Formalizing innovation-stimulating interventions for computer-based simulation within the DRIVE-AB project

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Abstract

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DRIVE-AB, funded by the IMI (Innovative Medicine Initiative), is a project where the goal is to preserve the development of antibiotics. From research papers and studies, a framework of 35 incentives were summed up, by proposing a series of economic incentives and models that would stimulate the investments in this area. Each incentive was described and divided according to Fund-related mechanisms, Grant-related mechanisms, Revenue guarantees or Assurances etc.

The purpose of this thesis is to develop a framework to formalize these economic incentives, also termed "interventions", so that they can be used as data for an input file in an agent based simulation model. In order for the framework to be developed certain questions needed to be answered. The central issue that will be analysed is how to create conditions required to formalize innovation simulating interventions.

Additional questions that will be determined are what requirements are needed for a valid executable input file considering the basic architecture of the simulator, and what type of parameters there are to extract and merge from the long list of interventions proposed by DRIVE-AB.

Each incentive was discussed and summarized into an ER-diagram. The ER-diagram is colored into different shades of blue where each shade represents pull, push or hybrid mechanisms.

This in turn, gives a clear picture of which aspects are looked at and how each incentive is connected and how they are necessary for simulating future antibiotic R&D.

From the ER diagram, a UML class diagram was created to visualize operations, constraints and execute software applications.

This resulted into one large class diagram, divided into push, pull and hybrid components, and one object diagram. This thesis is done in collaboration with Uppsala University and the DRIVE-AB team.
Summary

This bachelor thesis, Formalizing innovation-stimulating interventions for computer-based simulation within the DRIVE-AB project describes the process of interpreting and understanding a list of interventions given to us by DRIVE-AB. This list concludes different strategies and models to preserve the development of antibiotics while considering the aspect of patients, physicians and investors.

The collaboration with DRIVE-AB started in September in Ekonomikum, Uppsala where we first met the Uppsala team, consisting of Enrico Baraldi, Steve McKeever, Francesco Ciabuschi, Olof Lindahl, Christopher Okhravi and Carl Anderson Kronlid. This meeting was held to meet the team to get an introduction of DRIVE-AB and to specify our contribution. Together with our subject reviewer, Enrico Baraldi and supervisor, Steve McKeever a project plan was created and approved.

The first step was to describe the intervention list in ER diagrams, where we divided the list in half where Marina took the first 17 and Jeanette the later part. Different ER-diagrams have been made and remade, and presented to Enrico and Steve. The smaller ER diagrams have been merged together to create one large ER-diagram describing the list of intervention visualizing the pull, push and hybrid parts. This in turn have led to an UML class diagram, to visualize operations, constraints and how to execute software applications. The class diagram was divided amongst the authors were Marina was working on the push class diagram and Jeanette on the pull diagrams. The process of creating this thesis have been a collaboration between Jeanette and Marina. Conclusion and lessons learned addresses further work to be done and what this result can be used for.
Acknowledgment

The completion of this undertaking could not have been possible without the participation and assistance of the people of DRIVE-AB. Thank you for giving us this experience.

We gratefully want to acknowledge Enrico Baraldi, Steve McKeever and Christopher Okhravi for their leadership, guidance and input throughout this process. Thank you for the advice, support, and willingness that allowed us to pursue this research.
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List of Abbreviations

AMR- Antimicrobial resistance  
CSV- Comma separated values  
DRIVE-AB - DRIVING ReInVEstment in R&D and responsible AntiBiotic use  
IMI- Innovative Medicines Initiative  
MDR- Multiple drug resistance  
NPV- Net Present Value  
OMG- Object Management Group  
PDPs- Product development partnerships  
ROI- Return of investment  
R&D- Research and Development  
SME- Small Medium Enterprise  
TB- Tuberculosis  
UML- Unified Modeling Language
1 Introduction

In this thesis the aim is to improve how interventions to the pharmaceutical drug pipeline can be described with class diagrams. Furthermore the aim is to construct a framework to formalize interventions, so that it can be used as an input-file in an agent-based simulation model for the DRIVE-AB project. These innovation-stimulating interventions have been formulated to test and simulate various ways to raise revenues to incentivize the discovery and development of new novel antibiotics for present and future use. Class diagrams will make it efficient to extract parameters for the input-file and reduce the “Long List of Interventions” (See Appendix p. 34), proposed by DRIVE-AB. These innovation mechanisms have been included in the list by being targeted to fix one of antibiotic-related R&D root bottlenecks. The ambition is that the selected and proposed interventions will be implemented by public organizations, such as national government or transnational bodies (e.g., EU) to promote antibiotic R&D, all of which is part of innovation and health care policy. By experimenting with these interventions and identifying which parameters that may contribute to future development of the implementation of the software-based simulator and hopefully contribute to the study of solutions to address the problem of antibiotic resistance.

1.1 Delimitation

This research-thesis will be delimited within graphical representations of incentive mechanisms for simulating the development of new antibiotics. The long list of intervention mechanisms were analysed and translated from ambiguous text into UML-graphs. These graphs can be used as an input file for currently running version of the simulator.

This thesis has been divided by the authors among literature studies and result. Jeanette Castillo has done literature studies for Sections 3.1, 3.3, 4.1, 4.2, and has created diagrams in Section 5.1 Figure 9, Section 5.3 Figure 13 and Section 5.4 Figure 14. Marina Jaksic has done literature studies for 3.2, 4.3, 4.4, 4.5 Section 5.2 Figure 12, Section 5.4 Figure 15. A collaboration between the authors has been held throughout the whole project process, since the separate results have been combined in the end.

Chapter 1 is an introduction that presents the background to this thesis and delimitation. Chapter 2 introduces the methods used to develop this thesis. This chapter gives also information about the literature studies, meetings and discussions, and how the diagrams were created. In Chapter 3, we provide the background to antibiotics and the pharmaceutical pipeline, explain problems of antibiotics and bacterial resistance, and give an introduction of the large project DRIVE-AB. Chapter 4 is about theory and core-concepts, where we explain intervention mechanisms and criteria, UML diagrams, Agent-based models and present information about the simulator and input file. In Chapter 5 we present the results of our thesis with different sorts of diagrams. Chapter 6 is the conclusion where we analyse what we have created. Chapter 7 is about lessons learned where we suggest future work and presents what we would have done if we had more time. Chapter 8 is the appendix where all figures and attached documents can be found.
2 Method (Literature studies, meetings and discussions)

The DRIVE-AB project presented us with a list of thirty-five incentives (Drive-AB WP2: Long list of innovation mechanisms. See Appendix p. 34). Each incentive is a description of the factors it must consist of as well as the pros and cons.

Data has been collected through different ways on board in the process. This data has been discussed and analysed in this thesis, to get a better understanding about the antibiotic fields when creating UML-diagrams. Data is divided into two types of research areas: primary- and secondary data (Boykin, 2016). Primary data is the data collected by the investigator himself/ herself for a specific purpose, for example this thesis. Secondary data is when using information that has already been collected and compiled by others.

In this thesis, the key source of data is the existing literature on the topic, meetings and discussions. The information is the basis of the result and conclusion of this academic report.

Methods through which data has been collected for this thesis are the following three:

- Literature studies
- Meetings
- Discussions

Each of these methods are described below.

2.1 Literature studies

The process of this academic report began with the authors conducting a detailed information-gathering and fact-finding for two weeks in the beginning of the project. This was undertaken to inquire the field of antibiotic resistance and its economic consequences, especially the lack of innovative antibiotics. To create a framework for identifying parameters from the long list of interventions and for these to compile as an input, there needed to be information-gathering from a technical aspect (ER-, UML diagrams) and a business point of view (Antibiotic-pipeline and interventions). When combining these types of information, the effect of the result can be analysed and not only used as result, but as "lessons learned" for future development within the same field.

The literature study has been made from engines such as Google and Google Scholar, and reports that have been given to us by our supervisors. Scientific reports about the significance of Antibiotics, the Pharmaceutical pipeline and development and ER-, UML diagrams have been consulted for the theory and framework. The reports and journals that have been given to us by supervisors at DRIVE-AB have been useful for the problem formulation and has been the main material for this thesis. The theoretical background that has been broadly summarized, is founded on this literature study.

2.2 Meetings and discussions

Dialogues has been made with the DRIVE-AB Uppsala University-team to figure out how to make this project as efficient and useful as possible. There have been large meetings with the whole DRIVE-AB team with information about the progress of the whole project and feedback from different point of views. These large DRIVE-AB meetings has been held two times in Ekonomikum at Uppsala University. The first meeting was (8/9) where Anna Zorzet, partner in WP2 was invited, to give her opinion of her field of competence, and preparation was done for the annual meeting for DRIVE-AB in Oslo, to present their work with the simulator so far. The second large meeting held place at Ekonomikum as well, where important participants of the project were invited to contribute with their opinions and problem solving. Project managers and stakeholders such as Christine Årdal (Norwegian Institute of Public Health) came together with Ursula Theuretzbacher (Centre of Anti-infective Agents) and David Findlay (Glaxosmithkline Research and Development) and Chantal Morel (University of Geneva) who was with us on Skype, where discussions were held about what was expected and needed for the final delivery of the simulator. Smaller meetings with the DRIVE-AB Uppsala University team (Francesco Ciabuschi, Olof Lindahl, Steve McKeever,
Christopher Okhravi, Enrico Baraldi and Carl Anderson Kronlid) has been held two times in between these large meetings, to prepare what to present for the larger meetings.

