance value were partially quantified.) In addition, NICE acknowledged the high degree of uncertainty associated with these estimates. Even so, the estimates were more than sufficient to justify that the estimated value exceeded the cap included in the UK pilot programme. These estimates therefore provide a useful benchmark for the minimum value an antibiotic provides, while also demonstrating the complexity and challenges associated with attempting to quantify the value of an antibiotic to patients and society.

In light of these challenges, we explored the broader literature (as described in Section **¡Error! No se encuentra el origen de la referencia.**) to identify attempts to quantify the value elements listed

<sup>74</sup> Ibid; OHE (2017) [here](#); OHE (2019) [here](#); Rothery, C. et al. (2018) [here](#)

<sup>75</sup> National Institute for Health and Care Excellence (2022) *Cefiderocol for treating severe drug-resistant Gram-negative bacterial infections*. Available at: <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol> [Accessed 18 May 2022]

<sup>76</sup> National Institute for Health and Care Excellence (2022) *Ceftazidime with avibactam for treating severe drug-resistant Gram-negative bacterial infections*. Available at: <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam> [Accessed 18 May 2022]

above for recent antibiotics, which we use as ‘case studies’. In the following sections, we detail how we have translated these case study estimates from the literature to quantitative estimates of each value element, in the six MS. Given there have been a limited number of attempts to quantify each of the value elements for an antibiotic, it is necessary to draw across case studies of different antibiotics.

There are also significant issues associated with whether the components are additive and the degree to which they apply to different types of antibiotics. We first consider if there is any evidence of the magnitude of these benefits and then the degree to which they are likely to be representative. Subsequently, we consider how to apply these to our stylised TPPs.

### 3.3.1 Value elements in principle included in full HTA of new medicines

To estimate the value of antibiotics to treated patients, we examine case studies of the clinical benefit of the antibiotic in terms of QALYs gained, and the productivity benefit.

#### **Clinical benefit**

Quantification of clinical benefit is based on the UK Policy Research Unit in Economic Methods of Evaluation of Health and Social Care Interventions (EEPRU) assessments of cefiderocol and CAZ-AVI. Cefiderocol and CAZ-AVI are intravenous (IV) antibiotics that could treat pathogens such as metallo-beta-lactamase (MBL)-producing *Enterobacterales* or MBL-producing *Pseudomonas aeruginosa* and indications such as hospital acquired pneumonia or ventilator associated pneumonia (HAP/VAP) or complicated urinary tract infection (cUTI). These indications are usually treated in the hospital setting.

Based on categorisation of infection sites and predicted number of patients initiating these new antibiotics over 20 years, EEPRU’s assessments yielded a range of population-level QALYs gained.<sup>77,78</sup> Since the NICE draft guidance for cefiderocol and CAZ-AVI concluded that EEPRU underestimated the number of patients who would benefit from these antibiotics, we chose the largest population-level QALYs gained over 20 years that EEPRU provided (largest number of predicted patients initiating cefiderocol or CAZ-AVI due to clinical advisors’ categorisation of infection sites and model with persistent population growth rate), averaged them across cefiderocol and CAZ-AVI, and annualised them.

EEPRU provides the present value of the number of QALYs over 20 years, given the manufacturer’s assumptions of 5% annual growth rate for the patient population eligible for cefiderocol and CAZ-AVI and EEPRU’s assumption of 3.5% discount for QALYs. The following steps describe how we estimated the monetary value of clinical benefit for an antibiotic across six MS:

- We distribute the QALYs over 20 years to obtain a present value of QALY per year taking into account growth rate and discount rate.
- To obtain the present value of the total QALYs over 10 years, we sum the present value of QALYs per year realised in the first 10 years.

<sup>77</sup> Woods, B., Schmitt, L., Jankovic, D. et al. (2021) *Final report for the technology evaluation of cefiderocol for treating severe aerobic Gram-negative bacterial infections*. EEPRU. Available at: <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/cefiderocol-for-treating-severe-aerobic-gram-negative-bacterial-infections/committee-papers> [Accessed 18 May 2022]

<sup>78</sup> Harman, S., Kearns, B., Scope, A. et al. (2021) *Final report for the technology evaluation of ceftazidime with avibactam for treating severe aerobic Gram-negative bacterial infections*. EEPRU. Available at: <https://www.nice.org.uk/about/what-we-do/life-sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials/ceftazidime-with-avibactam-for-treating-severe-aerobic-gram-negative-bacterial-infections/committee-papers> [Accessed 18 May 2022]

- We calculate the monetary value of QALYs over 10 years by multiplying by €18K per QALY or €25K per QALY.<sup>79</sup>
- We calculate the present value of population-level QALYs over 10 years for each of the six MS using the UK estimate as a benchmark for the six MS by multiplying the UK QALYs by the ratio of the number of infections with antibiotic-resistant bacteria in 2015 (the latest available estimate) in each MS to the number of infections with antibiotic-resistant bacteria in 2015 in the UK.<sup>80</sup>

The results are shown in Table 8. The lower bound uses €18K per QALY whereas the upper bound uses €25K per QALY. For antibiotics that will likely be used in fewer patients than CAZ-AVI and cefiderocol (for example for CRAB in Table 5), this will be an overestimate.

### **Productivity**

Beyond the patient benefits, there is an impact on the patient's contribution to the economy. Quantification of productivity benefit is based on Codecasa et al. (2017), which calculates the productivity benefit of bedaquiline plus background drug regimens for multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis. Bedaquiline is an oral antibiotic used to treat MDR-TB along with other medications for tuberculosis. The present value of the total productivity benefit was €12,844 per patient in the cohort over 10 years.<sup>81</sup>

The following steps describe how we estimated the average productivity benefit of an antibiotic across six MS over 10 years:

- We calculated the average number of patients expected to receive an antibiotic in each MS over 10 years based on four novel antibiotics in France, estimated by the Haute Autorité de Santé (HAS).<sup>82</sup>
- To calculate the number in each of the six MS, we multiplied the mean annual target population of these four antibiotics in France by the ratio of the number of infections with antibiotic-resistant bacteria in 2015 for the other MS to the number of infections with antibiotic-resistant bacteria in 2015 for France.<sup>83</sup>
- We assume another cohort of patients receive the antibiotic each year.
- We calculate the monetary benefit per year by multiplying the number of patients per year in each MS and the productivity benefit per patient.

79 Rothery et al. (2018) states that £15,000 per QALY is used as an estimate of health opportunity cost. Converting this to EUR yields the €18K per QALY lower bound. NICE uses a cost-effectiveness threshold range between £20K and £30K ([here](#)). We introduced the upper bound of €25K per QALY in alignment with this range.

80 Cassini, A., Högberg, L., Plachouras, D. et al. (2018) Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*. 19(1): 56–66. [https://doi.org/10.1016/S1473-3099\(18\)30605-4](https://doi.org/10.1016/S1473-3099(18)30605-4)

81 Codecasa, L., Toumi, M., D'Ausilio, A. et al. (2017) Cost-effectiveness of bedaquiline in MDR and XDR tuberculosis in Italy. *J Mark Access Health Policy*. 5(1): 1283105. <https://doi.org/10.1080/20016689.2017.1283105>

82 Patient numbers were taken from HAS reports: Meropenem/vaborbactam [here](#), cefiderocol [here](#), ceftazidime/avibactam [here](#), imipenem/cilastatin/relebactam [here](#).

83 Cassini, A., Högberg, L., Plachouras, D. et al. (2018) Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*. 19(1): 56–66. [https://doi.org/10.1016/S1473-3099\(18\)30605-4](https://doi.org/10.1016/S1473-3099(18)30605-4)

- We sum the monetary benefit per year for the first 10 years to calculate the productivity benefit per antibiotics over 10 years.

The results are shown in Table 8. For antibiotics that will likely be used in fewer patients than oral bedaquiline (for example, the antibiotic for CRAB in Table 5), this is likely an overestimate.

