TANDVÅRDS- OCH
LÄKEMEDELSFÖRMÅNSVERKET

Comparative theoretical study of pull incentives for antibiotics development

The Dental and Pharmaceutical Benefits Agency,
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Preface

The Swedish Dental and Pharmaceutical Benefits Agency's (TLV's) mandate includes monitoring and analysing the development of prices on pharmaceuticals, as well as the overall spending on pharmaceuticals within Swedish health care. The goal of this is to ensure that Sweden is able to provide the best possible health outcome for the taxes spent on health care. As such, in the fight against antimicrobial resistance, TLV is seeking to ensure both that the conditions for developing new antibiotics are advantageous and that the public funding for this is limited and optimised.

In its 2023 Proposal for the Pharmaceutical Regulation, the European Commission suggested the introduction of a transferable exclusivity voucher to incentivise the development of novel antibiotics. While there has been an extensive debate on the suitability of using such vouchers for this purpose, there has been a lack of studies on this particular proposal. This report studies the Commission's voucher scheme and compares its investment to cost ratio to those of a market entry reward scheme and a subscription scheme. It especially accounts for the timelines involved in the various schemes and how they influence the cost of capital for investors. The report finds that the voucher scheme is the least cost-effective of the three schemes. This calls into question the economic suitability of such voucher, unless the other schemes are politically unfeasible.

The working group for this report consisted of analyst Carl Björvang and chief economist Douglas Lundin. This report is to be viewed as a pre-print that does not preclude later academic publication.

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Summary

To evaluate the voucher scheme presented by the European Commission, it is necessary to compare it to other possible incentive structures. TLV has chosen to compare it to two of the most common pull incentive models from the literature, the market entry reward (MER) and the subscription model. To be able to compare them, we estimated both the antibiotics development investments they are likely cause and their cost to society. This resulted in an investment to cost ratio that would reflect the efficiency of each model. The report found that:

The specifics are important

This report highlights the importance of looking at the details of any given voucher incentives scheme when assessing its value for money. Regarding the vouchers proposed by the European Commission, it is especially important to understand the impact of the time between the company's purchase of a voucher and the company's utility from it. With the proposed time of between two and seven years, depending on the pharmaceutical product to with the voucher is applied, this means a significant cost of capital for the buyer, decreasing the price they are willing to pay for the voucher and hence the incentives for the developer of the antibiotic (and therefore is the seller of the voucher).

Vouchers are comparatively cost-inefficient

The results of this report indicate that vouchers as a way to incentivise antibiotics development are associated with a number of inherent inefficiencies. One of these is that, due to the auction mode of selling vouchers, the price of the voucher and hence the size of the incentive is based on the willingness to pay of the second highest bidder, while the cost to society is based on the volume and price of the bidder with the highest willingness to pay. Another inefficiency is the uncertain price of the voucher, increasing the risk to investors and lowering the antibiotics development investments they would be willing to make.

The most cost-efficient option is the MER

Out of the three incentive models that were compared in this report, the MER was the most cost-efficient in terms of turning costs for society into funding for antibiotics development. The key factor for this efficiency is that the reward is paid out in full once the antibiotic has come to market, significantly reducing the cost of capital for the investors and hence increasing their willingness to invest into the development of new antibiotics. In addition, the fixed size of the MER reduces the risk for investors and the amount of investments

Subscriptions have added benefits

Subscriptions, commonly referred to as guaranteed revenue schemes, fall between vouchers and the MER in terms of social costs to antibiotics development incentives efficiency. Their spread-out payments impose some cost of capital inefficiencies, but

their fixed payment amounts make them similar to the MER in terms of risk profile. However, as the payments can be combined with availability and stewardship requirements, if structured properly the subscriptions can provide added benefits.

Terms and concepts

AMR – Antimicrobial Resistance, the evolved ability of microbes, such as bacteria, to resist substances that were previously used to treat infections by these microbes

Availability – The degree to which a pharmaceutical product is available for purchase to patients and health care providers

Cost of Capital – Alternative cost for binding capital in a given investment

Cost of Public Funding – Cost of the negative impacts of raising public funds, such as decreased incentives to work

Cost to Society – Cost that a given incentive is expected to burden society with, both in terms of monetary expenditures and lost health care gains

Investment to Cost Ratio – Ratio between the investment a given incentive is expected to cause and its cost to society

MER – Market Entry Reward, a specified monetary reward provided to the developer of a novel antibiotic upon its entry on a market

Novel Antibiotic – An antibiotic that is sufficiently different from previously discovered antibiotics to provide significantly better results in the treatment of infections by one or several strains of bacteria

Pull Incentive – An inventive that works by enticing investors to invest into antibiotics development to obtain a reward once the product is on the market

Push Incentive – An incentive that encourages and enables antibiotics development by supporting the developer during the process, often in relation to reaching pre-set milestones

Robustness Analysis – Analysis of how changes in various parameters affect the results of a study

Stewardship – The management of antibiotics so as to limit the development of AMR

Subscriptions – Also known as guaranteed revenue schemes, is a reoccurring fixed or minimum monetary payment paid out over a predetermined period

TEV – Transferable Exclusivity Voucher, a voucher that prolongs the exclusivity, in this context data exclusivity, of any pharmaceutical product it is applied to

Voucher – see TEV

1. Introduction

Antibiotics have become a staple of modern life. They have made most bacterial infections trivial, hindered many sever ones from becoming lethal and has enabled modern surgery by drastically lowering the risks of post-operative infections. Yet, the natural ability of bacteria to evolve in combination with unregulated use and a lack of newly discovered antibiotics have put the future supply of functional antibiotics at risk. Already, thousands of people die each year from antibiotics resistant bacteria. However, in the coming decades, millions of people will die prematurely from infections that were previously seen as treatable, with billions of associated healthcare expenses, in Europe alone.

This is an emergent global health crisis that requires political actions. To a great extent, these actions will be directed at various ways to ensure that there currently available antibiotics are used in a responsible way, so as to delay the spread of resistance towards them. However, another front in the battle against resistance is to encourage the development of new antibiotics so that there are new alternative treatments available for those bacteria that have become resistant to our current treatments.

The recently released proposals for an updated EU pharmaceutical legislation includes policies to address both the stewardship of existing antibiotics and the development of new ones. This paper will focus on the latter, for which the proposal suggests a so-called Transferable Exclusivity Voucher (TEV). This provides the developer of a new antibiotic with a voucher for the prolongation of regulatory data protection with 12 months, which can be used on any pharmaceutical fulfilling certain criteria. This voucher can either be used by the company that developed the antibiotic or sold to another pharmaceutical company.[1]

When evaluating the health economic merits of these vouchers, it would have been advantageous to compare the cost of the vouchers to European society with the value of the new antibiotics that would receive vouchers. However, there are two problems with this. First, as Simoens & Spriet notes, establishing the value of a new antibiotic is problematic and dependant on a range of assumptions.[2] Second, simply because a new antibiotic receives a voucher does not mean the voucher was the only contributing factor towards the development of that new substance.

Fortunately, there is another way to evaluate the merits of the vouchers and that is to compare them to other forms of antibiotics research and development incentives. If it is assumed that new antibiotics are going to provide hard-to-estimate, but substantial, societal value, we can instead study which incentive method that would contribute to their development in the most cost-effective manner. As such, this paper will compare the vouchers to two other proposed incentive schemes, namely a market entry reward (MER) and a subscription model.

