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Discrete choice experiment to investigate preferences for incentives to promote antimicrobial research and development

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ABSTRACT

Objectives: Without intervention, experts predict that antimicrobial resistance will rank among leading drivers of mortality by 2050. New drugs are desperately needed, but given the lengthy development timelines for antimicrobial research and development (R&D), existing economic incentives fail to support a robust pipeline of new products. This study aims to elicit the preferences of stakeholders for adequate antimicrobial R&D incentive programs.

Methods: A discrete choice experiment was conducted in which stakeholders (representatives from small or medium and large pharmaceutical companies, academics, clinicians, and policy makers) were asked in 12 choice tasks to select their preferred incentive combinations among two hypothetical options, differing in five attributes: form of monetary incentive, total amount of monetary incentive, market exclusivity extensions, transferable exclusivity extensions vouchers, and priority review vouchers. A subgroup analysis comprising only participants from the pharmaceutical industry was also conducted.

Results: A total of 50 stakeholders (including 24 from the pharmaceutical industry) completed the survey in full. Participants preferred longer transferable exclusivity extensions and larger amounts of monetary rewards. The levels that were perceived as having the highest utility were *$1 billion as total amount of incentives* and *transferable exclusivity extension for 18 months*. The subgroup analysis provided similar findings.

Conclusion: This study suggests that survey participants viewed transferable exclusivity vouchers for an 18-mo term and higher ($1 billion) monetary rewards as the preferred incentives to promote antimicrobial R&D. Further work is needed to design specific incentives and ensure they are implemented effectively.

1. Introduction

A future health crisis is creeping in gradually in the form of antimicrobial resistance (AMR). AMR occurs when a pathogen becomes resistant to an antibiotic, rendering the antibiotic ineffective, and if other therapeutic options are not available, making the infection untreatable [1]. The past decade has seen many researchers raising the alarm about AMR's potential threat to modern society [1–4]. Currently, around 700 000 people die annually worldwide from AMR pathogens, and experts predict that without intervention this will increase by 2050 to between 10 and 50 million deaths annually [2]. This means that AMR-related deaths will even surpass annual cancer deaths [3]. There is a high risk that if AMR is not addressed it is likely to result in a devastating impact on the global economy, as demonstrated by the crisis management for the severe acute respiratory syndrome corona virus-2 pandemic. The World Bank expects that the global economy will

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decrease by around 3.8% by 2050 if the AMR issue is not adequately addressed [1]. Despite the recognized threat and need for solutions, necessary policy measures are not in place to promote adequate investment in developing new drugs to ensure options remain for patients as older drugs lose their effectiveness, which has led many developers to exit the field [5].

The main reasons for this exodus are, firstly, the considerable demands involved in developing a novel antibiotic, such as high scientific complexity, long development periods, and resource intensity, particularly because many of the easier-to-develop antibiotics have already been found [6]. In addition, companies must overcome numerous regulatory barriers in bringing their antibiotic to the market, for example, the need for sufficient proof of noninferiority and balancing the drug's levels of toxicity so that it can pass the preclinical phase [4,7]. Even after an antibiotic has been approved and launched, companies are hard pushed to make a return on their investment, due to restricted reimbursement decisions, low recognition of value, consumer price expectancy, price benchmarks, delayed uptake of the antibiotic, short treatment duration, and so forth [7,8]; antibiotics are known for not being profitable. This view was further reinforced when Achaogen, a pharmaceutical company active in antibiotic development, declared bankruptcy in 2019, 10 mo after bringing to market their novel antibiotic addressing resistant pathogens [7]. Though the antibiotic from Achaogen, plazomicin, was effective against multidrug-resistant *Enterobacteriaceae*, the company was unable to make a return on its investment. In such circumstances, only a few major pharmaceutical companies are still actively developing and researching in this field.