### 3.3.2 Additional value elements for antibiotics

We used case studies to quantify four of the five STEDI elements for each of the six MS: transmission value, diversity value, enablement value, and insurance value. We have not quantified spectrum value; there is a lack of consensus in the literature as to an appropriate methodology for estimating it, and no attempts have been made to quantify it. It has been described as very difficult or impossible to model since it requires estimation of the impact of the alternative antimicrobial treatment strategies on health outcomes and costs of other future resistant infections.<sup>84</sup> Also, to be conservative we do not quantify novel action value. Although it is conceptually distinct from diversity value – novel action value is associated with an antibiotic that has a new mechanism of action, whereas diversity value stems from having a range of treatments available to reduce selection pressure – there is a debate as to whether its benefits are distinct from those of diversity value.<sup>85,86</sup>

#### Transmission value

Morton et al. (2019) attempted to model transmission value of a hypothetical antibiotic that targets carbapenem-resistant *Acinetobacter baumannii* (CRAB) in the intensive care unit (ICU) setting. The point estimate of the transmission value for this hypothetical antibiotic is 33,178 QALYs per year for Europe.<sup>87</sup>

- We used Morton et al.'s (2019) assumption of an 8% annual decay rate and applied it to QALYs for transmission value to incorporate the effect of increasing resistance. Additionally, we used EEPRU's assumption of a 3.5% annual discount rate to calculate the present value of QALYs (see above).
- We translated this point estimate into QALYs per year for the six MS by multiplying 33,178 by the ratio of the population of the MS to the population of Europe. We calculated the present value of QALYs per year across MS. We summed the present value of the QALYs per year for the first 10 years to calculate the transmission value per antibiotic over 10 years.
- We calculated the monetary value of QALYs over 10 years by multiplying by €18K per QALY or €25K per QALY (see rationale above).

The results are shown in Table 8. The lower bound uses €18K per QALY, whereas the upper bound uses €25K per QALY. For antibiotics that will likely be used in broader treatment settings than ICU

84 Rothery, C., Woods, B., Schmitt, L., Claxton, K., Palmer, S. & Sculpher, M. (2018) *Framework for value assessment of new antimicrobials: implications of alternative funding arrangements for NICE Appraisal*. EEPRU. Available at: [https://pure.york.ac.uk/portal/en/publications/framework-for-value-assessment-of-new-antimicrobials\(f0bc0ec9-9236-4cc7-9498-0002bd31f429\).html](https://pure.york.ac.uk/portal/en/publications/framework-for-value-assessment-of-new-antimicrobials(f0bc0ec9-9236-4cc7-9498-0002bd31f429).html) [Accessed 18 May 2022]

85 Ibid.

86 Simoens, S. & Spriet, I. (2021) Guidance for Demonstrating the Societal Value of New Antibiotics. *Frontiers in Pharmacology*. 11:618238. <https://doi.org/10.3389/fphar.2020.618238>

87 Morton, A., Colson, A., Leporowski, A., Trett, A., Bhatti, T. & Laxminarayan, R. (2019) How Should the Value Attributes of Novel Antibiotics Be Considered in Reimbursement Decision Making? *MDM Policy & Practice*. 4(2) <https://doi.org/10.1177/2381468319892237>

(for example, antibiotics for *S. aureus*, CRE, *Salmonella*, *N. gonorrhoeae* in Table 5), this is likely an underestimate.

### **Diversity value**

The same approach was used for diversity value. Morton et al. (2019) also provide an estimate of diversity value of a hypothetical antibiotic that targets CRAB in the ICU setting in addition to the transmission value shown above. The point estimate of the diversity value for this hypothetical antibiotic is 2,752 QALYs per year for Europe.<sup>88</sup>

- We used Morton et al.'s (2019) assumption of a 3% annual decay rate and applied it to QALYs for transmission value to incorporate the effect of increasing resistance. Additionally, we used EEPURU's assumption of a 3.5% annual discount rate to calculate the present value of QALYs.
- We translated this point estimate into QALYs per year for each of the six MS by multiplying 2,752 by the ratio of the population of the MS to the population of the EU. We calculated the present value of QALYs per year across MS.
- We summed the present value of the QALYs per year for the first 10 years to calculate the diversity value per antibiotic over 10 years.
- We calculated the monetary value of QALYs over 10 years by multiplying by €18K per QALY or €25K per QALY.

The results are shown in Table 8. The lower bound uses €18K per QALY, whereas the upper bound uses €25K per QALY. For antibiotics that will likely be used in broader treatment settings than ICU (for example antibiotics for *S. aureus*, CRE, *Salmonella*, *N. gonorrhoeae* in Table 5), this is likely an underestimate.

### **Enablement value**

There are three types of situation where a new effective antibiotic would generate enablement value: avoiding delay of procedures/treatments due to infection; decreasing incidence of infections and resulting deaths during or post procedures; and providing sufficiently effective infection risk reduction so that procedures/treatments can take place. Our analysis focuses on the second of these: the enablement value that a new antibiotic would bring via avoiding surgical site infections and infections after chemotherapy. This means that our estimate of enablement value is likely to be a significant underestimate of the true enablement value of an antibiotic.

Teillant et al. (2015) attempted to estimate enablement value as the number of additional deaths per year in the US under different scenarios of decreased efficacy of antibiotic prophylaxis.<sup>89</sup> Although there is scarce evidence that quantifies the relationship between antibiotic resistance and decrease in efficacy of antibiotic prophylaxis, it is evident that increased resistance leads to decreased efficacy of antibiotic prophylaxis.<sup>90</sup> Because antibiotic resistance to pathogens that cause surgical site infections has been increasing, we assume that a new antibiotic would decrease the reduction in

88 Ibid.

89 Teillant, A., Gandra, S., Barter, D., Morgan, D. & Laxminarayan, R. (2015) Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *The Lancet*, 15(12): 1529–1437. [https://doi.org/10.1016/S1473-3099\(15\)00270-4](https://doi.org/10.1016/S1473-3099(15)00270-4)

90 We understand that there is a submission for publication based on the experience from the UK pilots that will usefully supplement the existing literature.

efficacy of prophylaxis by 0.5% (lower bound) to 1.5% (upper bound).<sup>91</sup> According to Teillant et al. (2015), a 0.5% reduction in efficacy of prophylaxis results in 105 infection-related deaths in the US per year; these are the deaths that would be avoided if a new antibiotic decreased the reduction in efficacy of prophylaxis by 0.5%. With a 1.5% decrease in the reduction in efficacy, the number of deaths avoided in the US is 315 per year.

- We translated this number of deaths to each of the six MS by multiplying 105 and 315 by ratio of the population of the MS to the US population
- We multiplied the number of deaths per year for each MS by the value of a statistical life €1.5 million.<sup>92</sup>
- We applied a 3.5% discount rate per year and summed the monetary values over 10 years.

Results are shown in Table 8. For antibiotics that will not be used mainly for prophylaxis (for example, antibiotics for CRE, *Salmonella*, *N. gonorrhoeae* in Table 5), this is likely an overestimate.

### **Insurance value**

There are two components to insurance value: (1) the value associated with strategies to preserve the use of a new antibiotic until ongoing trends in resistance to all other existing antibiotics worsen and the prevalence of infections cannot be contained, and (2) the value associated with insuring against some exogenous shock to the system, such as an outbreak or pandemic, that could spike the prevalence of resistant infections.<sup>93</sup> In our analysis we focus on the second component. Megiddo et al. (2019) attempted to estimate insurance value of withholding use of a hypothetical novel oral antibiotic that can effectively treat *Staphylococcus aureus* infections until an outbreak occurs in the UK. The authors assumed that IV therapy exists, but the increased volume of cases would overburden the health system, meaning there would be value in having an oral treatment available. They modelled three levels of IV therapy capacity: 80%, 50%, and 20%. When IV therapy capacity during the pandemic was set to 50% or 20%, withholding wide use of the oral treatment until the pandemic event proved to be beneficial, providing a value of \$578m and \$2.2bn, respectively.<sup>94</sup>

- We translated these values for the UK into values for each of the six MS by multiplying €537.54m and €2.05bn by the ratio of the population of each MS to the population of the UK.<sup>95</sup>
- To obtain the expected value in each scenario, we multiplied the monetary value across MS by the probability of a bacterial outbreak occurring in a 10-year time frame. We assumed this

91 This was based on an assessment of recent trends in resistance over the last 10 years. ECDC (2019) *Data from the ECDC Surveillance Atlas – Antimicrobial resistance*. Available at: <https://www.ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc> [Accessed 20 May 2022]

92 OECD (2012) *Mortality Risk Valuation in Environment, Health and Transport Policies*. OECD Publishing. Available at: <http://dx.doi.org/10.1787/9789264130807-en> [Accessed 25 May 2022]

93 Rothery, C., Woods, B., Schmitt, L., Claxton, K., Palmer, S. & Sculpher, M. (2018) *Framework for value assessment of new antimicrobials: implications of alternative funding arrangements for NICE Appraisal*. EEPURU. Available at: [https://pure.york.ac.uk/portal/en/publications/framework-for-value-assessment-of-new-antimicrobials\(f0bc0ec9-9236-4cc7-9498-0002bd31f429\).html](https://pure.york.ac.uk/portal/en/publications/framework-for-value-assessment-of-new-antimicrobials(f0bc0ec9-9236-4cc7-9498-0002bd31f429).html) [Accessed 18 May 2022]

94 Megiddo, I., Drabik, D., Bedford, T., Morton, A., Wesseler, J. & Laxminarayan, R. (2018) Investing in antibiotics to alleviate future catastrophic outcomes: What is the value of having an effective antibiotic to mitigate pandemic influenza? *Wiley Health Economics*. 28(4): 556–571. <https://doi.org/10.1002/hec.3867>

95 Fx rate: 1 USD = 0.93 EUR

would be lower than the probability of a pandemic with similar impact to COVID-19 occurring in a 10-year time frame.<sup>96</sup>

- Assuming that the outbreak occurs in 2027 (five years from 2022), we used a discount rate of 3.5% to calculate present value.

