Work Package 2, Task 9: Preliminary Simulation Report

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Executive Summary

- This report presents the preliminary results from the antibiotic R&D pipeline simulator created within WP2/Task 9 of DRIVE-AB. The simulator is built using a combination of Agent Based and Monte Carlo simulation techniques and has been designed to explore intervention mechanisms aimed to stimulate the development of new antibiotics.
- The purpose of the simulator is to simplify the complexity of reality by focusing on important elements of the development process of future antibiotics at an aggregate level. The structure and components of the simulator mirror the typical core development phases and decisions in R&D projects, which are driven and influenced by different types of actors (e.g., small and medium size enterprises, big pharmas, and venture capitalists).
- The simulation provides results of the effects of intervention mechanisms currently being investigated by DRIVE-AB under the particular conditions specified in the report. These results are intended to support decision making in regards to these intervention mechanisms, but do not deal with any questions pertaining to their implementation.
- The simulation has explored variations and combinations of two kinds of intervention mechanism: Grants (a push incentive), and Market Entry Rewards (MERs, a pull incentive), with *full* or only *partial* de-linkage from sales and first *narrowly* focused on "hard to discover antibiotics" (which we term "Type A") and then *broadly* focused so to include also "easier to discover antibiotics" but still targeting societal needs (which we term "Type B").
- A **Fully Delinked Narrow MER** (whereby all revenues for a developer come from the MER and none from sales) awarded for bringing a "hard to discover antibiotic" of "Type A" to market shows positive effects over the status quo without intervention which presents on average less than two new Type A antibiotics reaching market in 30 years. Specifically, the introduction of $500Million MERs for such a type of antibiotics makes the number of market approvals double to 4 antibiotics over 30 years. Increasing the size

of MERs increases the number of market entries linearly up to $1500Million, where the effect reaches a plateau and 12 new antibiotics of Type A are expected to reach market in 30 years. This plateau indicates that *all* antibiotics surviving the attrition rates at the various stages are eventually made profitable by that size of the MER.

- Adding the current level of yearly grants ($600Million) available globally, enables somewhat lower Fully Delinked Narrow MERs of $1250Million to be sufficient to make all 12 Type A antibiotics still surviving in the simulator reach the market.
- The additive effect of an extra $300 Million in grants (focused to target only Type A antibiotics) further reduces the size of a MER required to reach the plateau to around $1000Million.
- The effect of a **Partially Delinked Narrow MER** (where only part of revenues come from the MER and the rest comes from sales) starts at $100Million when the number of new market entries doubles (from 2 to 4). It then increases linearly up to $750Million where it reaches a plateau and 12 Type A's are brought to market over 30 years.
- If combined with current grants ($600M), a Partially Delinked Narrow MER of $750Million is sufficient to bring to market more than 12 Type A's in 30 years; while the extra and targeted grants ($300M yearly on top of the existing $600M) makes MERs of $500Million to suffice in reaching the plateau.
- **A Fully Delinked Broad MER** reaches similar effects to the narrow one for Type A antibiotics. As the intervention now includes "easier to discover" Type B projects, the number of approved antibiotics after 30 years increases from 12 (without the intervention) to 47 where a plateau is reached at an intervention size of about $1500Million).
- Together with current grants ($600M), the required level of Fully Delinked Broad MERs that makes all surviving antibiotics profitable (i.e., reaches the above plateau) decreases to $1250Million
- Similarly, **a Partially Delinked Broad MER** reaches a plateau for Type B and A antibiotics (again 47 antibiotics) at around $1000Million (a higher level than the $750Million for the narrow MER focusing only on Type A antibiotics).
- Adding current grants reduces the level of a Partially Delinked Broad MER required to reach a plateau for Type B antibiotics to about $750Million.