[1] European Commission (2023a). For more, see section 2.1.
[2] Simoens & Spriet (2021)

2. Related Literature

In recent years, there have been a number of articles published that portray vouchers as a good method to incentivise research into novel antibiotics. The findings of Dubois, Moisson & Tirole show that many countries should favour vouchers to a MER, as it would be less expensive for them. [3] However, their conclusions depend on a skewed model that, for example, does not count the cost of public funding equally for the two incentive models.[4] It is also based on a form of voucher that is significantly different from the one proposed by the European Commission.

Boyer, Kroetsch & Ridley defend vouchers against a number of common claims against them. [5] However, they do not compare vouchers to other forms of incentive methods. Their voucher model is also different from that in the current EU legislation in some key regards.

Almost all proponents of vouchers have one thing in common and that is that they envision vouchers that work rather different from those proposed by the European Commission. Even sceptics of vouchers, such as Outterson & McDonnell, argue that if there have to be vouchers, they must be designed in a way that ensures their maximum efficiency.[6] One common feature, argued for by both Boyer et al. and Outterson & McDonnell is a multi-tier voucher system, where the duration of the voucher provided depend on the utility of the antibiotic it is rewarding. Another feature, argued for in different ways by both Outterson & McDonnell and Dubois, Moisson & Tirole, is to use the sale of vouchers as a way to fund MERs or other incentive methods. Dubois, Moisson & Tirole does this by arguing that the price of the voucher should be fixed, in essence making it a MER from the perspective of the developer of the antibiotic. Instead, it is the length of the voucher that should be determined by auction, so that the bidder demanding the shortest extension length would be given the voucher.

As such, even these authors who are in favour of vouchers are usually envisioning a different form of voucher than the European Commission has proposed. However, most academic literature is against vouchers as a method to incentivise research into and development of novel antibiotics. One of the more common arguments against vouchers is how expensive they will be, see e.g. Rome & Kasselheim.[7] However, simply arguing that vouchers would be expensive is not necessarily the same as saying that they should not be implemented. If vouchers were expensive but more cost-efficient than other incentive models, they would constitute an effective way of channelling substantial resources towards antibiotics development.

[3] Dubois, Moisson & Tirole (2022)
[4] Note that the authors are currently working on an improved version of their model.
[5] Boyer, Kroetsch & Ridley (2022)
[6] Outterson & McDonnell (2016)
[7] Rome & Kesselheim (2020)

Still, the sheer costs of the vouchers are far from the only argument against them raised in the literature. Årdal et al. brings up that the vouchers overcompensation the companies buying vouchers, that they address neither accessibility or stewardship issues and that they will have negative knock-on effects on the wider pharmaceuticals market.[8] Anderson, Wouters & Mossialos also address the overpayment and access issues as well as the problem of ensuring that the antibiotics rewarded have significant clinical value.[9] Another article, Van de Wiele et al. also touch on overcompensation, though its main argument is that vouchers such as those of the legislation offer data protection rather than patent extension, which means that they'll not be relevant for most pharmaceuticals, limiting the competition and hence price of the vouchers.[10] Then there is a host of articles and other papers, such as Årdal, Lacotte & Ploy, Médecins Sans Frontières et al. and the Netherlands pointing towards how various relevant stakeholder groups are opposed to vouchers, creating significant political barriers towards their implementation.[11]

While the arguments against vouchers listed above are important to consider, none of them are persuasive on their own. Overcompensation might point towards a source of inefficiency, but if other forms of incentives would have even greater inefficiencies, vouchers would still be preferable. Access and stewardship are both important for the utility of the rewarded antibiotic but could be handled through other means and it should hence be seen as a bonus, rather than a necessity, for an R&D incentive method to feature them. It is also important that the rewarded antibiotic has clinical significance, but this problem is shared with all other incentive methods that are decoupled from the use and sale of the substance.[12] The data protection versus patent extension issue need not be a problem on its own, especially since it might actually help in limiting the cost of the voucher scheme. Even the stakeholder opposition to vouchers need to be a deal-breaker, since other incentive schemes face their own political difficulties.

What is lacking in the literature, and what could provide a more definitive guide to the decision on whether to work towards vouchers or another incentive method, is a systematic and fair comparison between relevant incentive methods. This paper aims to provide such comparison. By creating models that use the same metric to compare the different incentives, the costs and benefits of each method can be studied, compared and evaluated.

2.1. The Proposed Voucher

To understand the potential effects of the proposed vouchers, the following section will outline the specifics of the current voucher proposal from the European Commission. In the Commission proposal for the Pharmaceutical Regulation, published on 26 April 2023, the European Commission proposed what they term a

[8] Årdal et al. (2023)
[9] Anderson, Wouters & Mossialos (2022)
[10] Van de Wiele et al. (2023)
[11] Årdal, Lacotte & Ploy (2021), Médecins Sans Frontières et al. (2022) and Netherlands (2022)
[12] See Outterson (2014) and Kotwani et al. (2022) for discussions on why this decoupling is necessary.

transferable data exclusivity voucher.[13] The proposed voucher has several features, outlined in articles 40-43, that are important for calculating how much investors will be willing to pay to obtain it and how much it will cost to society.

The first feature is that the voucher, as the name suggests, is transferable. This means that the voucher does not necessarily prolong the exclusivity of the antibiotic for which it was rewarded. Rather, it can be used on another pharmaceutical that the developer possesses or sold to a third party for use on their substance.

The second feature is, also as the name suggests, that the voucher extends the length of the data exclusivity of the pharmaceutical it applies to. This means that it does not extend the patent protection. Hence it will only extend the time that the substance is shielded from competition from generics if the data exclusivity, and its associated market exclusivity, extends beyond the period of the patent protection and its associated extensions.

The third feature is that the voucher is limited to one transfer. As such, it is only the company awarded the voucher or its first purchaser that could use it. This prohibits speculative investors to buy the voucher in the hope of selling it on for a profit.

The fourth feature is its length of 12 months. This means that there is a standardised data exclusivity extension length for each awarded voucher, independent of the medical value or other considerations concerning the underlying antibiotic. The market price of the voucher will hence correspond to how much 12 months additional data exclusivity will mean for the potential buyers.

The fifth feature is that a voucher can only be applied to a pharmaceutical within the first four years of its data exclusivity. As such, any potential buyer would have to purchase the voucher well before the expiration of the data exclusivity of their intended product. Since the proposed legislation also changes the data exclusivity length of pharmaceuticals, with a time span between 6 and 11 years, it will depend on the specificities of the given pharmaceutical how long in advance the voucher must be triggered.

[13] European Commission (2023a)