Separate meetings with supervisors has been conducted every two weeks for feedback and contact through email when needed. Regular contact with Christopher Okhravi who constructed the simulator has been important since it is an ongoing process with constant change of details, that might affect the result of the input file. Dialogues through email and live meetings has been the basis of this thesis when not finding answers on search engines or in the literature, and useful information from supervisors and their experiences has been used as material for this academic report.

2.3 Diagrams

The result and abstractions were made by creating different types of diagrams. ER diagrams were created of each incentive to get a deeper understanding of the meaning of text. This made it possible to pair up some incentives and reduce the amount of components. The new reduced diagrams were then created as UML class diagrams, to make them more efficient to present and more readable.

From the text in figure 2, the ER diagram in figure 1 was created. The abstraction of the intervention no. 30 was made by identifying key parameters and combining them with common relationships. The same procedure was made on intervention number 31 (Figure 3 and 4).

After creating ER diagrams for all the interventions from the list (See Appendix p. 34), the diagrams were reviewed to find common parameters. Several diagrams were merged together to decrease the amount of diagrams. One example is the Figure 5 below, where a combination of Figure 1 and Figure 3 became an UML diagram (See Section 5.2) and one Object diagram (See Section 5.3).
Figure 3: Example of a created ER diagram from Intervention no. 31 from the Long list of interventions.

31. Fully refundable R&D tax credit

<table>
<thead>
<tr>
<th>Description</th>
<th>Also Known As or Included In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under a fully refundable tax credit, companies report their annual investment in R&amp;D towards specified antibiotics, and the tax credit that the company would have received if it had taxable income is instead paid out in cash.</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4: Intervention no. 31

Figure 5: Example of a created UML class diagram reduced from several ER diagrams.
3 Background

This chapter is about the background and problems of antibiotics and gives an overview of the current antibiotic pipeline and the project DRIVE-AB. Antibiotics had their glory days between 1930-1960, since then the antibiotic pipeline has experienced a long-term fall. DRIVE-AB’s task is to reduce the problems caused by AMR (Antimicrobial resistance) through responsible use and identify new economic models of novel antibiotics.

3.1 Background of antibiotics

In 1928 Alexander Fleming discovered a mold on a staphylococcus culture, he named the substance penicillin (Nobel media, 2014). Between the period of 1930 and 1960 the development of antibiotics was at its highest point, also known as the golden era. The period is called golden since at that time success seemed to be unstoppable and is called an era as the success ended. When scientists tried pursuing making antibiotic drugs instead of making variants of old ones it resulted in failure, a few years later signs of resistance were observed (Michigan state university, 2011; Eastern Research Group, 2014).

Antibiotics such as penicillin was not introduced to the market until the 1940s, other antibiotics that were discovered were Bacitracin (1943), Oxytetracycline (1950) and Methicillin (1960), (Michigan state university, 2011). As the antibiotics were introduced to the market the treating of serious infections such as tuberculosis and meningitis has increased. A consequence to this phenomenon is the misuse of antibiotics, which have made serious diseases, such as Staphylococcus aureus hard to treat once again (Renwick et al, 2014; Eastern Research Group, 2014; Michigan state university, 2011). In addition, the pipeline for new antibiotic drugs has experienced a long-term fall. In other medical fields is it common to improve previous drugs as it is meant to be the first choice for patients when it is out on the market, this is not the case with antibiotics. The use of novel antibiotics is uncertain until previous antibiotic drugs are resistant. By the time a new antibiotic becomes the standard choice, it might be near or beyond the end of its patent life. Which means that it might be a struggle for the pharmaceutical company to generate revenues and recoup its development costs (O’Neill, 2015).

The resistance is not only bound to bacteria, but rather all microbes that have the potential to mutate. All effort to manage malaria or HIV could be reversed, with diseases once again spiraling out of control (O’Neill, 2014). According to O’Neill (2014), countries with high risk of malaria, HIV or TB are likely to suffer as resistance to current treatments increases. If the resistance of AMR is not taken seriously modern healthcare systems and treatments which rely on antibiotics to reduce the risk of bacterial infection will become far more risky to undertake than helpful.

The pace at which we discover antibiotics has slowed drastically while antibiotic use is rising. Antibacterial resistance is a problem and grows with the misuse of existing drugs. The increasing resistance has to do with overuse by physicians and patients which results in infections not responding to medical treatment (Renwick et al, 2014; O’Neill, 2014; Eastern Research Group, 2014).

Despite the potential in novel antibiotics, large pharmaceutical and biotechnology companies are reluctant to invest and develop novel classes of antibacterial drugs and therefore exiting the market. These market exits are based on insufficient returns of capital invested in the development of antibiotics. Governments across the globe are now searching for models and incentives which can stimulate and attract the development of novel antibiotics (Michigan state university, 2011, Renwick et al, 2014; O’Neill, 2014).
3.2 Antibiotic pipeline and development

3.2.1 Pipeline from discovery to profit

The current antibiotic pipeline is a group of 37 antibiotic candidates that several pharmaceutical companies have under clinical development, which are now clinical phases (I, II and III), for the U.S market. Figure 6, shows the different phases of the development of antibiotic life cycle (Eastern Research Group, 2014). The discovery of a antibiotic drug involves four different types of actors: SMEs, Publicly funded research institutes, Public-Private-Partnerships and Big Pharma (Theuretzbacher, 2014). For a drug to go from discovery to approval and for a company to gain profit, it has to go through various phases. These phases can broadly be grouped into four main stages: discovery, pre-clinical studies, clinical trials and marketing (or post-approval). In the pharmaceutical industry, potential new drugs might spend a decade or more in the pipeline. Each one of these stages in the pipeline involves a lot of costs and failure risks. A potential drug investor will evaluate these costs and risks against the potential ROI (return of investment) before beginning development of a new drug, through these phases.

![Diagram of New Drug Development and Commercialization Activities](image)

Figure 6: Model of New Drug Development and Commercialization Activities

- **Pre-clinical trials**

  For identification of a new drug, research is needed for the particular disease evaluated. In situations where the research finds a target that could deliver beneficial effects, the search begins for a potential new drug (D. Taylor, 2015).

- **Clinical trials**

  Clinical trials are divided into four major phases. The first three are before the drug is marketed and the last one begins when the drug is prescribed for the first time and continues for its life cycle.

  From the pre-clinical trial, a decision is taken whether moving the new potential antibiotic to the second phase, clinical development, where the costs rapidly grow. This decision is primarily commercial, with advice given from the scientific development team. Questions like "Have any negative aspects appeared during the pre-clinical studies? How good is the new potential antibiotic at meeting the medical criteria? What is known about the future competition? How large is the target market? What will the sale price be, etc. etc.?" are asked and with expectation that these questions are positively answered, the antibiotic candidate moves on to the first phase of clinical trials.

Pharmaceutical companies usually have many compounds in their pipelines at the same time. This is an important indicator of the market value and future prospect of a company that want to invest. The more compounds in the pipeline, and the more advanced stage that these are in, is a benefit for the company.

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Other factors are also considered when determining the value of a pipeline. For example, the size of the market of each potentially new drug, the market share, and the risk that this drug will not be approved and successfully go through all phases.

### 3.2.2 Challenges and value of the pipeline

So why are there so few antibiotics in the pipeline and what are the main challenges in the development of new antibiotics?

Drug discovery industry did a fantastic work with preventing natural bacterial threats, and numerous new substances of antibiotics were discovered in the middle of last century. Unfortunately, the progress slowed down, meanwhile bacteria kept developing resistance to the existing drugs on the market.

A shift has been recognized the past years, primarily because of the public health consequences of a declining pipeline of new antibiotics, according to Krans(2014). Policy-makers are recognizing the problems and are trying hard to increase research in this area.

There are many reasons why pharmaceutical companies largely abandoned the field of antibiotic research for many years (Buvailo, 2016).

One aspect of the problem is that antibiotics is extremely difficult to develop, as most of the identified substances were already discovered in the middle of last century, says Buvailo(2016) in his article about “Leadership in Antibiotics Discovery”.

He means that science today has more of a “lottery approach” to develop new antibacterial drugs: some research groups accidentally come across a potential candidate drug and try to develop it, with low success rate. Without a significant choice of lead compounds, there is not much for drug discovery researchers and pharmaceutical companies to test for human trials.

Another identified problem is the economic part of antibiotic development. Pharmaceutical companies spend enormous amount of money on discovery research, clinical trials and on the approval process, without the guarantee that the result will pay back.

