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Economic incentives for the development of new antibiotics

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Authors:

Enrico Baraldi, Francesco Ciabuschi, Simone Callegari and Olof Lindahl (Uppsala University)

E-mail: enrico.baraldi@angstrom.uu.se

Contact person at the Public Health Agency of Sweden: Mats Hedlin

Executive summary

This report responds to a request by the Public Health Agency of Sweden (Folkhälsomyndigheten) concerning which incentives for antibiotics research and development (R&D) Sweden should take into consideration for potential public investments. Based on discussions and interviews with experts, feedback from stakeholders (i.e. potential recipients of Swedish incentives), company case studies and computer-based Monte Carlo simulations, this report provides a set of recommendations about the economic incentives that can be relevant for Sweden.

The incentives identified for Sweden's portfolio meet the following criteria: improving Sweden's visibility in the antibiotics field, reinforcing Sweden's national R&D infrastructure in this area, leveraging Sweden's strengths and traditions, limiting the public expenditure per incentive, permitting rapid implementation and effects, providing highly needed support to the antibiotic pipeline in unique ways, and granting Sweden a key contribution and thus influence on the design and direction of each incentive.

Based on these criteria, a **Market Entry Reward** (MER) was not considered a viable alternative for Sweden if implemented by Sweden alone, especially because of its demanding financial engagement (close to 1 B USD), which is necessary for this incentive to produce relevant effects on the antibiotics R&D pipeline. However, if Sweden were to decide to pilot an MER, it should focus on a fully delinked MER, which entirely substitutes market sales with lump sums paid on a yearly basis. An MER should moreover be financed primarily from the healthcare budget to avoid crowding out other incentives. A fully delinked MER would allow testing several features of this incentive model, such as the evaluation procedures to set the overall amount of the MER, the definition of the unit prizes to be paid by local healthcare facilities to the central government, and periodic reviews to reassess the amount of yearly lump-sum payments according to the confirmed therapeutic efficacy of the antibiotic.

If Sweden were to collaborate with other countries, such as the G20 group or the 28 EU members, a reasonable amount for its share is 6 or 23 M USD, respectively, for a partially delinked MER and 9 or 34 M USD, respectively, for a fully delinked MER. There are, however, ways to combine push and pull incentives, which are quicker and more efficient than an MER, namely combinations of grants with milestone prizes, which are rewards paid to developers upon the successful completion of key R&D steps (e.g. Phase 1 clinical studies). In addition to producing better effects for the money spent, a combination of milestone prizes and grants also prevents large MERs from crowding out push investments as well as recipients such as small- and medium-sized firms (SMEs), who usually cannot wait for a reward that is delayed until the final approval of an antibiotic.

The recommended portfolio of incentives for Sweden includes three incentives: **grants**, **milestone prizes** and **Pipeline Coordinators**, to be used in combination with each other as a way to cover the antibiotics R&D pipeline and achieve important synergies. The following features should be considered when implementing and funding the three selected incentives:

1) Grants should be dedicated to early R&D projects (no later than Phase 2) and to reinforcing the national R&D infrastructure, with a longer-term perspective than the current 3-year timeframe. In this regard, Sweden should maintain and possibly increase its current yearly investments in antibiotics R&D grants of approximately 7 M USD/year (60 M SEK) over several years. These investments will pay off in the long run, both in terms of molecules that will enter the future R&D pipeline; and as a stock of competencies spread over an infrastructure of specialised R&D centres that can be leveraged

for future antibiotics research. These competences must be built up immediately and the seeds for future R&D projects need to be planted as soon as possible.

2) Two types of milestone prizes should be in focus for Sweden: first, a prize awarding a sum between 10 and 20 M USD at the **end of Clinical Phase 1** to highly innovative molecules addressing specific pathogens and, second, a prize for projects successfully **completing preclinical steps**. Establishing a prize at the end of Clinical Phase 1 is a much needed and unique initiative, with significant effects on the early R&D pipeline, granting also strong international visibility to Sweden. Sweden could also take major responsibility for such a milestone prize by covering a relatively large share. The other recommended milestone prize, awarded at the end of the preclinical steps, would help refill the clinical pipeline and would therefore have more of a long-term effect.

3) Pipeline Coordinators, that is, organizations that take an active role in selecting and supporting a portfolio of antibiotics R&D projects in various ways, are the last recommended incentive. Selecting among currently existing Pipeline Coordinators rather than creating a new one, Sweden should fund two types of such organizations: **R&D Collaborations,** which create collaboration platforms to perform early development activities for the antibiotic projects they support, and **Non-Profit Developers**, who conduct their own antibiotic projects with the aim of bringing antibiotics to market but without pursuing profit goals. The first type of Pipeline Coordinator, R&D Collaborations, is relevant for a Swedish public investment because they are potentially the most efficient incentive in making R&D projects profitable. However, to fully exploit this potential, R&D Collaborations must be refined to become more flexible, reduce bureaucratic burden and avoid conflicts between participants.

Non-Profit Developers provide the most extensive support to selected products by intervening across the entire antibiotic pipeline to ensure products reach the market. Moreover, this model strongly promotes both global availability and responsible use (stewardship). Therefore, Sweden may fund Non-Profit Developers through its international aid budget and in this way make important contributions to global health.

Both types of Pipeline Coordinators also offer the advantage that they can help connect Swedish antibiotics R&D centres to international platforms, which reinforce the effects of infrastructure-related grants. Moreover, all forms of Pipeline Coordinators are incentive models that can be used as tools to manage the other two incentives (grants and milestone prizes). In this capacity, they can, for instance, evaluate grant applications and the antibiotic projects eligible for milestone prizes, which require a deep insight into the details of a drug development project.

A fourth model, regulatory simplifications, which radically cut costs and times for Clinical Phase 3, can also be relevant for Sweden due to its contained costs, rapid implementation and effects and connection with Sweden's expertise. However, this incentive requires further analysis to fully grasp its implications for regulators and patient safety before being recommended for implementation.

The three incentives recommended by this report – grants, milestone prizes and Pipeline Coordinators – should be used in combination to exploit the synergies between them and their ability to push and pull molecules in different phases of the R&D pipeline. For instance, when grants and milestones are used together, the public investment per approved new antibiotic is lower than the combined spending if the two incentives were used in isolation. If it is not possible to introduce and use the three incentives simultaneously, the following priorities should be applied: first of all, grants need to be kept at current levels and possibly increased to fund both single antibiotic projects and competence development in the R&D infrastructure, while starting to invest in a Non-Profit Developer and a milestone prize at the end of Phase 1, followed by the development and funding of R&D Collaborations and, finally, a preclinical milestone prize.

Contents

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Key terms and concepts

Grants (research grants): Grants refer to funds (for example, scholarships) made available to developers of new antibiotics for the purpose of paying all or part of the costs of certain research and development activities, such as development costs for a particular clinical phase.

ENPV (Expected Net Present Value): A measure of an investment's profitability that calculates the present value of a project's future costs and revenues through a certain discount rate and takes into account the likelihood that a project will progress through the various R&D phases (see formula in Appendix B).

Efficacy: A measure of an incentive's effect that captures the improvement in the number of profitable R&D projects linked to a certain incentive model.

Efficiency: A measure that relates an incentive's cost to a certain improvement, such as a doubling of the number of profitable R&D projects.

R&D centres: Organizational units and laboratories in academia and other institutions possessing specialized expertise in research and development of antibiotics.

Delinkage: Delinkage is a feature of incentive models that means that an R&D reward disconnects the developer's revenues from the future sales of the developed antibiotics. This is important in the field of antibiotics because uncontrolled sales of new drugs may increase the risk of resistance development.

Market Entry Reward (MER): An MER is an innovation award for a new antibiotic with a certain profile. It is paid to, for example, the first new antibiotic with this profile in instalments over the first 5 years after the antibiotic has been released on the market. An MER can be fully delinked (FD) or partially delinked (PD).

Milestone prizes: Milestone prizes are an incentive that rewards development projects for successfully completing a specific preclinical or clinical phase. A milestone prize is paid after the preclinical or clinical phase in question is completed and can cover significantly more than the cost of this phase.

Partial delinkage: Partial delinkage is a feature of incentive models by which the reward for an innovation is only part of how developers can earn back the costs they incurred in R&D. This generally leads to the incentive amount being lower compared to 'full delinkage', but direct sales are allowed.

Pipeline: What is referred to in the report as a 'pipeline' is the current population of ongoing projects in the field of antibiotics and how they are spread over the different R&D phases (preclinical, Clinical Phase 1, Phase 2 and Phase 3). For a new antibiotic to evolve all the way from idea to approved drug, it is necessary for it to pass through a series of development phases often referred to as a pipeline.

Pipeline Coordinator: A Pipeline Coordinator is a public or non-profit organization that closely monitors the development of antibiotics, identifies gaps in the pipeline and actively supports (or directly conducts) R&D projects to fill these gaps with considerable flexibility in terms of tools and solutions applied. Usually, Pipeline Coordinators involve both public and private actors in various forms of collaboration.

Pull incentives: A pull-based model rewards developers for an accomplished result (e.g. the launch of a new antibiotic or successful test results). The developer bears the risk of losing his investment but his activity becomes more valuable if it succeeds.

Push incentives: A push-based model (such as a research grant) supports developers by partly or entirely covering the costs of an activity. A push-based model lowers the costs to carry out an activity and the risk of losing the investment in the absence of results is borne by the payer.

Full delinkage: Full delinkage is a feature of incentive models by which the reward for an innovation is formally and totally disconnected from the sale of the developed antibiotic. Therefore, direct sales of the new antibiotic are not permitted.

Simulation: Monte Carlo is a mathematical computer-based simulation that, through thousands of runs and reality-based input values, calculates probabilities and answers questions such as 'What improvement in ENPV can be achieved through a milestone prize?' or 'What public investment in grants is needed to get a new antibiotic approved?'

Small and medium-sized enterprises (SMEs): Companies with fewer than 250 employees and less than 50 M Euro in turnover, which often conduct projects in early R&D phases.

Stewardship: Responsible use of antibiotics, which includes prescribing the right antibiotic for the right infection.

1. Introduction

In October 2017, after considering the global threat of antibiotic resistance (AMR) and the current lack of new antibiotics, the Swedish Government tasked the Public Health Agency of Sweden (Folkhälsomyndigheten) to suggest how Swedish actors can support incentive models to stimulate the development of new antibiotics. The key problem is that developing new antibiotics is scientifically challenging and economically unprofitable, which has resulted in most of the large pharmaceutical companies leaving this field. Consequently, today there are too few antibiotic projects in the pipeline that can address future needs[1]. During the last 5 years, several experts and policy analyses have suggested that this market failure should be addressed by awarding antibiotics developers some kind of incentive that can turn the development of new antibiotics into a profitable business. In turn, in May 2018, the Public Health Agency of Sweden commissioned Uppsala University to investigate the kinds of economic incentives previously discussed in many international fora and reports that could be relevant for Sweden[2]. Therefore, the aim of this report is to identify, analyse and suggest a portfolio of push, pull and collaborative incentives that Sweden may support and introduce. Moreover, this report aims to specify how different stakeholders may react to these incentives, considering explicitly small and medium-sized enterprises (SMEs), which conduct most of the antibiotics R&D, especially in early phases[3].

Delimitations

When discussing with experts and analysing the many available incentive models[4], the focus has been on how Sweden can practically approach the various incentives, depending on their amount and time perspective. The selection of the portfolio of incentives proposed in this report is accordingly based on time and budget constraints, relevance for Sweden, synergies between the incentives (i.e. how they complement each other) and their effects on the various stages of the R&D pipeline (i.e. on projects that have reached different stages). Other criteria applied in selecting incentives were their visibility, uniqueness, coverage of a need in antibiotics R&D, and Sweden's contribution and influence on each model. Additional criteria considered were an incentive's impact on stewardship (rational antibiotic use) and the resulting drug's accessibility for patients (especially in low-income countries).

The incentive effects analysed in this report are delimited to improvements in the financial profile of an antibiotic project. A key assumption is thus that a developer chooses to continue or terminate a project only based on its profitability. Moreover, most incentives discussed in this report are still in the design and refinement stages, with a few undergoing testing. Therefore, further analyses and pilot testing will be necessary for any incentive model before it can be implemented.

[1] See Pew Charitable Trust, *Antibiotics Currently in Clinical Development*, 2017

[2] See, for instance, Outterson, K., *New Business Models for Sustainable Antibiotics*, Chatham House, 2014; The Review on Antimicrobial Resistance (AMR Review), *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, 2016; The Boston Consulting Group, *Breaking through the Wall: A Call for Concerted Action on Antibiotics Research and Development*, 2017; and DRIVE-AB Report, *Revitalizing the Antibiotic Pipeline*, 2018.

[3] Theuretzbacher, U., Market watch: Antibacterial innovation in European SMEs, *Nature Reviews Drug Discovery*, Vol. 15, 2016.

[4] For a list of 35 incentive models, see Appendix in DRIVE-AB Report, 2018.

Methodology

This investigation was conducted by a team at Uppsala University composed of Prof. Enrico Baraldi, Prof. Francesco Ciabuschi, Dr. Olof Lindahl and Dr. Simone Callegari. The work has been organized along the following seven activities:

1) Mapping the Swedish actors involved in antibiotics R&D to identify which academic units and companies are currently active in this area.

2) International comparison of Sweden's public investments in antibiotics R&D to identify Sweden's role and opportunities in supporting antibiotics R&D in the global arena, including a reasonable amount for Sweden's investments.

3) Swedish/Nordic expert panel: in June 2018, seven Swedish and Nordic experts (see list in Appendix A) gathered to discuss Sweden's role in supporting antibiotics R&D and the incentives that could be selected from a list of ten to be included in Sweden's arsenal (see Chapter 2 for details).

4) Interviews with international experts: to take an international perspective on Sweden's role and its opportunities in supporting antibiotics R&D, interviews were conducted with nine leading international experts (and one Swedish expert) in the areas of global health, international health policy, health economics, management, antibiotic development and law (see list in Appendix A).