Introduction

This report presents the preliminary results from the R&D pipeline simulator created within WP2/Task 9 and employed for large-scale simulation runs in May 2017. The simulation provides results of the effects of certain intervention mechanisms, currently being investigated by DRIVE-AB, under given circumstances (data, assumptions, etc.). These results are intended to support decision making in regards to these intervention mechanisms but do not deal with their implementation. Since the simulator is a software tool being continuously developed and upgraded, both in terms of parameters and functions, upcoming papers from Task 9 will present slightly different results based on new versions of the simulator. In general, the simulator models the innovation process inherent to the antibiotics industry, and has been designed to explore intervention mechanisms aimed to stimulate the development of antibiotics. The simulator is a combination of Agent Based and Monte Carlo simulation techniques and considers the various situations and processes that an antibiotic molecule (and the related R&D project) experiences from discovery through to market. The simulator reflects the central financial decision making process that pharmaceutical companies employ in order to bring molecules to market. In the simulation, discovery and early stage development occurs primarily in small biotech firms, often supported by venture capital investors, and their projects are later acquired by larger pharmaceutical companies that bring the product to market. We have explored primarily two kinds of intervention mechanisms: grants (a “push” incentive) and market entry rewards (a “pull” incentive). Our experiments show that: (1) the effect of fully delinked and partially delinked MER is 9 additional approved ABx at 1500M levels of MER and 750M MER respectively; (2) the different effect of a broad as opposed to a narrow MER is 35 additional approved ABx at similar MER sizes; (3) lower fully delinked MERs of $1250Million and partially delinked MER of $600Million are sufficient to make all ABx still surviving in the simulator reach the market.

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Outline of report

The report is structured as follows. We first describe the key structure and components of the simulator, namely the agents, projects, phases and decisions that make it up. Our methods then discuss the inner logic of our simulator (Agent based modelling and Monte Carlo) as well as the data used and assumptions that govern it. Having done so, we discuss the specific purposes of the experiments we performed, before presenting the experiments themselves and lastly, their results.

1. WHAT IS IN THE SIMULATOR

Our simulator includes five key elements: (1) Agents who invest in (2) Antibiotic R&D Projects. These projects move through various (3) Phases of development, in which a number of different (4) Decisions are made. These decisions are in turn based on the perceived profitability of projects that depend, next to their costs and uncertainty, on their future (5) Market.

1.1. AGENTS

The agents in this simulation are the developers and investors in antibiotic R&D. Specifically, the agents acting and making decisions in the simulation are SMEs (small- and medium-sized pharmaceutical firms), VCs (Venture Capital investors), and Big Pharmas (large pharmaceutical firms). The agents just described have different attributes which set them apart from each other.

First, they have different discount rates. These rates are taken into account by the agents when considering investment decisions. VCs are not looking long term, while SMEs and Big Pharma consider the combination of discount rates and risk-adjusted Net Present Value (eNPV) that reflect the alternate investment opportunities and investment risk. SMEs and Big Pharmas have the same distribution of discount rates for all phases, VCs have different discount rates for different product development phases, to reflect the varying levels of risk. The cost of capital for Big Pharma is in the range of 8% to 11%, while for SMEs it is in the range of 5% to 8%.

Second, Big Pharma are assumed to have funds but by having a threshold on their expected investments they also have alternative opportunities to choose from. They constantly need to acquire capital at costs ranging from a minimum of 8% and a maximum of 20% depending on the specific R&D phase. These costs of capital reflect the discount rates applied by VCs in evaluating projects at different R&D Phases. Specific ranges for discount rates for different agents and phases are available in Section 4.

Third, agents have different profit thresholds that a project must meet in order for the agent to decide whether to continue or not. These thresholds are manifested in the profit beyond a positive eNPV required by the agent. In this simulation, Big Pharma have a threshold of $100Million, while SMEs and VCs have no threshold but instead higher discount rates.

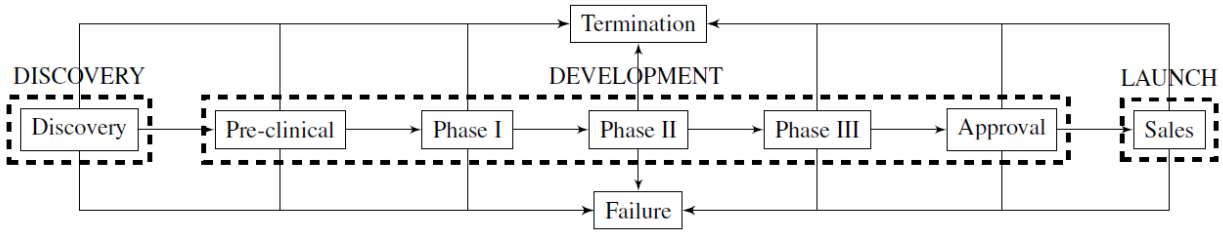
1.2. PROJECTS

Besides the agents just described the simulation also contains projects. These are antibiotic product development projects (molecules) that can be invested in by agents. The projects come in three types, A, B and C, characterized by different entry rates, i.e., the number of A, B, and C projects that enter the simulation in the Pre-Clinical phase each month. Type A are novel antibiotics, difficult to discover and hence with low entry rate (0,05 – 2,5 each month): they represent antibiotic against Gram-negative bacteria and of new class; Type B are slightly less novel antibiotics than Type A, with a medium entry rate (0,5 – 5 each month): they represent

antibiotic against Gram-positive and of new class or against Gram-negative bacteria but not of new class; Type C are finally me-too products, easy to discover, with a high entry rate (2 – 7 each month). These three types of projects populate the development pipeline where developers and investors are active and where projects need to go through a number of development phases (below) in order to reach the market. Further details on projects' entry rates are discussed in Section 4.