As a result, many governments and institutions have already implemented or are discussing the implementation of incentives or have set up research funding programs to eliminate some of the barriers and facilitate AMR research and development (R&D), but existing programs have not yielded a robust pipeline. One incentive being suggested is the subscription model, in which a company receives a monetary reward each year for a given period of time, say, 5 years, once the drug reaches the market, in order to ensure sustainable access. Another well-known incentive is a transferable exclusivity extension (TEE). This allows the company that brought a new antibiotic, A, to the market to choose another drug, B, which they hold the patent on, and extend the duration of its patent term [9]. However, to our knowledge, there are no studies available yet on what incentives are preferred. Figuring out the preferred incentives could provide information useful to a variety of stakeholders, especially the policy makers evaluating different incentives. Identified preferences may suggest which incentive, if implemented and used properly, could have the greatest effect in bringing the relevant stakeholders back to the table and enabling investment in antimicrobial R&D.

To determine preferences among participants, discrete choice experiments (DCEs) have gained in popularity as a methodology, especially in the field of health policy [10]. A DCE is a quantitative method to identify the preference of participants by letting them choose repeatedly between two hypothetical scenarios. In addition to identifying what a participant's preference is, a DCE can also measure trade-offs, showing exactly what is preferred over something else [11]. This study aimed to determine stakeholders' preferred incentives for promoting antimicrobial therapeutic development by using a DCE methodological approach.

2. Materials and methods

DCE methods were used to identify the preferences of different stakeholders regarding certain economic incentives for developing antimicrobials. In the DCE, respondents must choose between two hypothetical scenario combinations. The different scenarios contain the same attributes but with different levels. Before the survey can be created, a list of attributes and levels needs to be identified. The current study was approved by the Maastricht University Ethics committee (REC number: FHML/HPIM/2021.024). A protocol was developed prior to conducting the search and is available upon request.

Table 1
List of attributes and their corresponding levels.

Attributes	Levels
Form of monetary incentive	No monetary incentive
	Early-stage research grants
	One-time payment after market approval
	Milestone monetary rewards
	Annuity payment over 5 y
Total amount of monetary incentive	No monetary incentive
	$20 million*
	$100 million*
	$500 million*
	$1 billion*
Market exclusivity extension	No market exclusivity extension
	Extension for 1 y
	Extension for 3 y
	Extension for 5 y
Transferable exclusivity extension	No extension
	Extension for 6 mo
	Extension for 12 mo
	Extension for 18 mo
Priority review vouchers	No priority vouchers
	Priority review vouchers

* These monetary rewards would be per novel antimicrobial drug

2.1. Attributes and levels

Four steps were taken to identify and select the attributes and their corresponding levels:

1 An umbrella review was conducted to identify pre-existing literature that investigated incentives being implemented or proposed for promoting antimicrobial development. An umbrella review looks at previously published systematic literature reviews (including meta-analysis and scoping reviews) to fill a knowledge gap [12]. Combination of keywords and subject headings, such as "'antibiotic development incentives' AND 'pharmaceutical industry,' 'antibiotic development' AND 'antibiotic resistance,' AND 'economic barriers,'" were used to search the databases PubMed and Web of Science in April 2021. Only English articles published from 2010 onwards reporting on antimicrobial development barriers and proposed incentives were included. The umbrella review identified a total of 53 resources that were used for analysis. An initial list of potential incentives and levels was derived from this review.
2 Interviews with experts from the pharmaceutical industry (n = 6) were undertaken in parallel to validate and complement the findings from the umbrella literature review.
3 Based on the first two steps, the research team, including DCE experts (n = 2), experts in AMR, and individuals from the pharmaceutical industry (n = 4), finalized the list of attributes and their corresponding levels. Five attributes, out of 34, were identified as being the most relevant and prevalent from the interviews and the literature review. The corresponding levels were also based on pre-existing literature and expert opinions.
4 The list was then reviewed by academic experts in the field of antibiotic incentives (n = 2) and industry experts (n = 3) to ensure accuracy and relevance. Only minor adjustments were made to the levels of the attributes. The final list of attributes and levels can be found in Table 1.