5) Interviews and discussions with stakeholders: the same incentives discussed with the previously mentioned experts were also discussed with representatives of three groups of stakeholders who may be the recipients of Swedish incentives, namely SMEs (via their European association, the BEAM Alliance), large pharmaceutical firms (via the Swedish Association of the Pharmaceutical Industry, LIF) and public R&D organizations, including Pipeline Coordinators[5]. The discussions and analyses with the experts and stakeholders (activities 3, 4 and 5) led to the selection of seven incentives that were then simulated with a large population of virtual projects (activity 6) and concretely assessed through case studies with current antibiotic developers (activity 7).

6) Computer-based simulation of the incentives' effects: a Monte Carlo simulation created a variation in the ENPV (Expected Net Present Value), which is a formula used in the pharmaceutical industry to measure the profitability of antibiotics R&D projects and to decide whether to continue or terminate a project at the start of every R&D phase. To gauge how ENPV and, consequently, a project's profitability improves due to the various incentives, 50,000 virtual projects were generated. The necessary public investments for the various incentives were also calculated to compare their efficiency (see Section 3.1 for details and Appendix B for the input parameters applied in the ENPV formula).

7) Case studies of current antibiotics R&D projects: these analyses complement the general and average effects that can be measured in the simulation's large project population (activity 6) because they reveal how certain particular SMEs and large companies still active in this field would react to the same incentive, considering the R&D phase in which they currently operate. A sample of four companies (two SMEs and two large firms; two with early- and two with late-stage development projects) considered the same incentives, which were simulated during activity 6, and decided whether each of them offered sufficient economic simulation to continue their project or not. The four companies also indicated how high the various incentives needed to be to continue to the next decision

[5] Pipeline Coordinators are new organizations usually created with public funds with the purpose of connecting several public and private actors to improve the coordination of activities within international antibiotic R&D. For more information, see DRIVE AB Report, 2018, and Baraldi, E., Lindahl, O., Savic, M., Findlay, D. & Årdal, C., Antibiotic Pipeline Coordinators, *Journal of Law, Medicine and Ethics*, Vol. 46 S1, pp. 25–31, 2018.

point in their project (see Section 3.2). Thus, the cases offer an important reality check of various incentives by considering how actual companies would react to specific incentives.

Sweden's role and investments addressing AMR and antibiotics R&D

Sweden has historically had a major role in the fight against AMR, making it a key issue during the Swedish EU Presidency in 2009, when the very first study on incentives for antibiotics R&D was commissioned[6]. Sweden is also among the most advanced countries in the area of antibiotic rational use and stewardship. Globally, Sweden plays a major role in the GLASS system, which monitors resistance outbreaks and development, and the funding organization JPIAMR (Joint Programming Initiative on Antimicrobial Resistance), which it helped start and currently hosts. Research within AMR and antibiotics is conducted at several Swedish universities and institutes, such as RISE, Lund University, Karolinska Institute, Umeå University, Gothenburg University and Uppsala University, which is also the host of the R&D collaboration platform ENABLE, financed by the EU program Innovative Medicines Initiative (IMI). However, there are currently only four Swedish SMEs with active new antibiotic development projects and these are all in the earliest R&D phases.

Between 2009 and 2018, Sweden invested about 144 M Euro in nationally funded R&D projects[7] in the broader area of AMR, of which about 42 M Euro were specifically dedicated to antibiotics development. As Sweden also contributed to funding antibiotics R&D within international programs, such as JPIAMR and IMI's ND4BB (New Drugs for Bad Bugs), at an estimated 13 M Euro, the Swedish total public investment in the last 9 years or so amounts to approximately 55 M Euro[8]. Therefore, Sweden's public average investments in antibiotics R&D are about 6 M Euro per year (corresponding to 60 M SEK/year or 7 M USD/year). These investments are mainly in grants, that is, a form of *push* incentive. Sweden invests a minimal share of these yearly 6 M Euro (estimated at about 0.3 M Euro/year, based on a total 6-year investment of 1.8 M Euro) indirectly in IMI's international project ENABLE, which is an incentive belonging to the Pipeline Coordinators category (see Section 2.2). However, Sweden has not yet made any investments in *pull* incentives, such as milestone prizes or Market Entry Rewards (MERs).

This report includes three chapters. Chapter 2 presents the three incentives that are proposed for Sweden's portfolio to stimulate antibiotics R&D. Chapter 3 discusses and analyses the effects of these incentives based on simulations and case studies, as well as their pros and cons. Finally, Chapter 4 summarizes the report and offers recommendations on the three proposed incentives.

[6] Mossialos, E., Morel, C. M., Edwards, S., Berenson, J., Gemmill-Toyama, M., & Brogan, D., *Policies and Incentives for Promoting Innovation in Antibiotic Research*, European Observatory on Health Systems & Policies, 2010.

[7] Grants from the following Swedish funders: VR, Vinnova, Formas, Forte, SSF, Energimyndigheten, Ragnar Söderberg and Riksbankens Jubileumsfond. Source: www.swecris.se

[8] For details on these figures, see Section 2 in the Swedish version of this report: Baraldi, E., Ciabuschi, F., Callegari, S., & Lindahl, O., *Ekonomiska Incitamentsmodeller för Utveckling av Nya Antibiotika*, Uppsala Universitet, 2018.

2. Presentation of the incentives proposed for Sweden

This chapter reviews and discusses the three incentives – grants, milestone prizes and two versions of Pipeline Coordinators – that are proposed as relevant for Swedish investments to stimulate antibiotics R&D. Section 2.1 describes how these three models were selected in cooperation with a group of Swedish and international experts in the areas of antibiotic resistance, antibiotics R&D, global health and incentives for R&D. Next, Section 2.2 presents each of the three incentives and describes how they were designed based on the experts' suggestions. Here, we introduce a fourth incentive model – regulatory simplifications – which can be potentially relevant for Sweden but needs to be examined further before being recommended. Finally, Section 2.3 summarizes this arsenal of incentives and explains how they complement each other.

2.1 Expert group discussions on ten incentive models

To support the selection of incentive models presented in Section 2.2, 17 Swedish and international experts (see details in the Introduction and Appendix A) discussed whether the ten models under review could be considered relevant for Sweden to stimulate antibiotics R&D[9]. These ten models were: (1) grants, (2) fully delinked MER, (3) partially delinked MER, (4) milestone prizes, (5) increased unit prices of sold antibiotics, (6) regulatory simplifications (which were not included in the original proposal but were suggested by experts in a panel discussion) and four variants of Pipeline Coordinators (PiCoor), namely (7) an 'Accelerator' PiCoor, which focuses on providing counselling and funding for preclinical or Phase 1 studies, (8) an 'R&D Collaboration' PiCoor, which creates a collaboration platform through which early R&D studies are conducted for the benefit of its members, (9) a 'Non-Profit Developer' PiCoor, which manages its own R&D projects for non-profit purposes, and (10) a 'Public R&D Procurer' PiCoor, acting as a governmental client for, and/or performer of, R&D activities if no private actors are interested in conducting complete R&D projects (from early phases to market approval).

To evaluate the ten incentive models in discussions with experts, which were followed by conversations with stakeholders (i.e. representatives of small and large pharmaceutical companies, academics and representatives of existing Pipeline Coordinators), certain criteria were considered that could make the models more or less attractive for Sweden. In addition to the basic idea that an incentive should be relevant for Sweden, the criteria included the following: (1) amount of necessary investment and thus possible budget constraints; (2) turnover time, which refers to the time it takes to introduce and generate the intended effects and hence temporal constraints; (3) global public visibility of incentives; (4) uniqueness, which means that an incentive is currently absent; (5) needs, which indicates that an incentive tackles an important barrier in antibiotics R&D; (6) Swedish contribution, which means that Sweden has an opportunity to play a decisive role in the incentive when operational; (7) complementarity, which refers to the current effects of various incentives on different parts of the R&D pipeline; and (8) stewardship and access, two central aspects involved in dealing with antibiotic resistance.

Based on these criteria, the evaluation led to the elimination of five incentive models: MERs (both partially and fully delinked), increased unit prices and Pipeline Coordinators devised as 'Accelerators' and 'Public R&D Procurers'. The MERs were excluded by experts mainly because they demand at

[9] These models are taken from the long list (35 models) of the DRIVE-AB project. See Appendix B, pages 81–93 DRIVE-AB Report, 2018.

least 1 B USD[10], which makes it impossible for Sweden alone to guarantee their funding. In addition, in international cooperation with the G20 or EU, the Swedish contribution (respectively, 6 or 23 M USD for a partially delinked MER and 9 or 34 M USD for a fully delinked MER) would be limited to a few percent of the total amount of an MER and therefore would not allow Sweden to play a decisive role. Furthermore, an innovation-promoting MER would take several years to produce the desired effect and thus have a turnover that does not increase Swedish visibility in the field in the near future. However, if Sweden still chooses to conduct an MER pilot study, several experts suggested that this should be done with full delinkage, as this would align with Sweden's involvement in stewardship issues. Moreover, an MER should be financed from the healthcare budget to avoid crowding out other incentives, such as grants, if funds were to be taken from the national research and innovation budget. A fully delinked MER would allow testing several features of this incentive model, such as the evaluation procedures to set the overall amount of the MER, the definition of the unit prizes to be paid by local healthcare facilities to the central government, and periodic reviews to reassess the amount of yearly lump-sum payments according to the confirmed therapeutic efficacy of the antibiotic.

Increased unit prices were eliminated because most experts estimated that an increase in prices in Sweden alone would not generate sufficient revenues to motivate antibiotic developers to start or continue an R&D project, as the Swedish market is too small in terms of sold volumes. Hence, a price increase aimed at stimulating R&D would only result in increased costs for Swedish healthcare, as well as possibly negative consequences for access to antibiotics. The Accelerator PiCoor was excluded even though it was found to be of interest according to many of the established criteria (e.g. being a reasonable investment, having fast turnaround and meeting high demand), mainly because significant international funding for this kind of Pipeline Coordinator began in 2017[11]. Because of this, a Swedish contribution to an Accelerator PiCoor would not be decisive or create sufficient visibility for Sweden. Finally, the Public R&D Procurer PiCoor was dropped in discussions with the experts mainly because it was pointed out that what is really needed today is international cooperation, rather than an individual country, especially a small one such as Sweden, trying to take full responsibility for the entire development of an antibiotic. Some experts stated that a small country does not have the capacity and resources to implement this, especially considering the risk and costs involved, knowing that most early molecules in the R&D process will fail [12]. In other words, a Public R&D Procurer PiCoor would certainly create visibility as well as provide a unique and strong contribution but it would also pose a high risk and, ultimately, a likely unsustainable financial commitment for a small country. However, it was expressed that a small country's often specialized resources can greatly benefit from combining with other countries' resources in, for example, an R&D Cooperation PiCoor acting earlier in the pipeline or a Non-Profit Developer PiCoor acting throughout the entire pipeline.

Ultimately, this selection process left four incentive models that were considered relevant for Sweden to invest in and can increase visibility, strengthen the national infrastructure, allow for early implementation and are based on Sweden's strengths and traditions. These incentive models are grants, milestone prizes, and two variants of Pipeline Coordinators, namely R&D Collaboration PiCoor and Non-Profit Developer PiCoor. The fourth model, regulatory simplifications, might be

[10] See DRIVE-AB Report, 2018; Rex, J.H. & Outterson, K., Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach, *The Lancet Infectious Diseases*, Vol. 16, No. 4, pp. 500–505, 2016.

[11] CARB-X, the largest Accelerator in existence, has been awarded more than 500 M USD until 2021. See www.carb-x.org and CARB-X Annual Report 2017–18.

[12] Several experts assessed the Public R&D Procurer PiCoor as the last resort for R&D in antibiotics if all private actors were to withdraw. In addition, some company representatives expressed that such an incentive contradicts their business models because pharmaceutical companies do not perform contract research (as a CRO, Contract Research Organization, does) but aim to develop, license or launch to market their own products.

relevant after further analyses and discussions. These incentive models are described in more detail in the next section.

2.2 Three incentive models for Sweden: grants, milestone prizes and Pipeline Coordinators

Grants (push incentive)

Design and focus: According to the experts, it is important that the grants that Sweden invests in focus on building a research infrastructure and on early R&D phases, preferably preclinical research, where the greatest need exists to fill the antibiotic pipeline. In the current infrastructure, some of these grants should focus on rebuilding and strengthening a permanent base of research centres in Sweden with high specialization in selected areas of R&D on antibiotics (e.g. centres of excellence). Thus, these infrastructure grants should be investments of millions of Euro (tens of millions of SEK) per centre and extend over five to ten years, that is, be long-term oriented. Even grants to individual antibiotic projects should be early (around the preclinical phase) and long-term, that is to say, they can be spent over several years, longer than the current average of three to five years. In addition, the funding financed with grants should focus on important medical needs, such as the WHO's Priority Pathogen List[13]. Based on both expert discussions and company case studies (see Section 3.2), it was also estimated that a coverage ratio of between 50 and 80% of R&D costs should be sufficiently motivating for academic recipients as well as private recipients of these grants.

In summary, grants match several of the criteria set out: they are highly needed, may constitute a limited investment, can be implemented in the near future, can provide Sweden sufficient visibility even in view of its important role in international initiatives such as JPIAMR[14], and complement pull incentives (see Sections 3.1 and 3.4). An even more important point regarding the relevance of this incentive model for Sweden is the need for long-term initiatives to strengthen the Swedish R&D infrastructure for antibiotics, which is crucial for Sweden to be able to play a key role in this field in the future. This appears to be in line with the increased resources of approximately 60 M SEK (i.e. 6 M Euro) that the Swedish Research Council will award within the framework of the National Research Program on Antibiotics Resistance[15] in the coming 3 years. However, as previously mentioned, there is a need to build a longer-term program, which likely means devoting even more resources to the development of a Swedish R&D infrastructure.