1.3. PHASES

Antibiotics projects progress by going through a number of sequential phases typical for all pharmaceuticals: Pre-Clinical, Phase 1 Clinical Trials, Phase 2 Clinical Trials, Phase 3 Clinical Trials, and Approval (Thompson et al. 2004). These phases differ in terms of their duration, their cost, and the probability of projects successfully completing the phase. Upon creation of a project, the simulator draws random samples from triangular distributions for the stage-specific parameters duration, cost, and probability of success. These distributions stem from Sertkaya et al. (2014) that presents an analytical decision-tree model framework for antibacterial development.



Additionally, moving through the development phases, certain projects suffer setbacks, such as toxicity or lack of therapeutic effects in human trials. Therefore, projects going through each phase have a certain risk also of failing for technical reasons, which is expressed as the complement of the success probability. A project which fails does not proceed in the simulated pipeline but becomes a "failure" due to techno-scientific reasons and is thus terminated.

1.4. DECISIONS

In the simulation, a number of different decisions are taken by agents with regards to the future of their projects. These decision concerns whether a project should proceed, terminate, hibernate (wait), be sold, or be entered into a partnership with another firm. These decisions are taken at the end of each time step, which approximates to one month, of the simulation. Decisions are taken in isolation for each project, we do not currently consider combinatory project effects.

The factor triggering these decisions is the eNPV (expected net present value) of the project in question as calculated by the relevant agent(s) who are about to make the investment

decision. NPV is calculated as in Equation 1 where it is a discrete time period, N is the number of time periods of the investment, Ct the (out-of-pocket) cash flow (revenue or cost) at period t, and i the discount rate of the evaluator. The discount rate in NPV reflects the firm's opportunity cost and the perceived risk of the investment, Atrill, McLaney, and Harvey (2014). eNPV is the sum of each cash flow used in an NPV calculation multiplied by the probability that it occurs, which according to the multiplication rule of Bayesian probability equates to the expected value (in terms of NPV) of the investment. eNPV is calculated as in Equation 2 where $P0 \rightarrow \omega$, (and ω is the end of patent) is the probability of reaching the final cash flow from the point of investment, and $Pt \rightarrow \omega$ the probability of reaching the final cash flow from time t (Stewart, 2002; Okhravi, 2017).

$$NPV_N^i = \sum_{t=0}^{N} \frac{C_i}{(1+i)^t} \qquad (1) \qquad\qquad eNPV_N^i = \sum_{t=0}^{N} \frac{C_i P_{0\rightarrow\omega}}{(1+i)^t P_{t\rightarrow\omega}} \qquad (2)$$

The eNPV captures the perceived profitability of an investment given how much money needs to be invested today and how much is expected to be repaid in the form of net revenues, such as sales, in the future. The eNPV varies depending on each investor's cost of capital (the higher the cost of capital, the lower the eNPV will be), the size of the revenue and the time it will take before revenues appear (the longer time, the lower eNPV will be), the risk that the project fails, and the cost of development. The alternative investments available to the investor are considered in the form of "thresholds", which are compared to the eNPV to judge whether an agent is willing to invest or not in a particular project.

If the eNPV is positive and above the eNPV threshold of the agent(s) controlling the project, then the project may proceed. If it is not, the project is terminated for financial reasons, namely lacking or poor profitability. If instead the agent is an SME who wishes the project, that is above the threshold, to proceed but does not have sufficient funds, then the agent will attempt to get such funds from a VC, by partnering with other firms (namely Big Pharma) or by selling the project to them. If the SME agent fails in partnering, selling the project, or securing a venture capital investment, the project is "hibernated" for some time and then tries again. The time spent in hibernation increases exponentially with every failed attempt. The main factor influencing the survival of technically viable projects throughout all these decisions is the eNPV of each single project.