	Incentive Combination A	Incentive Combination B
Form of monetary incentive	One-time payment after market approval	Annuity payments over 5 years
Total amount of monetary incentive	$100 million	$20 million
Market exclusivity extensions	Extension for 1 year	No extension
Transferable exclusivity extensions	Extension for 18 months	Extension for 6 months
Priority review vouchers	No priority review vouchers	Priority review vouchers
Which of the two-incentive combination best promotes antimicrobial R&D? *(Tick one box only)*	Incentive Combination A ☐	Incentive Combination B ☒

Fig. 1. Example choice set.

2.2. Experiment design

A total of 36 choice sets were created and put into three surveys with 12 choice sets each. An efficient design (maximizing D-efficiency) was created using the program Ngene to ensure statistical accuracy and to exclude implausible combinations from the design (e.g., no monetary incentive with $20 million, $100 million, $500 million, or $1 billion; one-time payment after market approval, milestone monetary rewards, and annuity payment over 5 years with $20 million; early-stage research grants with $100 million, $500 million, and $1 billion). In addition to the 12 choice sets, a dominance test was included to test for the reliability of participants' responses. A dominance test is when one of the hypothetical incentive combinations is significantly better compared to the counterpart [13]. Therefore, a total of 13 choice sets were included in each survey. An example choice set is shown in Fig. 1.

2.3. Questionnaire development

The questionnaire was developed online using the software Qualtrics and consisted of four parts. The first part explained the task to the participant and then presented the list of attributes and levels along with an example question to further illustrate the question format. Additionally, participants could opt to view additional information regarding the different attributes and levels to ensure that all participants understood each incentive correctly. In the second part of the questionnaire, participants completed the 13 choice sets. In the third part, participants were asked about their opinion on the feasibility of certain incentives being implemented within 5 years and by what amount. The first question required the participant to rank seven incentives based on their feasibility of being implemented within the next 5 years on a seven-point Likert scale. Additionally, participants had to indicate which monetary amount was most likely to be introduced by the relevant regulatory body in the next 5 years. These questions were added to determine whether a difference exists between what incentive participants prefer and what incentive participants view as feasibly implemented. Finally, some questions regarding the participants' current field of occupation and the region of occupation were added.

The questionnaire was developed and reviewed by the research team (n = 7), which consisted of academic experts (n = 4) and pharmaceutical company experts (n = 3). Furthermore, a pilot test was conducted with participants from the pharmaceutical industry (n = 5) and academics (n = 3) to ensure the questionnaire was clear and understandable, free of errors, and took roughly 10 min to complete. After conducting the pilot survey, only minor language modifications were made.

2.4. Study population, data collection, and sample size

The study was aimed at participants in the United States and in the European Union/United Kingdom who belonged to a defined stakeholder group such as a pharmaceutical company representative, academics, policy makers, or others. The target sample size was to collect a minimum of 50 responses and to have at least 20 of those responses from the pharmaceutical sector to conduct a subgroup analysis [14]. The subgroup analysis consisted of the combined responses from small or medium (SME) and large pharmaceutical companies. To ensure a large sample size, multiple methods were used to identify participants. One method was purposive sampling, in which participants were identified by reviewing articles about AMR incentives and contacting them via email [15]. An additional mailing list was compiled by the authors from our own network because we are well connected within the field of antimicrobials. Participants were then invited by email to undertake the survey. In addition, various stakeholders circulated the questionnaire within their own organizations and to their contacts.