Milestone prizes (pull incentive)

Design and focus: Milestone prizes are a pull incentive that is much lower than an MER; the experts therefore perceived them as less problematic to test. There are different ways to design milestone prizes but in the discussions with the experts, a variant was analysed according to which the developer would be awarded an amount equal to three times the R&D costs for the successfully completed phase in question. Such an amount was considered to not only cover costs but also provide a substantial profit that can be reinvested in the next phase or, more specifically, must be reinvested as a condition for receiving the milestone prize. Furthermore, it was considered relevant to allocate such prizes on three occasions relatively early in the R&D process, namely (1) at the end of preclinical studies (what

[13] http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/
[14] See www.jpiamr.eu
[15] https://www.vr.se/analys-och-uppdrag/nationella-forskningsprogram/antibiotikaresistens.html

we call a 'PC Prize'), (2) at the end of Clinical Phase 1 ('P1 Prize'), and (3) at the end of Clinical Phase 2 ('P2 Prize'). By multiplying the R&D cost parameters in the simulation by three (see Complementary Table 1 in Appendix B), the amount available at the end of the preclinical studies is approximately 29 M USD, at the end of Phase 1 is 24 M USD, and at the end of Phase 2 is 46.5 M USD.

A milestone prize at the end of Phase 3 was considered less interesting because an MER is more attractive at that stage of an R&D process, and it should be a possibly lower MER than the MER which needs to be promised to very early-stage projects. Some experts were even more precise and pointed out that the most attractive milestone prize should be given at the end of Phase 1, that is to say, the P1 Prize. However, it was considered more relevant to continue the analysis and simulations with all three types of milestone prizes (their prioritization scheme is shown in Sections 3 and 4). The previous amounts proved to be very attractive for smaller companies according to the responses from stakeholders as well as the case studies (see Section 3.2). Positive effects for the entire pipeline of these milestone prizes can also be seen in the simulation (see Section 3.1).

In summary, milestone prizes meet several of the criteria for selection of incentive models for Sweden. The costs fall within the budget framework, as they only represent a smaller proportion of an MER (24–46 M USD compared to around 1 B USD). Milestone prizes can be quickly implemented and generate effects over the course of a few years. They are seen as highly needed by SMEs, as well as in early R&D phases, in which milestone prizes provide a good complement to grants (see the simulation results on combinations of incentives in Section 3.1). Furthermore, these incentives are unique as they are not yet implemented and, due to their limited amount, would give Sweden the opportunity to make a decisive contribution to a particular milestone prize. Finally, Sweden would have high global visibility if the prize were to set up as what one international expert called 'The Swedish/Nobel Prize for Phase 1 Antibiotic Development'. In addition, this could be achieved with approximately 24 M USD, which was tested in the simulation, or only 10–15 M USD, which representatives of SMEs considered an attractive prize for completing Phase 1. In addition, this prize should primarily be devoted to the development of the most valuable molecules that are particularly innovative (e.g. new classes of antibiotics) and focus on those that address the WHO's priority pathogens.

Pipeline Coordinators (collaborative, push/pull incentive)

Design and focus: There are several Pipeline Coordinators already active in the antibiotic field, such as CARB-X (an 'Accelerator'), ENABLE (an 'R&D Collaboration') and GARD-P (a 'Non-Profit Developer')[16]. All these organizations are rather newly established or operate as projects that will soon be concluded (e.g. ENABLE). Therefore, several features of these incentive models need to be tested and further developed and the presence of these structures, combined with the need to extend their timeframe, offers an opportunity for a Swedish investment. However, the specific role of Sweden within such structures needs to be defined in detail, which can happen while their functions, design and mission become more specified.

Pipeline Coordinators were evaluated by experts as innovative solutions that provide customized opportunities to support the development of new antibiotics. However, as mentioned earlier, two alternative designs (Accelerator and Public R&D Procurer) PiCoors were excluded in favour of focusing on R&D Collaboration and Non-Profit Developer PiCoors. Both of these latter types of Pipeline Coordinators create collaboration platforms that coordinate several R&D organizations but the difference is that the R&D Collaboration PiCoor performs early R&D steps for molecules owned

[16] For details, see www.carb-x.org; http://nd4bb-enable.eu/; and www.gardp.org .

by other developers, whereas the Non-Profit Developer PiCoor performs all R&D steps up until the market launch for its own molecules. The experts were clear to emphasize that Sweden should not start its own Pipeline Coordinator. Because R&D in antibiotics is very resource-intensive, this requires deep and broad knowledge of a kind that is rarely found in smaller countries and, if the goal is to bring the products to market launch, several projects need to be run in parallel, as many will fail. This, in turn, entails prohibitively high costs for a small country managing such a large portfolio of R&D projects. In addition, R&D in antibiotics needs improved international cooperation, rather than a growing number of local and partially competing Pipeline Coordinators. Therefore, a smaller country such as Sweden should not create its own Pipeline Coordinator. Conversely, the experts suggested that Sweden should combine its limited but specialized resources with other countries. Moreover, and above all, Sweden should do this within existing international structures and possibly in connection with work to refine and further develop these structures. In summary, experts suggested that Sweden should finance existing international Pipeline Coordinators by supporting either their continuation or further development.

Collaborative structures such as an R&D Collaboration PiCoor should be permanently established internationally, either at the EU or Nordic level, and Sweden could try to anchor parts of such an international organization to Swedish universities or research institutes. In addition, there are ongoing collaborations and competencies that involve Swedish actors (e.g. within ENABLE) that could be further developed. Moreover, Swedish participation in an international R&D Collaboration PiCoor could be combined with Sweden's national efforts to strengthen its R&D infrastructure for antibiotics, as mentioned in the grants section. By strengthening national R&D centres with national grants and thus making them better equipped for international cooperation, this can in turn help them receive additional international resources and thereby create a positive feedback loop.

As the simulation results show (see Section 3.1, Table 1), an R&D Collaboration PiCoor is the strongest and most effective of all simulated incentives, with a public cost of only about 12 M USD to double the number of profitable R&D projects. Despite these strong potential results, it is also important to refine the R&D Collaboration PiCoor initiatives that Sweden chooses to invest in to make them more efficient, flexible and capable of taking into account the needs of smaller companies in the form of fast delivery times, quality and a wide network of R&D laboratories. Because such collaborative incentive models are relatively new, mechanisms still need to be introduced for resolving conflicts between the public academic side and industry. This includes control mechanisms that minimize conflicts of interest and promote openness in key decisions and other evaluations. Solving these practical obstacles is seen as a prerequisite for R&D Collaboration PiCoors to achieve their potential effects and cost-efficiency as previously described.

The reason for choosing to invest in a Non-Profit Developer PiCoor differs entirely from cost-efficiency or impact. An important feature of this type of Pipeline Coordinator is that, unlike the R&D Collaboration PiCoor, it fully or partially takes over the rights of a molecule and strives to lead it to market launch by following it throughout the entire pipeline. Thus, this model represents a very powerful intervention to ensure that products that are economically unattractive – but are strongly needed in low-income countries with a weak ability to pay – can still be taken to market. Experts highlighted this as a relevant model for Sweden to invest in, in view of Sweden's proven goodwill, commitment and contribution to global health with a particular focus on low-income countries. This would certainly create high international visibility for Sweden. In addition, SIDA (The Swedish International Development Cooperation Agency) could potentially provide funding, which would mean less competition for funds, compared to the other proposed incentives, which must be financed through the national innovation and research budget or healthcare budget.

Another reason to finance a Non-Profit Developer PiCoor is that, as a member of such an organization, Sweden can also engage Swedish healthcare providers, such as hospitals, in the organization's R&D projects. In the long run, Swedish healthcare may also need antibiotics developed by a Non-Profit Developer PiCoor, thus providing Sweden with an advantageous asset. The lack of profit targets ultimately means that this incentive model promotes both global access and rational use of new drugs. From a budget point of view, this type of Pipeline Coordinator requires a significant investment of up to 271 M USD to get a new antibiotic approved (see Section 3.1, Table 1) but, as it is in the nature of this organization to build on global cooperation, the Swedish share is approximately 2 to 8 M USD in cooperation with the G20 and EU, respectively (see last row in Table 1). This is a reasonable level of investment for this type of venture for Sweden.

In sum, the two types of Pipeline Coordinators described match the criteria found in Section 2.1 that make incentive models attractive to Sweden. Neither constitutes an excessive investment and the money could be invested directly to support ongoing R&D projects or create more favourable conditions for the global pipeline and better global health. Both mechanisms are relatively new and unique and need funding to either continue their business or be rebuilt in new forms. In addition, both forms of Pipeline Coordinators meet clear needs in the R&D of new antibiotics: an R&D Collaboration PiCoor would support early R&D projects, often driven by SMEs, whereas a Non-Profit Developer PiCoor would support unprofitable yet particularly important R&D projects throughout the development process to ensure global access. Both incentive models would provide Sweden with high international visibility and, in both models, Sweden could play an important role in the fight against AMR. Finally, investing in an international R&D Collaboration PiCoor complements well the national initiative on infrastructural grants to reinforce national R&D centres.

A fourth model considered to be potentially relevant to Sweden by some experts was regulatory simplifications, which could make Phase 3 considerably less costly and shorter for antibiotic developers and thereby stimulate them strongly in this final and decisive phase. The experts argued that Sweden has extensive experience in regulatory issues and considerable competence in regulatory process innovation. Thus, Sweden could take a leading role in Europe for such simplifications that could benefit the entire antibiotic field. Although such an incentive would save considerable money and time for companies, unlike any other incentives, it would not involve any public investment. However, there are some legal, medical and technical issues that need further investigation before one can define this incentive and its potential more specifically. As these issues are beyond the scope of this assignment, it was decided not to include regulatory simplifications as a fourth tool in the Swedish arsenal to stimulate R&D on antibiotics. However, given its potential, this is an incentive that should be further investigated by regulatory specialists.

2.3 Final comments on the selected incentive models for Sweden

Three incentive models that are considered relevant to Sweden have been identified. The amount of investment, turnover time, visibility, uniqueness, need, Sweden's contribution, mutual complementarity and stewardship and access were all taken into account. The incentives considered to best match these criteria and also strongly stimulate antibiotic development are grants, milestone prizes and Pipeline Coordinators. The proposed portfolio of incentive models includes both push (grants) and pull (milestone prizes) as well as collaborative mechanisms (Pipeline Coordinators) that increase the precision of the stimulus on the global R&D pipeline. It is particularly important that the incentives in the Swedish arsenal also complement each other and can work with precision through large parts of the R&D pipeline. Figure 1 shows the phases of the pipeline in which the three selected incentives intervene (as well as regulatory simplifications and MERs).

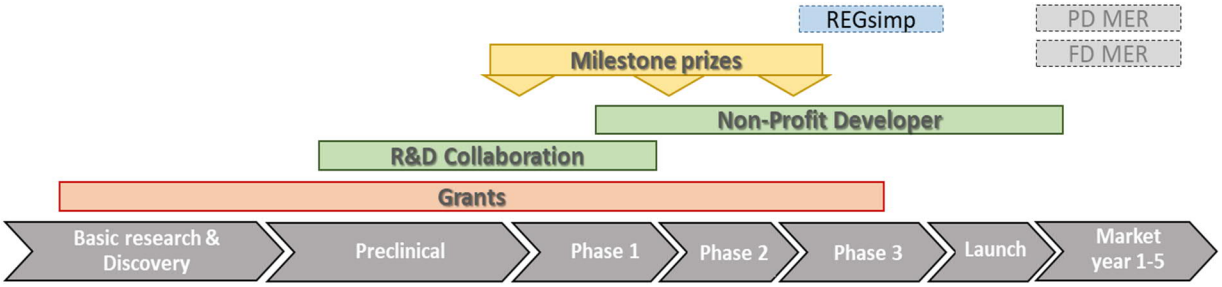

Figure 1: Placing the three proposed incentives over the antibiotics R&D pipeline

More specifically, grants intervene in early stages, including basic research and infrastructure construction. Later on, milestone prizes intervene from preclinical stages up to Phase 2. The R&D Collaboration PiCoor also works mostly on the preclinical stages and up to Phase 1, whereas the Non-Profit Developer PiCoor extends its influence from Phase 1 to market launch. The other two incentive models act further down in the pipeline: regulatory simplifications act on Phase 3 and MERs act at the market launch. As the simulation results in Section 3 show, the three selected incentives are particularly effective in different phases of the R&D pipeline, that is, for projects that have progressed along the development pipeline to different extents. A noteworthy result is that it is of considerable importance to incorporate incentives targeting early R&D phases, as most antibiotic projects fail in those phases; moreover, because of the high risks, those projects have the lowest profitability. It is because of this problem that the arsenal proposed to Sweden for incentive models is primarily aimed at the early pipeline.

Although the simulation and case studies in Section 3 cover all incentive models shown in Figure 1 (including the MERs), the discussion of effects, combinations and synergies focus on the three incentive models that are crucial to stimulate the early R&D pipeline.

3. Analysis and comparison of the incentives' effects

In this section, we present and analyse the effects of the three selected incentives (grants, milestone prizes and Pipeline Coordinators) along with three additional incentives (two types of MERs, i.e. with partial or full delinkage, respectively PD MER and FD MER, and regulatory simplifications), which were discussed in Section 2. We first present the results from a computer-based simulation (Section 3.1) and follow with in-depth case studies (Section 3.2). Both analyses show effects connected with specific amounts of public investments in each incentive. Whereas the simulation shows general and average effects in terms of improved profitability per project, the case studies show how a particular company would react to each incentive when it comes to the decision to continue or not a particular R&D project. We proceed then with a comparison of the three selected incentives in terms of their advantages and disadvantages (Section 3.3). Finally, we discuss the synergies that Sweden may obtain by combining the three incentives.

3.1 Results from the simulation

A Monte Carlo simulation was performed to create variation in the function ENPV, Expected Net Present Value (see Appendix B for details), by means of a large number of virtual projects, each one with different costs, times, revenues, risks and discount rates, which vary randomly between a minimum and maximum. These min-max parameters are based partly on publicly available information on R&D in the antibiotic field and partly on further information collected for this mission (see all parameters in Complementary Table 1 in Appendix B).