1.5. MARKETS

The market simulated is the global market as of today and is based on Sertkaya et al. (2014). This global market, in turn, reflects High-Income Countries (HICs, with approximately 90% of global buying power) and Low- and Middle-income Countries (LMICs) with the remaining buying power. However, worth noting is that although Low- and Middle-income Countries may have

buying power, the profit potential as perceived by pharmaceutical firms is generally negligible, since the costs for licenses, registration, and logistics are comparatively large. Therefore, we can make the assumption that the net contribution of Low- and Middle-income Countries to the global (profitable) market for novel antibiotics is negligible. As a consequence, the global numbers used in the simulation thereby can be said to encompass the entire global markets for antibiotics.

2. METHODS

Assessing the effects of various intervention mechanisms on antibiotics R&D requires a large number of possible scenarios, that is alternative realities to be considered for a given set of inputs, each one being performed during one "run" of the simulator. Moreover, many of the inputs are stochastic. Intervention mechanisms occur within an existing antibiotic landscape and with strict regulatory control. Predicting the effect of such intervention mechanisms can only be solved analytically by making so many generalizations that the vast majority of scenarios are not considered and the emergent behavior of the system is not exposed. We need to be able to amalgamate the outcomes of scenarios in order to assess each intervention mechanism both individually and against each other. As there are tens of thousands of scenarios per experiment, it is not feasible to undertake this by hand. This naturally leads to the adoption of computer based simulations to explore each incentive model thoroughly to gauge its effects. Much of our antibiotic landscape is extracted from Sertkaya et al (2014) as this is the landmark study based on extensive industry data collection. We have supplemented and revised their parameters through interviews and discussions as part of the DRIVE-AB project.

2.1. AGENT-BASED SIMULATION

An agent-based model includes distinct agents who interact with the environment or with each other and aims to assess the effects of such interactions on the system as a whole. The research area evolved from discrete event simulation that models the operation of a system as a discrete sequence of events in time. A good summary of the field is given in Robinson (2004). Our agents are pharmaceutical developers (SMEs and Big Pharma), who are seeking to bring molecules from discovery to market by navigating through the costly pharmaceutical pipeline. They adapt and migrate from one state to another, as described in Holland & Miller (1991), but have limited negotiation skills.

SMEs are created whenever new molecules are discovered, and can only own a single molecule. The number of Big Pharma organizations remains constant within any given experiment, however they can own multiple molecules. An agent can either transfer any of its molecules to a different agent, or transition the molecule into a different state (as described in the section State Transitions). In simplistic terms, our agents either develop the molecules provided to them themselves, or transfer them to someone who can. The goal of an agent-based simulation is to determine the collective behavior of agents obeying simple rules. In our case market ready antibiotics emerge from agents making eNPV-based go/no-go decisions upon molecules that are simultaneously subjected to the risk of scientific failure. By introducing policy driven intervention mechanisms into such a system we are able to gain better insight into their relative efficacy.

2.2. MONTE CARLO SIMULATIONS

Monte Carlo methods, Eckhardt (1987), are a broad class of computational algorithms that rely on repeated random sampling to model phenomena with significant uncertainty in inputs. For instance, the entry rate for a new antibiotic molecule into the pipeline is described by a probability distribution. We could have modeled this entry rate using a discrete number but then we would only observe the effects of a very regular R&D process, which we know not to be representative of reality. This holds also for all other input parameters to the simulation, such as R&D costs and market sizes. Exploring the vast space of possible inputs and the ensuing outcomes instead allow us to reason about the effects of policy interventions in multiple potential realities.

2.3. OUR SIMULATION

Following the above reasoning our simulator is a combined Monte Carlo and Agent-Based model. It behaves in the following manner:

1. We have a domain of possible inputs that represent the relevant environment of an antibiotic molecule and project.
2. We generate inputs randomly from a probability distribution over the domain.
3. The simulator then performs an agent-based computation on the inputs.
4. Finally, we aggregate the results and present the data in a form suitable for human interpretation.

3. THE MODELLING

3.1. STATE TRANSITIONS

A project in the simulator will at any given time be in one of the seven possible states listed below and displayed in Figure 1. Every state entails some specific behavior that will necessarily either move the project to another state or make it remain in the same. At every simulation time step (month), all agents subject all their projects to one and only one state transition. In Figure 1, green states are initial states, and red states final. In other words, every project finds itself in an initial state when it enters the simulation and exits the simulation when it reaches one of the final states. Below we describe what the different states entail.