2.5. Statistical analysis

The data were analyzed using the software Nlogit 6.0. Incomplete surveys and those in which participants failed the dominance test were excluded from the data sheet. The data sheet was double-checked by a member of the research team to ensure the accuracy of the data entry. Effect coding was used to model categorical variables. With effect coding, the sum of all coefficients, including the reference coefficient, is zero. The higher the value of the coefficient, the higher the perceived utility of the attribute level. Hence, the value of the coefficient represents the importance the attribute level has for the participant. The *P* value measures the statistical significance of the preference weight of the attribute level compared with the mean effect of the same attribute [16]. The 95% confidence interval (CI) provides further information regarding the preference weight. The preference weight between two levels is considered statistically different if the 95% CIs do not overlap.

A random parameter logit model was used to estimate the coefficient and a standard deviation for the variation between respondents, helping to capture heterogeneity. Heterogeneity indicates whether there is variation in preference between respon-

Table 2
Results from the random parameter logit model.

Attributes and levels	Coefficient	Standard deviation	Conditional relative importance
Form of monetary incentive:			16%
No monetary incentive	−1.99 CI [−3.80, −0.19]	-	
Early-stage research grants	2.13** CI[0.3, 3.96]	2.18** CI[0.16, 4.2]	
One-time payment after market approval	−1.46** CI[−2.77, −0.15]	0.74 CI[−0.26, 1.73]	
Milestone monetary rewards	0.86 CI[−0.23, 1.96]	1.7** CI[0.34, 3.06]	
Annuity payment over 5 y	0.46 CI[−0.23, 1.14]	0.95 CI[−0.26, 2.15]	
Total amount of monetary incentive:			40%
No monetary incentive	−4.96 CI[−8.8, −1.13]	-	
$20 million	−2.69*** CI[−4.49, −0.88]	0.3 CI[−0.64, 1.23]	
$100 million	−1.2** CI[−2.34, −0.05]	2.51*** CI[0.68, 1.23]	
$500 million	3.2** CI[0.72, 5.69]	1.41** CI[0.26, 2.54]	
$1 billion	5.64*** CI[1.86, 9.42]	1.79** CI[0.02, 3.56]	
Market exclusivity extensions			11%
No extension	−1.46 CI[−2.73, −0.19]	-	
Extension for 1 y	−0.2 CI[−0.76, 0.36]	0.41 CI[−0.4, 1.22]	
Extension for 3 y	0.1 CI[−0.5, 0.72]	1.46*** CI[0.4, 2.51]	
Extension for 5 y	1.55** CI[0.2, 2.9]	1.17** CI[0.19, 2.2]	
Transferable exclusivity extensions			28%
No extension	−4.02 CI[−7.31, −0.72]	-	
Extension for 6 mo	−0.7** CI[−1.25, −0.14]	0.54 CI[−0.11, 1.2]	
Extension for 12 mo	1.42*** CI[0.4, 2.44]	1.2** CI[0.11, 2.3]	
Extension for 18 mo	3.29** CI[0.56, 6.02]	3.74*** CI[1.21, 6.28]	
Priority review vouchers			5%
No priority review vouchers	−0.62 CI[−1.1, −0.14]	-	
Priority review vouchers	0.62** CI[0.14, 1.09]	0.06 CI[−0.26, 0.38]	

*$P < 0.10$
** $P < 0.05$
*** $P < 0.001$Pseudo R-square: 0.344Log-likelihood: −272.73

dents. If the standard deviation of an attribute or level is significantly different from zero, then this indicates a significant preference heterogeneity. Normal distributions were used for all attributes. A panel model was used to consider that each participant answered 12 choice sets.

In addition, the conditional relative importance of each attribute was calculated using the range method. In this method, one first measures the difference between the highest and lowest coefficient of the level of one specific attribute. Then, the attribute-specific level range is divided by the sum of all attribute level ranges, providing the value of the conditional relative importance [13]. A subgroup analysis including only participants from the pharmaceutical industry was also conducted. Furthermore, the frequency with which participants chose a certain incentive and amount was examined using Microsoft Excel, by calculating the average Likert-scale score per incentive.