It is easier for companies to concentrate on developing drugs in areas where there are regularly demanding users, such as pills to keep cholesterol in order which would be used by a lot of people on regular basis. That is why antibiotics are among the harder candidates in development.

Antibiotics have strict prescription limits and are relatively cheap, compared to anti-cancer drugs and which makes them compete in an area of inexpensive generics (E. Sukkar, 2013).

The third problem is overuse of antibiotics. Bacteria have effective defense mechanisms, giving them a chance to mutate over time and become resistant to many medicines available on the market today. Resistance has increased because of the regular misuse of antibiotics, for example when using them to treat viral infections like colds, which they are not able to cure. Another significant obstacle of developing new antibiotics in the pipeline, exists in the clinical trial process that is used to test new medicines (Mezher, 2016). To prove the value of new antibiotics, it is necessary to test them against bacterial infections that are resistant to the medicines that are typically prescribed. Finding patients with these specialized infections can be very challenging and current diagnostics cannot identify them quick enough.
3.3 DRIVE-AB

According to O’Neill (2015), companies have to make investment decisions years before an antibiotic drug is available on the market. It takes approximately 15 years for an antibiotic drug to go from the start, initial research to the end, a marketable product. The failure rates in new antibiotics are high, which means that in a majority of cases there is no financial return (Harbarth et al, 2015; O’Neill, 2014).

There are three economic incentives that needs to be met before the antibacterial crisis becomes urgent. These are:

- To attract companies to invest in the R&D market and bring new products.
- To protect the valuable resources from misuse and premature resistance.
- And to ensure global access of antibiotics (Outterson, 2014).

A tool to address these problems is the project DRIVING Re-InVEstment in R&D and responsible AntiBiotic use, (DRIVE-AB). It is a three year long project that started in October 2014 and is founded by the IMI. A collaboration between European Union and the European Federation of Pharmaceutical Industry Association (EFPIA), and is composed in 12 different countries where there are 16 public and 7 private partners (Drive-AB, 2014).

According to DRIVE-AB’s website (2014), the project is to provide and search answers in the following areas:

1. Reducing AMR through responsible use and
2. Identifying new economic models of novel antibiotics for now and the future.

DRIVE-AB will produce models step wise where the first step is to develop an evidence-based definition, of ‘responsible use of antibiotics’. This will provide a framework for later steps. Data from surveillance systems, databases of antibiotics, and literature studies will provide estimations of today’s situation of antibiotic resistance from the perspective of both clinical and economic. Simulation models based on collected data will estimate the need and impact for future public health needs in socioeconomic settings (Harbarth et al, 2015; Drive-AB, 2014).

DRIVE-AB’s main task is to preserve the development of antibiotics. By methodically concluding different existing strategies, thirty-five interventions were summed up. The most promising simulation model will be presented and tested with policy makers and investors in late 2017 (Renwick et al, 2014; Harbarth et al, 2015).
4 Theory and Coreconcepts

This chapter is about the intervention mechanisms and criteria, UML diagrams and a brief summary of agent-based models. The current existing simulator and input-file will be introduced, together with an illustration of the contribution from this thesis.

4.1 Intervention mechanisms

In the beginning of DRIVE-AB’s project there were forty-four identified incentives which were categorized in push, pull and hybrid incentives depending on where in the pipeline the affect.

Push incentives is to increase the research and development of new antibiotics. Push methods reduces the costs by providing research grants, tax incentives and establishing partnerships for sharing R&D outlays. This benefits smaller companies that often lack the capital to go from pre-clinical research into clinical development. A majority of the risks with R&D is borne by the investors since the possibility that push incentives will fund projects that will fail. A major problem is that it gives the developer sole knowledge regarding a project’s progress which permits the developer to act in its own interests (Renwick et al, 2014).

Pull methods are defined as outcome-based or lego-regulatory, and aims to reward development of novel drugs by increasing and ensuring future revenues. Outcome-based pull incentives motivates companies to work efficiently in launching a drug that meet the developer’s requirements. Compensation is made to the developer as long as the drug is successful and removes all financial risk from the investor.

The uncertainty and financial risks deterrents potential market investors. While price setting and market authorization often are difficult to estimate, a good outcome-based pull incentive is defined to frequently motivate developers to undertake the R&D risks. Examples of outcome-based strategies are monetary prizes, advanced market commitments, and patent buyouts (Renwick et al, 2014).

Lego-regulatory pull strategies only reward successful research which maximizes motivation and efficiency. This means that companies are offered higher market returns and as outcome-based pull incentives, the developer bears all the risks of R&D except from companies who lacks resources such as capital. Lego-regulatory pull mechanisms includes market exclusivity extensions which might reduce innovation and competition.

Pull methods depend on investors remaining committed to the project despite changes in funding priorities. While a challenge with pull incentives is defining the optimal set of drugs that does not result in a mismatch with the goals (Renwick et al, 2014).

Hybrid incentives is a combination of push and pull methods (Renwick et al, 2014).

4.2 Intervention criteria

According to Renwick et al (2014), there are four market criterias that has to be met for an incentive to be reviewed by the DRIVE-AB.

1. Improve the overall net present value (NPV) for new antibiotics.
2. Enable greater participation of SMEs.
3. Encourage participation by large pharmaceutical companies.
4. Facilitate cooperation and synergy across the antibiotic market.
1. Improve the overall net present

From Renwick et al (2014), NVP is the sum of all costs and measured in the profitability of a project. The estimated NVP in different research fields are $50 million dollars in antibiotics, +$1.15 billion dollars in the musculoskeletal drug and +$720 million in the neurological drug. Stakeholders are reluctant to invest in the antibiotic market as long as the revenues are low. To increase investment a suggested NVP for antibiotic drug is +$200 million.

2. Enable greater participation of SMEs

The increment of drugs in the late 1980s and early 2000 prevented SMEs to participate in antibiotic R&D, since SMEs does not have the capital larger pharmaceutical companies have. Since antibiotic projects are dropped in the research or early clinical trials, payments and cost reduction is an important aspects for SMEs (Renwick et al, 2014).

3. Encourage participation by large pharmaceutical companies

Unprofitable, size, risks and regulations are factors that makes larger companies hesitate investing in antibiotic projects. Pharmaceutical companies need approximately $800 million in revenues from a single project/product opposed to SMEs which needs between $100 million to $200 million per year. To attract companies as Big Pharma, financial rewards and policies awards from the government should be in focus (Renwick et al, 2014).

4. Facilitate cooperation and synergy across the antibiotic market

According to Renwick et al (2014), to encourage pharmaceutical companies and governmental holders sharing information, resources and expertise can be cost effective and help align public and private priorities. The antibiotic delinkage is one attempt to change the current business model. It is a method that can offer a sustainable and global approach and seeks to solve three problems simultaneously. The first is to provide market incentives for companies to invest in R&D and contribute with new products to the market. Second is to provide market incentives to protect valuable resources from being overused and premature resistance. And finally to ensure global access to life-saving antibiotics (Outtersson, 2014).

4.3 UML

UML stands for Unified Model Language. It is a generalizing language for specifying, visualizing and documenting the design systems that was created by Object Management Group (OMG) and UML 1.0. The goal was to define a general language that could be used by all modelers and simple to understand. Although UML is not a programming language, there are tools that generate code in various languages using UML diagrams (Tutorialspoint, 2016).

4.3.1 Object oriented concepts

Object oriented systems generally uses UML since the language follows the object oriented methodology and concepts. An object contains data and methods, where data represents the state of the object. A class forms a hierarchy to model real world systems and describes the object (Tutorialspoint, 2016). According to Fakhroutdinov (2016) and Tutorialspoint (2016), object, classes and attributes are described as:

- An object is an instance of a class, it contains the state and behavior, where a state is the attributes and relationships. The behavior are defined as operations and methods.
- A class is a blueprint of the object. It describes objects that share the same features, constraints and semantics.
- An attribute is defined as values that can be connected to a class or interface.
4.3.2 UML diagrams

UML diagrams can be divided into two categories, Structural diagrams and Behavioral diagrams. Structural diagrams represents the static aspect of the system. It is used in documenting software architecture and the static parts has the following four structural diagrams (Tutorialspoint, 2016).

• Class diagram,
A class diagram describes attributes, operations and constraints of a class. In addition to visualizing, describing and documenting different areas of a system, class diagrams can execute code of software applications. It is the only UML diagram which can be mapped with object oriented language (Tutorialspoint, 2016; Ambler, 2014).

• Object diagram,
Object diagrams represents an instance of class diagrams, which means that object diagrams depends on class diagrams. A side from the basic concepts, object diagrams represent the static view of a system. The difference between the two diagrams is that class diagrams represents an abstract model consisting of classes and their relationships while object diagram represent an instance at a particular moment (Tutorialspoint, 2016).

• Component diagram,
A component diagram is used to illustrate the physical of a system such as libraries, files and documents. Used to visualize, it illustrates the architecture and the functionality between the components (Tutorialspoint, 2016; Visual paradigm, n.d).