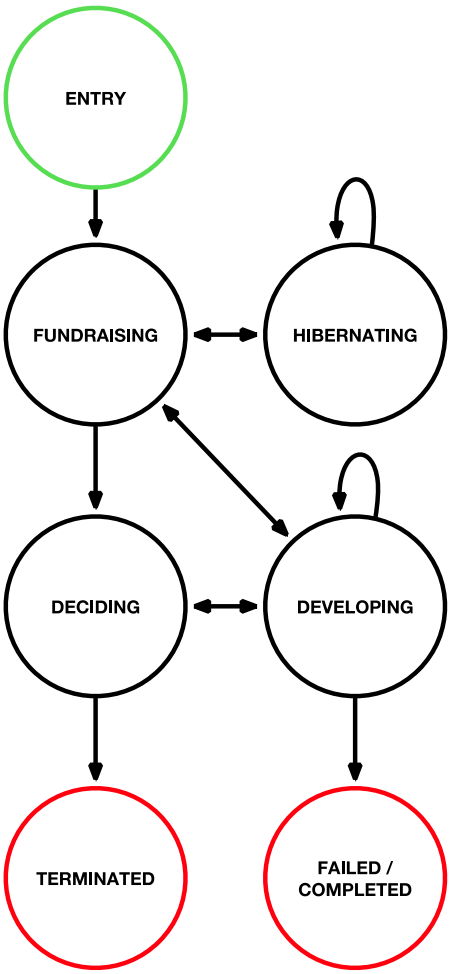


Figure 1 State space of any given project in the simulator.

3.1.1. Entry

Every project enters the simulation in this state and will only remain in this state for the first time step.

3.1.2. Fundraising

Given the assumption that Big Pharma have an eNPV threshold greater than zero, they only need to secure funding internally and not externally. They have funds but also alternative investment opportunities. If an investment opportunity is sufficiently promising (eNPV $\geq$ threshold), capital will be granted. Thus, we assume that Big Pharma always have the funds available to continue and thus always leave the *Fundraising* state and instead move to *Deciding* or *Developing* depending on whether it is facing a decision-point (corresponding to a stage gate in the R&D process, such as prior to starting Phase 2 of Clinical Trials) or not.

If the project however is not owned by a Big Pharma but by an SME then it can move into *Deciding* or *Developing* only if the agent has enough funds to pay for the next R&D stage (i.e. a month's worth of project development). If the SME agent does not have the necessary funds then it will look for either 1) an investment from a VC, 2) a Partnership with a Big Pharma, or 3) an Exit to a Big Pharma.

During a single time step an agent can only explore one of these options, and which one it explores is selected randomly. If during *Fundraising*, an exit, partner, or investor is found then the agent transitions into *Deciding* if the project is at a decision-point, but to *Developing* if not.

Investors and Big Pharma will decide to fund only if a project meets their eNPV requirements based on their specific discount rate and (if applicable) profitability threshold. If the SME agent instead fails to find a funder for the project, it transitions to the *Hibernating* state.

In the case of a VC investment the project will be granted sufficient funds to pay for the remainder of the impending stage. In case of a *Partnership* the project will be granted sufficient funds to pay for development all the way to market entry. In case of an *Exit* the project will be transferred from the SME to the Big Pharma acquiring the project who can afford to bring the project all the way to market entry. In this situation no previous investors will affect future decisions since the agent in question from that moment and onwards now is the Big Pharma project rather than the SME one.

3.1.3. Hibernating

We assume that the difficulty of finding someone to invest in your project grows exponentially with every failed attempt. An agent stays in the *Hibernating* state, while awaiting a new chance to attempt to attract funding. Concretely, the agent (i.e., an SME) may attempt to attract funding every 1st, 2nd, 4th, 8th, 16th, and so forth. In other words, at the start of month that is a power of 2 from the time that it entered the *Hibernating* state. If the agent is at a time step that allows it to attempt to raise funds, it moves back into the state *Fundraising*.

3.1.4. Deciding

The agent (both SMEs and Big Pharma) calculate whether the eNPV of the project's projected future is above (or equal to) the agent's threshold. When making go/no-go decisions we do not simply employ the agent's discount rate and threshold but rather combine that of the agent and its current investors (if any) and partner (if one). If eNPV is above or equal to the threshold, then the project enters the *Developing* state. If not, then it is marked as *Terminated* and will be removed from the simulation.