Diagram 1. Voucher application and use timeline

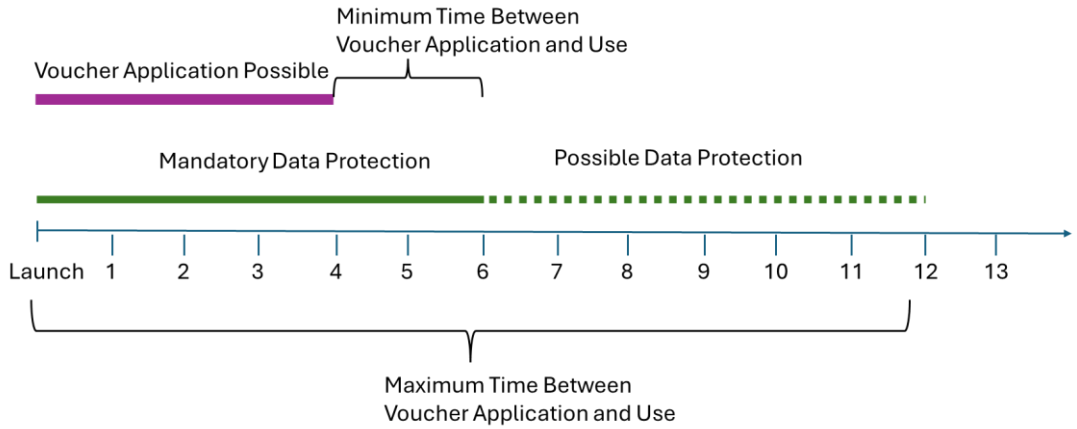
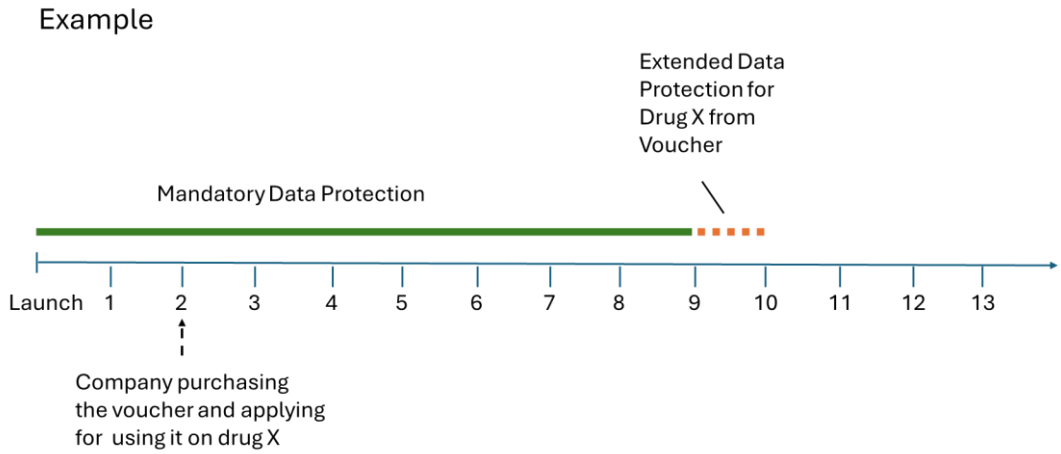


Diagram 2. Example of a voucher application and use



As can be seen above, the difference between the data protection times and the period in which voucher application is possible means that there is a substantial range of possible lengths between voucher application and use. On the one extreme, if a company buys a voucher the same year the launch of the product they want to apply the voucher to, and that product receives the full 11 year data protection, it would mean that the company would have to wait 11 years until they received any utility from the voucher. On the other hand, if the company bought the voucher on the fourth year after launch, and the product only received six years data protection, they would only have to wait two years between application and utility.

The sixth and last relevant feature is that the voucher awarding is limited in both numbers and timeframe. There can be no more than 10 voucher awarded. Nor can there be any voucher awarded after 15 years have passed since the regulation entered into force.

3. Method

In order to be able to compare the voucher, MER and subscription models, we have to realise that these incentives are not there to outright 'buy' a new antibiotic. First, as with any research and development spending, there is no magic amount of investment that will guarantee a new antibiotic will become available, let along guarantee its quality in the fight against resistance. As such, we can only estimate how much money would have to be allocated to a portfolio of novel antibiotics R&D projects for one of them to bear fruit.

Second, we have to keep in mind that virtually no new antibiotic is likely to have its complete funding based on the incentive methods discussed here. The initial research that came up with a lead substance will almost always have been conducted within an academic environment based on governmental and non-profit funding for basic research. Both governments and charities might also provide alternative assistance or incentives to push or pull the substance towards completion.[14, 15] Even once business interests provide the majority of funding, these will take the full post-launch income spectrum into consideration when making their investment decisions, including the incentives discussed here, possible other incentives and global sales.

For these reasons, it is overly simplistic to calculate a cost to society per novel antibiotic figure for each of the incentives (C_i) and compare these to each other. Instead, we also need to take into account how much investment each incentive method would be able to provide (I_i). We calculate this as the maximum investment amount that is expected to yield a profit to the investor. By then dividing this investment by the cost to society, we can arrive at a measure of efficiency (E_i) that would accurately reflect the economic desirability of each of the incentives:

$$E_i = \frac{I_i}{C_i}$$

To keep the incentives comparable, the general construction of both the investments and costs for each of the incentives should follow the same structure. However, because the incentives work in different ways, we will have to construct separate models for each of them.

[14] For current alternative funding sources, see for example GARDP (2023) and CARB-X (2023).

[15] Indeed, as of the current EU legislative proposal, it is fully possible for an antibiotic fully funded through means that are completely independent of the voucher, such as US, Chinese or other foreign government assistance, to still receive a voucher and hence put a substantial strain on European healthcare spending without the voucher having played any part in incentivizing the research and development of that antibiotic.

3.1. Vouchers

Voucher schemes can be set up in a number of different ways.[16] As outlined in section 2.1, the recent EU legislative proposal has a rather specific structure to it, with implications for the economic performance of the vouchers issued under it. To ensure that this paper is relevant to the current debate on this proposal, the vouchers analysed here will follow this structure as specified in the legislative proposal.

In order to calculate the investment to cost ratio for the form of voucher suggested in the recent EU legislative proposal (E_V), we need to take a number of variables into account. The first step is to understand how the price of the voucher ought to be established. To do so, we have to assume that the seller is aiming for the highest price possible, and that the buyer would be aiming for as low a price as possible. For the seller, this means that they would sell to the highest bidder and the buyer would pay no more than the next highest bidder would be willing to pay. As such, the price will be determined by the max price the 2nd highest bidder would be willing to pay. This ought to correspond to the point at which they would no longer make a profit by buying the vouchers.

This break-even point can be found by calculating how much gain they would make from the voucher, or the difference between their profit with and without it. We can denote this as their sales during monopoly (S_{V2nd}^{M}) minus their expenses during monopoly (X_{V2nd}^{M}), from which we then subtract their sales during competition (S_{V2nd}^{O}) minus their expenses during competition (X_{V2nd}^{O}), altogether (S_{V2nd}^{M}-X_{V2nd}^{M})-(S_{V2nd}^{O}-X_{V2nd}^{O}). We then have to acknowledge that this profit is earned a number of years into the future, so it has to be adjusted by the cost of capital over that period of time ($(1-Z)^{J}$).

Beyond this, research and development funding does not occur at the time a product is launched, but rather over the years leading up to the actual launch and subsequent potential sale of the resulting voucher. As such, we have to adjust for the cost of capital over that time period ($(1-Z)^{Y}$). This investment is also associated with significant risks. Although these risks can be mitigated to some extent by investing in several antibiotics projects simultaneously, there is still a risk that a given project will not result in an approved pharmaceutical or that the substance will not fulfill the criteria for receiving a voucher, as well as uncertainties associated with the potentially substantial variation in the price of the vouchers. If we denote this risk ($1-R_V$), we end up with the following equation:

$$I_v = \left(\left(\left(S_{V2nd}^{M} - X_{V2nd}^{M}\right) - \left(S_{V2nd}^{O} - X_{V2nd}^{O}\right)\right) * (1-Z)^{J} * ((1-Z)^{Y}) * (1-R_V)\right)$$

In order to calculate the societal cost (C_v) of a voucher, we have to estimate the monetary loss associated with purchase of the substance under monopoly rather than competition. This can be calculated as the sales of the original during monopoly (S_V^{M}) minus the sale of the original (S_V^{O}) and the generics (L) during competition. We also have to estimate the value of the health loss associated with being able to serve fewer patients (U). In addition, we have to account for that this

[16] For some examples, see Dubois, Moisson & Tirole (2022), Boyer, Kroetsch & Ridley (2022) and Outterson & McDonnell (2016).

expense is incurred a number of years after the voucher is purchased by adjusting the sum of these costs with a societal discount rate ($(1\text{-}D)^J$). Hence, we get to following equation:

$$C_V = \left(S_V^M - \left(S_V^O + L\right) + U\right) * (1 - D)^J$$

Hence, to calculate the investment to cost ratio for vouchers, we arrive at the following equation:

$$E_V = \left(\frac{\left(\left(\left(S_{V2nd}^M - X_{V2nd}^M\right) - \left(S_{V2nd}^O - X_{V2nd}^O\right)\right) * (1 - Z)^J * ((1 - Z)^Y) * (1 - R_V)\right)}{(S_V^M - (S_V^O + L) + U) * (1 - D)^J} \right)$$

3.2. Market Entry Reward

One of the reasons for MERs being an often-considered way to fund antibiotics R&D is their simplicity. At their core, they represent a one-off payment to an organisation that it able to produce an antibiotic that fulfil certain criteria. Although there are suggestions for potentially improved, but more complex MERs, this paper will base its model on a simple MER structure.