The results are shown in Table 8. The lower bound reflects the 50% IV coverage situation, whereas the upper bound reflects the 20% IV coverage situation. For antibiotics that will likely be used in a limited number of patients (for example, antibiotics for CRAB and *S. aureus* in Table 5), this is likely an overestimate.

### 3.3.3 Summary of results of case study analysis

We summarise the results of the case study analysis of antibiotic value by MS in Table 8. Benefits are represented as the present value of benefits over 10 years. This assumes that each antibiotic's value is realised over 10 years. This is an underestimate as the benefits of the antibiotics brought to the market because of the TEE will extend well beyond the 10-year horizon here, especially if careful stewardship prolongs the effective life of the drug.

There is agreement across experts that various value elements interact with one another, and it is not possible to simply aggregate the benefits from the STEDI framework applied to any individual antibiotic. In addition, the value of any given antibiotic will depend on the type of antibiotic but also how it is used. For example:

- If the antibiotic is held back as insurance in case of an outbreak, the insurance value would be maximised but the other benefits arising from using the antibiotic would not be fully realised until the outbreak occurs.
- If the antibiotic is used extensively, then clinical and productivity benefits, transmission value, and enablement value are realised today, but diversity value and insurance value will be limited.

In practice however, it is likely to be a middle ground. If a new antibiotic benefits patients now, especially those who are critically ill and have no other treatment options, it is unlikely that the new antibiotic will be completely held back. Indeed, we were told this would be unethical. It is also unlikely that any new antibiotics will be used extensively, as this would contradict antibiotic stewardship practices.

For the purposes of this study we assume the antibiotic would be used sparingly (as they are on the WHO list of priorities), in accordance with stewardship practices; the diversity value and insurance value would be significant; but there would also be a value in terms of transmission and enablement value. However, given the challenges associated with quantifying the STEDI elements, and the limited case studies we have as evidence, we suggest focusing on the most significant benefits for each of our stylised TPPs introduced in Chapter 2. It would be inappropriate to include both insurance and transmission value for a particular example.

**Table 8: Net present value of benefit of TEE per antibiotic over 10 years by Member State**

Value element	Benefits of TEE by MS (€ M present value)
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Penn, M. (2021) *Statistics Say Large Pandemics Are More Likely Than We Thought*. Duke Global Health Institute. Available at: <https://globalhealth.duke.edu/news/statistics-say-large-pandemics-are-more-likely-we-thought#:~:text=It%20found%20the%20probability%20of,of%20experiencing%20one%20by%20now> [Accessed 24 May 2022]

	France	Germany	Italy	Spain	Greece	Poland
<b>Clinical benefit</b>	54–75	23–33	87–120	18–25	8–11	18–25
<b>Productivity</b>	69	30	111	23	10	23
<b>Spectrum</b>	<i>Not estimated*</i>					
<b>Transmission</b>	335–466	414–575	296–411	236–327	53–74	189–262
<b>Enablement</b>	277–644	342–684	245–489	195–390	44–88	156–312
<b>Diversity</b>	57–79	70–97	50–69	40–55	9–13	32–44
<b>Insurance</b>	43–165	54–204	38–146	30–116	7–26	24–93
<b>Novel action</b>	<i>Not estimated*</i>					

Source: CRA analysis of various sources, see text for details. Parameters used to calculate upper and lower bounds (see body text for more details): Clinical benefit, transmission value, diversity value: lower bound = €18k/QALY, upper bound = €25k/QALY. Enablement value: lower bound = 0.5% decrease in the reduction in efficacy of prophylaxis, upper bound = 1.5% reduction in efficacy of prophylaxis. Insurance value: lower bound = 50% IV capacity, upper bound = 20% IV capacity. \*See section 3.3.2 for rationale for not estimating spectrum value and novel action value. The value elements that are realised depend on antibiotic characteristics and how widely antibiotics are used and should not be treated as additive (see 3.3.4).

### 3.3.4 Applying the value elements to potential novel antibiotics

As set out in Section 2.3, we created example antibiotic profiles of products which could receive a TEE (Table 5). Now, we contextualise the case studies quantified above by describing how the value elements may apply to the example antibiotics. For each antibiotic, we set out below the key value elements that would likely drive value (described below and in Table 9).

- For antibiotic #1, for CRAB, the value would be in the critical care setting and predominantly driven by the clinical and productivity benefits, transmission value and insurance value.
- The value of antibiotic #2, for *S. aureus*, would be driven to a large extent by enablement value, since *S. aureus* commonly causes surgical site infections and infections after cancer chemotherapy. There is also a significant insurance value, but this is limited by the IV ROA.
- The clinical and productivity benefits and transmission value of antibiotic #3, for CRE, would depend on the oral ROA, with a significant insurance value if efficacy is preserved through careful stewardship.
- The value of antibiotic #4, for FQ-*Salmonella*, predominantly arises from insurance value, as it would have greatest value in an outbreak of food-borne infections.
- For antibiotic #5, for *N. gonorrhoeae*, the value is driven by the clinical and productivity benefits and transmission value.

**Table 9: Relevance of each value element for the five example antibiotics**

Value Element	Applicability of Case Study Estimate for Example Antibiotics				
	Antibiotic #1 CRAB	Antibiotic #2 <i>S. aureus</i>	Antibiotic #3 CRE	Antibiotic #4 <i>Salmonella</i>	Antibiotic #5 <i>N. gonorrhoeae</i>
<b>Clinical benefit</b> <i>France:</i> €54m–€75m	✓		✓		✓
<b>Productivity</b> <i>France:</i> €69m	✓		✓		✓
<b>Diversity value</b> <i>France:</i> €57m–€79m					
<b>Transmission value</b> <i>France:</i> €335m–€466m	✓		✓		✓
<b>Enablement value</b> <i>France:</i> €277m–€644m		✓			
<b>Insurance value</b> <i>France:</i> €43m–€165m	✓	✓	✓	✓	

Source: CRA analysis. Note: a tick indicates that the value element is a key driver of the value for that particular example antibiotic; however, all antibiotics will likely derive benefit from all value elements.

### 3.4 Benefits of supporting infrastructure for antimicrobial development

The R&D on antibiotics stimulated by implementing the TEE policy would have wider benefits to society, beyond the benefits arising from the individual TEE recipient antibiotics. This is because medical countermeasures for future health crises, such as growth in AMR, are developed over years of innovation. This was demonstrated in recent years in the case of COVID-19 vaccines. The rapid vaccine development in response to the COVID-19 outbreak and subsequent pandemic was enabled by years of prior research and innovation on emerging viruses and to develop the mRNA vaccine platform.<sup>97</sup> Similarly, antibiotics against resistant infections are not developed ‘overnight’ but require years of innovation and investment in the overall research infrastructure for antimicrobial development. Implementing TEE in Europe would stimulate R&D, which would ensure continued investment in this, ensuring antibiotics are available when we need them in the future. We have not been able to quantify the benefit to society of continued investment in the antimicrobial innovation

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Ball, P. (2021) The lightning-fast quest for COVID vaccines — and what it means for other diseases. *Nature*. 589:16–18. <https://doi.org/10.1038/d41586-020-03626-1>

infrastructure, but this is a key benefit of TEE and should be considered when evaluating it for implementation in Europe.

### 3.5 Summary of the benefits of TEE

To summarise, the potential benefits of implementing TEE in Europe are substantial. An appropriately designed TEE policy has the potential to incentivise development of novel antibiotics which would help reduce the rate of AMR development, ensure that our antibiotic arsenal remains effective against the most dangerous pathogens, and equip us to deal with inevitable future outbreaks of bacterial infections. Although the value to society of each individual TEE will vary by the characteristics of each recipient antibiotic and is therefore difficult to quantify, it is clear that the overall societal value of implementing a policy that helps to fix the 'broken' antibiotic market is significant.<sup>98</sup>

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Wellcome Trust (2020) *It's time to fix the antibiotic market*. 1 November. Available at: <https://wellcome.org/news/its-time-fix-antibiotic-market> [Accessed 20 May 2022]

To estimate costs at the EU / EEA-level, we scale the costs per MS by the population of that MS and the EU / EEA population, then we average across these numbers to yield an average lost genericisation savings per TEE (2024–2033). For example this is €592M for two 12-month TEE.