• Deployment diagram,
Deployment diagrams is used to illustrate the topology of the physical components. It focus on the distribution of components in an application and the run-time configuration in a static view (Tutorialspoint, 2016; Visual paradigm, n.d).

Behavioral diagrams is the dynamic aspect of systems, meaning the functionality of the software system when it is running. The dynamic part is represented by the five UML diagrams (Tutorialspoint, 2016).

• Use case diagram,
Use case diagram consists of actors, an entity that interacts with the subject. There are internal and external actors where the use case diagram gathers the essence of a system and models the system and subsystem of an application. It describes the behavior of the system from an external point of view (Tutorialspoint, 2016; Visual paradigm, n.d).

• Sequence diagram and Collaboration diagram,
Sequence diagram and Collaboration diagram is also known as Interaction diagram. The two diagrams are used to capture the different angles of systems dynamic behavior, to model how the object interacts in a particular scenario (Tutorialspoint, 2016; Visual paradigm, n.d).

• Statechart diagram,
A state diagram is an illustration of different states an object can encounter during its lifetime. It is useful to model reactive systems that can be both internal and external events (Tutorialspoint, 2016).

• Activity diagram,
An activity diagram is the dynamic aspects of a system. Described as a flowchart, it goes from one activity to another (Tutorialspoint, 2016).
4.4 Agent-based models

Agent-based modeling is a form of computational social science simulation. That is, it involves building models that are computer programs and is particularly suited to topics where understanding process and their consequences is important (Gilbert, 2008). The DRIVE-AB project is developing a simulator according to this kind of modeling. This method has been chosen because computational models are formulated as computer programs in which there are some inputs (independent variables or parameters) and outputs (dependent variables), while the program itself represents the processes that are thought to exist in the social world (Macy & Willer, 2002 p. 2).

Figure 7: A tick diagram that shows the process when simulating a tick in each alive project, from the simulator DRIVE-AB is developing. See Appendix p. 55 for a larger picture.

Agents interact within an environment and can be either separate computer programs or, more commonly, distinct parts of a program that are used to represent actors such as individual people or organizations. Their aim is to react to the computational environment in which they are located, where this environment is a model of the real environment in which the social actors operate. They can interact by passing messages (dialogue between people or information flow) to each other and act on the basis of what they learn from these messages.

4.5 Simulator and Input-file

For the simulator to execute, there will be an input file needed with relevant information. Most programs require a user input in some form, in order to be useful in a real-world setting. An input file for the DRIVE-AB simulator, is a file that contains data that serves to the current version of the simulator.

The preparatory work with diagrams that this thesis has been about, is meant to contribute to the input file that is serving the DRIVE-AB simulator.

The top level of the input file contains the following five elements:

1. Number of runs: How many times to run with the same initial conditions.
2. Number of ticks: How long the simulation runs, 1 tick = 1 month.
3. Seed: Two otherwise identical input files will yield the same output if seeds are identical but possibly not, if not identical.
4. Organizations: Currently existing organizations and their corresponding projects.
5. Interventions: The interventions whose effects one seeks to explore.

The simulation is built using the language Ruby with a few RubyGem dependencies. When running a simulation, input is a JSON-file, and output is a number of csv (Comma separated values) files. The csv files can then be ran through standard statistical software to explore hypotheses. The aim is to have the input parameters abstracted so it can be used by any given simulator model, hence it is an ongoing process with changes on the simulator.

The picture below (See Figure 8) is an over-view of our contribution to the DRIVE-AB project. The blue rectangle represent the work done for this thesis, where the list of intervention (See Appendix p. 34), could generate into a class diagram and an object diagram, (See Figure 12 and 13). The input file will contain data from the diagrams and other relevant information to simulate and produce a bar chart with the result.
Figure 8: An illustration of the entire project process. The marked blue square is the contribution of this thesis.
5 Result

5.1 ER-diagram

The given list of interventions (See Appendix p. 34) intended to increase innovation in antibiotic-related R&D have been analysed and merged in different steps. To identify the class hierarchy, a “divide and conquer” model was used to break the ambiguous text, and analyze each intervention separate to gain a deeper level of understanding and extracting common parameters.

Each mechanism was first drawn as a ER diagram, to find common entities and attributes among the others. These diagrams were combined to one reduced ER diagram (See Figure 9).
Figure 9: ER diagram.
5.2 UML diagrams

As the research was moving forward, it was identified that UML diagrams would be a better way to visualize the design of a system, since class diagrams with relationships are fairly easy to understand. The aim is to provide a class diagram that could use any chosen intervention from the text, and run it through the framework. The class diagram (See Figure 12) consists of push, pull and hybrid mechanisms, to see where it effects the antibiotic pipeline. Since class diagrams evolve as real world systems, there have been a lot of changes as the development process moved forward and several drafts have been made. To show an example of an intervention being run in the final UML class diagram, an Object diagram (See Figure 13) was created from a chosen incentive to represent an instance of a class.

There is a general convention when implementing a class diagram. Figure 10 illustrates the relationship between classes used for the class diagram in figure 12. According to Vernon (2014) and Fakhroutdinov (2016),

- **Association** is a relationship between two classes to show how they can be linked to each other.
- **Aggregation** represents a shared ownership relationship where each object have their own life cycle.
- **Containment** (also called composition) is a strong type of aggregation where the object does not have its life cycle if the connected object is deleted.
- **Inheritance** is a specific classifier that inherits part of its definition from the general classifier. Subclasses inherits data from the superclass, such as operations, associations and attributes. Inheritance is also called generalization.
- **Dependency** is a relationship that shows when a class refers to another class. It needs another class for its implementation.

Cardinality constraints between relationships:

The relationship between classes visualizes the connection the classes have. In the class diagram below, there are four relationships types (See Figure 11) that demonstrates the endpoints notations between classes (Gravelle, 2010; Kettunen, 2010).

- **1..1** One-to-one, occurs when a class is related to exactly an occurrence in another class.
- **1..*** One-to-many, occurs when a class is related to many occurrences in other classes.
- ***..1** Many-to-one, occurs when a class with many occurrences is related to one other class.
- ***..*** Many-to-many, occurs when a class with many occurrences is related to one other class with many occurrences and vice-versa.
Figure 12: The interventions represented in a class diagram.
The main class of the hierarchy called **Intervention**, represents all numbers of interventions listed in the given text (See Appendix p. 34). All interventions have **Conditions** for each incentive to be fulfilled. These conditions are depended on different periods of **Time** and are identified with an **InterventionName**.

If these conditions in the pre-clinical development have been successfully fulfilled, the user might want to enter different **Stages** of possible investment. If not, there is a possibility of closing this phase by entering **EXIT**.

The class **Stages** is a superclass that represents possible factors of producing an antibiotic through all phases of the pharmaceutical pipeline, from pre-clinical trials to marketing the drug. This class has three subclasses: **Market**, **Investing** and **Marketing**, that are different paths to reaching the target of the chosen incentive. The subclasses inherits methods and attributes from its superclass.

**Market**
The class Market is evaluated upon possible investment and marketing of a product.

- **Alteration**
  The Alteration class is constantly changing depending on the market. It has a composite relationship which means that Alteration class will be obliterated when the Market class is destroyed.

- **Price**
  The class Price is determined depending on the current Market.

- **Unit**
  The class Unit is determined depending on the current Market.

**Investing**
The class Investing is divided into different ways of providing capital for investing in a new developed Antibiotic.

- **Payment**
  The class Payment have specified milestones for the incentive to fulfill before any payment is awarded.
    - **Milestones**
      Several conditions needs to be fulfilled depending on which class to enter below.
      - **Prize**
        The class Prize are different forms of Monetary prizes. This class highlights the completion of high priority problems and is a form of payment.
      - **Loans**
        The class Loans is providing loans for high-risk projects by the Government.
        - **Risk**
          The class Risk is only entered if the target are high-risk projects.

**Funding**
The class Funding are different forms of financing the new developed antibiotic and tax related incentives. The funding’s might be done through either funds or grants.

- **Funds**
  The class Funds includes all fund-related mechanisms such as antibiotic venture capital fund, the antibiotic corporate bond and an antibiotic government bond.

- **Grants**
  The class Grants includes all grant-related mechanisms, such as cash-grants, interest free loans and incubator/accelerator services.

- **TaxCredit**
  The class TaxCredit are tax reduction mechanisms with different ways of tax deferral or incentives.
    - **TaxIncentive**
      The TaxIncentive class is a subclass to the taxCredit class.
– TaxDeferral
    The TaxDeferral class is a subclass to the taxCredit class.

ProductAccess
The class ProductAccess is a combined class of different mechanisms where the developer can apply for either patent, license or voucher, or have access to different types of platforms.

• Platform
    There are three types of platforms: PDPs (Product development partnerships), R&D and Collaboration platforms that might be accessed through this class, from the perspective of a developer.