Due to their relative simplicity, the calculations for determining the investment to cost ratio of a market entry reward (E_R) is rather limited.[17] To calculate the expected investment (I_R), we use the size of the MER (A) as the base. Like with the voucher, this is then adjusted by the cost of capital over between investment and reward ($(1\text{-}Z)^Y$), as well as the MER specific risk premium ($1\text{-}R_T$)[18]. As such, we end up with the following equation:

$$I_R = A * (1 - Z)^Y * (1 - R_T)$$

The expected cost of the MER (C_R) is simply equal to that of the size of the MER (A):

$$C_R = A$$

Hence, to calculate the investment to cost ratio for an MER, we arrive at the following equation:

$$E_R = \frac{\left(A * (1 - Z)^Y * (1 - R_T)\right)}{A}$$

3.3. Subscription

Like the vouchers, but unlike the MER, subscriptions can be constructed in a myriad of ways. In this paper, we will consider a basic form of subscription that is constituted of a fixed nominal annual payment for a predetermined number of years. Like with a MER, the size of the payment would be made known in advance. This model is also based on the assumption that the reward part of the subscription

[17] Under Appendix I, we will introduce a few variables that will make it a bit more complex.
[18] The risk premium for the MER and subscriptions are lower, since the value of these are known to the investor prior to making the investment, while that of the voucher is only revealed after the investment is done. As such, the risk that remains is that of a failed development process or a failure to meet the criteria of the reward. See the Results section for further explanation.

is decoupled from the access and stewardship aspects that are often brought up as the main advantages of a subscription scheme. As such, the model will disregard both the costs and benefits of these aspects, assuming that they are addressed separately from the reward aspect.[19]

To establish the investment to cost ratio of subscriptions (E_S), the most important part to account for is that, unlike the MER, the reward is provided over a longer period of time. As such, to calculate the expected investment (I_S), we have to adjust the yearly reward (B) by the cost of capital (Z), so that it reflects the average value of the reward to the company. This can be done by adding the value of first year of subscription payment (B/N) and the present value of the payments that follow, until the end of the subscription ($(B/N)*((1-(1+Z)^{(1-N)})/Z)$. Then, like with the voucher and MER, this is then adjusted by the cost of capital over between investment and reward ($(1-Z)^Y$), as well as the subscription specific risk premium ($1-R_S$). As such, we end up with the following equation:

$$I_S = \left(\left(\frac{B}{N} + \frac{B}{N} * \frac{(1-(1+Z)^{1-N})}{Z}\right) * (1-Z)^Y * (1-R_S)\right)$$

The cost of the subscription to society (C_S) must, in a similar manner, take account of the duration of the subscription. This can be done by adjusting the cost in a similar manner as above, using the discount rate to society (1-D) instead of the cost of capital. As such, we end up with the following equation:

$$C_S = \frac{B}{N} + \frac{B}{N} * \frac{(1-(1+D)^{1-N})}{D}$$

Hence, to calculate the investment to cost ratio for a subscription, we arrive at the following equation:

$$E_S = \frac{\left(\left(\frac{B}{N} + \frac{B}{N} * \frac{(1-(1+Z)^{1-N})}{Z}\right) * (1-Z)^Y * (1-R_S)\right)}{\frac{B}{N} + \frac{B}{N} * \frac{(1-(1+D)^{1-N})}{D}}$$

[19] Under Appendix I, we will discuss how including these might affect the investment to cost ratio of subscriptions.

4. Results

In order to be able to compare the investment to cost ratios of the various antibiotics R&D incentive schemes, we need to put values to the various variables that we have identified for each of the incentive models. As such, we will go through each incentive scheme, to see how much they would cost and the amount of antibiotics investments they would produce. We will then study how robust these results are by changing some of the variables and introducing some potential additional variables. Last, we will compare these results and their robustness.

4.1. Vouchers

To calculate the amount of investments that the voucher scheme is likely to produce, we will use data provided by the European Commission in their impact assessment for the vouchers.[20] They assessed that $((S_{V2nd}^{M}-X_{V2nd}^{M})-(S_{V2nd}^{O}-X_{V2nd}^{O}))$ would amount to €253 million.[21] The impact assessment also assumed a cost of capital (Z) at 10%, which we will also adapt.

However, the impact assessment did not feature an assessment of the investment risk premium for the investors, so we have to assess one. For the vouchers, there are three elements to the risk calculation. One is the risk of the investment not leading to a functional antibiotic, the developed antibiotic does not receive a voucher,[22] and the price volatility risk of the vouchers. The investor can manage the first two risks by spreading investments over a large number of products, hence they can each be made fairly low.[23] However, the voucher price volatility can not be significantly avoided through diversification, as it applies only to the limited number of antibiotics that will potentially be awarded a voucher. As such, if we make rather conservative estimates, we can assume that the first two risk factors require a combined risk premium of 5%, while the third risk alone requires a risk premium of 5%. As such, we would end up with a total risk premium for the vouchers (R_V) of 10%.

In addition to this, we have to assess the time periods involved the potential antibiotics R&D investments. First, as seen in section 2.1, the proposed EU legislation mandates that a voucher is used within the first four years of a product's data protection. Assuming that the voucher is bought and used at the end of the

[20] European Commission (2023b)
[21] The European Commission's Impact assessment gave a value of €205 million. However, this was taking two years of cost of capital (at 10%) into account. As our model takes the cost of capital into account separately, we needed to remove this from the profit calculation, which results in an estimated €253 million ($205/(1-0{,}1)^2 = 253$)
[22] This can happen either as a result of the antibiotic being approved after the expiry of the voucher scheme, it being approved after the maximum number of vouchers (10) have already been issued or because it does not live up to the standards required for a voucher.
[23] For further deliberation on how diversification can decrease investment risks in pharmacuetical research and development, see U.S. Congress, Office of Technology Assessment (1993: 276-280).

fourth year of this protection, which would be the most advantageous time for the buyer, this would mean that the actual utility of the voucher would occur two to seven years after it is bought. Taking into account that the product has to be one that relies on data protection rather than patents and patent extensions to ward of generics competition, it is likely that such a product would have a longer rather than shorter data protection, so that the data protection is able to surpass the patent protection. Hence, we will assume that the average product that a voucher will be applied to will have 5 years from purchase to utility (J). Most likely, investment will occur in several batches depending on the needs of the antibiotics developer. However, for simplicity we will assume that, on average, there will be 4 years between investment and realisation (Y).

If the bring the above values into the model for calculating expected investment from a voucher, we find that:

$$I_v = (253) * (1 - 0.1)^5 * ((1 - 0.1)^4) * (1 - 0.1) = 88.22$$

So, for every antibiotic that receives a voucher, the voucher scheme should lead to about €88 million in antibiotics R&D investment.