## 4 Cost of TEE to European Member States

In addition to the benefits of TEE, it is also important to consider the costs to European MS. In this chapter, we quantify the cost of a TEE, and the cost of the TEE policy over the first 10 years of implementation to each of the six selected MS (France, Germany, Italy, Spain, Greece, and Poland). We consider three areas:

1. Lost genericisation savings resulting from the marketing exclusivity extension of a product which uses the TEE voucher
2. Administrative costs of implementing TEE
3. Wider impacts of the marketing exclusivity extension of a product which uses the TEE voucher, on patient access to this product and others in its class

We use the assumptions set out in Chapter 2 regarding the length of TEE (9 or 12 months) and the number of TEEs (1 or 2 TEEs per year).

### 4.1 Lost genericisation savings

The first element of the cost of TEE to MS that we estimate is the savings from genericisation that are lost when a TEE user receives a marketing exclusivity extension for 9 or 12 months. To do this, we first examine which products would be likely to use a TEE, and then estimate for each MS the average genericisation savings forgone by marketing exclusivity extension.

#### 4.1.1 Expected TEE users

Since the intention is for TEE to be implemented at the EU/EEA level, we determined which products would be likely use a TEE at EU/EEA level to then understand the cost of this to MS. As set out by Berdud et al. (2019), the company with the highest WTP at any given time (based on the present value of their expected sales in the year of marketing exclusivity expiry ('loss of exclusivity', LOE)) will likely use each TEE (depending on the application of guardrails). Therefore, we obtained EU/EEA and country-specific pharmaceutical sales data to estimate which products would likely use a TEE each year for the period 2024–2033.<sup>99</sup> European sales data obtained included forecasted sales up to 2026, which was then extrapolated until LOE.<sup>100</sup>

To determine which products would likely use a TEE each year, we follow the approach of the OHE.<sup>101</sup> We calculate WTP for a TEE for each product in each year from 2024 to 2033 by multiplying

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<sup>99</sup> This was based on product-level data from Evaluate Pharma. Accessed April 2022.

<sup>100</sup> The 30 products with greatest EU/EEA forecasted sales in 2024 were identified and selected for the analysis to determine which products would likely use TEE from 2024–2033. Forecasted sales in 2024 were used to rank products because we assume that TEE will be implemented in 2024. Products with patient expiration prior to 2024 and vaccines were excluded.

<sup>101</sup> Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics.

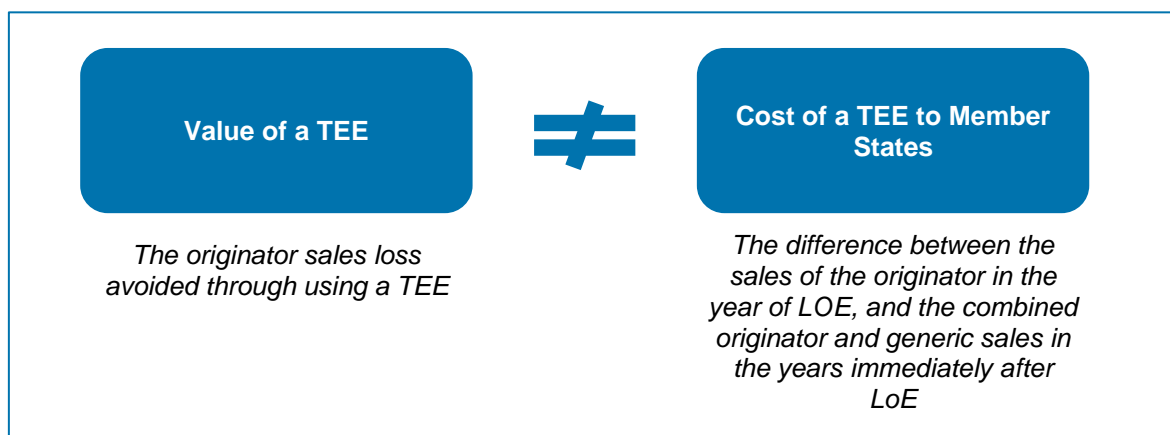
net sales (70% of gross sales) by a 47% reduction in sales in the year after LOE.<sup>102,103</sup> We assume two new entrants per year into the top 30 list, with sales in the first year of entry of €727m and €632m respectively, based on average sales of entrants into the top 30 list from 2017 to 2021 and growing at the average compound annual growth rate (CAGR) of the top 30 list.

As the TEE does not need to be used immediately, it can be purchased by a company losing market exclusivity in the future. We therefore estimate the present value of WTP for a TEE for each product using a discount rate (cost of capital) of 10%.<sup>104</sup> The value of the TEE depends on how many are sold. If one is sold this will go to the manufacturer with the higher WTP. If two are sold, the second TEE will go to the manufacturer with the next-highest WTP. Two scenarios (1 TEE per year and 2 TEEs per year) were then developed by selecting the products with the highest WTP each year from 2024 to 2033. These products are the 'expected TEE users'. This reflects that a company can have 1 TEE per product. In practice, other additional guardrails could be applied to the TEE users, but these are not assumed in our analysis.

#### 4.1.2 Estimating lost genericisation savings

The approach above is used to determine the products that will have a TEE applied to them. It has determined the WTP and hence the value of the TEE, and whether this delivers the necessary incentive. However, the value of TEE is not the same as the cost to MS. They pay through the lost genericisation of the product during the period of the TEE. This difference is illustrated in Figure .

**Figure 8: Illustration of the difference between the value of a TEE and the cost to Member States**



Source: CRA analysis

As the off-patent market varies from MS to MS, we need to estimate this at the country level. For example, a country that does not experience any generic entry would have no forgone cost savings and would not pay a cost for the TEE. We assume that generics or biosimilars enter the market as soon as the originator loses marketing exclusivity, and we calculate what the MS would have paid for medicine if genericisation occurred as expected and compare this to the cost if a TEE means it is

<sup>102</sup> Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics.

<sup>103</sup> In reality the WTP would be based on expected profitability rather than loss sales and therefore we should include an allowance for costs. However, given this would be equally applied to all bidders of the TEE, this would not change the identification of the highest bidder and therefore would not change our analysis.

<sup>104</sup> Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics.

delayed for a period of time. This will overestimate the cost of forgone savings if there is a delay – so, for example, in a country like Poland, where generic entry is often delayed,<sup>105</sup> the cost of the TEE is overstated.

Having determined the expected TEE users at EU/EEA level, we calculated the MS's associated lost genericisation savings from one TEE due to marketing exclusivity extension. The genericisation savings are the difference between what the MS would have paid with and without the TEE in the years after LOE. Since most of the products that the TEE will be used for are biologics, we have focused on analysis of biosimilar competitive dynamics. We calculated the genericisation savings using estimates for key parameters from the literature, including:

- The ratio of the sales of an originator, one year, two years and three years after LOE to the sales of originator in year of LOE; these parameter estimates are based on OHE's 2019 report that estimates a 47% reduction in gross sales as a result of generic entry<sup>106</sup>
- Generic/biosimilar uptake one year, two years and three years after LOE based on percentage of treatment days of a group of biosimilars; these parameter estimates are based on IQVIA's 2021 white paper that provides Europe-level biosimilar uptake rates for one year, two years and three years after biosimilar launch<sup>107</sup>
- The ratio of the price of the generic or biosimilar and the originator one year, two years and three years after LOE to the existing price of the originator by MS; these parameter estimates are based on IQVIA's 2018 assessment that provides the percent difference between biosimilar and originator price at biosimilar launch across various countries<sup>108</sup>

A detailed explanation of the methodology and how we use these parameters is available in the Appendix.

As genericisation occurs gradually over a number of years, TEE has an impact in the first year but also affects cost savings in subsequent years.<sup>109</sup> The objective, as with the benefits of TEE, is to model the lost genericisation savings over the first 10 years after the TEE is applied. We assume that the cost is negligible after the first three years as the market will be fully genericised so the

105 Simoens, S. (2009) Developing Competitive and Sustainable Polish Generic Medicines Market. *Croat Med J.* 50(5): 440–448. doi: 10.3325/cmj.2009.50.440 but supported by more recent analysis IQVIA (2022) Protection expiry for pharmaceuticals in Europe full report

106 Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D.* Office of Health Economics.

Note that these parameters do not vary by Member State based on source.

107 Troein, P., Newton, M., Scott, K., & Mulligan, C. (2021) *The Impact of Biosimilar Competition in Europe.* IQVIA. Available at: [https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?\\_ =1640100592119](https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119) [Accessed 25 May 2022]

Note that these parameters do not vary by Member State based on source.