ENPV is a formula that assesses a project's profitability and is commonly used in the pharmaceutical industry to make 'Go-No Go' decisions before starting every R&D phase and, hence, decide if a project will proceed to the next phase or be terminated. Moreover, companies in this industry also apply a certain profitability threshold that defines the value that a project's ENPV needs to exceed if a developer is to consider it profitable. Such a threshold is accordingly applied to the projects in this simulation (see the last row in Complementary Table 1 in Appendix B). Within the frame of this simulation, next to the risk of technical failure, it is only a project's ENPV amount – that is, strictly its financial profitability – that decides if a project will continue or stop. Because a new decision to continue or terminate is made before every new R&D phase, the simulation allows assessing the ENPV amount of all projects in the various stages of the R&D pipeline. This, in turn, allows tracing the profitability profile of all these projects and how it varies after the introduction of various economic incentives, which all modify every project's ENPV in a particular way.

In this simulation, we conducted 50,000 runs to generate the necessary variation in R&D projects, as previously mentioned. These 50,000 virtual projects were then exposed to the nine incentives, which were tested (grants, three types of milestone prizes, two versions of Pipeline Coordinators, PD MER, FD MER and regulatory simplifications). In other words, every incentive has changed the economic profile of all the simulated R&D projects in a unique way, that is, their costs, times, revenues and risks (see the red numbers in Complementary Table 1 in Appendix B). For instance, a milestone prize at the end of the preclinical stage ('PC Prize') increases the revenues for Phase 1 with 29.4 M USD, whereas an R&D collaboration PiCoor ('R&D Coll') reduces the times and risks for the preclinical stage and Phase 1 by a random value between 0 and 30%, while simultaneously covering all costs for these two stages (which, accordingly, become 0 in Complementary Table 1 in Appendix B). Furthermore, regulatory simplifications reduce costs, times and risks for Phase 3 by 50%. Finally, a fully delinked (FD) MER corresponds to 1,100 M USD paid in equal yearly instalments of 220 M USD for 5 years, which substitutes for all other kinds of revenues from market sales, and a partially delinked (PD) MER

corresponds to 750 M USD[17] paid in equal yearly instalments of 150 M USD for 5 years, which add on to yearly market sales.

Next, the *effects* of the various incentives were measured in terms of the changes their new parameters caused to the ENPV of every project, considering all R&D projects at every single stage in the R&D pipeline. Moreover, we assessed how each incentive can improve ENPV in every R&D stage to compare the various incentives and understand in which stage of the R&D pipeline each incentive could create the strongest effects. We present first the effects of each single incentive if applied in isolation and then the effects of couples of incentives used in combination.

Although effects in terms of improved ENPV are important, this does not necessarily imply that the antibiotic project will proceed all the way to market launch. It is, in fact, necessary that the improved ENPV also exceed the profitability threshold for a 'Go' decision to be made at all remaining phases until market launch. Therefore, the simulator also calculates the effects of the various incentives in terms of the number of projects that become profitable through all phases and consequently reach the market. The improvement in profitable R&D projects generated by every incentive must then be placed in relation with the public investments required by every incentive, which varies from nearly zero for regulatory simplifications to 24 M USD for a milestone prize at the end of Phase 1 ('P1 Prize') and 1,100 M USD for an FD MER (see the second column in Table 1). We seek to determine the public investment that is needed to reach a certain improvement in the number of profitable antibiotic projects. Finally, to compare the effects of the various incentives, we calculated their *efficiency* expressed as the public investment that is connected to doubling the number of profitable R&D projects (see the last column in Table 1).

The results presented aim to support general policy decisions on economic incentives and consequently do not include details about the design and implementation of each incentive. The size of the effects[18] identified in the simulation is dependent on how each incentive was modelled in terms of its amount and other conditions. For instance, the amount and distribution of an MER is 750 M USD for PD and 1,100 M USD for FD spread over 5 years; and, in this simulation, milestone prizes were paid at the beginning of the following phase and entailed an amount corresponding to three times the R&D costs of the previous phase (see Complementary Table 1 in Appendix B). MERs and milestone prizes with other conditions and amounts would generate other effects than those presented in this report. Therefore, an important task for public actors investing in these incentives is not only to choose a specific incentive but also to design it to generate optimal effects in relation, for instance, to its public costs.

Effects of single economic incentives

The simulation shows that all incentives clearly improve ENPV but have different effects at various R&D stages (see Figure 2 and Complementary Table 2 in Appendix B). These improvements – from a scenario without incentives (which is called the 'base') – vary considerably between the incentives because they intervene in very different ways (i.e. they entail different changes in the input parameters

[17] These monetary amounts for MERs are based on the DRIVE-AB report, 2018, and on Okhravi, C., Callegari, S., McKeever, S., Kronlid, C., Baraldi, E., Lindahl, O., & Ciabuschi, F., Simulating Market Entry Rewards for antibiotics development, *Journal of Law, Medicine & Ethics*, Vol. 46, No. 2, Suppl., 32–42, 2018. In particular, Okhravi et al. (2018) show that, when increasing the amount of an MER from its lowest effective level of 400 M USD, the maximum incremental improvement in the number of profitable antibiotic projects is reached at 750 M USD for a PD MER and at 1,100 MUSD for an FD MER.

[18] These results are based on a specific configuration of the software and algorithms applied in the simulation and how the input values are processed. As this simulation software is constantly developed and new functions are added or discarded, future results may differ from those presented here.

of Complementary Table 1 in Appendix B) and in different stages of the R&D pipeline. **Grants**, an **R&D Collaboration PiCoor** ('R&D Coll') and the **milestone prize at the end of the preclinical stage** ('PC Prize') are the **strongest incentives in the preclinical stage** because they directly address the problems that usually inhibit profitability (i.e. ENPV) in this stage. These three incentives intervene mainly by reducing R&D costs (grants) and the times and risks for technical failure ('R&D Coll') and offer revenues if a preclinical stage is successfully completed (milestone prize, see Figure 2).

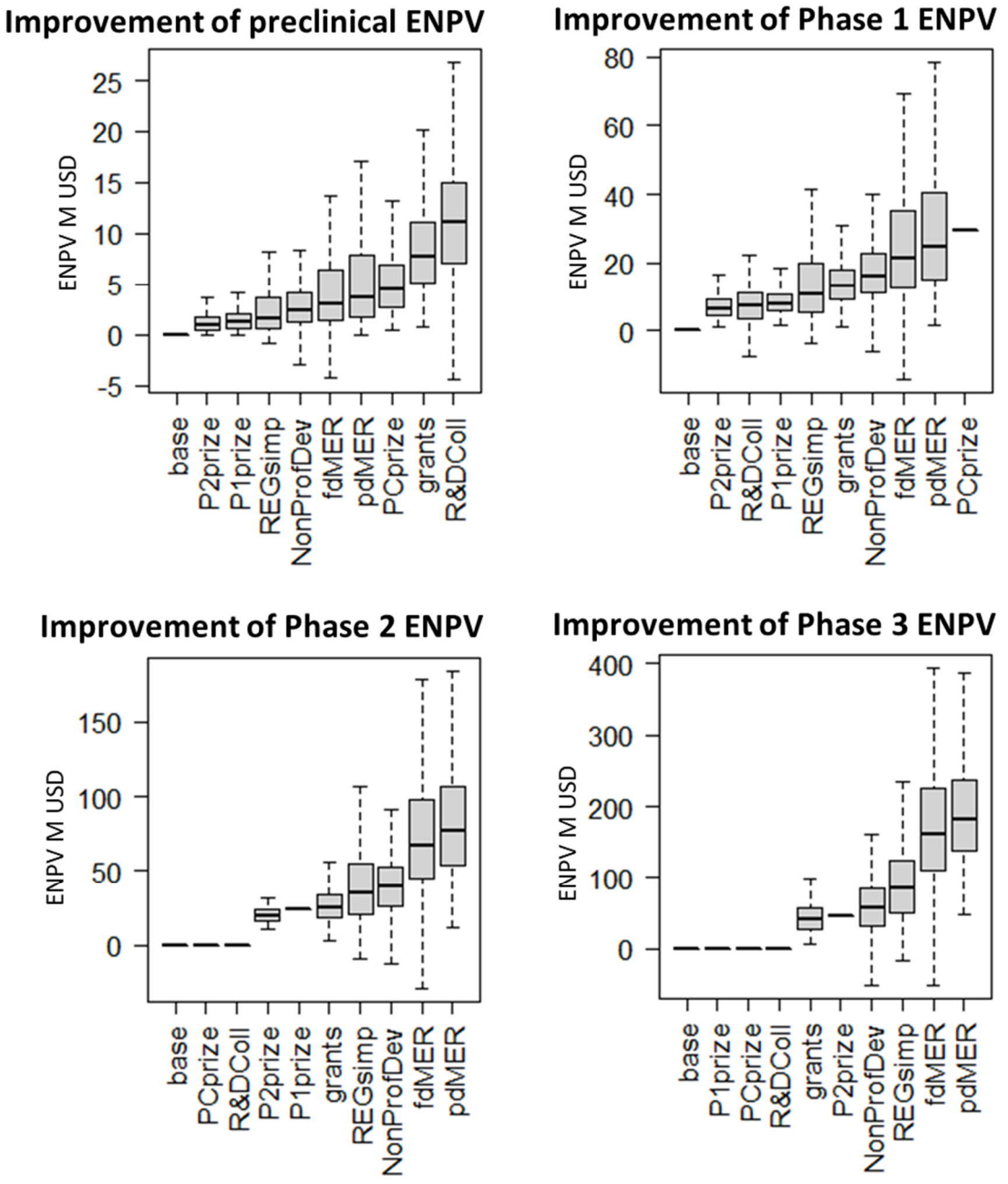

Figure 2: ENPV improvement from 'base' after nine incentives and in various R&D stages (grants; PCprize: milestone prize at the end of preclinical; P1prize: milestone prize at the end of Phase 1; P2prize: milestone prize at the end of Phase 2; R&DColl: Pipeline Coordinator of R&D Collaboration type; NonProfDev: Pipeline Coordinator of Non-Profit Developer type; fdMER: fully delinked MER; pdMER: partially delinked MER; and REGsimp: regulatory simplifications). The box-plots show median values, along with the first and third quartile in the boxes. Outliers are not shown in Figure 2 but are in Complementary Table 2, which also shows mean values (see 'min', 'mean' and 'max').

The improvement in the preclinical ENPV connected with the R&D Collaboration PiCoor is the highest of all incentives, with an average of approximately 11 M USD, followed by grants with 9 M USD and the milestone prize 'PC Prize' with 5 M USD (see 'mean' in Complementary Table 2 in Appendix B). Considering that the lowest and negative ENPV are found in the preclinical stage, in which most projects are terminated due to lack of profitability, it is particularly important to improve the profitability in this stage of the pipeline, when developers evaluate the cash-flows of many future stages. The results in Figure 2 show that an R&D Collaboration PiCoor can considerably improve profitability in this important stage, which is pivotal for the future of most antibiotics R&D projects. If too many such projects are terminated because of too low ENPV in such an early stage, it will be very difficult to maintain a healthy pipeline in the following phases and all the way to market.

For antibiotics projects **entering Phase 1, the strongest incentive is a milestone prize at the end of the preclinical stage** ('PC Prize'). This incentive increases ENPV the same amount as its nominal value, that is, 29.4 M USD, followed by (after the MER, which was excluded in Section 2.1) a Non-Profit Developer PiCoor ('NonProfDev'), which substantially improves ENPV by about 18 M USD (see Complementary Table 2 in Appendix B for details). The same **Non-Profit Developer** provides even better results and is (again after the MER) the **best alternative for antibiotics projects in Phase 2**, with an average ENPV improvement of 40 M USD compared to a scenario without incentives ('base'). Next come regulatory simplifications ('REGsimp') that, through reduced costs, times and risks of technical failure in Phase 3, increase ENPV by an average of 41 M USD and, lastly, grants with an improvement of about 27 M USD (see the lower-left image in Figure 2 and the numbers in Complementary Table 2 in Appendix B). At the last development phase analysed, that is, before starting Phase 3, many antibiotic projects display higher profitability than in previous phases – namely, an average positive ENPV of 17 M USD – and the relative improvement of ENPV caused by the selected incentives is lower than in the previous phase. For instance, regulatory simplifications provide an average improvement of 92 M USD, followed by the Pipeline Coordinator 'Non-Prof Dev' with about 56 M USD and, finally, a milestone prize at the end of Phase 2 with 47 M USD (see Complementary Table 2 in Appendix B).

Although an improvement of ENPV is important, it is even more important to identify how many profitable antibiotic projects an incentive can create, that is, how many antibiotics an incentive can support all the way from the preclinical stage to the market launch by generating an ENPV high enough at every decision point that the developer continuously decides to bring the project to the next phase. The percentage improvement in the number of profitable antibiotics connected to each incentive indicates its efficacy but these effects can entail very high costs (such as for an MER). Therefore, the effects and efficacy must be placed in relation to the costs of each incentive to calculate its efficiency. This kind of efficiency is shown in the last columns of Table 1 in the form of the public investment that is connected to doubling the number of profitable antibiotics for every incentive. Therefore, in this table, the incentives are listed in order of their efficiency, starting from the most efficient (the cheapest) and moving to the least efficient (the most expensive). Table 1 also shows the public investments necessary for each incentive to bring a new antibiotic to market launch, which is almost always higher than the costs connected to doubling the number of profitable antibiotics. This is because it is usually necessary to more than double the number of such projects to reach market launch, as many profitable antibiotics fail because of technical problems.