3. Results

A total of 53 questionnaires were completed. In three, the participants failed the dominance test and were therefore excluded. A total of 50 questionnaires were thus included in the analysis. Of the participants, nine worked at an SME pharmaceutical company (fewer than 250 employees), 15 were from large pharmaceutical companies (more than 250 employees), 13 were academics, three were nonacademic clinicians, four were policy makers, and six indicated “other.” The majority of participants were active in the European Union (n = 25), 20 in the United States, and the other five respondents indicated “UK” or “other.”

3.1. Participants’ preferences

The results of the random parameter logit model are presented in Table 2, and the coefficients are further illustrated in Fig. 2. As expected, participants preferred larger amounts of monetary rewards and longer TEEs terms over the other options given. The most preferred levels (associated with the highest coefficients) were, in order of preference, *$1 billion as total amount of incentives* (5.64; CI [1.86–9.42]), *transferable exclusivity extension for 18 months* (3.29; CI [0.56–6.02]), and *$500 million as total amount of incentive* (3.20; CI [0.72–5.69]). For the attribute *form of monetary incentive*, the level with the highest coefficient was early-stage research grants (2.30; CI [0.3–3.96]).

The attributes whose levels showed a significant difference from one another were: total amount of monetary incentive, transferable exclusivity extension, and priority review vouchers. For the attribute total amount of monetary incentive, the levels no monetary incentive (95% CI; −8.80 to −1.13), $20 million (−4.49 to −0.88), and $100 million (−2.34 to −0.05) had a significant difference from the levels $500 million (0.72–5.69) and $1 billion (1.86–9.42). Of the attribute transferable exclusivity extensions, the levels no extension (−7.31 to −0.72) and 6 months (−1.25 to −0.14) overlapped with each other, and the levels 12 months (0.40–2.44) and 18 months (0.56–6.02) overlapped. The CI did not overlap for the levels of the attribute priority review vouchers.

When looking at the relative importance of each attribute, total monetary reward (40%) was considered as the most important aspect followed by transferable exclusivity extension (28%) and then form of monetary incentive (16%). Additionally, each attribute had at least one level with a significant standard deviation, which indicates that variations exist in preferences among participants.

When looking at what monetary amount is most feasible to be implemented, the majority of participants chose the amount of $500 million (36%), followed by $100 million (30%). Participants were then asked to rate the feasibility of the following incentives being implemented within 5 years on a Likert scale, with one being “not very likely” and seven being “very likely.” The average Likert scale score for the feasibility of specific incentives being implemented within the next 5 years was as follows: milestone monetary reward (4.90), priority review voucher (5.00), market exclusivity vouchers (4.66), annuity payments over 5 years (4.54), one-time payment after market approval (4.26), and transferable exclusivity extensions (4.02).