108 IQVIA Institute for Human Data Science (2018) *Advancing Biosimilar Sustainability in Europe – A Multi-Stakeholder Assessment.* Available at: [https://www.biosimilars-nederland.nl/wp-content/uploads/2018/10/okt\\_2018\\_IQVIA\\_Pfizer\\_Advancing-Biosimilar-Sustainability-in-Europe.pdf](https://www.biosimilars-nederland.nl/wp-content/uploads/2018/10/okt_2018_IQVIA_Pfizer_Advancing-Biosimilar-Sustainability-in-Europe.pdf) [Accessed 25 May 2022]

Note that these parameters do vary by Member State based on source.

109 Boyer, B., Kroetsch, A. & Ridley, D. (2022) *Design of a Transferable Exclusivity Voucher Program – Incentives for drug and vaccine development for neglected diseases.* Duke Margolis Center for Health Policy. Available at: <https://healthpolicy.duke.edu/publications/design-transferable-exclusivity-voucher-program>

impact of the delayed genericisation is not seen. We therefore calculate the lost cost savings for the first three years after LOE. The cost savings forgone across MS for the year after LOE, two years after LOE, and three years after LOE are shown in Table 10. **Error! No se encuentra el origen de la referencia.**, as a percentage of what the MS spends in the year of LOE. It should be noted that the cost savings forgone are smaller than the lost sales of the originator company. This is because the MS pays for the genericised sales of the generic companies.

**Table 10: Cost savings factors for one TEE across Member States for the first three years after loss of exclusivity (LOE)**

	France	Germany	Italy	Spain	Greece	Poland
<b>% cost savings forgone in year after LOE</b>	15.2%	14.5%	19.8%	18.4%	14.3%	23.9%
<b>% cost savings forgone two years after LOE</b>	20.5%	19.7%	25.5%	23.9%	19.5%	29.9%
<b>% cost savings forgone three years after LOE</b>	27.0%	26.2%	32.2%	30.6%	26.0%	36.9%

Source: CRA analysis

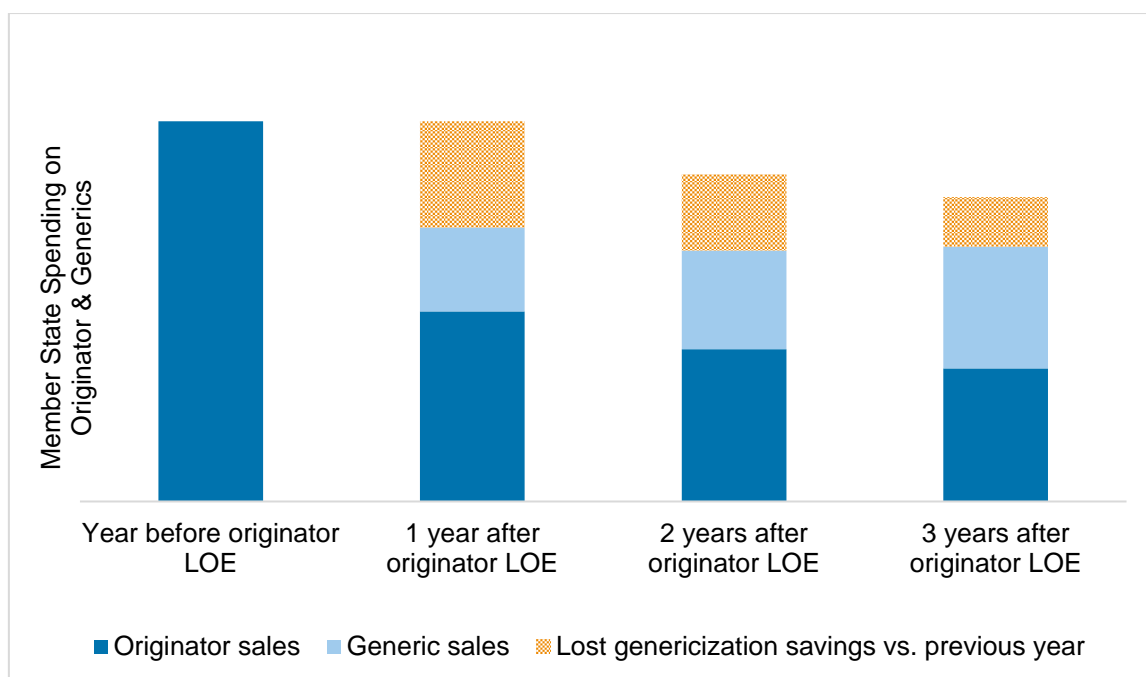
Figure 9 illustrates the approach, with the orange segment representing loss cost savings for a 12-month TEE.

To estimate the originator sales after LOE, we analysed historical sales in year of LOE and in years post LOE of products that have lost exclusivity in the anti-TNF (adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade)) and oncology (bevacizumab (Avastin), trastuzumab (Herceptin)) spaces. This is based on five products but has the advantage of being relatively recent and representing products with a high level of sales.<sup>110</sup>

**Figure 9: Illustration of lost genericisation savings**

110

The analysis could be developed to include country-specific analysis of how genericisation depends on the type of medicine that is losing market exclusivity.



Source: CRA analysis

We calculate the present value of the costs using a discount rate of 3.5%, which is aligned with the discount rate for QALYs in the benefits calculations. Next, we sum the three years together to produce the lost genericisation savings for each TEE in each MS. To calculate the average lost genericisation savings per TEE (2024–2033) when TEE extends market exclusivity by 9 months instead of 12 months, we scale the average lost genericisation savings for the 12-month TEE scenario by the ratio of the TEE lengths. The average lost genericisation savings per TEE are shown in Table 11; **Error! No se encuentra el origen de la referencia..**

**Table 11: Average lost genericisation savings per TEE (2024–2033)**

TEE Scenario	TEE Length	Average lost genericisation savings per TEE (2024–2033) (€ M Present Value)					
		France	Germany	Italy	Spain	Greece	Poland
1 TEE per year	12 months	105	121	105	66	15	14
	9 months	79	91	79	50	11	10
2 TEEs per year	12 months	73	88	74	48	19	11
	9 months	55	66	55	36	14	9

Source: CRA analysis

This is a simplified analysis:

- Since we assume generics or biosimilars enter the market in the year of LOE, and this is not always the case, our estimate of the cost of TEE to MS is likely to be an overestimate (particularly in markets where genericisation is often delayed). However, for some products, originator sales will decrease more quickly than we have estimated, which may lead to a higher cost of TEE.

- It is also worth noting that this is based on average lost genericisation savings; the lost savings for any individual TEE will vary depending on the sales and market dynamics of the particular TEE user product.

## 4.2 Administrative cost of implementing TEE

A number of different administrative costs are associated to the TEE policy. There will be regulatory costs in setting out the products that will qualify for the TEE, assessing whether the products are eligible, and allocating and monitoring the TEE. There will also be administrative costs associated with selling the voucher. We have estimated these as follows:

- We assume that the **cost of assessing potentially eligible products, assigning vouchers and ongoing monitoring** would be the responsibility of the European Medicines Agency (EMA). One way of estimating the EMA-level administrative costs for implementing TEE is to base this on the cost to the FDA of implementing Tropical Disease Priority Review Vouchers (PRVs) and Rare Pediatric Disease PRVs, as a proxy. The FDA 2022 budget indicates that \$13.4m was allocated to PRVs for fiscal year 2021.<sup>111</sup> Assuming the EMA is funded by MS proportionally to MS population size, we estimated the cost to each MS based on the ratio between its population and the total EU population (Table 12). The administrative costs of TEE in Europe would likely be smaller than the estimate shown in Table 12 because it is likely only 2 or 3 TEEs will be awarded each year, compared with the seven PRVs granted by the FDA in 2019.<sup>112</sup> Furthermore, unlike the PRV programme, implementing TEE will not involve conducting priority reviews or other resource-consuming regulatory activity for the EMA. We assume that administrative costs are fixed for each year. Although this appears the most appropriate available analogue, using the FDA PRV programme as a proxy for the administrative costs of TEE could, according to experts consulted for this project, be a considerable overestimate of the cost of TEE, as the activities that would need to be undertaken by EMA would be less than those conducted for priority reviews.
- The **cost of selling the voucher** would predominantly fall under the purview of the TEE recipient as they are responsible for identifying a buyer and negotiating the voucher sale. We assumed an administrative cost to the TEE recipient of selling the voucher of \$1m (€0.9m) per TEE.<sup>113,114</sup> This has been accounted for in the calculation of the required value of a European TEE in Chapter **¡Error! No se encuentra el origen de la referencia..**

Based on the interviews conducted, it is likely that the administrative costs estimated for TEE could be considerably lower than those for alternative pull incentives that have been proposed, such as subscription models, which have a significant administrative cost involved in their set-up and maintenance. In addition, much of the administrative cost of TEE is borne at the European level, while for subscription models, the administrative cost is borne at the MS level.