Incentive	*Public cost per incentive*** (M USD)*			*Total public investment per 1 launched antibiotic (M USD)*			*Percentual improvement of profitable antibiotic projects*	*Public investment per 100% improvement of profitability (M USD)*		
	Total	Swedish share EU[19]	Swedish share G20	Total	Swedish share EU	Swedish share G20		Total	Swedish share EU	Swedish share G20
REG simp*	(32.9)	(1.02)	(0.27)	(35)	(1.09)	(0.29)	385%	(9.1)	(0.28)	(0.08)
R&D Coll	**17.8**	0.55	0.15	110.6	3.44	0.92	**896%**	**12.4**	0.39	0.1
Grants	83	2.6	0.7	240	7.5	1.99	409%	59	1.8	0.49
PC prize	29.4	0.91	0.24	188	5.85	1.56	283%	66.7	2.07	0.55
PD MER	750	23.3	6.2	750	23.3	6.23	855%	88	2.7	0.73
P1 prize	24	0.75	0.2	**83.5**	2.6	0.69	70%	119.4	3.71	0.99
P2 prize	46.5	1.45	0.39	88.1	2.74	0.73	61%	143.2	4.45	1.19
FD MER	1,100	34.21	9.13	1,100	34.21	9.13	479%	231.8	7.21	1.92
Non-Profit Dev*	149.2	4.64	1.24	270.6	8.42	2.25	(77%)	(354.5)	(11.02)	(2.94)

** The amounts of R&D cost reduction allowed by REGsimp are listed for comparative purposes even if they are not public investments.*

*** A Non-Profit Developer does not apply the ENPV formula for its decisions. The calculation of profitable projects is made for this incentive only to allow comparison and is accordingly put between parentheses.*

**** This column indicates the amount that each incentive pays for every R&D project that it stimulates.*

Table 1: Improvements of profitable antibiotic projects for nine incentives and public investments per incentive and per launched antibiotic

Before discussing the efficiency of the selected incentives, we consider their efficacy – that is, their effects – independently from their cost. According to the simulation, the incentive with the strongest effects is an R&D Collaboration PiCoor, which increases the number of profitable R&D projects about ten times (896% in the fourth column of Table 1). The Non-Profit Developer PiCoor shows instead much weaker effects, as it does not even double the number of profitable antibiotics (only a 77% increase). However, one should consider that improving profitability is not the goal of a Non-Profit Developer. Grants are also a strong incentive, which can increase the number of profitable projects five times (a 409% increase), closely followed by regulatory simplifications (385% increase). Among the three milestone prizes, the prize at the end of the preclinical stage ('PC Prize') seems to be the strongest, with an increase in the number of profitable antibiotics of almost four times (283% increase), which is more than four times better than milestone prizes offered at later stages in the pipeline, such as at the end of Phase 1 ('P1 Prize' with 70% improvement) and Phase 2 ('P2 Prize' with only 61% improvement).

If we consider the efficiency of the various incentives, that is, we relate the improvement in the number of profitable or approved antibiotics with the necessary public investments, an R&D Collaboration PiCoor not only produces the strongest effects but is also **the most efficient** of all incentives. This incentive requires a limited investment for each R&D project it supports (about 18 M USD) and the total public cost to make one of these projects reach market launch is among the lowest (approximately 111 M USD, see the third column in Table 1). Moreover, an R&D Collaboration PiCoor has the highest efficiency measured as the lowest cost for doubling the number of profitable antibiotics, with about 12 M USD (see the last column in Table 1). The second-best efficiency (i.e. cost for doubling profitable projects) belongs to grants, with 59 M USD, but these are more expensive when it comes to taking an antibiotic all the way to market, with 240 M USD.

The incentive that is the most efficient per launched antibiotic is a milestone prize at the end of Clinical Phase 1 ('P1 Prize'), with 84 M USD per approved antibiotic (see the bold figure in Table 1). However, comparing the efficiency of all milestone prizes is a more complex issue. A 'PC Prize'

[19] The Swedish share in collaboration with the EU and G20 was calculated by defining the ratio between Sweden's GDP (gross domestic product) and the sum of the GDPs of all EU countries (including UK) and, respectively, all G20 countries. This ratio is 3.11% for the EU and 0.83% for the G20. Based on figures from World Bank, *GDP current US$, World Development Indicators.* Downloaded 3 July 2018.

awarded at the end of the preclinical stage costs less per project (29 M USD, see the second column in Table 1) than a 'P2 Prize' awarded at the end of Phase 2 (47 M USD) but a 'P2 Prize' requires lower investment to bring a new antibiotic to market launch (see 88 M USD vs. 188 M USD in the third column of Table 1). This is because many more R&D projects that are awarded a 'PC Prize' are eventually terminated because of technical failures compared to those that receive a 'P2 Prize' at a later R&D stage. However, a 'PC Prize' is the most efficient of the three milestone prizes when it comes to the costs of doubling the amount of profitable antibiotics, with a total of only 67 M USD, which makes 'PC Prize' the third best alternative for doubling profitable antibiotics, compared to slightly over 100 M USD to reach the same result for both 'P1 Prize' and 'P2 Prize' (see the last column in Table 1).

It is interesting that all three milestone prizes seem to have better efficiency per approved antibiotic than both kinds of MER (PD and FD) and much lower investments in general, which makes milestone prizes a very cost-efficient alternative to MERs as a pull incentive. The better efficiency of milestone prizes (measured as public investment needed per launched antibiotic) depends both on the effect of discounting future cash-flows and on where exactly they intervene in the pipeline compared to MERs. The discounting effect implies that incentives that are paid later in the future are perceived as less attractive than those paid earlier and, accordingly, need to be higher in nominal amount. However, the 'where' issue depends on the fact that different stages of the pipeline are characterized by different costs and risks, which implies varying profitability barriers that need to be addressed in each stage. In this context, an MER intervenes at the end of the pipeline and not in any specific phase, which means that its effects are spread across the entire pipeline and do not appear strongly in its earliest stages (see also Figure 2), whereas milestone prizes intervene at a specific point of the pipeline and can provide strong incentives, specifically when there are high profitability barriers that need to be overcome, which occurs in the preclinical stages and at the start of Phase 1 (see the higher part of Figure 2). This explains the result that one can obtain better efficiency by investing about 24 M USD at the end of Phase 1 and by distributing this amount to a sufficient number of projects to ensure at least one reaches market, rather than by attracting projects from all possible phases with a much higher MER. In other words, milestone prizes are a tool that acts with greater precision in the 'financially most sensitive' position in the pipeline and, accordingly, requires considerably lower amounts to achieve the same result as an MER.

Finally, the Non-Profit Developer PiCoor has low efficiency because it allocates 150 M USD for each antibiotic it handles and is expected to spend 271 M USD to bring one project to market launch. However, as already mentioned, the choice of this incentive model is not motivated by its efficiency or effectiveness but by other issues such as access, rational use (stewardship) and visibility for Sweden. Table 1 shows each incentive's total cost in terms of public investment and the possible Swedish share if it were funded through collaborations within the G20 or EU. Compared with both types of MER, the amounts of the Swedish share of all other incentives is much lower. For instance, the Swedish share of a milestone prize at the end of Phase 1 ('P1 Prize') is about one-tenth of the share of a PD MER, which in collaboration with the G20 or EU is, respectively, 6 and 23 M USD (see the third column in Table 1). The latter amount is close to what Sweden alone would need to invest if it decided to introduce a prize at the end of Phase 1, that is, 24 M USD. By avoiding massive investments in an MER, Sweden would be able to cover higher shares of the other incentives. It would likely be too expensive for Sweden to provide all funding needed by the other incentives on its own (i.e. to invest the amount needed for a newly approved antibiotic, shown in the third column of Table 1, or the nominal value of an incentive, shown in the second column of Table 1). However, with the same budget, Sweden would be able to cover more than 0.8–3% of the other incentives, which applies to much higher MERs. For instance, Sweden would need 6 to 34 M USD to cover a share up to only 3%

of an MER but similar amounts would allow Sweden to entirely fund a milestone prize at the end of the preclinical stage (29.4 M USD) or Phase 1 (24 M USD) or cover up to one-third of the investments needed in the several Phase 1 milestone prizes (83.5 M USD), which are required to have a new antibiotic approved. A higher Swedish share of investments for a given incentive should give Sweden higher visibility and greater influence in how an incentive is designed and targeted.

Effects of combinations of incentives

Various incentives are expected to be used together to stimulate antibiotics R&D across the entire pipeline and, as shown in Figure 2, different combinations of incentives work better in different R&D stages. One can also demonstrate that combining incentives, that is, using them together with each other, can improve both their effects and efficiency. Therefore, we show the synergies that emerge when one combines the selected pull incentives (three types of milestone prizes) with push incentives (grants) and the collaborative incentives (two types of Pipeline Coordinator). We also show combinations that include MERs to demonstrate that there are stronger and more efficient combinations that do not include an MER.

ENPV achieves higher improvement throughout the entire R&D pipeline if one combines push with pull incentives (i.e. grants and milestone prizes or MERs) or pull incentives with Pipeline Coordinators (see the difference between mean values in Complementary Table 2 for single incentives and in Complementary Table 3 for selected combinations, both in Appendix B). The combination of pull and collaborative incentives can entail, for instance, an R&D Collaboration PiCoor awarding milestone prizes (for instance, after the preclinical stage or after Phase 1) or a Non-Profit Developer receiving an MER or milestone prizes that can finance its future operations. Looking at the enhanced effect of combinations of incentives, the strongest ENPV improvements in the preclinical stage are higher than the sum of the effects of single incentives and are obtained by combining milestone prizes with an R&D Collaboration PiCoor, with average values between 13 and 18 M USD (see Complementary Tables 2 and 3 in Appendix B). The ENPV improvement of this combination is followed by combinations of milestone prizes with grants, which provide an ENPV improvement between 10 and 14 M USD, and then by combinations of milestone prizes and Non-Profit Developer PiCoor, with values between 5 and 8 M USD. In Phase 1, milestone prizes together with an R&D Collaboration PiCoor improve ENPV by between 16 and 37 M USD on average and combinations of milestone prizes and grants do even better, with improvements between 22 and 44 M USD; however, the highest improvements in Phase 1 derive from combinations of milestone prizes and Non-Profit Developer PiCoor and are between 25 and 47 M USD (see Complementary Table 3 in Appendix B). These combined mean ENPV improvements in Phase 1 are also higher than the improvements obtained from single incentives in the same phase.

Looking at the efficacy of the various combinations over the entire pipeline, our simulation shows that milestone prizes and R&D Collaboration PiCoor taken together offer among the strongest improvements in terms of number of profitable R&D projects, which increase by approximately 12 and 17 times, respectively, with a Phase 1 and preclinical prize (see 1,151% and 1,591% in the fourth column of Table 2). Combinations of milestone prizes and R&D Collaboration PiCoor are also the most efficient because they entail the lowest cost to bring an antibiotic to market launch (319, 212 and 218 M USD, respectively, for ‘PC Prize’, ‘P1 Prize’ and ‘P2 Prize’, as shown in the third column in Table 2). The most efficient combination for doubling the number of profitable antibiotics is an R&D Collaboration PiCoor together with a milestone prize at the end of Phase 1 (‘P1 Prize’), with a combined cost of only 18 M USD for such a doubling. This significantly improves the efficiency of ‘P1 Prize’ compared to when it is used alone (which was a cost of 119 M USD, as shown in Table 1,

last column) but does not improve the efficiency of the R&D Collaboration PiCoor compared to when it is used alone (which was already as efficient as costing only 12 M USD, as shown in Table 1).

Combination of incentives	Public cost per incentive**	Total public investment per 1 launched antibiotic	Percentual improvement of profitable antibiotic projects	Public investment per 100% improvement of profitability
	M USD	M USD	%	M USD
Grants+PD MER	833	904	1,860%	49
Grants+FD MER	1,183	1,221	1,514%	81
Grants+PC prize	112	407	1,211%	**34**
Grants+P1 prize	107	**307**	562%	55
Grants+P2 prize	130	311	535%	58
*Non-Prof Dev+PD MER**	899	934	(1,146%)	(82)
*Non-Prof Dev+FD MER**	1,249	1,250	(1,125%)	(111)
Non-Prof Dev+PC prize*	178	436	(612%)	(71)
Non-Prof Dev+P1 prize*	173	337	(174%)	(194)
Non-Prof Dev+P2 prize*	195	341	(166%)	(205)
R&D Coll+PD MER	768	1,016	3,655%	28
R&D Coll+FD MER	1,118	1,441	3,143%	46
R&D Coll+PC prize	47	**319**	1,591%	**20**
R&D Coll+P1 prize	42	**212**	1,151%	**18**
R&D Coll+P2 prize	64	**218**	1,129%	**19**

**A Non-Profit Developer does not apply the ENPV formula for its decisions. The calculation of profitable projects is made for this incentive only to allow comparison and is accordingly put between parentheses.*

*** This column indicates the amount that each incentive pays for each R&D project that it stimulates.*

Table 2: Calculated improvements of profitable antibiotic projects for combinations of eight incentives and public investments per incentives and per launched antibiotic

Milestone prizes also provide strong effects when combined with a Non-Profit Developer PiCoor but lose some of their strength compared with combinations with an R&D Collaboration PiCoor, with an increase of profitable antibiotic projects between about three times (166%) for 'P2 Prize' and seven times (612%) for 'PC Prize' (see fourth column in Table 2). The costs to bring a new antibiotic all the way to market for these combinations vary between 337 and 436 M USD (see third column in Table 2), which does not improve the efficiency of either the Non-Profit Developer or milestone prizes (see Table 1, third column for comparison); this indicates that there are no clear synergies between these two incentives. Thus, milestone prizes do not seem essential for this kind of developer because a non-profit driven developer would not decide to continue a project based on the increased revenues derived from a milestone prize (even if such revenues would be attractive for financing the broader operations of a Pipeline Coordinator, an effect that is not simulated in this report).

An interesting result is that there are combinations of grants with other incentives that are more efficient than their combinations with MERs – a more efficient way is to combine grants with other pull incentives such as various kinds of milestone prizes. The combination of grants with a prize at the end of the preclinical stage ('Grants+PC Prize' in Table 2) results in an increase in profitable projects that may be lower than the combination with an MER (1,211% vs. 1,860%) but this increase is obtained with a much lower amount invested (112 M USD vs. 833 M USD). This implies that a combination of grants and 'PC Prize' requires an investment of only 407 M USD to bring a new antibiotic to market, as opposed to 904 M USD, which is necessary for the combination of grants and PD MER. 'Grants+PC Prize' is also the combination of pull and push incentives with the highest efficiency in terms of costs for doubling the number of profitable projects, that is, 34 M USD (see the bold figure in Table 2). Finally, the combination of grants with a milestone prize at the end of Phase 1

('Grants+P1 Prize' in Table 2) entails a much lower cost per approved antibiotic (307 M USD) than grants together with PD MER (904 M USD).