    – Collaboration
        The class Collaboration represents the relation between countries and companies working on the platform.

• Patent
    The class Patent is used when applying for a patent on a new developed antibiotic or to extend an existing patent.

• License
    The class License is applied or paid to have access to a specific antibiotic or portfolio of antibiotics.

• Voucher
    The class Voucher is awarded to increase revenue for the company investing.

Marketing
The class Marketing is providing a marketing value and exclusivity for a new developed product.

• Value
    The class Value is used to evaluate whether a product is profitable. It is connected with two classes: Profit and Cost.

    – Profit
        The class Profit calculates the profit value.

    – Cost
        The class Cost calculates the cost of marketing the product.

• Exclusivity
    Market and Data exclusivity is a class used for completing clinical trials and encourages companies to maximize sales.

    – MarketExclusivity
        The class MarketExclusivity is used to give a company exclusive marketing rights.

    – DataExclusivity
        The class DataExclusivity protects the clinical trial data.
5.3 Object diagram

The object diagram is created to give a snapshot of the class diagram at a particular moment. The purpose with the object diagram is to get us close to the actual framework behavior. To demonstrate the “thinking process” of the class diagram, one example with two incentives shown below is reviewed in an object diagram. An example is a snapshot of intervention No.30 ‘Tax credits and deferrals’ and No.31 ‘Fully refunded R&D tax credit’, from the list of interventions (See Appendix p. 34). The object TaxCredit (F3) is identified with three TaxCredit objects: (T1), (T2) and (T3) TaxCredit. The objects are identified with (I1) TaxIncentive, (I2) TaxIncentive and (D1) TaxDeferral.

The following three TaxCredit objects has variables x,y,z that will be static in the actual snapshot, but are changeable in the figure depending on the refundable amount that is entered. The investors can increase the private cost to a level that is equal or below the threshold of the tax revenue. They can also delay paying taxes, through the object TaxDeferral.

![Diagram](image)

Figure 13: The object class diagram
5.4 Mechanisms

In the UML class diagram, the incentives have been categorized in classes depending on where in the pipeline they affect the result. Each class is divided in pull, push or hybrid mechanisms and will be described below with one example for each category.

5.4.1 Pull diagram

![Pull diagram](image)

Figure 14: The Pull class diagram
The classes MarketExclusivity and DataExclusivity have the pull mechanism class Exclusivity in common. These classes are incentives for completing clinical trials. DataExclusivity protects the clinical trial data, preventing other organizations from seeking regulatory approval of a product using the same data as the originating organization for a specified period of time. MarketExclusivity gives a company exclusive marketing rights for a particular drug for a specified period of time. This class is used to incentivize R&D in fields that otherwise may not be pursued, for example medicines for rare diseases.

Marketing is an excellent example of a pull mechanism, since these types of mechanisms aims to reward development of novel antibiotics by increasing and ensuring future revenue. The aim of the marketing phase in the antibiotic pipeline, is to reward successful research and development which maximizes motivation and efficiency. By protecting clinical trial data and giving companies exclusive marketing rights, it encourages companies to maximize sales which gives a high possibility of future revenue.

5.4.2 Push diagram

The push class diagram starts in the Funding and ProductAccess class diagram. The Funding class is connected to three classes, Grants, Funds and TaxCredits which defines ways an antibiotic project can be funded or ways to postpone paying taxes. Since push incentives occurs in the beginning of the antibiotic pipeline, they affect the incentives by reducing the costs and supporting early phase startups. Funds provide financial resources such as grants while grants motivates innovation in the private sector. ProductAccess is a generic name for ways to protect the investment, in this case the antibiotics. There are patent rights that gives the rights to exclude other organizations from making or using the product information for a set period of time. Patents can also extend the life of any patents drugs or be bought by the government. This is an option to save the molecules that are not yet needed. Licenses can be used to seek patent to develop a new drug or to keep the drug of the market until it is needed. Vouchers gives an antibiotic regulatory approval of a non-related drug. It is not a patent you gain money from but a possibility to raise more money.
Figure 15: The Push class diagram
5.4.3 Hybrid diagram

Hybrid mechanisms is a combination of both push and pull mechanisms. The example of risk-sharing loans provides both of these mechanisms in one incentive.

The class Loans is provided by governments or publicly funded institutions for high-risk projects within a specified profile at lower-than-market interest rates. If the milestones for the contract have been achieved, the loans are expected to be paid in full. If not, portions of the entire loan are written off. These kinds of loans are meant to attract co-investment from other investors by reducing the risk profile. This incentive promotes greater public and private investments. Since push incentives are aimed to increase the research and development of new antibiotics, these kind of loans is one way of reducing costs and establishing partnerships for sharing R&D outlays. If the milestones are achieved or not achieved, the loans could be paid in full or portions of the entire loan could be written off. This would secure future revenue and attract co-investment and by that reduce the risk-profile, which makes it a pull incentive as well.

Figure 16: The Hybrid class diagram
6 Conclusion

The framework that was developed to formalize interventions, is a combination of translating ambiguous text into diagrams and identifying overlapping incentives. When creating ER-diagrams of the given text, it was easier to separate key parameters from the ones that would not affect the output as much. A large task of this project was doing research on the complexity of the words in each intervention, concluding the output of each mechanism and identify key parameters from each incentive. The valuable, identified parameters were captured to the mechanisms of the pipeline and reduced to one large UML class diagram (See Section 5.2, Figure 12). Since the theory of object oriented systems often uses UML (Tutorialspoint, 2016), the structure follows the object oriented methodology and concepts. The objects contains data and methods.

The hierarchy in the class diagram is represented as inheritance, consisting of classes and their mutual relationships. The created object diagram (See Section 5.3, Figure 13) is a representation of an instance at a particular moment and is more close to the actual system behavior (Tutorialspoint, 2016). The aim is to capture the static view of an intervention in the system at a particular moment. The object diagram was initially created in this research, to show an example of how to choose one particular intervention from the list (See Appendix p. 34) and capture the view of it running through the class diagram.

The main class “Intervention” in the class diagram, uses methods from classes below to identify what incentive the user wants to use. There were many incentives that had similar parameters, which made it possible to identify overlapping in the diagrams. According to Renwick’s et al (2014) definition of intervention mechanisms, analysing whether they were affecting the pipeline as pull, push or hybrid mechanisms (See Section 5.4), is not only important for extracting parameters, but also useful for future research, depending on whom each incentive will be presented to. We also needed to take the four market criteria that needed to be met for an incentive to be reviewed by DRIVE-AB (Renwick et al, 2014) in consideration when creating the diagrams.

The creation of the diagrams and the input file are two separate projects, abstracted from each other. The creation of the input file might be in Section 7, if time allows. The aim was to prepare key parameters for a input file, that could be run through any simulator. The architecture of the simulator is unknown since it is a developing process that will change during time. The output consisting of diagrams, that we have provided for this project (See Section 5) is a preparatory work for the input file used to run the DRIVE-AB simulator.
7 Lessons learned

This work can be further extended by testing the identified class parameters as variables for the creation of an input file, and evaluate the result. Since the parameters have not been tested, it is not clear that they will provide valid statistical data when executed through the DRIVE-AB simulator.

The framework that we have provided needs to be validated as well. The purpose was to choose any number of incentive and run it through the class diagram. This was shown with one example with the object diagram (See Figure 13), but needs to be tested with all number of incentives.

If we had more time, we would create a model for the input file, that could be run through any simulator. Since the complexity of the words took a lot more time to understand than we expected, and the class diagrams had to be remade a number of times, we did not have time to develop a methodology even further. In appendix p. 57-58 one can find figures of how the class- and object diagrams changed over time, to the result that we have provided now.
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Background
This document is a part of DRIVE-AB WP2 Task 7 (Develop and assess alternative reward and business models, including review proposed models). This document is a list of mechanisms intended to increase innovation in antibiotic-related research and development (R&D), i.e., innovation mechanisms. These have been gathered from literature searches regarding pharmaceutical innovation incentives, extracted from the World Health Organization’s Consultative Expert Working Group on Research and Development: Financing and Coordination and supplemented by additional models suggested by experts. Additionally, the final report for DRIVE-AB WP2 Task 4 (Solutions from other industries applicable to the antibiotic field) has been reviewed and additional innovation mechanisms have been added if they were not already included in the list.

The innovation mechanisms in this document have been boiled down to core concepts. There are many proposed mechanisms in the literature that are a combination of multiple mechanisms, e.g., orphan drug legislation is a combination of several mechanisms including extended exclusivities and tax exemptions. In this document we look at each mechanism on its own. How to combine them will come at a later stage of our work.

The innovation mechanisms have been grouped into types to facilitate reading and processing. Some mechanisms could be placed under more than one of the group types. In these cases, the mechanism was placed under the perceived primary group type.

In order for an innovation mechanism to be included on this list, it must target to fix one of antibiotic-related R&D root bottlenecks. The bottleneck theoretically resolved is listed under the group heading.