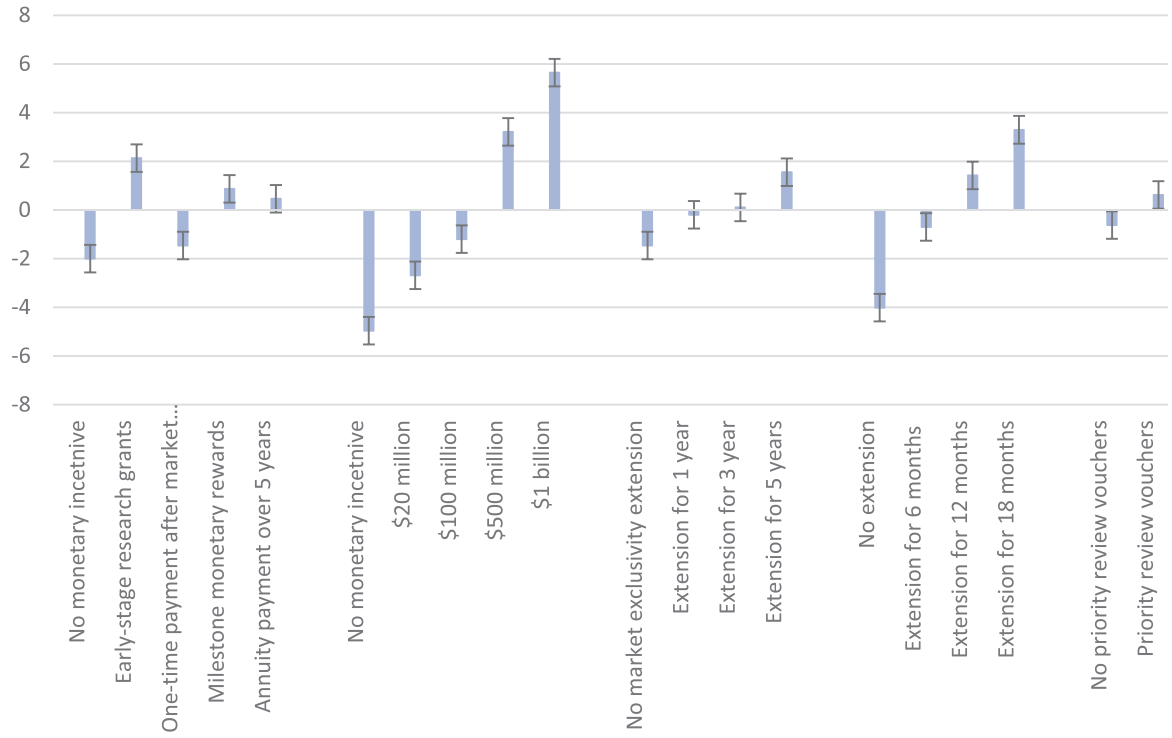

Fig. 2. Participant's preference coefficients.

Table 3
Subgroup analysis of the pharmaceutical industry (n = 24)

Attributes and levels	Coefficient	Standard deviation	Conditional relative importance
Form of monetary incentive:			8%
No monetary incentive	−0.53 (−2.01, 0.95)	-	
Early-stage research grants	1.45* (−0.12, 3.02)	0.67 (−0.59, 1.94)	
One-time payment after market approval	−1.97*** (−3.39, −0.55)	0.77 (−0.36, 1.9)	
Milestone monetary rewards	0.51 (−0.43, 1.46)	0.1 (−0.53, 0.72)	
Annuity payment over 5 y	0.54 (−0.37, 1.45)	0.52 (−0.73, 0.83)	
Total amount of monetary incentive:			42%
No monetary incentive	−3.92 (−6.37, −1.46)	-	
$20 million	−2.49*** (−4.15, −0.84)	2.26** (0.03, 4.48)	
$100 million	−1.03* (−2.07, 0.01)	1.15*** (0.35, 1.95)	
$500 million	1.25** (0.21, 2.29)	1.97** (0.22, 3.72)	
$1 billion	6.19*** (2.97, 9.4)	3.03*** (1.38, 4.67)	
Market exclusivity extensions			9%
No extension	−0.99 (−2.09, 0.1)	-	
Extension for 1 y	0.19 (−0.5, 0.88)	0.19 (−0.69, −1.06)	
Extension for 3 y	−0.37 (−1.3, 0.56)	1.6*** (0.55, 2.65)	
Extension for 5 y	1.18** (0.14, 2.23)	0.72* (−0.18, 1.59)	
Transferable exclusivity extensions			38%
No extension	−4.89 (−7.48, −2.31)	-	
Extension for 6 mo	−0.43 (−1.25, 0.39)	0.3 (−0.73, 1.33)	
Extension for 12 mo	0.98** (0.09, 1.87)	0.59 (−0.62, 1.8)	
Extension for 18 mo	4.35*** (2.17, 6.52)	2.73*** (1.31, 4.15)	
Priority review vouchers			3%
No priority review vouchers	−0.34 (−0.83, 0.15)	-	
Priority review vouchers	0.34 (−0.15, 0.83)	0.66*** (0.2, 1.12)	