111 Food and Drug Administration (2022) *Fiscal Year 2022: Justification of Estimates for Appropriations Committees*. Available at: <https://www.fda.gov/media/149616/download> [Accessed 20 May 2022]

112 US Government Accountability Office (2020) *Drug Development: FDA's Priority Review Voucher Programs*. Available at: <https://www.gao.gov/products/gao-20-251> [Accessed 20 May 2022]

113 Fx rate: 1 USD = 0.93 EUR.

114 Årdal, C., Lacotte, Y. & Ploy, M.-C. (2020) Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe. *Clinical Infectious Diseases*. 71(8):1994–1999. Available at: <https://doi.org/10.1093/cid/ciaa153>

**Table 12: Estimated administrative costs by Member State**

	Estimated administrative cost of TEE (€ M present value)					
	France	Germany	Italy	Spain	Greece	Poland
<b>Cost per TEE (1 TEE per year)</b>	1.6	2.0	1.4	1.1	0.3	0.9
<b>Cost per TEE (2 TEEs per year)</b>	0.8	1.0	0.7	0.6	0.1	0.5
<b>Total fixed cost over 10 years (2024–2033)</b>	16.3	20.1	14.4	11.5	2.6	9.2

Source: CRA analysis. Note: total cost over 10 years is not dependent on the number of TEEs per year; cost per TEE for 1 TEE per year and 2 TEEs per year are calculated by dividing the fixed cost per year by the number of TEEs each year.

### 4.3 Impact of TEE on number of patients treated

There are other potential costs of a TEE. A TEE could delay generic entry into markets, and this could reduce patient access in these markets, harming patients. It could have knock-on impact on therapeutic competition. This would depend on market dynamics in different MS and could therefore have country-specific impact.

To address the concern that the extension of marketing exclusivity of TEE users could result in reduced patient access to medicines, we investigated the change in number of patients treated in the first year after LOE compared with the year before LOE. To do this, we used IQVIA data on treatment days per capita (TD/capita) in 2021 and in the year before biosimilar entry for a variety of biosimilars in various therapeutic areas.<sup>115</sup> Due to the class size, availability of data and several products recently losing marketing exclusivity in Europe, we analysed this data for two classes: tumour necrosis factor inhibitors ('anti-TNF') and oncology. In the oncology category, products included bevacizumab (Avastin), rituximab (Mabthera), trastuzumab (Herceptin) and corresponding biosimilars. In the anti-TNF category, products included adalimumab (Humira), etanercept (Enbrel), infliximab (Remicade) and corresponding biosimilars.

Based on the TD/capita in 2021 and in the year before biosimilar entry, and the year in which first sales of biosimilars were recorded, we calculated the relative difference between TD/capita one year after biosimilar entry and TD/capita in the year before biosimilar entry. We took into account current growth rates (by assuming a constant rate of change of TD/capita from the year of biosimilar entry to 2021 – as might be expected without genericisation). Percentage change in TD/capita was averaged across anti-TNF and oncology categories for the six MS (Table 13). This is consistent with prior work done by Lakdawalla and Philipson (2012).<sup>116</sup>

**Table 13: Estimated change in total market volume in first year after biosimilar entry by Member State**

TEE Length	Average percentage change (%) in treatment days for anti-TNF and oncology categories in first year after biosimilar entry by Member State
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<sup>115</sup> Troein, P., Newton, M., Scott, K. & Mulligan, C. (2021) *The Impact of Biosimilar Competition in Europe*. IQVIA. Available at: [https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?\\_=1640100592119](https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119) [Accessed 25 May 2022]

<sup>116</sup> Lakdawalla, D. & Philipson, T. (2012) Does Intellectual Property Restrict Output? An Analysis of Pharmaceutical Markets. *The Journal of Law & Economics*. 55(1). Available at: <https://doi.org/10.1086/663345>

	France	Germany	Italy	Spain	Greece	Poland
<b>12 months</b>	6.5	-3.3	-0.1	5.6	0.0	11.1
<b>9 months</b>	6.2	-3.2	0.5	5.3	0.0	10.6

Source: CRA analysis. Note: only retail panel data is available for Greece; Greece data was not available for oncology category.

We find that the change in volume is relatively small across all markets (~5%), with the highest number in Poland. However, as described above, the cost of TEE has been overestimated for Poland due to expected delays in generic entry, so the impact of TEE on patients in Poland may not be as great as Table 13 suggests.

There could also be a knock-on impact on therapeutic competition, as the prices of other products in the same class as the TEE user may not decrease as they would have done had a TEE not been applied. Our estimate of the lost genericisation savings does not account for this; however, this is taken into account in the change in total market volume estimates in Table 13. It is likely that the impact of this on lost genericisation savings will be minimal, especially in the countries with low overall volume change, as this indicates most of the new generic uptake comes from patients previously on the originator rather than patients switching from other products.

#### 4.4 Summary of estimated cost of TEE

The cost of TEE to MS includes lost genericisation savings and administrative costs. Table 14 shows the cost of TEE per antibiotic by MS across TEE lengths and scenarios.

**Table 14: Cost of transferable exclusivity extension (TEE) per antibiotic by Member State**

TEE scenario	TEE length	Average cost of TEE per antibiotic (2024–2033) (€ M present value)					
		France	Germany	Italy	Spain	Greece	Poland
<b>1 TEE per year</b>	12 months	105	121	105	66	15	14
	9 months	79	91	79	50	11	10
<b>2 TEEs per year</b>	12 months	73	88	74	48	19	11
	9 months	55	66	55	36	14	9

Source: CRA analysis

Table 15 shows the per 100,000 persons costs. Aside from the administration costs, the costs of TEE (lost genericisation savings and impact on number of patients treated) only materialise if an eligible antibiotic is approved in Europe and the voucher is used to extend marketing exclusivity by the recipient or a purchaser.

**Table 15: Cost of transferable exclusivity extension (TEE) per antibiotic per 100,000 persons by Member State**

TEE scenario	TEE length	Average cost of TEE per antibiotic (2024–2033) per 100,000 persons (€ M present value)					
		France	Germany	Italy	Spain	Greece	Poland
<b>1 TEE per year</b>	12 months	0.16	0.15	0.18	0.14	0.14	0.04
	9 months	0.12	0.11	0.13	0.10	0.10	0.03
<b>2 TEEs per year</b>	12 months	0.11	0.11	0.12	0.10	0.18	0.03
	9 months	0.08	0.08	0.09	0.08	0.13	0.02

Source: CRA analysis

## 5 Discussion

### 5.1 Implications of the analysis

The analysis above sets out an approach to estimating the costs and benefits of a new incentive, such as TEE, for EU MS. It attempts to address the potential differences in costs and benefits across MS, and that there are different types of antibiotics needed. Although we have not been able to estimate all the costs and benefits, and there is still uncertainty around many of the estimates, the results are strongly indicative that the benefits of TEE to each MS will outweigh the cost to a considerable degree, and that the cost of a TEE to MS is considerably lower than has been previously estimated. The results also help address concerns around the potential impact of TEE on patients. We discuss each of these implications below.

First, the benefits to each MS, on the level of each individual TEE and the policy as a whole, will outweigh the cost to a considerable degree. As described above, the benefits to society of each individual TEE will depend on the clinical characteristics of the recipient antibiotic. However, assuming appropriate clinical criteria are put in place to determine which antibiotics can receive a TEE, such as efficacy against WHO priority pathogens, on average TEE-recipient antibiotics will provide a very high degree of value to society, which exceeds the average cost of each TEE. The challenges related to anticipating the benefits of each TEE, due to the complexity of estimating the value of an antibiotic to society, have meant that we have not been able to quantify the full extent of the value that antibiotics provide to society, either individually or as a collective arsenal against future infections and AMR development. However, even if only two or three of the value elements are considered, the benefits of a TEE to each MS outweigh the costs. Compared with the total size of the incentive required to stimulate development of the antibiotics TEE makes available in Europe, each country's payment for the TEE is small. In addition, we have not been able to quantify the combined impact of an effective portfolio of antibiotics, and the benefit to society of continued investment in the innovation infrastructure, which are additional benefits on top of the benefits of each individual antibiotic.

In addition, development of a new antibiotic will have significant value not just for patients and populations in Europe, but globally. By stimulating development of antibiotics in Europe, the European Commission and MS would be helping to provide low- and middle-income countries (LMICs) with valuable medicines; indeed, the QALY benefits of antibiotics are likely to be greater in these countries than in European countries. When considering the benefits of TEE, it is important to consider not just the benefits to Europe directly, but those which are realised around the world. If TEE is implemented in Europe in a timely manner (and before PASTEUR in the US), Europe will be considered a leader in incentivising antibiotic innovation, while bringing antibiotics to market which protect Europeans and support global development.