This long list of innovation mechanisms will be voted on by WP2 members to determine which innovation mechanisms have the greatest internal support across a different range of criteria. The results of this voting will be discussed at a meeting in London on February 4-5, 2016.
**Fund-related mechanisms**

The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small.

1. **Antibiotic Health Impact Fund**

<table>
<thead>
<tr>
<th>Description</th>
<th>Also Known As or Included In</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>The Antibiotic Health Impact Fund (HIF) is a mechanism where governments create a joint fund that will pay for the actual global health impact of the antibiotic including conservation. The fund runs parallel to the traditional reimbursement system. If a company opts into HIF, it agrees to sell the antibiotic at cost globally. It then receives an annual payment based upon the amount of financing in the fund, divided formulaically by the health impact of the antibiotic. This annual payment continues for the lifetime of the patent.</td>
<td>Unmet medical need determines the size of the reward; access is improved; reinforces global health priorities</td>
<td>Requires significant up-front financial commitment and collaboration; measurement of the relative health impact requires costly administration (and may be very difficult since it deviates from standard QALY assessments); significant overhead costs to administer HIF</td>
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2. **Antibiotic tax**

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<tr>
<td>The antibiotic tax is a mechanism that imposes a fee or tax on antibiotic use to offset negative externalities, with the proceeds used to fund conservation and R&amp;D for new antibacterials. The tax can be selectively applied, e.g., only to antibiotics used for animals and/or only to antibiotic consumption in high-income countries. One option for implementation is to tax antibiotic active pharmaceutical ingredients</td>
<td>Sustainable funding mechanism; higher prices may lead to improved conservation, especially in veterinary sector</td>
<td>No global tax mechanisms exist today so this is essentially a coalition of countries agreeing to a finance antibiotic R&amp;D (the focus of the national tax becomes irrelevant); challenging to implement</td>
<td></td>
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### 3. Antibiotic corporate bond

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<tbody>
<tr>
<td>The antibiotic corporate bond is a mechanism where developers performing antibiotic-related R&amp;D market their corporate bonds as antibiotic-related. The aim is to increase social-impact investors.</td>
<td></td>
<td>Social-impact investing can attract specialized investors.</td>
<td>Many developers work across different therapeutic areas so there may be fungibility issues.</td>
</tr>
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### 4. Antibiotic government bond

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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>An antibiotic government bond is a government-issued bond meant to raise funds specifically for investment into antibiotic R&amp;D. Governments would pay out proceeds as either grants or non-dilutive capital for SMEs and larger developers. Bonds could be partially or fully repaid through future profits (including on corporate profits from the innovation incentives like transferable patent extensions).</td>
<td></td>
<td>Social-impact investing can attract specialized investors.</td>
<td>It would be cheaper for the government to provide R&amp;D grants (no need to pay interest). Most of the innovation incentives in this document are publicly funded so any repayment is likely to be at the expense of government-funded health systems. Governments do not typically issue earmarked bonds.</td>
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### 5. The Fast Track Option

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<tr>
<td>The Fast Track Option is a variant of the Priority Review Voucher (#18). It gives companies the option to purchase an expedited regulatory review for a drug of their choice. The funds raised as a result are used to support public sector R&amp;D, for example through a PDP.</td>
<td></td>
<td>None</td>
<td>It expedites market entry based upon ability to pay rather than medical need. The value of the Fast Track Option would be greatly diminished if many manufacturers purchased it as the regulatory agency would not be able to expedite all applications. Therefore, it is questionable if anyone would purchase it since it is a prisoner’s dilemma.</td>
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### 6. Joint antibiotic R&D public fund and infrastructure

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<tr>
<td>Two or more countries finance a common antibiotic R&amp;D platform/infrastructure consisting of equipment, facilities and manpower as well as ongoing operating costs. This platform can be used both by “member” and “non-member” countries to run specific projects, whose running costs are covered by the specific countries taking the initiative for each project. Any revenues generated from the R&amp;D are divided as per the agreement between countries.</td>
<td>Jointly financed R&amp;D infrastructure and antibiotic supply</td>
<td>The payer countries can align the R&amp;D with public health priorities.</td>
<td>The public sector is the sole payer, i.e., it may reduce private sector investments. It would likely require a treaty in order to secure long-term financing commitments. Treaties requiring pooled funds are extremely difficult to achieve. It requires setting up a large, new public entity.</td>
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### 7. Publicly-financed venture capital

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<tr>
<td>One or more governments would establish an antibiotic venture capital fund. Investments would be made mainly on commercial terms but also be based on clinical need and for the purpose of supporting early phase start-ups. Exit is done by selling individual shares, or by transferring entire portfolios to other investment funds. Initially, the fund would need public funding, but private capital could be invited to participate from an early stage. Later on, exits and gains from previous investments could possibly make the fund self-sustaining and profitable.</td>
<td>Potentially self-sustaining</td>
<td>In order to be self-sustaining, the fund would need to encourage high prices and volumes. Additionally, the government as the ultimate medicines purchaser (for most countries) is placed in a conflict of interest with this mechanism since the motives of a standard VC are to maximize revenues.</td>
<td></td>
</tr>
</tbody>
</table>
Grant-related mechanisms
The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small. (The cost of development is reduced.)

8. Grants and subsidies

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<th>Advantages</th>
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<tr>
<td>Direct governmental or other publicly-financed subsidies can include cash grants and interest-free loans. This includes grants to SMEs in order to stimulate national private sector innovation. Grants provide non-dilutive capital and can be made conditional with advance agreement to meet specific goals like conservation.</td>
<td>BARDA; Global innovation fund for AMR; Direct funding of research; 21st Century Cures Council; IMI; NIH Innovation Fund; Small Business Innovation Research</td>
<td>Time-honored; promotes knowledge generation with no expectation of return on capital</td>
<td>Governments may not be best suited to judge the viability of research programs or SMEs. There may be an information asymmetry between the government and the researchers. Politics may play a role in selection.</td>
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9. Incubator/accelerator services

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<tr>
<td>Incubators typically provide business mentoring, financing advice, office space and other services to start-ups. Accelerators assist small companies to achieve rapid growth (for example, securing venture capital or achieving specific milestones) also through mentoring and other services. Incubators tend to be government funded and also earn income from office rents. Accelerators typically expect equity in the company. An antibiotic-related incubator or accelerator can focus not only on antibiotics but also diagnostics, preventive measures and all other supplementary and complementary technologies.</td>
<td>Antibiotic Innovation Platforms</td>
<td>Assists start-ups to progress an idea towards commercialization</td>
<td>Does not provide enough investment to contribute to R&amp;D in a significant way</td>
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### 10. Product development partnerships (PDPs)

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<tr>
<td>Product development partnerships (PDPs), typically grant funded through development aid, are collaborations between a non-profit entity (the PDP) and private sector industry to develop drugs on a not-for-profit basis.</td>
<td>WHO’s Global Antibiotic Research and Development Facility; BIC’s Global antibiotics public–private partnership</td>
<td>Successful in developing cost-effective, incremental innovation for neglected areas</td>
<td>PDPs have not yet excelled at the innovation of novel medicines (although this may simply be an issue of time).</td>
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### 11. Public procurement, single-buyer scheme for antibiotic R&D

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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>A “central public body”, either a national state or a transnational organization, procures specified R&amp;D activities from a range of actors via an open, competitive tender. The R&amp;D delivery contract specifies the deadlines for the various R&amp;D stages and milestones covered by the agreement, with rigorous requirements on quality, reliability, and safety. Ownership of the R&amp;D results is retained by the central public body commissioning the R&amp;D activities, including patents.</td>
<td></td>
<td>Aligns R&amp;D with public health priorities</td>
<td>The public sector is the sole payer, i.e., it may reduce private sector investments. It requires setting up a large, new public entity. Governments are inexperienced with developing and commercializing new medicines.</td>
</tr>
</tbody>
</table>
Mechanisms for increasing the sales price per unit
The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small.

12. DRG top-up payment or bypass

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<tr>
<td>With a DRG (Diagnosis-Related Group) top-up payment or bypass, payers top-up the hospital reimbursement amount (the DRG) to compensate for the use of a high-priced, novel antibiotic. Alternatively payers can ring-fence and supplement the hospital's antibiotic budget as a whole to encourage the use of novel antibiotics. These payments can be contingent upon conservation-promoting conditions.</td>
<td>RADARS; DISARM</td>
<td>Works with existing systems which increases the viability of implementation</td>
<td>Hospital- centric; promotes immediate usage of a novel antibiotic which may not be warranted or promote conservation; hard to restrict only to antibiotics – other therapeutic areas also have expensive medicines</td>
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</tbody>
</table>
**Monopoly protections**

The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small.