To understand the societal cost of a voucher, we have to first estimate the cost of to society of an extra year of monopoly (S_V^M- (S_V^O+L)). Continuing using the data from the voucher impact assessment, we will use their estimate of this of €283 million. Then we have to know the monetized cost of untreated patients (U), which the impact assessment estimates to €158 million. We then have to assess the social discount factor (D), which is commonly held as approximately 3% per year. Using these values, and with the previously established J, the cost to society of one voucher is estimated as follows:

$$C_V = (283 + 158) * (1 - 0.03)^5 = 378.7$$

So, for every antibiotic that receives a voucher, the voucher scheme should cost society €390 million. Hence, if we trust the values used in these models, we should arrive at the following investment to cost ratio:

$$E_V = \frac{\left(253 * (1 - 0.1)^5 * ((1 - 0.1)^4) * (1 - 0.1)\right)}{\left((283 + 158) * (1 - 0.03)^5\right)} = \frac{88.22}{378.7} = 23\%$$

Thus we can conclude that, for every €1 the voucher scheme is likely to cost the European society, in purchase costs and lost health gains, it is estimated to return 23 cents in antibiotics R&D investment.

4.2. MER

Both the projected investment from, and societal cost of, a MER is significantly easier to calculate than the corresponding values for a voucher. To assess the investment part, we first have to know the size of the MER. Since this is set politically, rather than by the market, it could be any value that is assessed to be optimal. However, for the purposes of easy comparison, we will assume that the value of the MER (A) is set at the monopoly cost of the voucher, excluding the cost of untreated patients, €283 million. We then use the same Z and Y as for the vouchers, that is 10% and 4 years. Last, we assess the risk premium required for the

MER. Since the MER is not subject to price volatility, it is only subject to the fairly diversifiable risks of not failure to develop a viable product and of not receiving a MER. Hence, since the combined risk premium required for these risks was earlier established at 5%, that will be used as the risk premium for MER investment (R_T). As such, we can estimate the investments associated with a MER as follows:

$$I_R = 283 * \left((1-0.1)^4 - (1-0.05)\right) = 176.39$$

So, for every antibiotic that receives a MER, the MER scheme should lead to about €176 million in antibiotics R&D investment.

The cost of the vouchers is extremely simple to calculate, as it is equal to the size of the MER:

$$C_R = 283$$

So, for every antibiotic that receives a MER, the MER scheme should cost society €283 million. Hence, if the trust the values used in these models, we should arrive at the following investment to cost ratio:

$$E_R = \frac{\left(283 * \left((1-0.1)^4 - (1-0.05)\right)\right)}{283} = \frac{176.39}{283} = 62\%$$

Thus we can conclude that, for every €1 the MER scheme is likely to cost the European society, it is estimated to return 62 cents in antibiotics R&D investment.

4.3. Subscription

The subscription is in many ways similar to the MER, but with a time delay element. As such, we will assume that the nominal sum of the reward in the subscription is the same as for the MER, at €283 million. We will then assume that the scheme be based on 20 years of subscription (N). The cost of capital (Z) will be 10%, the same as in all of the schemes. We also assume that the scheme is legally binding, so that there is no added risk of payment failure over the years of subscription, meaning that the risk premium for the subscription (R_F) ought to be 5%, just as with the MER. As such, we can estimate the investments associated with a subscription as follows:

$$I_S = \left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.1)^{1-20})}{0.1}\right) * (1-0.1)^4 * (1-0.05)\right) = 82.6$$

So, for every antibiotic that receives a subscription, the subscription scheme should lead to about €83 million in antibiotics R&D investment.

With a subscription amount of €283 million and a runtime of 20 years, and assuming that the discount rate to society (D) at 3%, the same as with the vouchers, the cost to society of one subscription is estimated to be:

$$C_S = \frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.03)^{1-20})}{0.03} = 216.83$$

So, for every antibiotic that receives a subscription, the subscription scheme should cost society €217 million. Hence, if the trust the values used in these models, we should arrive at the following investment to cost ratio for subscriptions:

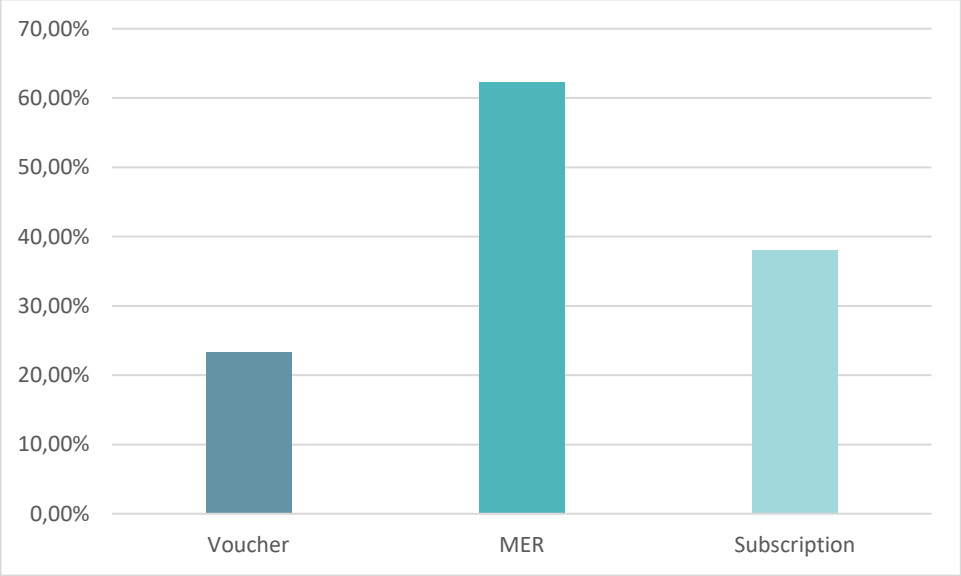
$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.1)^{1-20})}{0.1}\right) * (1-0.1)^4 * (1-0.05)\right)}{\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.03)^{1-20})}{0.03}} = \frac{82.6}{216.83} = 38\%$$

Thus we can conclude that, for every €1 the subscription scheme is likely to cost the European society, it is estimated to return 38 cents in antibiotics R&D investment.

4.4. Comparison

The results show substantial differences between the various novel antibiotics R&D incentives schemes considered in this paper. As seen below, vouchers have the least efficient investment to cost ratio, while MER has the most efficient ratio, with subscriptions in between them:

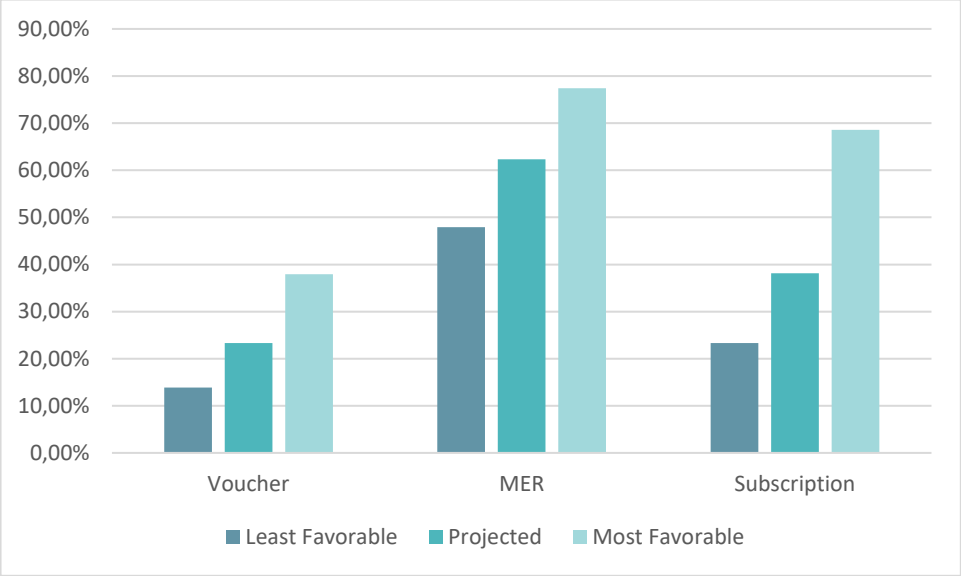
Diagram 3. Projected investment to cost ratio



Moreover, the robustness analysis indicate that the results are fairly stable.[24] As shown below, the least and most favourable scenarios for each of the models following the same pattern as their projected scenarios, with the most favourable scenario for vouchers still not achieving the same efficiency as the least favourable scenario for MER:

[24] See Appendix I.