* $P < 0.10$
** $P < 0.05$
*** $P < 0.001$Pseudo R-square: 0.40Log-likelihood: −119.63

3.2. Subgroup analysis

The subgroup analysis of the pharmaceutical company participants comprised 24 responses. The results are reported in Table 3. Similar to the full sample size, the levels with the highest coefficient were total amount of monetary incentive $1 billion (6.19) and transferable exclusivity extension for 18 months (4.35). Compared with the full sample, the attributes *total amount of monetary incentive* and *transferable exclusivity extension* were more important (42% vs. 40%, 38% vs. 28%). Furthermore, the pharmaceutical company participants did not view the other attributes as being very important.

When asked what incentive is most likely to be implemented within the next 5 years, results were similar between the pharmaceutical industry subgroup and the full sample. The subgroup viewed milestone monetary rewards (4.96) and transferable exclu-

sivity extension (3.67) as being the most feasible. The other incentives had the following Likert scale scores: one-time payment after market approval (4.29), annuity payments over 5 years (4.29), market exclusivity vouchers (4.33), and priority exclusivity vouchers (4.67).

4. Discussion

This study investigated certain stakeholder preferences regarding specific attributes of incentives to promote antimicrobial therapeutic R&D. The most important attributes for survey participants were the total amount of the monetary incentive and TEE.

Based on earlier literature findings, a monetary reward was anticipated to rank highly, but our study results provide new insights into the relative value of award timing. Survey participants preferred earlier monetary awards over later ones, which could indicate the desire to de-risk investment in development. Early-stage research funding supports small companies and research institutions to start developing new drugs, and this type of incentive has led to around 300 small companies entering the field of antimicrobial R&D [17]. It is also one of the most effective ways of promoting research and increasing the total body of knowledge in a research area fast. This, however, may not translate into further attempts at commercialization unless the economic environment offers a higher degree of certainty for generating returns. When looking at only the responses of the pharmaceutical company representatives, preferences on early research grants ranked lower than in the full cohort. However, another reason why early-stage research grants are preferred could be that many of the participants were academics who would benefit from research grants and therefore also view this as one of the most effective ways of promoting research. Often, academic research requires funding from external organizations, and if more funds are available more research can be undertaken. This argument is further supported by the fact that when looking at the responses of the pharmaceutical company representatives, preferences on early research grants ranked lower than in the full cohort.

Early-stage research grants would not address the underlying issue of companies' inability to make a return on their investment in antibiotics, as was the case with Achaogen. It is estimated that for a company, basic operations and meeting regulatory commitments during the first 10 years costs $350 million, but including stewardship programs, development risks for further studies, and market or regulatory delays, the real cost is likely to be $450 million and above [17]. Additionally, there is a very high failure rate during development: it is estimated that only 1.5% to 3.5% of antibiotics make it from early research to marketing authorization [8,18]. This failure rate can result in many of the early-stage research grants funding research that in the end will not lead to a marketable drug. There need to be incentives that support the few drugs that get past the development phase and reach the market.

The second most preferred incentive is a TEE of 18 months. A TEE allows companies to transfer the exclusive selling right, and therefore protect their business from generics, for an additional 18 months. In case of no drugs to transfer it to, a developer can sell the right and receive a cash return. It allows a company to capture a net return of investment through sales of another drug and does not require direct cash funding for antibiotics. A TEE voucher is anticipated to be worth $1 billion or more and make up for the expenses incurred during the development of a series of antimicrobial compounds that may lead to a successful product [19]. However, this can vary from study to study. A retrospective modeling study found that a median gain was $187 million, but the exact value is heavily dependent on which drug the voucher is transferred to [20]. Considerations of cost-effectiveness of the incentive should include the notion of value, estimated at $29 billion in the United States alone looking at the current burden of disease [21]. However, participants considered TEEs not very feasible to be passed within the next 5 years. The reason for this might be that a bill to enact TEE in the United States (REVAMP Act) was introduced in 2018, but it never advanced to a vote. It has not been reintroduced.