### 13. Exclusivities

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<tr>
<td>Data exclusivity protects the clinical trial data, preventing other organizations from seeking regulatory approval of a product using the same clinical trial data as the originating organization for a specified period of time (from 5–8 years for new chemical entities and up to 12 years for biological products). Since it is unethical to perform redundant clinical trials on patients, data exclusivity gives a company an automatic, temporary monopoly on the medicine in countries where data exclusivity has been granted.</td>
<td>GAIN Act, Antibiotic Conservation and Effectiveness; Supplementary Protection Certificates; Orphan Drug Legislation; Qualified Infectious Disease Product</td>
<td>Incentive for completing expensive clinical trials; no LMIC country has implemented data exclusivity protections so there is no impact on access</td>
<td>Encourages companies to maximize sales and therefore discourages responsible use</td>
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</tbody>
</table>

Market exclusivity gives a company exclusive marketing rights for a particular medicine for a set period of time. It is used to incentivize R&D in areas that otherwise may not be pursued such as pediatric medicines or medicines for rare diseases. It can be conditioned on meeting conservation targets.
### 14. Transferable patent extensions

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<tr>
<td>A transferable patent extension would grant a legal right to extend the life of one patent, on any patented drug, in exchange for the successful regulatory approval of a specified antibiotic. For example, if a company developed “Antibiotic A” it would receive a patent extension for its blockbuster cholesterol medicine. If the patent extension is fully transferable; it can be sold.</td>
<td>Wild card patent extensions</td>
<td>This can be a very lucrative asset.</td>
<td>Indirectly paid through the healthcare system through prolonged high prices for a popular drug; may require changes to WTO’s TRIPS Agreement</td>
</tr>
</tbody>
</table>
Prizes
The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small.

15. Lump sum payment

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<tr>
<td>A global or national body agrees to pay a lump sum (fixed, predictable amount) to a developer that achieves regulatory approval for a pre-specified target product profile (TPP). The payment may be given at once or split up into multiple payments. The payment may be given to the first developer to meet the TPP or to the first several developers. The payment is conditional on responsible use and potentially equitable availability provisions. For example, the developer may be required to sell the antibiotic at cost with no marketing. A hybrid option of this model allows for a smaller lump sum payment with the ability for the developer to sell the resulting antibiotic at higher prices. This hybrid may be combined with a specified threshold, i.e., if the manufacturer’s sales exceed the threshold, it reimburses the government part of the lump sum.</td>
<td>Shared risk model</td>
<td>Delinked model which incentivizes development and commercialization of new antibiotics for specified clinical need but does not incentivize sales</td>
<td>Can result in a perverse incentive if novel antibiotics are cheaper than older ones – therefore, may require an additional pricing mechanism for hospitals</td>
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16. Lump sum diminishing payments

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<tr>
<td>Similar to the lump sum hybrid mechanism (#15), developers would receive smaller annual payments at time of marketing approval and thereafter for a new antibiotic meeting a specific target product profile. In exchange the developer would agree to a price cap on the antibiotic. Over time the price cap would be increased and the annual lump sum payment decreased. The aim is that by the end of the exclusivity period, the price is high and prescription volumes may remain relatively low. Therefore, there will be an incentive for generic manufacturers to enter the market.</td>
<td>The more modest payment amounts will encourage more national authorities to participate.</td>
<td>Complicated to determine appropriate lump sums and price caps as well as annual changes</td>
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17. Payer Licenses

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<tr>
<td>Governments, healthcare systems or hospitals buy or tender out an annual license to have access to a specific antibiotic or portfolio of antibiotics irrespective of volumes sold or up to a maximum annual quantity. The antibiotic(s) are then available free-of-charge. A variation on this model is that governments pay the license to keep the antibiotic off the market until needed clinically.</td>
<td>Insurance model; Service or supply contracts based on fixed annual subscription fee; value-based subscription</td>
<td>Full delinkage possible; saves very important molecules for a rainy day</td>
<td>Can result in a perverse incentive if novel antibiotics are cheaper than older ones – therefore, may require an additional pricing mechanism for hospitals</td>
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18. Priority review vouchers

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<tr>
<td>A priority review voucher is awarded upon marketing authorization for a specific novel antibiotic. The voucher creates a transferable/saleable right to have a regulatory agency evaluate the approval of a non-related drug in a more expedited time frame.</td>
<td>Qualified Infectious Disease Product; GAIN Act</td>
<td>Can raise between USD 50-350 million; the receipt of the voucher is predictable</td>
<td>Since the voucher is only valuable when used for non-priority medicines, it has the predictable effect of diluting the benefits of priority approval for actual priority medicines, and creating a risky rush to judgement on a non-essential drug. Additionally regulatory approval is becoming quicker with evaluating nearly all new drug applications within 6 to 10 months.</td>
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19. Traditional prizes

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<tr>
<td>Monetary prizes can take a number of different forms, including those that enable the manufacturer to retain the patent, those that require the manufacturer to forego the patent, elective systems such as the optional reward scheme, milestone monetary prizes and best entry tournaments, amongst others. Prize allocations can be reduced by company sales receipts. Prizes can be awarded to one or more top-ranked participant. Prize systems have successfully funded innovations in the aeronautical and space industries.</td>
<td>RADARS; Antibiotic Innovation Funding Mechanism</td>
<td>Incentivize the completion of high priority problems, typically those that are difficult to solve; since several entities compete to win the prize, prizes can be cost-effective resulting in significantly more R&amp;D than would occur in a grant-based system</td>
<td>Difficult to determine the appropriate size of reward to attract investment whilst not overpaying; prizes likely will not work where the investment is considered too large to justify the risk</td>
</tr>
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</table>
Regulatory mechanisms
The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small. (The cost of development is reduced.)

**20. Limited Population Antibacterial Drug Approval Mechanism**

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<tr>
<td>Through the Limited Population Antibacterial Drug Approval Mechanism, where an urgent, unmet clinical need exists, an antibiotic’s safety and effectiveness can be tested in substantially smaller, more rapid, and less expensive clinical trials. Successful trials give the antibiotic a narrow indication for use in small, well-defined populations of patients for whom the drugs’ benefits have been shown to outweigh their risks.</td>
<td></td>
<td>The realities of the medical need (small numbers of patients, serious unmet medical need) adapt the regulatory process so that there may be at least one treatment available to patients.</td>
<td>Gives marketing authorization to products of which little is known and could be ineffective or even dangerous; it is difficult to perform a health technology assessment since the benefit may be highly uncertain.</td>
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**21. Regulatory harmonization**

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<tr>
<td>Regulatory harmonization means that countries agree to standardize their documentation requirements and processes for marketing authorization. This allows a company to seek regulatory approval in many countries more expediently. For example, Europe has implemented a centralized procedure for applying for marketing authorization in all EU and EEC countries.</td>
<td></td>
<td>Avoids potentially unnecessary clinical trials which are aimed only at one country’s population; streamlines paperwork</td>
<td>In some countries (e.g., Brazil) there are legal rights to access approved medicines. So marketing authorization may impact national healthcare system budgets if a very expensive treatment is approved for a low-priority indication.</td>
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Revenue guarantees or assurances
The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small.

22. Advance market commitment (AMC)

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<tr>
<td>An Advance Market Commitment (AMC) is a legally enforceable commitment by a government or a private/international organization to purchase a specified quantity of a drug or a vaccine that meets certain criteria pre-specified by the purchasers at a pre-determined price. There are two approaches to an AMC: the “winner takes all” approach or the “multiple winners” approach.</td>
<td>Market uncertainty is reduced; R&amp;D is directed towards specific, unmet needs</td>
<td>An AMC is a purchasing obligation which may be undesirable for antibiotics where the new antibiotic may only be used as a last resort.</td>
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23. Call options for antibiotics (COA)

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<tr>
<td>Governments (and/or private actors/philanthropies) offer to buy rights to purchase drugs at fixed affordable prices, during earlier stages of development. The money from the option is used by developers to defray R&amp;D costs. This is comparable to the Advance Market Commitment. Whereas AMC requires governments to commit to buy, the COA requires developers to sell.</td>
<td>Upfront payment of R&amp;D by public global consortium / supernational organization</td>
<td>Provides cash funding at earlier stages of development; Market uncertainty is reduced; R&amp;D is directed towards specific, unmet needs</td>
<td>Governments (or others) pay for R&amp;D that may never come to market; it may be cheaper to provide a grant instead; unclear how COA would transfer between companies if the IP is sold or out-licensed</td>
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<td>The creation of a global purchaser for antibiotics in line with the GAVI/UNICEF model for vaccines or the Global Fund to Fight AIDS, Tuberculosis and Malaria. Health systems would then purchase some or all antibiotics needed from this entity. It may be restricted to only those antibiotics that are considered as medical last resorts.</td>
<td>Greater control; facilitates monitoring of antibiotic usage; simplifies commercialization of antibiotics with no current medical need or very small patient populations</td>
<td>Creates a large, expensive monopoly; governments may be unwilling to give so much control to a third party entity for life-saving medicines; GAVI and GFATM are financed through development aid – global antibiotics need to be financed through health budgets; there are relatively few vaccine, antiretroviral and antimalarial producers, whereas there are hundreds to thousands of antibiotic producers</td>
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<tr>
<td>A government (or coalition) purchases the national patent rights to an antibiotic once the antibiotic has received national marketing authorization. Then the actual antibiotics are sold by the government, which may or may not outsource the production. Governments may choose this option for particularly important molecules that are not yet needed.</td>
<td>Strategic Antibiotic Reserve (SAR); Antibiotic Innovation Funding Mechanism (AIFM)</td>
<td>Full delinkage; one transaction per molecule per country; government can manage the molecule for long-term public health</td>
<td>Difficult to negotiate appropriate price; political risk; governments are not experienced at manufacturing or controlling the manufacturing of medicines</td>
</tr>
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</table>
Risk-sharing mechanisms
The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small. (The cost of development is reduced.)