Second, the cost of a TEE to MS is considerably lower than has been previously estimated. This predominantly arises from the fact that previous estimates of the cost of TEE to MS have focused on the products with the highest sales in Europe and assumed no originator sales in the year after LOE. Our analysis, however, has used data on the gradual decline of originator sales and uptake of generics post-LOE to develop a more accurate model of the expected cost of a TEE to MS. We have also demonstrated that while the cost of an individual TEE may vary, the cost of TEE used in the debate so far is not representative of the group of products that would likely receive a TEE in the coming years. This can help to address concerns about the cost of TEE to MS.

Third, our analysis helps address concerns related to the impact of TEE on patients being treated by TEE user products. TEE has been critiqued as not benefitting the patients who would pay for it. Our analysis helps address this concern in two ways:

- We demonstrate how investment in antibiotic innovation benefits the whole population, including patients in ‘other’ therapy areas (e.g. oncology), as effective antibiotics are necessary to enable treatments and procedures as well as prevent and treat infections in patients in a wide variety of therapy areas (enablement value). We estimate the significant enablement value of an antibiotic, and we discuss the value to the healthcare system as a whole of investing in maintaining an effective portfolio of antibiotics. Narratives that make a distinction between ‘AMR patients’ and ‘other patients’ are unhelpful because they fail to recognise the benefit that reducing the development of AMR would bring to the healthcare system and society. Given the burden of AMR on ‘other’ therapy areas, and the benefits of antibiotics for these patients, it is reasonable to expect these therapy areas to contribute towards the cost of developing new antibiotics to help combat AMR.
- We show that the change in total treatment volume in the years immediately following LOE of a product is small. This indicates that when a TEE is applied to a product, there is unlikely to be a large negative impact on patient access to the TEE user product or other products in the class.

## 5.2 Future directions

This study provides a framework which could inform development of a methodology for a comprehensive cost-benefit analysis and impact assessment, which would be able to quantify the benefits and costs more precisely. However, our analysis also demonstrates the associated challenges given the uncertainties surrounding which antibiotics would receive a TEE, the future epidemiology of the target bacteria and the methodology for quantifying the value of an antibiotic to patients, healthcare systems and society.

As outlined above, one of the main components of the value of an antibiotic is its insurance value: the value to society of having effective antibiotics ready to treat an outbreak of bacterial infections. The expected value to society of this insurance value is partially dependent on the probability of such an outbreak occurring, and the severity of the outbreak. To improve future estimates of the insurance value of antibiotics, these are two dimensions that would be worth exploring.

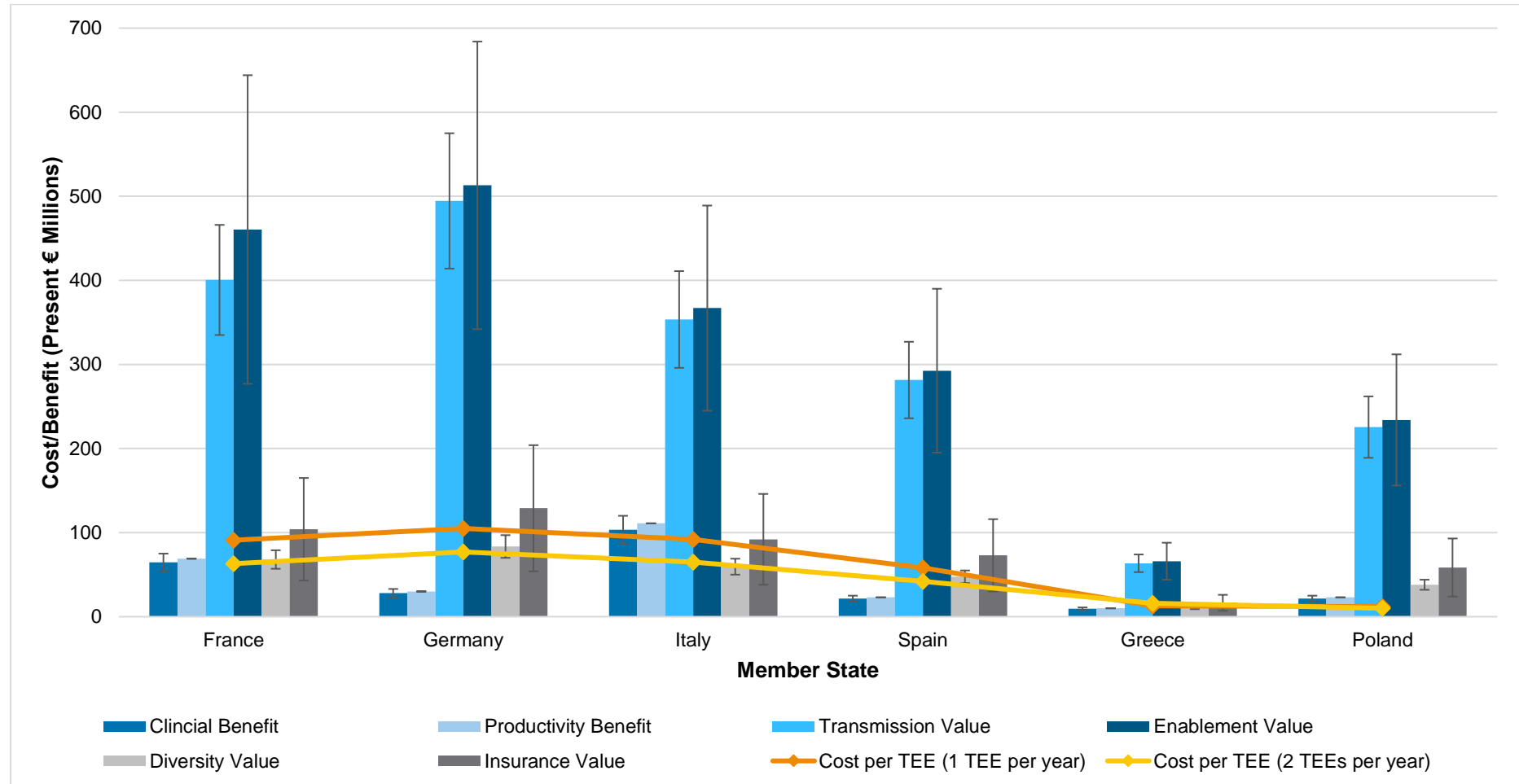
Our analysis also demonstrates the importance of estimating the costs and benefits of a pull incentive policy, and suggests that a similar analysis for other policies under consideration in Europe (e.g. joint procurement) could be beneficial to facilitate informed policy decision-making.

It is worth noting that this study has not directly assessed the impact of different access mechanisms for antibiotics in Europe. However, in conjunction with considering incentives for the R&D of novel antibiotics, including TEE, the European Commission should ensure that appropriate access mechanisms and reimbursement rules for antibiotics are in place in MS, so that the benefits of pull incentives can be realised through patients having access to novel antibiotics.

## 5.3 Conclusions

We need to invest in maintaining our arsenal of effective antibiotics. When evaluating and comparing potential pull incentives for implementation in Europe, it is important to consider both the costs and benefits. TEE has the advantage of providing a sufficiently powerful incentive to stimulate development of new antibiotics that is feasible and relatively straightforward to implement at the joint EU-level with minimal up-front administrative costs to the EMA, and a cost that is spread across all European MS. Our analysis suggests that the benefits of TEE to society are likely to exceed the costs to a considerable degree, and that the costs are lower than previously predicted.

Figure 10: Summary of costs and benefits of TEE across Member States



Source: CRA analysis of various sources, see text for details. Error bars represent upper and lower bounds of benefits estimates. Parameters used to calculate upper and lower bounds (see body text in Section 3.3 for more details): Clinical benefit, transmission value, diversity value: lower bound = €18k/QALY, upper bound = €25k/QALY. Enablement value: lower bound = 0.5% decrease in the reduction in efficacy of prophylaxis, upper bound = 1.5% reduction in efficacy of prophylaxis. Insurance value: lower bound = 50% IV capacity, upper bound = 20% IV capacity. Average cost per TEE of 12-month TEE duration and 9-month TEE duration are displayed for costs per TEE for 1 TEE per year and 2 TEEs per year.

## Appendix

### Scaling factors used for 'case study' method for estimating the benefits of TEE

Table 16 shows the data that we used to scale the value elements in Section 3.3.