Diagram 4. Robustness of results



Hence, we can be confident in the conclusion that, from the payer perspective, the MER scheme provides the most effective investment to cost ratio, followed by subscriptions and that the voucher scheme is the least cost-efficient option.

5. Discussion and concluding remarks

From this study we can conclude that the investment to cost ratio of the voucher scheme, as outlined in the proposed EU legislation, is significantly lower than other schemes investigated by this paper. This low ratio is largely due to the extensive cost of capital caused by the delay between the purchase of a voucher and the utility gained from it, the discrepancy in pay willingness between the highest and 2nd highest bidder, as well as the direct and indirect costs of longer market exclusivities. Due to the combination of these factors and others, vouchers are about half as effective at translating societal cost into antibiotics R&D investments as subscriptions and a third as effective as market entry rewards. As such, from a payer perspective, vouchers are to be viewed as the least preferable options for incentivising the development of novel antibiotics.

A further problem with vouchers, compared to the other schemes, is that the actual reward level is not directly adjustable. Unlike the MER and subscription schemes, where a nominal monitory reward level can be set, the vouchers can only be adjusted through length and other conditions. As such, with the low investment to cost ratio of vouchers, there is a substantial risk that the conditions of the voucher will be set so that no investments will occur due to it, since the rational upper investment limit would not be able to cover the needed R&D expenses and hence any investment would be wasted.

Hence, there is a risk of creating a situation where the introduction of vouchers is politically seen as having dealt with the antibiotics development issue, while failing to actually produce any investment. In this case it is likely that it would take years to determine confirm that the voucher programme had failed and even further to work out the structures of a new scheme. As such, the voucher programme could end up delaying the implementation of a properly functional incentive scheme by many years.

Another risk it that new antibiotics will be developed, but that the vouchers will have had little to no impact on their development process. While each of the incentive methods induces a risk of over-incentivising investors, vouchers run a risk of not incentivise investors yet still come at a cost to society. The antibiotics in question might have been funded through other means, such as through workable schemes launched by other governments or because the demand for new antibiotics becomes so severe that market prices make new developments profitable. Still, since there is no provision in the current EU legislative proposal to ensure that the voucher scheme made a significant impact on an antibiotic that received the voucher, it might simply cause added societal cost for little to no benefit.

However, this is not to say that the two other schemes modelled in this paper do not have their own issues. Mainly, while the vouchers can be introduced as a legal measure, with no upfront cost to the payers, both the MER and subscription schemes require political decisions that allocate specific funding for their schemes. This means that, while they obscure the cost to patients and tax-payers and might

contribute to the sense of lack of democratic accountability that has long plagued the EU, the vouchers are likely to require less political capital to implement than the other schemes. Also, because the vouchers are EU-wide by necessity, they do not suffer from the potential free-rider and coordination challenges that MER and subscription schemes could face, since they would both need to be supported by an EU-wide coalition of states to become financially viable.

If such a coalition cannot be created, the MER or subscription schemes might not be functional options. In that case, the choice might be between the voucher scheme and no solution. If so, it might be beneficial for the EU to explore how the vouchers scheme could be improved, for example along the lines of some of the suggestions found in the current literature on the topic. However, if no changes are made, the current voucher scheme is so inefficient that this paper cannot conclude whether it is preferable to no solution.

6. Appendix

6.1. Robustness Analysis

This paper presents calculations for how to evaluate the value of three incentive methods for stimulating antibiotics research, namely vouchers, MERs and subscriptions. While it finds that the various methods have markedly different investment to cost ratios, it is important to understand that these ratios are both dependant on the specifics of the models used and on assumed values for some of the variables. As such, it is important to study the robustness of the results to reasonable changes to these models and variable values.

The models presented in this paper present the most the most important variables for calculating the costs of the various incentives. However, some other considerations have been made in the literature around antibiotics research promotion. Some of these will be used to study the robustness of the conclusions from the main models.

6.1.1. Cost of public funding

A common consideration when dealing with public spending is that there is a cost of raising public funds, as many taxes disrupt the economy through e.g. lessening the incentives to work. As such, economists like Dubois, Moisson & Tirole apply a variable to take account of this (G).[25] If we take this into consideration, both the MER and the subscription would have to be adjusted in order to account for how they use public funds to create their incentives:

$$C_R = A * (1 + G)$$

$$C_S = ((B + (B * (1 - D)^N))/2) * (1 + G)$$

However, vouchers are not immune to the effects of the cost of public funding. Large parts of European health care is funded either through taxes or tax-like mandatory social insurance schemes that scale with income. As such, the cost of vouchers also needs to take into account the proportion of healthcare spending that is publicly funded (H), so that the adjustment becomes (1+G*H):

$$C_V = ((S_V^M - (S_V^O + L)) * (1 + G * H) * (1 - D)^J$$

6.1.2. Voucher to finance MER

There have been several suggestions in the literature, such as Outterson & McDonnell and Dubois, Moisson & Tirole, that instead of providing the developer of a novel antibiotic with a voucher that they can use or sell, vouchers should be sold as a way to finance other incentive methods.[26] If we assume that the voucher is used to provide the developer with a MER, this alters the investment to cost calculations significantly. For the investors, the investment decision would be the same as that of a MER. For the societal costs, these consist of the difference between the reward

[25] Dubois, Moisson & Tirole (2022)
[26] Outterson & McDonnell (2016) and Dubois, Moisson & Tirole (2022)

amount and the proceeds from the sale of the voucher, as well as the regular societal cost of the voucher. As such, the expected investment and social cost from such a voucher scheme would be:

$$I_V = A * (1 - Z)^Y * (1 - R_V)$$

$$C_v = A - \left(\left(\left(S^M_{V2nd} - X^M_{V2nd}\right) - \left(S^O_{V2nd} - X^O_{V2nd}\right)\right) * (1 - Z)^J * ((1 - Z)^Y) * (1 - R_V)\right) + \left(S^M_V - \left(S^O_V + L\right) + U\right) * (1 - D)^J$$

6.1.3. Availability and stewardship

One common criticism of both vouchers and MER are that they don't provide insurance that the novel antibiotic being rewarded will be available to those who provide the incentive. Nor do they guarantee that the antibiotic will be used in a way that minimises resistance development and ensures its continued efficacy. Subscriptions could, if structured in such a way, be used to ensure both of these. Hence, the value of the investment gained from subscriptions ought to be multiplied by an affordability (Q) and a stewardship (W) factor.

$$I_S = \left(\frac{\left(B + (B * (1 - Z)^N)\right)}{2} * (1 - Z)^Y * (1 - R_F)\right) * Q * W$$

However, if the subscription includes availability and stewardship provisions, this will also impact the profitability of the developer. To maintain the same profitability, the scheme would have to offer compensation for this (Å). As such, we would end up with the following model:

$$C_S = \frac{\left(B + (B * (1 - Z)^N)\right)}{2} * Å$$

The above models introduce new elements that might significantly change the outcomes to the various investment to cost ratios. However, to understand the influence these might have on the conclusions made in this paper, we would have to introduce values to the new variables. As such, below follows a range of robustness calculations both of these models and of variations to the values in the original models.