3.2 Results from the case studies

The Monte Carlo simulation provides results from a large population of virtual projects rather than covering the reaction of specific developers to a certain incentive. Therefore, it is difficult to distinguish between large pharmaceutical companies (Big Pharma) and small and medium-sized companies (SMEs). Making such a distinction is important because these two kinds of developers are known to react differently to the various incentives, depending heavily on the different parameters in their projects and varying ways of applying, for instance, the ENPV method. Thus, it is useful to conduct *case studies* to analyse in detail how specific actors make investment decisions and how they would react to a particular incentive in terms of 'Go' or 'No Go' decisions for their existing antibiotic projects. In particular, we conducted four in-depth case studies with companies directly involved in antibiotics R&D and purposefully selected two large pharmaceutical firms and two small ones. As shown by the simulation, the R&D phase of a project implies different effects of the various incentives. Therefore, we applied as additional sampling criterion that two of the selected companies had a project in early R&D stages, namely preclinical, and two had a project in later R&D stages, namely after a completed Phase 1.

Altogether, our cases feature four companies: a small one with an R&D project in an early R&D stage, a small one with a project in a later phase, a large company with a project in an early R&D stage, and finally, a large company with a project in a later phase. This sample is shown in the 2x2 matrix of Table 3, which also indicates the four companies' reactions to five incentives: grants, Pipeline Coordinators of two types ('R&D Coll' and 'Non-Prof Dev'), milestone prizes, MERs and regulatory simplifications.

These cases show clear differences in how small as opposed to large companies react to the various incentives. A clear pattern in Table 3 indicates that SMEs are convinced more easily to continue their R&D projects (see the green text for the 'Go' decisions, the orange text for 'Maybe' and the red text for 'No Go' decisions). More incentives and lower public investments encourage the two small companies to continue their projects compared to the large companies. The only incentives that attract the large companies are MERs or much higher amounts for the other incentives.

	SME	BigPharma
Early Phase	**SME – early phase (preclinical)** -Grants: YES for GO Phase 1, 1.5-3M USD -PiCoors: YES both R&D Coll + Non-profit dev. -Milestone prizes: YES after Phase 1 (4.5-15M USD depending on Phase 1 costs) -MER: YES both PD 50 M USD and FD 200 M USD -Regulatory: YES if 80% cheaper/faster Phase 3 -Favourite: x10 higher prices for new antibiotics	**BigPharma – early phase (preclinical)** -Grants: YES for GO Phase 1 min 100% coverage -PiCoors: NO R&D Coll (acad), NO Non-profit d. -Milestone prizes: NO (3x Vs 33% success, against business model, not a CRO) -MER: YES PD 3B USD or 2B USD+40%grants, NO FD -Regulatory: NO (insufficient, Phase 4 costs) -Favourite: Transf. Excl. Vouchers (TEVs)
Later Phase	**SME – later phase (clinical Phase 1-2)** -Grants: YES for GO Phase 2, if 50% coverage -PiCoors: too late R&D Coll, YES Non-profit Dev -Milestone prizes: YES at least costs prev. phase -MER: YES PD 1B USD, NO FD (VCs are against it) -Regulatory: YES if 50% cheaper/faster Phase 3 -Favourite: NA	**BigPharma – later phase (clin. Phase 2-3)** -Grants: YES for GO Phase 3, 100% coverage -PiCoors: too late R&D Coll, NO Non-profit dev -Milestone prizes: maybe after Phase 3 (as first MER instalment) -MER: YES both PD 100-500 M USD & FD 1-2B USD -Regulatory: YES, but insufficient alone -Favourite: TEVs, new valuation/reimbursement

Table 3: Four companies of different sizes and in different R&D stages and their reactions to five incentives

An important result is that large companies in early R&D stages seem to require much higher MERs to be stimulated compared to small companies in the same stages and other large companies in later R&D stages (3,000 M USD vs. 1,000–2,000 M USD or lower). This is probably because small companies usually have only one project on which they bet all their resources and, consequently, can accept relatively lower profitability and, hence, lower incentives, whereas large pharmaceutical companies also operate in other therapeutic areas with high profitability, which implies high alternative costs and places higher financial requirements on each antibiotic project. Large pharmaceutical firms also seem to apply the assumption and explicitly expect that most early R&D projects will fail on their way to market, which is a less clear assumption for a small company. Therefore, large companies always account for high costs to cover all failed projects (the so-called 'cost of failures'), which small companies seldom do. In sum, it seems economically more difficult to stimulate large companies in early stages than companies in the other three situations analysed in the case studies.

Another interesting result from Table 3 is that the amounts that appear attractive for the small companies are much lower than those employed in the simulation for most incentives. More precisely, grants lower than 3 M USD would be enough to stimulate an SME to start Phase 1 and grants that only cover 50% of the costs are generally enough to start Phase 2. These amounts can be compared with 10 M USD for early phases and 20 M USD for later phases, which were applied in the simulation (see Complementary Table 1 in Appendix B). In addition, the milestone prizes that seem attractive for SMEs in the cases are much lower than those applied in the Monte Carlo simulation – around 15 M USD or simply coverage of the previous phase's costs, compared to 24–29 M USD in the simulation. These results from the real context of case studies suggest that the positive effects identified in the simulation may be an underestimation of the positive effects that the selected incentives can have for small companies. However, the opposite may hold for large pharmaceutical companies, which seem to require higher coverage by grants (100%) and even for late R&D phases, which were excluded from

the simulation (see Complementary Table 1 in Appendix B). Further, it seems like large companies are not interested in milestone prizes because they clash with these companies' business model, which entails aiming for rewards for product launches, rather than receiving minimal compensation only for some R&D activity. A business model based on low payments for an R&D phase would more closely fit a CRO (Contract Research Organization) rather than a complete pharmaceutical company.

Pipeline Coordinators are also not attractive for large companies because they are considered too 'academic' (R&D Collaboration PiCoor) or because these companies are not interested in engaging with products that completely lack profit potential (Non-Profit Developer PiCoor). Instead, small companies are interested in Pipeline Coordinators of both kinds. The last proposed incentive, regulatory simplifications, was considered attractive by small companies but not large ones. In fact, large companies pointed out that this incentive would not be enough on its own and it risks causing higher costs for additional studies after market launch. The case companies also indicated their own favourite incentive models: a small company pointed at increased unit prices (up to ten times higher than current prices), which was excluded during the discussion with experts (see Section 2.1), and the large companies proposed Transferrable Exclusivity Vouchers (TEVs), which were omitted from the initial list for discussion with the experts. TEVs are an incentive that awards an extension, usually one year, of the market exclusivity for a product selected by the holder of the voucher, which would likely be used for a 'blockbuster', that is, a product with yearly sales of several billion USD. TEVs are intensively discussed now in the US but were excluded from early discussions (as they were in the DRIVE-AB project, see footnote 9) because TEVs create great uncertainty for the public payers.

3.3 Pros and cons of the various incentive models

After looking at the effects of the proposed incentives, both in a broad sense in the simulation and more concretely in the case studies, we can now discuss their respective advantages and disadvantages based on the results presented in Section 2.2. MERs are not discussed further as they were ruled out after discussions with the experts. The simulation has also shown that MERs are not the most cost-efficient option. However, large pharmaceutical companies seem to be attracted to this type of incentive, which means that if one wants to engage these types of actors to develop new antibiotics, MERs may need to be considered. However, this should happen in an international rather than a Swedish context. Regulatory simplifications were considered an interesting option for Sweden and the simulation has shown that they can have strong effects, which are partly confirmed by the case studies, at least for SMEs. However, the legal and technical complexity of this option is such that deeper analysis is needed before this type of incentive can be proposed, especially if the aim is to completely abolish Phase 3 studies. Regulatory simplifications of this kind may also include major changes and potential risks for patients and should only be introduced gradually and under strict review. Thus, the pros and cons for only the three selected incentive models are discussed here (see Table 4 for a summary).

Incentive Model	Pros	Cons (and risks)	Risk Management
Grants (long-term, infrastructure, early phases)	- Simple and well known - Lower amount - Can be received by many actors - Strengthens the whole pipeline - Direct motivation for SMEs - Helps build competences - Enhances future innovation capability - Allows Swedish organizations to participate in international projects	- Bureaucratic for SMEs - A weaker type of incentive - Not the most effective to support market launch - Does not highly influence the direction of the next R&D phases - Difficult to control accessibility and stewardship after launch	- Simpler application procedure - Combine with pull incentives (milestone prizes) for more effectiveness - Terms and need for paybacks during following R&D stages and market launch - Connecting grants to a Pipeline Coordinator ('Accelerator')
Milestone Prizes (Preclinical, Phase 1, Phase 2)	- Relatively manageable sums - Quick effect on recipient - Among the most effective to support market launch - Easy to test - Very attractive for SMEs - Can be combined with grants to increase their effect	- Not tested yet for antibiotics - Risk of 'gaming' - Early prizes with many applicants can be complex to manage - May have to be paid to foreign developers - Big Pharma not interested	- Pilot testing, comparison with existing prizes - Chargeback requests and control by Pipeline Coordinator alt. authority - Targeted prizes just for special types of antibiotics - Require availability of new antibiotic for Sweden
Pipeline Coordinators (R&D Collaboration, Non-Profit Developer)	- Already existing to a certain extent - R&D Collab. most effective of all incentives - Can combine mechanisms - Can apply suitable mechanism for the single antibiotic project - Can make portfolio choices - Contributes to national competence basis - Non-Profit Dev. best to enhance access and stewardship	- Not operating at full scale yet - Too bureaucratic for SMEs - Potential conflicts between parties (academics/companies) - Risk for conflicts of interest - Risk to exclude certain potential partners	- Pilot testing of certain new roles and functions - Simplification of organizational structures and external interfaces - Functioning control mechanisms against conflicts of interest

Table 4: Pros and cons (and risks) of the three incentive models proposed

Grants have the advantage of being well-known instruments that are relatively easy to use and administer; they also require lower funds than, for example, an MER and can be given to several developers at the same time. A major advantage of grants, as shown by the simulation, is that they have strong effects in early R&D phases, thus strengthening all subsequent stages in the pipeline by keeping multiple R&D projects alive (projects that would otherwise be terminated due to financial reasons). Grants also satisfy SMEs' needs for quick access to financial resources. At the national and system levels, grants are very important for building R&D competence for future antibiotics, including support to enhance the national innovation capacity through a strong infrastructure of R&D centres. Such R&D centres would provide additional benefits, as they may participate more actively in international platforms such as different forms of Pipeline Coordinators. Thus, it is proposed here that grants should be devoted to building a national R&D infrastructure; they should also be long-term and focus on early R&D phases (potentially up to but not further than Phase 2).

Grants, however, show some disadvantages: considerable bureaucracy in the application process creates barriers for smaller companies when applying and they need to be managed through simplified procedures. Furthermore, according to the simulation results (see Table 1), grants also represent a weaker incentive in terms of efficiency per launched antibiotic compared to pull incentives. This is a

disadvantage that can be managed by combining grants with pull incentives, which would also increase their overall effectiveness (see Table 2). Two related disadvantages of grants are that they do not allow the financier to influence subsequent R&D phases or the availability and stewardship of the drug after market launch. These two issues could be addressed through paybacks that may apply if the recipient in the following R&D phases or after market launch does not accomplish certain results or behaviours. Another option is to link grants to a Pipeline Coordinator, such as an 'Accelerator' that can monitor the behaviour of the recipient.

A tangible advantage of milestone prizes is that they act as a pull incentive without expending as many resources as those required by an MER. In addition, they have a more direct positive effect for developers from a time perspective. According to the simulation results (see Table 1), they are also among the most effective incentives per market-launched antibiotic. Milestone prizes are also easy to test and particularly appreciated by SMEs. Finally, as previously mentioned, these incentives can be combined with grants to significantly increase their efficiency.

Milestone prizes also show some disadvantages. First, they have not yet been tested on antibiotics; however, this should be relatively easy to do using references to existing prizes for similar technologies (e.g. diagnostics and tuberculosis[20]). Furthermore, milestone prizes represent a greater risk for fraudulent reporting ('gaming') than, for example, an MER because information asymmetry between the developer and financier is greater in earlier R&D phases. To counteract this risk, several actions could be taken: (1) introduce clear and rigorous criteria for allocation; (2) evaluate the test results and the molecule thoroughly through a specialized Pipeline Coordinator or competent authority (e.g. the Swedish Medical Products Agency); (3) introduce reimbursement requirements upon submission of fabricated information or reduction of payment if the information subsequently proves not to be correct. Another possible risk is that early prizes can attract many applicants and create a demanding evaluation process. This can be mitigated by the introduction of specifically targeted prizes that would be available only for unique antibiotics with high innovation content and minimal risk of resistance. Milestone prizes should be given to the best candidates, which may lead to payments to foreign applicants. In such cases, Sweden could secure a societal return for this investment by requiring foreign recipients to provide favourable access to Sweden in the event of a future launch of an antibiotic that has received a Swedish milestone prize. Finally, there is the disadvantage that 'Big Pharma' do not seem motivated by milestone prizes. However, thanks to these incentives, there will be several SMEs that take their products further into the R&D pipeline so 'Big Pharma' will have several options for investments or acquisitions.

Because milestone prizes cover various types of payments in different R&D steps, it is also necessary to discuss exactly which prize is most relevant for Sweden. The options are a prize at the end of the preclinical stage ('PC Prize'), one at the end of Phase 1 ('P1 Prize') and one at the end of Phase 2 ('P2 Prize'). These three alternatives also have pros and cons in relation to each other that are not discussed in detail but the proposal here is based primarily on results from the simulation. According to Table 1, the strongest prize, if measured as doubling of profitable antibiotics, is 'PC Prize', followed by 'P1 Prize' and then 'P2 Prize'. However, 'P1 Prize' is the most effective of all nine evaluated incentives measured in terms of cost per approved antibiotic. Thus, one could exclude 'P2 Prize' and focus on a 'PC Prize', which strongly helps projects get out of the preclinical stage (see Figure 2, top left), and a 'P1 Prize', which works more efficiently in terms of approved antibiotics. In addition, a 'P1 Prize'

[20] For instance, the Longitude Prize will award 10 M GBP to the rapid diagnostic tool that, at the end of 2019, best matches the criteria for speed, precision, simplicity and availability. See https://longitudeprize.org/challenge. The Life Prize is instead awarded to those who can develop a treatment that can cure, within one month, all types of tuberculosis. See https://twitter.com/TheLifePrize.

paid at the end of Phase 1 would create high visibility for Sweden and be relatively easier to administer than a 'PC Prize', which may attract many more applicants.