**Table 16: Data used to scale benefit value elements**

Description	Numbers Used to Scale to MS Estimates		Source
Number of infections with antibiotic-resistant bacteria in 2015	FR	124,806	Cassini et al. (2018) <sup>117</sup>
	DE	54,509	
	IT	201,584	
	ES	41,345	
	GR	18,472	
	PL	41,069	
Population of the MS and Europe	FR	67,379,908	World Bank (2020) <sup>118</sup>
	DE	83,160,871	
	IT	59,449,527	
	ES	47,363,419	
	GR	10,700,556	
	PL	37,899,070	
	Europe	747,636,026	

Sources: see footnotes

### Method for estimating genericisation savings forgone by each member state

We set out here how we estimate the % cost savings forgone by a TEE for each MS. We define an equation and estimates for the key parameters involved. Several variables were defined before outlining the equation (Table 17).

**Table 17: Variables for calculating lost genericisation savings**

Variable	Description
$P_0, V_0$	Price, volume of originator in year of LOE
$P_1, V_1$	Price, volume of originator one year after LOE
$P_g, V_g$	Price, volume of generic or biosimilar one year after LOE

Source: CRA analysis

Based on the variables defined, the following equation describes the cost to a MS due to timely generic or biosimilar entry. The left side of the first equation represents the originator sales in the year of LOE, i.e. the cost the MS is paying when only the originator is available and generics or biosimilars have not entered the market. The right side of the equation represents the cost to the MS in the year after LOE (i.e. the sales of the originator in that year plus the sales of the generic or biosimilar) plus the genericisation savings. The genericisation savings are therefore the difference between what the MS pays in the year of LOE and the year after LOE.

<sup>117</sup> Cassini, A., Högberg, L., Plachouras, D. et al. (2018) Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet Infectious Diseases*. 19(1): 56–66. [https://doi.org/10.1016/S1473-3099\(18\)30605-4](https://doi.org/10.1016/S1473-3099(18)30605-4)

<sup>118</sup> World Bank (2020). Population. Available at: <https://data.worldbank.org/indicator/SP.POP.TOTL>

$$P_0V_0 = P_1V_1 + P_gV_g + \text{Genericisation Savings}$$

$$\text{Genericisation Savings} = P_0V_0 \times \underbrace{\left(1 - \frac{P_1}{P_0} \times \frac{V_1}{V_0} - \frac{P_g}{P_0} \times \frac{V_g}{V_0}\right)}_{\text{Cost savings factor}} \quad (1)$$

This can be written as:

$$\text{Genericisation Savings} = \text{Sales of TEE Purchaser in Year of LOE} \times \text{Cost Savings Factor}$$

This 'cost savings factor' is a unique multiplier for each MS for each year after LOE and defines the relationship between the lost genericisation savings and the sales of the TEE user in that year. The cost savings factor is a fixed number for each MS each year, determined by the genericisation dynamics in each MS. We estimate the lost genericisation savings by calculating the cost savings factor for each MS each year and multiplying this by the expected sales of the TEE user that year, as represented by the equation above. Below we set out the method for estimating the cost savings factor.

There are not estimates in the literature for all the variables in equation (1) above, so we define additional variables based on the estimates available in the literature, shown in Table 18. We then manipulate equation (1) above so the cost savings factor can be defined in terms of these variables.

**Table 18: Additional variables for calculating cost savings factor**

Variable	Description
$V_t$	Total market volume (originator and generic or biosimilar) one year after LOE
$u$	Generic uptake (percentage of total market volume) one year after LOE
$g$	Growth of total market (percentage change in volume) one year after LOE
$r$	Ratio of sales of originator one year after LOE to sales of originator in year of LOE

Source: CRA analysis

Because

$$V_t = V_1 + V_g = V_0(1 + g)$$

Therefore,

$$\frac{V_g}{V_0} = V_g \times \frac{1 + g}{V_t} = u(1 + g) \quad (2)$$

Because

$$r = \frac{P_1V_1}{P_0V_0} \quad (3)$$

So,

$$\frac{P_1}{P_0} = r \times \frac{V_0}{V_1} = \frac{r \times \frac{V_t}{1 + g}}{V_t - V_g} = \frac{r \times \frac{V_t}{1 + g}}{V_t - uV_t} = \frac{r \times \frac{1}{1 + g}}{1 - u} = \frac{r}{(1 + g)(1 - u)}$$

Therefore,

$$\frac{P_g}{P_0} = \frac{P_g}{P_1} \times \frac{P_1}{P_0} = \frac{P_g}{P_1} \times \frac{r}{(1 + g)(1 - u)} \quad (4)$$

Substituting equations (2), (3) and (4) into (1) yields:

$$\text{Cost Savings} = P_0 V_0 (1 - r - \frac{P_g}{P_1} \times \frac{r \times u}{1 - u})$$

Cost savings factor (5)

Estimates for parameters  $r$ ,  $\frac{P_g}{P_1}$ , and  $u$  were taken from the literature for each MS and for each of the first three years after LOE, shown in Table 19.

**Table 19: Estimations for additional variables for calculating cost savings factor**

Variable	Estimation						Source
	First year post LOE		Second year post LOE		Third year post LOE		
<b>r</b>	53%		45%		37%		Berdud et al. (2019) <sup>119</sup>
<b>u</b>	40%		50%		60%		Troein et al. (2021) <sup>120</sup>
<b>P<sub>g</sub>/P<sub>1</sub></b>	FR	90%	FR	78%	FR	66%	IQVIA Institute for Human Data Science (2018) <sup>121</sup>
	DE	92%	DE	77%	DE	65%	
	IT	77%	IT	65%	IT	56%	
	ES	81%	ES	69%	ES	59%	
	GR	93%	GR	79%	GR	67%	
	PL	65%	PL	55%	PL	47%	

Sources: see footnotes

These were used to calculate the cost savings factor in equation (5) for each of the six MS for the first three years after LOE. A 15% decrease was applied to parameter  $\frac{P_g}{P_1}$  each year.<sup>122</sup> A 10% increase was applied to parameter  $u$  each year.<sup>123</sup>

The results of this analysis are shown in Table 10 in Section 4.1.2 above.

119 Berdud, M., Ferraro, J., Mestre-Ferrandiz, J. & Towse, A. (2019) *Study of the potential use of an EU Transferable Exclusivity Extension (TEE) to incentivize antibiotic R&D*. Office of Health Economics

120 Troein, P., Newton, M., Scott, K. & Mulligan, C. (2021) *The Impact of Biosimilar Competition in Europe*. IQVIA. Available at: [https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?\\_=1640100592119](https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119) [Accessed 25 May 2022]

121 IQVIA Institute for Human Data Science (2018) *Advancing Biosimilar Sustainability in Europe – A Multi-Stakeholder Assessment*. Available at: [https://www.biosimilars-nederland.nl/wp-content/uploads/2018/10/okt\\_2018\\_IQVIA\\_Pfizer\\_Advancing-Biosimilar-Sustainability-in-Europe.pdf](https://www.biosimilars-nederland.nl/wp-content/uploads/2018/10/okt_2018_IQVIA_Pfizer_Advancing-Biosimilar-Sustainability-in-Europe.pdf) [Accessed 9 May 2022]

122 European Commission (2007) *Pharmaceutical Sector Inquiry – Preliminary Report; Fact Sheet "Prices, time to generic entry and consumer savings."* Available at: [https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/fact\\_sheet\\_1.pdf](https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/fact_sheet_1.pdf) [Accessed 25 May 2022]

123 Troein, P., Newton, M., Scott, K. & Mulligan, C. (2021) *The Impact of Biosimilar Competition in Europe*. IQVIA. Available at: [https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?\\_=1640100592119](https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2021.pdf?_=1640100592119) [Accessed 25 May 2022]

## Abbreviations

AMR	antimicrobial resistance
Anti-TNF	tumour necrosis factor inhibitor
CAZ-AVI	ceftazidime with avibactam
CRAB	carbapenem-resistant <i>Acinetobacter baumannii</i>
DALY	disability-adjusted life year
cUTI	complicated urinary tract infection
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EEPRU	Policy Research Unit in Economic Methods of Evaluation of Health and Social Care Interventions
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
EU4	France, Germany, Italy, Spain
FDA	US Food and Drug Administration
FQ	fluoroquinolone
GDP	gross domestic product
HAP	hospital-acquired bacterial pneumonia
HAS	Haute Autorité de Santé
HHS	US Department of Health and Human Services
HTA	health technology assessment
ICU	intensive care unit
IV	intravenous
LMICs	low- and middle-income countries
LOE	loss of exclusivity
MBL	metallo-beta-lactamase
MDR-TB	multidrug-resistant tuberculosis
MER	market entry reward
MS	Member State
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OECD	Organisation for Economic Co-operation and Development
OHE	Office of Health Economics
PRV	priority review voucher

QALY	quality-adjusted life year
R&D	research and development
ROA	route of administration
STEDI	spectrum value, transmission value, enablement value, diversity value, insurance value
TD	treatment day
TEE	transferable exclusivity extension
TPP	target product profile
VAP	ventilator-associated bacterial pneumonia
WHO	World Health Organization
WTP	willingness to pay

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