6.1.4. Calculations

One of the most extensively debated factors when it comes to vouchers are their price. However, here just as in the European Commission's impact assessment, there is a recognition that the sale price of the voucher alone gives rather limited information on the actual efficacy of the vouchers. Instead, the sale price has to be contrasted with the price that society pays in increased pharmaceutical prices and in unmet healthcare needs.

One of the factors that could change the relationship between the price of the vouchers and the cost to society is if more than one voucher was issued in a given year. To see how their results would vary with the number of vouchers issued within a year, the Commission's impact assessment studied how up to three vouchers in a year would influence this relationship. They found that the this would result in a combined, unadjusted sales price of €330 million for the vouchers, with a combined

unadjusted cost of €839 million.[27] If we adjust these with cost of capital, risk premium and the social discount rate, we end up with the following investment to cost ratio:

$$E_V = \frac{\left(330 * (1-0.1)^5 * ((1-0.1)^4) * (1-0.1)\right)}{\left((589+300) * (1-0.03)^5\right)} = \frac{115.06}{763.42} = 15\%$$

However, we should also consider a scenario where less than one voucher is issued per year. This means that the competition for the vouchers would be higher and that the difference in willingness would be lower between the highest and 2nd highest bidder. This could drive up the price of the voucher significantly. If we assume that this increased competition would cut the buyer's rent by two thirds from the original scenario, we end up with an unadjusted voucher price of €380 million. If we assume that this does not affect the cost to society, this leads to the following investment to cost ratio:

$$E_V = \frac{\left(380 * (1-0.1)^5 * ((1-0.1)^4) * (1-0.1)\right)}{\left((283+158) * (1-0.03)^4\right)} = \frac{132.5}{378.7} = 35\%$$

As such, it is reasonable to assume that the investment to cost ratio of vouchers may vary between 15% and 35% depending on how many vouchers investors think will be released per year.

Apart from how many vouchers that will be released per year, another variable that could be varied is the years from purchase to utility (J). This is a political decision linked to the conditions on when the voucher has to be activated. As the legislation is designed now, it forces the voucher to be used within the first four years of the data protection for the extended pharmaceutical. This means a timespan of two to seven years between purchase to utility, with what we have here assumed is an average of five years.

As this a politically set variable, it can be either increased or decreased through the legislation. The furthest this could be extended would an average of eight years, by requiring the voucher to be activated in the first year of data protection. On the other end, the variable could become null and void by abolishing this criterion. A span of eight to zero years from purchase to utility would give the following span of investment to cost:

$$E_V = \frac{\left((253) * (1-0.1)^8 * ((1-0.1)^4) * (1-0.1)\right)}{\left((283+158) * (1-0.03)^8\right)} = \frac{64.31}{345.63} = 19\%$$

$$E_V = \frac{\left((253) * (1-0.1)^0 * ((1-0.1)^4) * (1-0.1)\right)}{\left((283+158) * (1-0.03)^0\right)} = \frac{149.39}{441} = 34\%$$

As such, it is reasonable to assume that the investment to cost ratio of vouchers may vary between 19% and 34% depending on how many vouchers investors think will be released per year.

[27] $267/(1\text{-}0{,}1)^2 = 330$; €539 million + €300 million. For more information, see European Commission (2023b) p.48.

Throughout this whole study, we have assumed a cost of capital of 10%. This is a rather standard approximation, but various factors such as inflation, interest rates, industry developments, market fluctuations and CCR investment could change this number. To study how such fluctuations could affect the investment to cost ratios of the various schemes, we will see how a 5% and a 15% cost of capital would influence their results. If we first look at the 5% case, the investment to cost ratios would be:

$$E_V = \frac{\left((253) * (1-0.05)^5 * ((1-0.05)^4) * (1-0.1)\right)}{\left((283+158) * (1-0.03)^4\right)} = \frac{143.51}{378.7} = 38\%$$

$$E_R = \frac{\left(283 * \left((1-0.05)^4 - (1-0.05)\right)\right)}{283} = \frac{218.98}{283} = 77\%$$

$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.05)^{1-20})}{0.05}\right) * (1-0.05)^4 * (1-0.05)\right)}{\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.03)^{1-20})}{0.03}} = \frac{143.27}{216.83} = 66\%$$

If we instead look at the 15% case, the investment to cost ratios would be:

$$E_V = \frac{\left((253) * (1-0.15)^5 * ((1-0.15)^4) * (1-0.1)\right)}{\left((283+158) * (1-0.03)^4\right)} = \frac{52.74}{378.7} = 14\%$$

$$E_R = \frac{\left(283 * \left((1-0.15)^4 - (1-0.05)\right)\right)}{283} = \frac{140.34}{283} = 50\%$$

$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.15)^{1-20})}{0.15}\right) * (1-0.15)^4 * (1-0.05)\right)}{\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.03)^{1-20})}{0.03}} = \frac{50.51}{216.83} = 23\%$$

As we see above the investment to cost ratio changes for each of the schemes. The ratio for the vouchers change from between 38% and 14%, the MER between 77% and 50% and the subscription between 66% to 23%. As such, we can see that all schemes are affected by cost of capital fluctuations, but that these are most influential for the voucher scheme and least influential for the MER.

Another factor that two of the schemes, vouchers and subscriptions, are affected by is the social discount value. This is a hard variable to properly estimate, as it depends on a range of factors such as inflation, political systems and social preferences. As such, it is reasonable to assume that the discount rate could be as low as 0% and as high as double our most likely estimate, 6%. If we first look at the 0% case, the investment to cost ratios would be:

$$E_V = \frac{\left((253) * (1-0.1)^5 * ((1-0.1)^4) * (1-0.1)\right)}{\left((283+158) * (1-0.00)^4\right)} = \frac{88.22}{441} = 20\%$$

$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.1)^{1-20})}{0.1}\right) * (1-0.1)^4 * (1-0.05)\right)}{283} = \frac{82.6}{283} = 29\%$$

If we instead look at the 6% case, the investment to cost ratios would be:

$$E_V = \frac{\left((253) * (1-0.1)^5 * ((1-0.1)^4) * (1-0.1)\right)}{\left((283+158) * (1-0.06)^4\right)} = \frac{88.22}{323.65} = 27\%$$

$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.1)^{1-20})}{0.1}\right) * (1-0.1)^4 * (1-0.05)\right)}{\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.06)^{1-20})}{0.06}} = \frac{82.6}{172.04} = 48\%$$

Here we see that the effect of changes to the social discount value has varying degrees of effect on the voucher and subscription investment to cost ratio. For vouchers, a shift from 0% to 6% social discount rate means a change in ratio from 20% to 27%. For subscriptions it means a swing from a 29% to a 48% ratio.