Pipeline Coordinators offer several advantages. They exist already or are under construction in the two forms proposed here: 'R&D Collaboration' and 'Non-Profit Developer'. In addition, an R&D Collaboration PiCoor is the most effective of all incentives regarding the cost of doubling the number of profitable antibiotics and is among the most effective in terms of cost per approved antibiotic. This high efficiency is combined with the flexibility of the incentive, which allows it to adapt the given support to the needs of the individual R&D project. A Pipeline Coordinator also makes active and informed choices to provide special support, depending on the entire product portfolio it manages, which means that synergies between projects can also be achieved. Both types of Pipeline Coordinators can also help connect Sweden's R&D centres and clinical units to international structures, thus obtaining additional funding and skill development. Finally, a Non-Profit Developer PiCoor represents the best option for promoting the availability of developed antibiotics to patients worldwide and for stewardship.

Pipeline Coordinators also imply certain disadvantages or risks. Existing Pipeline Coordinators are not fully developed in all their possible functions, but this can be remedied by testing various features and new parts of their organizations step by step, with the help of pilot projects. Furthermore, SMEs indicate that an intensive form of Pipeline Coordinator, such as an R&D Collaboration PiCoor, also entails obstacles such as crippling bureaucracy and presents some conflicts (for example, between academic parties and companies), including conflicts of interest when major resource allocation decisions are made. These problems can be addressed by simplifying the structures, procedures and external interfaces created by a Pipeline Coordinator, as well as by developing control models that minimize conflicts or can solve such problems when they occur. Open and inclusive rules would also counteract the risk that some developers are potentially excluded from cooperation in these platforms, as shown in Table 4.

3.4 Synergies and combinations between incentive models

After discussing the various incentives individually, one can now build on the results from the simulation, case studies and analysis of pros and cons to suggest how and why they can be combined. There are three lines of thought one can follow to create synergies between the three proposed incentive models: a time perspective, an investment perspective and a perspective that follows the underlying nature of the models. These three aspects are discussed in turn next.

From a time perspective, it is important that the selected mechanisms attack all barriers that occur at different R&D phases in the antibiotic pipeline, from the preclinical stage to market launch. To ensure that many new antibiotics are ultimately approved, it is necessary to foster as many as possible through the earliest phases because, unfortunately, many R&D projects will fail in later phases due to technical problems. To create this positive dynamic, early grants can be combined with subsequent milestone prizes (at the end of the preclinical stage or Phase 1) so these two incentives can act together to push and pull the molecules through the early stages. Pipeline Coordinators can take over later in the pipeline, including in Phase 1, and ensure that the development of medically valuable molecules is not interrupted solely because of lack of financial attractiveness for the developers (see Figure 1 in Section 2.3 for an overview of where in the pipeline the different incentives appear). Thus, a combination of the three proposed incentives (grants, milestone prizes and Pipeline Coordinators), especially through a Non-Profit Developer PiCoor, can balance and reinforce each other over the entire pipeline to bring new antibiotics closer to the market (see Table 2).

In addition to the time horizon of the incentives, we need to consider the speed with which incentives can be introduced and when they will generate effects in terms of newly approved antibiotics. Is there then a priority pattern that can be followed to introduce these three mechanisms? Obtaining quick approvals implies utilizing the existing clinical pipeline (which, however, contains very few truly innovative molecules), which can best be done through a Non-Profit Developer PiCoor. Providing milestone prizes at the end of Phase 1 ('P1 Prize') is the second fastest alternative and can also stimulate the progress of new molecules in the clinical pipeline. However, it is important to think long-term as well and start investing as soon as possible to support an inflow in this pipeline of innovative projects from the preclinical stages, which requires the introduction of prizes at the end of the preclinical steps ('PC Prize'), targeted grants and the development and broadening of R&D Collaboration PiCoors. In other words, a prioritization of either long-term effects or rapidity in the effects means that precedence should be given to different incentive models. Overall, one can see both the Non-Profit Developer PiCoor and 'P1 Prize' as two new mechanisms that should be prioritized in terms of timing because of their relative speed, whereas the 'PC Prize' and an enhancement of R&D Collaboration PiCoors can come directly thereafter due to their long-term effect. Grants, on the other hand, have such a pivotal role for the entire system that they must be prioritized, which means that they need to come in a steady flow and, if possible, be raised to progressively strengthen the national R&D infrastructure and entire antibiotic pipeline, which are important long-term effects of grants.

Looking at combinations of incentives depending on the amounts invested and their effectiveness, the simulation has shown (see Section 3.1) that the most effective combination for obtaining an approved antibiotic is an R&D Collaboration PiCoor and 'P1 Prize' or the other types of milestone prizes, followed by a combination of grants and 'PC Prize' (see Table 2).

How can one combine the three incentive models based on their nature and functions? It should be borne in mind that Pipeline Coordinators are active and highly committed mechanisms that take a holistic view of the entire pipeline in ways that the more reactive and automatic grants and milestone prizes cannot. Therefore, Pipeline Coordinators are the incentive models that have the best ability to create synergies because they can intervene within the entire pipeline and have the capacity to coordinate, share and monitor both grants and milestone prizes. More specifically, a Pipeline Coordinator could conduct analyses similar to those that we made for the case studies in this assignment, that is, it could review specific R&D projects and identify the incentives and amounts that best suit the particular project. Which incentives creates the greatest stimulus and maintains the right risk profile for public investments – a grant or milestone prize? Here, the same Pipeline Coordinator could decide to allocate and use different shares of the other two mechanisms: for some projects, a milestone prize of the amount corresponding to the R&D cost of the previous phase may suffice if a grant has also been assigned earlier to the same project.

To emphasize the importance of synergies from combining the three proposed incentive models, one might consider what would happen if one of the incentives was not implemented. Excluding grants would cause long-term problems because there would be few early-stage R&D projects that could be helped to the market (i.e. the pipeline would be 'dry'). If one excludes milestone prizes, molecules that just entered the clinical pipeline would suffer from the current market situation with no stimulus unless a Pipeline Coordinator chooses them and creates a customized support plan. Finally, if one chooses not to support Pipeline Coordinators, one would lose the only incentive that can follow a molecule from early stages to launch and forgo major improvements in terms of effectiveness of grants and milestone prizes that Pipeline Coordinators offer.

4. Conclusions and recommendations

The purpose of this report was to identify, analyse and suggest a portfolio of incentives that Sweden and Swedish actors can invest in during the coming years. Relying on discussions with experts and stakeholders (i.e. potential recipients of Swedish incentives), computer-based simulations and case studies with relevant companies, this investigation produced a set of results that can be summarized in a series of conclusions presented here.

Discussions with experts on antibiotics R&D, global health and innovation helped in the selection of a portfolio of incentives that fits Sweden and consists of three models: grants, milestone prizes and two forms of Pipeline Coordinators – R&D Collaboration and Non-Profit Developer. By excluding a Market Entry Reward (MER), Sweden can cover a larger proportion of the funds for other incentives needed for a new approved antibiotic, significantly higher than 0.8–3%, which is the reasonable Swedish share for an MER. Contributing more to a certain incentive provides Sweden with higher visibility and greater influence over how the incentive is designed and directed. This applies to all three incentives proposed. A fourth incentive model, regulatory simplifications (a significant reduction in time and cost for Phase 3) was also considered relevant for Sweden but, due to the major changes and potential risks for patient safety this would imply, further analysis of this incentive's regulatory and medical implications is necessary. Regulatory simplifications could be based on Sweden's expertise and experience in regulatory issues and also showed strong effects in the simulation, especially in late R&D phases. An advantage is that these effects would come without significant investments from public actors. Following this, a series of recommendations for each of the three models proposed for Sweden's incentive portfolio is presented:

1) Grants should be assigned to early-stage projects, have a long-term focus and be oriented towards infrastructure building (see Section 2.2). Sweden's average annual investment in R&D for antibiotics of 7 M USD (60 M SEK, see Section 1) is in line with the Swedish share (about 2–7.5 M USD) of the total investment in grants of 240 M USD that are needed to obtain one new antibiotic's approval (see the third column of Table 1). However, a long-term perspective and repeated investments are needed in this type of incentive because its effects require time to manifest. Grants are also important because they can help Sweden build and strengthen its R&D infrastructure for antibiotics (for example, through targeted investments in selected centres of excellence) and can be put into use immediately for this purpose and to improve the early R&D pipeline. Overall, there is a need to maintain and, if possible, increase grants to finance both individual R&D projects and the development of competences and R&D infrastructure.

2) Milestone prizes are, according to the simulation, very effective pull incentives and the most attractive mechanism for SMEs, which play an increasingly important role in R&D on antibiotics and thus need an incentive to suit their needs for early reward of their efforts. Of the three milestone prizes tested in the simulations, Sweden should first invest in a prize at the end of Phase 1 and later also on a prize at the end of the preclinical stage. The reason for starting with a Phase 1 prize is that it would have a relatively quick effect at the beginning of the clinical pipeline, which is in dire need of immediate replenishment. In addition, a Phase 1 prize would be easier to handle compared to a preclinical prize (which would certainly have a much higher number of applications that are difficult to assess). Such a Phase 1 prize, with high and clear demands on the degree of innovation of the molecule and focusing on specific pathogens, would give Sweden high visibility, especially if Sweden could cover a larger proportion of the 10–20 M USD deemed attractive for such a prize (according to the response of the SMEs participating in the case study; see Section 3.2). In a second moment, Sweden could also engage in the

introduction of a prize at the end of the preclinical stage to focus more on longer-term results and help fill the clinical pipeline.

3) Pipeline Coordinators is the incentive that offers the highest flexibility in tackling the gaps in the R&D pipeline and is particularly suitable to support specific antibiotic projects (see Section 2.2 for details of the two Pipeline Coordinator designs recommended here). In addition, an R&D Collaboration PiCoor is the most effective of all incentive models if it achieves its full potential, which, however, requires managing the potential risks of complicated bureaucracy and conflicts between parties, including conflicts of interest. A Non-Profit Developer PiCoor is the mechanism that can cover the entire R&D pipeline and provide maximum support for selected projects, including ensuring global availability of these products and rational use without sales pressure. In addition to these important effects, a Non-Profit Developer PiCoor could be funded through the international aid budget (e.g. SIDA) and strengthen Sweden's role in improving global health. Pipeline Coordinators also provide a mechanism for linking national Swedish R&D centres to major international initiatives, thereby strengthening the effects of national grants. Sweden is already involved through the EU's IMI program in terms of human resources and funding of this kind of initiative, with approximately 2 M USD (1.8 M Euro, see Section 1), representing an important share of the approximately 12 M USD needed, according to the simulation, to double the number of profitable projects through an R&D Collaboration PiCoor (see Section 3.1, Table 1). It is therefore relevant to continue with these types of investments and to further develop Pipeline Coordinators to their full potential.

The disadvantages and risks of the three aforementioned models have been discussed and none are considered significant enough to prevent Sweden from using any of the three models (see Section 3.4). Rather, it is highly relevant to use the three incentives together to obtain optimal results. First, the three incentive models complement each other as they intervene and generate their main effects in different parts of the R&D pipeline (see Figure 1 in Section 2.3 and Figure 2 in Section 3.1). Second, there are other synergies that make these three mechanisms valuable to use together, such as the reinforced effects in terms of reduced costs per approved antibiotic. For example, valuable synergies may be gained by combining grants and milestone prizes, as well as by using a Pipeline Coordinator to manage and customize these other two incentives. If the three incentives cannot be introduced all at the same time, the following time schedule is recommended: grants should be retained at current amounts or increased to create long-term effects on the national R&D infrastructure and eventually to reinforce the antibiotic pipeline. At the same time, one should start investing in the Non-Profit Developer PiCoor and set a milestone prize at the end of Phase 1 to exploit the relatively rapid effects of these two incentives, followed in time by the development and strengthening of the R&D Collaboration PiCoor and the establishment of a prize at the end of the preclinical stage.

Overall, the three incentive models and their combined use offer a set of innovative and powerful incentives that have a strong impact on different parts of the R&D pipeline. The costs are also reasonable and would allow Sweden to cover larger shares and thus be responsible for some of the proposed incentives. Finally, these efforts are based on Sweden's strengths, tradition and history in the field of antibiotics and can increase Sweden's international visibility and strengthen Swedish R&D infrastructure for antibiotics in the long term.

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Appendix A – Experts in the Nordic panel and international experts

Experts in the Nordic panel:

Helle Aagaard, Richard Bergström, Otto Cars, Lars Jonsson, Anders Karlén, Ivar Vågsholm och Christine Årdal.

Alexandra Waluszewski, Swedish expert who participated with written comments.

International experts:

Grania Brigden, Aleks Engel, Ramanan Laxminarayan, Jasper Littmann, Chantal Morel, Kevin Outterson, Jens Plahte, John-Arne Røttingen och Ursula Theuretzbacher.

We thank all experts for highly valuable opinions and comments on the incentives which were discussed. We take full responsibility for how we interpreted their views. This report does not aim to reproduce exactly the experts' support or critique of the incentives which were under scrutiny.

Appendix B – Methods and parameters for the simulation

In this study, we have built a Monte Carlo simulation that explores the present values according to the ENPV formula (Expected Net Present Value) that different antibiotics can have under various circumstances or scenarios from the time of preclinical studies to launch in the market. These scenarios correspond to virtual R&D projects and may, in turn, vary in terms of, for example, technical likelihood of success, overall probability of success, development costs, development times, expected future revenue, financial expectations of the developer, and the impact of different incentive models.