26. Cost sharing for clinical trials

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<tr>
<td>Governments would share the cost of clinical trials with pharmaceutical companies, perhaps with conditions on responsible use and/or price. Financing could be determined on a matching basis. Alternatively governments could commit to support the trial in public hospitals and clinics. Governments may choose this option for particularly important molecules or indications.</td>
<td>De-risks investments in R&amp;D, especially expensive Phase III trials; promotes greater public and private investments; may add greater transparency to trials; governments can play a role in trial design to ensure that typical patients are included and drug comparators are appropriate for the national profile</td>
<td>Governments are not experienced in designing or performing clinical trials; it may be difficult for governments to prioritize where their funding is in greatest need</td>
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27. Risk-sharing loans

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<tr>
<td>Governments (or publicly funded institutions like the European Investment Bank) provide loans for high-risk projects within a specified profile at lower-than-market interest rates. If the contractual project milestones are achieved, then the loans are expected to be paid in full. If not, portions or the entire loan are written off. These risk-sharing loans are meant to attract co-investment from other investors by reducing the risk profile.</td>
<td>Infectious Disease Finance Facility; Public soft loans for late-stage R&amp;D</td>
<td>Incentivizes specific R&amp;D; promotes greater public and private investments</td>
<td>Potential information asymmetry where the government (or agency) may lack information regarding the contractual milestone; supports only private sector as PDPs are poorly positioned to loan funds; IDFF is seeded with public money and then meant to be self-sustaining which encourages the use of high prices and volumes</td>
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### 28. Liability protection

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<tr>
<td>A program that would fairly and efficiently compensate individuals harmed by certain antibiotics that were properly manufactured. This type of liability protection has been applied to childhood vaccines in the US under the Vaccine Injury Compensation Program. This is especially relevant in cases where there are only few patients with the resistant pathogen (i.e., very small clinical populations) and therefore practically impossible to perform a full clinical trial.</td>
<td>De-risks investments for R&amp;D directed at unmet, clinical needs for resistant pathogens that may one day threaten greater numbers of individuals</td>
<td>Given the public outcry regarding safety concerns with products authorized and subsequently removed from the market, it should be expected that proposals on liability limitations will face significant public, and hence political, opposition.</td>
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</table>
**Tax reduction mechanisms**
The core bottleneck resolved by the following mechanisms is that the market size and future profitability for a novel antibiotic are uncertain and/or small. (The cost of development and/or production is reduced.)

29. **Regulatory fee exemptions**

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<tr>
<td>A developer is given an exemption from the regulatory fees when applying for marketing authorization of a specified antibiotic.</td>
<td>Orphan drug legislation</td>
<td>Allows for small savings; may be particularly important for a SME</td>
<td>It is difficult to argue that one type of medicine is more deserving and should not pay for regulatory approval than others.</td>
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30. **Tax credits and deferrals**

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<tr>
<td>A tax credit is a tax incentive which allows certain taxpayers to subtract the amount of the credit from the total they owe the state. Another variation is to allow the tax credit to be transferrable to a future year. Tax deferral refers to instances where a taxpayer can delay paying taxes to some future period. Tax incentives are thought to increase private expenditure to a level equal or just below the level of the lost tax revenue (negative price elasticity).</td>
<td>Patent box; Orphan drug legislation</td>
<td>Tax reductions have proven positive in stimulating action by large pharmaceutical companies.</td>
<td>Tax incentives are a less transparent method of government funding; often favors companies with taxable profits and near-term rather than longer-term investments</td>
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31. **Fully refundable R&D tax credit**

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<tr>
<td>Under a fully refundable tax credit, companies report their annual investment in R&amp;D towards specified antibiotics, and the tax credit that the company would have received if it had taxable income is instead paid out in cash.</td>
<td></td>
<td>Especially benefits SMEs as a predictable cash flow</td>
<td>Tax incentives are a less transparent method of government funding; it may be more efficient to finance the R&amp;D through grants</td>
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</table>
Collaboration mechanisms
The core bottleneck resolved by the following mechanisms is too few scientists, physicians and students are participating in infectious disease R&D.

32. Collaboration platforms

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<tr>
<td>Collaboration platforms facilitate collaboration during drug discovery and</td>
<td>ENABLE; Open source drug discovery; Establishing a Drug Discovery Platform for Sourcing Novel</td>
<td>If the platform attracts enough participation, it can accelerate the innovation and provide cost savings. Collaboration platforms can be designed flexibly to either create public goods (with open IP) or protect an organization’s IP. It can avoid duplication in efforts.</td>
<td>Monitoring and oversight of closed collaboration platforms may be required to ensure adherence to anti-trust regulations. It may be challenging for companies to change their normally proprietary culture.</td>
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<tr>
<td>development, although typically they function best at pre-competitive phases. They may assist with testing and optimizing molecules that are still in the earlier stages of drug discovery but have the potential to become future drug candidates. Platforms can be open (so anyone can contribute) or closed (so that only invited individuals can contribute). Open platforms may place the knowledge and collaboration in the public domain so that anyone else can freely utilize or further develop it. If collaboration is targeting late stage development, exemptions to anti-trust laws may be required. Another variation is to allow the collaboration to be performed through regular gatherings where knowledge is shared.</td>
<td>Novel Classes of Antibiotics as Public Goods; Building a Diagnostic Innovation Platform to Address Antibiotic Resistance; Standardization Bodies: pre-competitive R&amp;D coordination for common challenges</td>
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### 33. Joint, multilateral, non-pooled financing and coordination of R&D targets

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<tr>
<td>A group of willing countries would form a non-binding coalition to finance antibiotic R&amp;D priorities. Countries would select one or more priorities in which they commit to finance R&amp;D. Smaller countries may choose to consolidate their financing. Commitments and “ownership” would be pledged publicly for accountability. Countries could then internally determine the best route of financing the R&amp;D for the targets they have selected, e.g., some countries may pair with industry. There is no pooled funding.</td>
<td></td>
<td>The payer countries can align the R&amp;D with public health priorities. The coalition can be formed quite quickly since it is non-binding and countries may exit at any time.</td>
<td>The coalition can be short-lived since it is non-binding. Countries may be unable or unwilling to finance the large amounts required.</td>
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### 34. InnoCentive

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<tr>
<td>InnoCentive is an online marketplace where organizations with specific innovation needs post challenges along with an appropriate award. The award is paid to the solver who best meets the solution requirements.</td>
<td></td>
<td>Attracts outsiders to focus on discrete challenges; allows developer to gather different perspectives and ideas</td>
<td>Requires someone to sift through all the contributions to determine if there is truly something useful</td>
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### 35. Patent pools

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<tr>
<td>A patent pool enables the collective acquisition and management of IP for use by third parties for a fee. Patent holders from the public or private sector may contribute patents to the pool. Subsequently, a developer wanting to use the patent to develop a new product can seek a license from the pool against the payment of royalties to produce the medicines. This allows for incremental innovation.</td>
<td></td>
<td>It reduces transaction costs and barriers to market entry resulting from IP protection.</td>
<td>In the antibiotic market, where incremental innovation is unlikely to be a long-term solution, one could argue that such an arrangement may not bring the necessary innovation to produce truly novel products. Another limitation arises when we consider whether royalties would be perceived as sufficient compensation for relinquishing IP rights, especially if the patented technology has any chance of contributing to the development of a novel product.</td>
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</table>
Simulator flowchart

1. Simulation Tick
2. For each alive project
3. Calculate financial value of a) developing the project to the end, and b) exiting at each potential exit (which entails potential buyers calculating their buy price, which entails recursively allowing each buyer to calculate their highest utility exit points).
4. Remove options that cannot be afforded given the current amount of claimable external capital.
5. Does any option have a utility value above 5 (the utility of doing nothing)?
   - Yes: Save path with highest value as exit point, and reduce available external capital with the amount needed if needed.
   - No: Do nothing. (Non-terminal)
6. Has the project reached the organisation's exit-point for the project?
   - Yes: Sell project to (previously calculated) highest bidder.
   - No: Incur the cash flow for the next step.
7. Flip a coin: Yes or No.
8. Step the project forward, corrected for the organisation's efficiency for the particular stage.
First version of the object diagram

Figure 17: The object class diagram
First version of the pull incentive

Figure 18: An illustration of a Pull incentive
References