Last among the variables that are in the models, we want to see how changes to the risk premiums would impact the schemes. The risk premiums used in the above results are already fairly conservative, so the reasonable potential for decreasing them is limited. What could be done, politically, is to make the requirements for the novel antibiotics less stringent and to remove the cap on the number of vouchers, MERs or subscriptions. If this was done to an extreme, this could essentially remove the risk of a finished antibiotic not receiving a reward, decreasing the risk premium needed by 2.5%, to 7.5% for the vouchers and 2.5% for the MERs and subscriptions. This would result in the following investment to cost ratios:

$$E_V = \frac{\left((253) * (1-0.1)^5 * ((1-0.1)^4) * (1-0.075)\right)}{\left((283+158) * (1-0.03)^4\right)} = \frac{90.67}{378.7} = 24\%$$

$$E_R = \frac{\left(283 * \left((1-0.1)^4 - (1-0.025)\right)\right)}{283} = \frac{181.03}{283} = 64\%$$

$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.1)^{1-20})}{0.1}\right) * (1-0.1)^4 * (1-0.025)\right)}{\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.03)^{1-20})}{0.03}} = \frac{84.77}{216.83} = 39\%$$

We should also consider the opposite possibility, that the criteria are made more stringent or that the number of rewards is further restricted. In that case, the risk premiums necessary to compensate for the decreased likelihood of a novel antibiotic receiving an award can easily double, from 2.5% to 5%. We should also consider the scenario where investors find the variability in the potential prices of the vouchers significantly riskier than we have assumed here, potentially leading to a doubling of the risk premiums demanded due to it. If we add in these extra risks, we end up with risk premiums of 7.5% for the MERs and subscriptions and 17.5% for the vouchers. This would result in the following investment to cost ratios:

$$E_V = \frac{\left((253) * (1-0.1)^5 * ((1-0.1)^4) * (1-0.175)\right)}{\left((283+158) * (1-0.03)^4\right)} = \frac{80.86}{378.7} = 21\%$$

$$E_R = \frac{\left(283 * \left((1-0.1)^4 - (1-0.075)\right)\right)}{283} = \frac{171.75}{283} = 61\%$$

$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.1)^{1-20})}{0.1}\right) * (1-0.1)^4 * (1-0.075)\right)}{\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.03)^{1-20})}{0.03}} = \frac{80.42}{216.83} = 37\%$$

From the above, we can see that, while the risk premium changes have some influence on the outcome of the schemes, these are all rather limited. For vouchers they lead to a investment to cost ratio of 21% to 24%, for MERs between 61% and 64% and subscriptions between 37% and 39%.

Having looked at how adjustments to the current variables in the models could change the investment to cost ratios for the antibiotics innovation schemes, we also have to introduce some variables that are not part of the current models. The first of these is the cost of public funding (G). If we assume that G is 30%[28], this leads to the following investment to cost ratios for the MER and subscription schemes:

$$E_R = \frac{\left(283 * \left((1-0.1)^4 - (1-0.05)\right)\right)}{283 * (1+0.3)} = \frac{176.39}{367.9} = 48\%$$

$$E_S = \frac{\left(\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.1)^{1-20})}{0.1}\right) * (1-0.1)^4 * (1-0.05)\right)}{\left(\frac{283}{20} + \frac{283}{20} * \frac{(1-(1+0.03)^{1-20})}{0.03}\right) * (1+0.3)} = \frac{82.6}{281.88} = 29\%$$

To include the cost of public funding for the voucher scheme we also have to see how much of the healthcare spending, specifically concerning high-cost pharmaceuticals, is funded either publicly or through other mandatory, tax-like systems such as most European social or health insurance schemes. Since most Europeans receive high-cost pharmaceuticals this way, especially if they are considered in-patient pharmaceuticals, we can make a rough estimated proportion of 80% of the high-cost pharmaceutical being publicly funded (H). This would lead to the following investment to cost ratios for the voucher schemes:

$$E_V = \frac{\left((253) * (1-0.1)^5 * ((1-0.1)^4) * (1-0.1)\right)}{\left((283+158) * (1+0.8*0.3) * (1-0.03)^4\right)} = \frac{88.22}{437.03} = 20\%$$

Hence, we can see that the introduction of a cost of public funding does reduce all investment to cost ratios, but that the impact is significantly less noticeable with the voucher than with the MER and subscription scheme, bringing the former down to 20% and the latter by 48% and 29% respectively.

If vouchers were used as a way to fund a MER, we do not have to introduce any new variables. Instead, we have to rearrange the current variables to reflect this approach. If we do so, we reach the following investment to cost ratio:

$$E_V = \frac{283 * \left((1-0.1)^4 - (1-0.05)\right)}{283 - 253 * (1-0.1)^5 * \left((1-0.1)^4 * (1-0.1)\right) + (283+158) * (1-0.03)^5} = \frac{176.39}{573.49} = 31\%$$

[28] A common estimate used by e.g. Dubois, Moisson & Tirole (2022)

Finally, if we look at including the potential value of availability and stewardship from a subscription scheme, we have to consider a set of new variables. First, we have to establish the value of the availability and stewardship that the subscription can provide. While both are highly valuable, a subscription is much more suitable for availability than stewardship. Not only is it easier for the producer to ensure availability, as they are in control of their own supply lines but not of the prescription or usage of the antibiotics. It is also easier for the payer to ensure adherence, as they can see if products are arriving and apply sanctions if deliveries are missed, while prescription and usage outside of their own institutions is difficult. This, in combination with that it is essential to have access to a product in order to gain direct medical benefits from it, means that we can estimate a high value for availability. As such we will assume that the availability that the subscriptions can provide increases the value of a novel antibiotic to the reward provider by 80%.

Even if it is harder for both the producer and the payer to ensure stewardship, there are some actions that can be taken by the payer and verified by the payer. These include providing best practice support to prescribers and users, enforce patent and other market regulations to prevent unlicensed usage and limiting or banning exports to countries with substantial stewardship shortcomings. Neither the provision nor the enforcement of these measures can ever be as tight as those for availability, but they can still significantly contribute to maintaining the efficacy of the novel antibiotic over time. As such, we estimate the value of the stewardship that the subscription can provide to 30%.

Last, we have to estimate how much more the payer would have to pay in order for the provision of availability and stewardship to be cost-neutral to the producer, in comparison to the original subscription scheme that did not mandate the provision of these added benefits. A common estimate for provision of pharmaceutical products under monopoly is 20% of the sales price, which in this case can be estimated as 20% of the value of the original subscription.[29] The cost for providing stewardship is harder to estimate. However, if we follow the logic above, where stewardship is difficult to enforce but that there are a few measures that can be taken, it follows that the stewardship requirements should only include these measures. As such, we will assume that these limited measures will cost 10% of the value of the original subscription. As such, we would have a combined cost of 30% of the original subscription. Including all these variables, we reach the following cost to benefit ratio:[30]

$$E_S = \frac{\left(\frac{\left(283 + (282 * (1-0.1)^{20})\right)}{2} * (1-0.1)^4 * (1-0.05)\right) * 1.8 * 1.3}{\frac{\left(283 + (283 * (1-0.03)^{20})\right)}{2} * 1.3} = \frac{193.27}{281.88}$$
$$= 69\%$$

[29] See e.g. European Commission (2023b).

[30] Note that this does no longer represent a pure investment ratio to cost, as the availability and stewardship benefits are other gains to the payer, rather than purely investments into antibiotics R&D.

As we can see, the robustness measures that we have carried out do change the investment to cost ratio of each of the schemes. However, apart from including availability and stewardship aspects into subscriptions, these do not change the relative ratios of the schemes. As such, we can be fairly certain that the results of this paper are robust.

6.2. List of variables

X:Production Cost	*A: MER amount*
Z: Cost of Capital	*B: Total subscription amount*
Y: Years from investment to realisation	*D: Social discount value*
J: Years from purchase to utility	*T: Relating to MER*
N: Years of subscription	*F: Relating to Subscription*
M: During monopoly	*G: Cost of public funding*
O: During competition	*H: Proportion of pharmaceutical spending paid through public or semi-public funding*
R: Systemic risk	*Q: Affordability*
U: Cost of untreated patients	*W: Stewardship*
L: Sales of Competitors	*Å: Compensation for Availability and Stewardship costs*

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