The technical likelihood that the development of a new antibiotic succeeds in each phase of development was assumed to comply with reported standards and is attributed as a probability-based chance of success according to a uniform distribution of values (see PoS = Probability of Success, Complementary Table 1, Appendix B). For those projects that do not fail for technical reasons, it is assumed that antibiotic developers decide whether to continue the project (i.e. continued financing) based on the project's ENPV. ENPV is a widely used measure to support decision-making about the profitability of major investments. The use of ENPV for these purposes is very common especially in large pharmaceutical companies and has previously been applied to model the decision-making of pharmaceutical companies[21].

Our simulator applies the formula here to calculate ENPV:

$$ENPV(i,n) = P(n)\sum_{t=0}^{n}\frac{C(t)}{(1+i)^t}$$

In this calculation: *i* symbolizes the discount rate (cost of capital) of the developer, *n* represents the last month of sales (in our simulation, this corresponds to the end of the patent), *P(n)* symbolizes the probability of reaching the last month of sales, and *C(t)* symbolizes the positive or negative cash flow at the end of each simulated month *(t)*.

Moreover, we assume in this simulation that projects are evaluated on the basis of their ENPV only when they are about to enter a new development phase. To capture differences among developers of new antibiotics, we introduced a 'Yes / No' decision before the start of each new development phase. This decision is based on the project's ENPV. An ENPV-based valuation of a given development project means there is an alternative cost for this investment. This alternative cost therefore needs to be taken into account, which is done by simulating a constant need to find capital at a cost that varies between 8% and 30%. This alternative cost is reflected by the discount rate used by developers in the evaluation of investments in R&D. To reflect the variation between the alternative costs of different developers, projects are assigned different discount rates to be used in these ENPV-based investment decisions. Finally, different developers are assumed to use different profit thresholds that a project must overcome to be eligible for further investment. These profit thresholds are translated in the simulation as the additional profitability (about 0–200 M USD) that a developer requires, in

[21] See, for instance, Blau, G.E., Pekny, J,F., Varma, V.A., & Bunch, P.R., Managing a portfolio of interdependent new product candidates in the pharmaceutical industry, *Journal of Product Innovation Management*, Vol. 21, No. 4, pp. 227–245, 2004, and Okhravi, C., McKeever, S., Kronlid, C., Baraldi, E., Lindahl, O., & Ciabuschi, F., Simulating market-oriented policy interventions for stimulating antibiotic development, *Simulation Series*, Vol. 49, No. 1, pp. 12–23, 2017.

conjunction with a positive ENPV, to decide to finance another development phase of the new antibiotic[22].

R&D in antibiotics is conducted through a number of formalized development steps: preclinical stage, Phase 1, Phase 2, Phase 3 and approval. These phases vary in terms of duration (time), cost and likelihood of success (PoS). When a new project is created in the simulator, a random variation of these parameters is drawn from a uniform distribution of data, which in turn is sourced from two comprehensive empirical studies[23]. Data relevant for the calculation of ENPV are based on a uniform distribution in which the lowest possible income is 0 (reflecting antibiotics lacking a market at approval) and the highest is 1,900 M USD. In the simulation, we assume that the size of a new antibiotic market grows linearly for 10 years or until the patent expires. Average revenues of 950 M USD were used to focus on antibiotics that have small markets and are therefore assumed suitable to receive the various incentives. All data in the two aforementioned empirical studies have been reviewed and, where necessary, adjusted based on critical comments from experts and panels composed of representatives from both large and small pharmaceutical companies, health authorities, and academia. The input parameters of the simulation are presented in their entirety in Complementary Table 1 in Appendix B.

We report here the results of a Monte Carlo simulation of antibiotics R&D, which was designed for this particular study to be applied in a large-scale simulation, with a total of 50,000 runs. In addition to simulating current antibiotics R&D, the results also include the effects of different incentive models discussed with Nordic and international experts, as well as with stakeholders (i.e. potential recipients of the Swedish incentives). Furthermore, the impact of the different incentive models on antibiotics R&D projects has been discussed in terms of input values, simulation parameters, and assumptions concerning developers' behaviours. The simulator reflects the effects of introducing nine different incentive models as follows:

- a '**push**' incentive in the form of **grants**;
- two '**pull**' incentives in the form of an **FD** (fully delinked) **MER** and **PD** (partially delinked) **MER**, which guarantee developers high revenues in the form of cash payments if the developer successfully finalizes the development of a new antibiotic that meets certain conditions for approval;
- three variants of the '**pull**' incentives **milestone prizes**, more specifically, a '**PC Prize**', '**P1 Prize**' and '**P2 Prize**', which are payments given upon successful completion of a specific development phase (respectively, preclinical, Phase 1 and Phase 2);
- two **Pipeline Coordinators**, including a collaborative R&D organization, '**R&D Coll**', and a non-profit developer, '**Non-Prof Dev**'; and

[22] In the simulation, each project is evaluated without comparing its ENPV value with those of other projects that a developer could have in its R&D portfolio. In reality, developers who carry out several projects at the same time tend to prioritize projects with higher ENPV values, which means that companies operating in several therapeutic areas will allocate resources to drugs other than antibiotics. In the simulation, it is also assumed that for each project that reaches a phase in which a certain incentive applies (e.g., the end of Phase 1 for a 'P1 Prize' or market launch for an MER), the entire amount will be awarded. In other words, it is assumed in the simulation that the various antibiotic projects do not compete with each other to obtain a certain incentive but the incentive is directly assigned to them if they meet its requirements and have survived to the particular phase.

[23] Sertkaya, A., Eyraud, J.T., Birkenbach, A., Franz, C., Ackerley, N., Overton, V., & Outterson, K, *Analytical framework for examining the value of antibacterial products*, 2014, and Årdal, C., Baraldi, E., Theuretzbacher, U., Outterson, K., Plahte, J., Ciabuschi, F., & Røttingen, J-A., Insights into early stage of antibiotic development in small- and medium-sized enterprises: a survey of targets, costs, and durations, *Journal of Pharmaceutical Policy and Practice*, Vol. 11, No. 8, 2018.

• a legal incentive, **REGsimp**, reflecting a possible simplification of the regulations for Phase 3.

The aforementioned incentive models are simulated as follows:

• Grants are simulated as a 20–100% reduction in preclinical development and Phase 1 costs, as well as a 20–80% reduction in Phase 2 and Phase 3 costs;

• FD MER is simulated as a replacement of all revenue from sales in the form of a payment of 220 M USD per year for 5 years after approval;

• PD MER is simulated as an annual payment of 150 M USD for 5 years in addition to the expected revenue from sales;

• PC Prize, P1 Prize and P2 Prize are simulated as payments at the start of Phase 1, Phase 2 and Phase 3, respectively, and correspond to three times the average cost of the previous phase;

• R&D Coll is simulated as a 100% reduction of development costs, a 0–30% lower risk of technical failure and 0–30% less time for the preclinical stage and for Phase 1;

• Non-Prof Dev is simulated as a 20% reduction in Phase 1 costs and 100% reduced costs from Phase 2 through approval but also as a 30% reduction in all revenues; and

• REGsimp is simulated as a 50% reduction in costs, development time and risk of technical failure in Phase 3.

Complementary tables and figures for Appendix B

		Economic incentive									
			Push	PiCoors		Pull					Legal
		Baseline	*Grants*	*Non-Prof Dev*	*R&D Coll*	*PCprize*	*P1prize*	*P2prize*	*FD MER*	*PD MER*	*REGsimp*
Preclinical	Duration (years)	2-10	2-10	2-10	1.4-10	2-10	2-10	2-10	2-10	2-10	2-10
	Costs (MUSD)	2.1-17.5	0-14	2.1-17.5	0	2.1-17.5	2.1-17.5	2.1-17.5	2.1-17.5	2.1-17.5	2.1-17.5
	PoS* (%)	18-69	18-69	18-69	23-69	18-69	18-69	18-69	18-69	18-69	18-69
	Revenues/prizes (MUSD)	0	0	0	0	0	0	0	0	0	0
Phase 1	Duration (years)	0.5-5	0.5-5	0.5-5	0.35-5	0.5-5	0.5-5	0.5-5	0.5-5	0.5-5	0.5-5
	Costs (MUSD)	1-15	0-12	0,5-15	0	1-15	1-15	1-15	1-15	1-15	1-15
	PoS* (%)	25-84	25-84	25-84	33-84	25-84	25-84	25-84	25-84	25-84	25-84
	Revenues/prizes (MUSD)	0	0	0	0	29,4	0	0	0	0	0
Phase 2	Duration (years)	1-1.67	1-1.67	1-1.67	1-1.67	1-1.67	1-1.67	1-1.67	1-1.67	1-1.67	1-1.67
	Costs (MUSD)	1-30	0.2-24	0	1-30	1-30	1-30	1-30	1-30	1-30	1-30
	PoS* (%)	35-74	35-74	35-74	35-74	35-74	35-74	35-74	35-74	35-74	35-74
	Revenues/prizes (MUSD)	0	0	0	0	0	24	0	0	0	0
Phase 3	Duration (years)	1.33-4.42	1.33-4.42	1.33-4.42	1.33-4.42	1.33-4.42	1.33-4.42	1.33-4.42	1.33-4.42	1.33-4.42	0,66-2,21
	Costs (MUSD)	16-115	3.2-92	0	16-115	16-115	16-115	16-115	16-115	16-115	8-57,5
	PoS* (%)	31-79	31-79	31-79	31-79	31-79	31-79	31-79	31-79	31-79	47-91
	Revenues/prizes (MUSD)	0	0	0	0	0	0	46,5	0	0	0
Approval	Duration (years)	1-1.58	1-1.58	1-1,58	1-1.58	1-1.58	1-1.58	1-1.58	1-1.58	1-1.58	1-1.58
	Costs (MUSD)	40-88	40-88	0	40-88	40-88	40-88	40-88	40-88	40-88	40-88
	PoS* (%)	83-99	83-99	83-99	83-99	83-99	83-99	83-99	83-99	83-99	83-99
	Revenues/prizes (MUSD)	0	0	0	0	0	0	0	0	0	0
Market exclusivity	Duration (years)	10	10	10	10	10	10	10	5	10	10
	Top sales	10 linear	10 linear	10 linear	10 linear	10 linear	10 linear	10 linear	1-5	10 linear	10 linear
	Revenues/prizes (MUSD)	0-1,900	0-1,900	0-1,330	0-1,900	0-1,900	0-1,900	0-1,900	1,100	750-2,650	0-1,900
ENPV	Discount rate (%)	8-30									
	Threshold (M USD)	0-200									

* Probability of Success

Complementary Table 1: Input parameters for the simulation in the various R&D phases and for different incentives (see red figures)

		Preclinical			Phase 1			Phase 2			Phase 3		
		min	mean	max	min	mean	max	min	mean	max	min	mean	max
ENPV without incentive ("baseline")		-51,3	-11,1	65,9	-76,2	-9,5	192	-117	-7	358	-155	17	627
ENPV improvement (worsening) per incentive (M USD) from "baseline"													
Economic incentives	*Grants*	0,7	8,5	36,5	1,3	14,3	61	4	27	79	6	44	124
	R&D Coll	-5,1	11,2	46	-12,5	7,5	56	0	0	0	0	0	0
	Non-Prof Dev	-15,4	3,1	35,6	-36	17,7	80	-83	40	122	-148	56	164
	PDMER	0,04	6	94,1	1,3	30,6	191	12	84	300	45	190	459
	FDMER	-7,7	5,1	101,4	-17,4	27,3	233	-29	76	378	-54	175	604
	PC prize	0,5	5,1	16,9	29,4	29,4	29	0	0	0	0	0	0
	P1 prize	0,05	1,5	9	1,7	8,4	19	24	24	24	0	0	0
	P2 prize	0,03	1,3	10,9	0,9	7,2	24	11	20	32	47	47	47
	REGsimp	-1	2,9	55,3	-3,4	14,9	150	-12	41	224	-18	92	378

Complementary Table 2: ENPV without and with nine incentives and at various R&D stages (50,000 runs)

		Preclinical			Phase 1			Phase 2			Phase 3		
		min	**mean**	**max**	**min**	**mean**	**max**	**min**	**mean**	**max**	**min**	**mean**	**max**
ENPV without incentive ("baseline")		-51,3	-11,1	65,9	-76,2	-9,5	192	-117	-7	358	-155	17	627
ENPV improvement (worsening) per incentive combination (M USD) from "baseline"													
Combined economic incentives	***Grants+PD MER***	0,81	14,5	120	4	45	232	19	111	350	59	234	537
	Grants+FD MER	1,07	13,6	120	1	42	277	-4	103	414	-19	219	679
	Grants+PC prize	1,25	13,6	51	31	44	92	4	27	88	6	44	120
	Grants+P1 prize	0,71	10	45	3	23	75	28	51	105	6	44	124
	Grants+P2 prize	0,85	9,8	45	3	22	83	14	47	111	53	90	168
	Non-Prof Dev+PD MER	0,16	9,1	116	5	48	232	28	124	379	68	247	614
	Non-Prof Dev+FD MER	0,16	9,4	145	6	50	285	10	130	505	10	263	825
	Non-Prof Dev+PC prize	-2,84	8,3	51	-7	47	110	-83	40	122	-148	56	164
	Non-Prof Dev+P1 prize	-10,43	4,7	44	-24	26	98	-59	64	146	-148	56	164
	Non-Prof Dev+P2 prize	-9,9	4,5	46	-23	25	102	-56	60	150	-101	103	210
	R&D Coll+PD MER	2,21	20,6	137	0	44	213	12	84	282	46	191	466
	R&D Coll+FDMER	2,54	19,4	148	-1	40	236	-27	77	399	-46	176	664
	R&D Coll+PC prize	3,08	18,1	59	19	37	90	0	0	0	0	0	0
	R&D Coll+P1 prize	-1,74	13,6	56	-3	18	68	24	24	24	0	0	0
	R&D Coll+P2 prize	0,39	13,3	57	-3	16	63	11	20	32	47	47	47

Complementary Table 3: ENPV without and with combinations of eight incentives and at various R&D stages (50,000 runs)