The incentive that was deemed by participants as being the most feasible was the milestone monetary reward. The reason for its high feasibility is most likely that milestone monetary rewards do not only benefit larger pharmaceutical companies but also SMEs, making it very attractive for a variety of stakeholders. Annuity payments were not seen to be as feasible as milestone rewards, even though there are already forms of annuity payments being piloted as contractual agreements.

A milestone monetary reward would support and immediately compensate researchers and developers at each phase of R&D, rewarding the significant investment required to complete each step in the antimicrobial's development and allowing continuation to the next phase. Thus, if the drug fails to attain market approval, at least some of the R&D costs are covered. Additionally, these monetary rewards could be used to fund the next steps to reach the next milestone and might be deemed a more predictable funding mechanism. Such risk-sharing arrangements lower the barriers to start development projects and positively impact net present value (NPV) calculations and support continued financing of the development programs [22]. According to Simpkin et al [22]., there is a need for continuous funding of the antimicrobial product line and not just at the very beginning. Milestone monetary rewards can be applied by small research institutions and large pharmaceutical companies without favoring one over the other [9]. However, our results showed that the pharmaceutical industry respondents seemed to view milestone monetary rewards as not having a high utility. A reason for this might be that large pharmaceutical companies often acquire mature drugs that are already in phase 1 or phase 2, and therefore would rarely make use of milestone rewards, and therefore they are more focused on incentives in the commercial stage.

Participants indicated that the most feasible amount a monetary incentive would have is $500 million. However, according to previous research this amount would still be insufficient and $1 billion or more is needed to properly stimulate R&D [2,23]. Considering this, TEE would be more effective than monetary incentives because the direct payments would presumably not be high enough. The pharmaceutical industry respondents perceived that the most likely amount to be implemented within the next 5 years is $100 million. This indicates that the pharmaceutical industry respondents are not very optimistic regarding the antimicrobial incentives, which is probably why many companies have exited the field.

There are some limitations to this study. First, although most coefficients were statistically significant, the sample size was small. One reason for a low response rate is that the target population was rather specific and small, because not many academics and pharmaceutical employees are active in the field of antimicrobials. In addition, participants are often very busy and have a tight schedule, which makes it difficult for them to take the time to fill out the survey. This could lead to the sample not being representative of the target population. That is why the survey was kept short, so that participants could participate without spending a lot of time. Furthermore, because participants were able to volunteer to take the survey there was a possibility of self-selection bias. That is why this study included a variety of stakeholder groups that were expected to have different preferences regarding the incentives.

Another limitation is that there is a plethora of different incentives aimed at promoting antimicrobial R&D, making it unwieldly

to include all the incentives in the DCE. However, a strong methodology was followed to select the most important and relevant attributes in the study. A further limitation is that the survey only solicited preferences relative to the options given and did not allow participants to include their preferred incentive if not included in the DCE. Additionally, the way an incentive is implemented often determines its effectiveness but a DCE does not allow for this sort of detail, looking rather at whether the general idea of the incentive is preferred. Consequently, the study only identified the most preferred incentives relative to the options given. More research would be needed on the implementation aspect of each incentive option.

5. Conclusion

To fight against AMR, a stable antimicrobial drug pipeline needs to be obtained. One way this could be achieved is through the implementation of new incentives. This study revealed that stakeholders have preferences for longer TEEs and higher monetary amount. These preferences could help in designing appropriate incentives to promote antimicrobial R&D and bring pharmaceutical companies back into the field, although further work needs to be conducted regarding the specific incentives and how they would be implemented.

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