3.1.5. Developing

The agent attempts to move the project one step forward, thereby pursuing one month of development progress. Development may probabilistically fail, causing the project to into the *Failed* state. If development succeeds and the agent has enough funds to perform the next step, then the next state depends on whether the next step is a decision point or not. If the next step is a decision point, then the agent moves back into *Deciding*, while if it is not then the agent stays in Developing. If on the other hand, the agent does not have enough funds to perform the next step, then it transitions into the Fundraising state. So our simulator will decide to pursue a project at every phase but funds and technical success is required to ensure each step.

3.1.6. Terminated

Termination means that the project was cancelled on the basis of being a poor financial prospect (i.e., eNPV < the combined threshold of the agent, its investors and its partner).

3.1.7. Failed

Failure means that the project was cancelled on the basis of scientific/technical issues (e.g. toxicity).

3.1.8. Completed

When a project is *Completed*, it has successfully reached market.

3.2. SIMULATION LOOP AND KEY ALGORITHMS

Any simulation run is composed of a series of time steps. The total length of a simulation run is 360 steps, each one corresponding to one month of "human time" and hence to a total span of 30 years for our simulation. At every time step the following three events occur:

1. Grants are handed to agents, owning eligible projects (depending on their type, see above), and the grant pool corresponding to the current levels of yearly grants to antibiotic R&D is renewed at the start of every year (every 12th time step).
2. All agents subject all their projects to a single state transition (as explained in the section State Transitions).
3. New projects owned by new SMEs enter the simulation.

Grants are not requested by agents, but rather handed out to them on the basis of the costs of their impending stage (which they cover either fully, for the earliest stage of pre-clinical, or only partly for the remaining stages). Thus, we model grants as supplementary money. These funds are particularly important for SMEs, since in our simulation, grants are the only possible way for an SME to avoid the *Fundraising* state and thus ultimately tireless *Hibernation*.

When describing the state transitions above, we referred to the employment of a few algorithms such as *fundraising* and *decision making (Deciding)*. What follows, are pseudo code explanations of some key algorithms previously mentioned as well as an algorithm for how grants are handed out and how the grant "pools" are renewed yearly. We assume investors play a role over the lifetime of the project. The relative impact of an investor is affected by how many previous investors the project has had. The investor with the greatest financial input affects the decision making the most.

3.2.1. Decision-making (Deciding)

```
    discount_rate = max(partner.discount_rate, mean(investors.discount_rate, owner.discount_rate))
    threshold = max(partner.threshold, mean(investors.discount_rate, owner.threshold))
    value = max(
        enpv(intervention(project), discount_rate),
        enpv(project, discount_rate))
    if value + project.unspended_grants ≥ threshold
        project.transition_to(DEVELOPING)
    else
        project.transition_to(TERMINATED)
```

3.2.2. Investments (Fundraising)

```
investor = pick_random(investors.filter(i => i.invests_in(project.stage))
value = max(
  enpv(intervention(project), investor.discount_rate),
  enpv(project, investor.discount_rate))
if value + project.unspended_grants >= investor.threshold
  project.add_capital(project.stage.remaining_cost)
  associate(investor).with(project)
  if project.is_at_decision_point?
    project.transition_to(DECIDING)
  else
    project.transition_to(DEVELOPING)
```

3.2.3. Exits (Fundraising)

```
buyer = pick_random(all_orgs_with_infinite_capital)
value = max(
 enpv(intervention(project), buyer.discount_rate),
 enpv(project, buyer.discount_rate))
if value + project.unspended_grants >= buyer.threshold
  transfer(project).to(buyer)
  if project.is_at_decision_point?
    project.transition_to(DECIDING)
  else
    project.transition_to(DEVELOPING)
```

3.2.4. Partnerships (Fundraising)

```
if (project.number_of_partners == 1)
  project.transition_to(HIBERNATION)    # Because: not eligible
else
  partner = pick_random(all_organizations.filter(o => o.has_infinite_capital))
  value = max(
    enpv(intervention(project), partner.discount_rate),
    enpv(project, partner.discount_rate))
  if value + project.unspended_grants >= partner.threshold
  project.add_capital(project.remaining_cost)
  associate(partner).with(project)
    if project.is_at_decision_point?
      project.transition_to(DECIDING)
    else
      project.transition_to(DEVELOPING)
    end
  end
end
```

3.2.5. Grants

```
for every grant

  if tick % grant.cycle == 0
    grant.available_amount = grant.size      # reset available amount if in cycle
  end

  if grant.available_amount > 0
    project = pick_random(projects.filter(p => p.has_not_received_grants_in_current_stage))
    if project != NIL
      claim = project.stage.remaining_cost
      granted = min(claim, grant.available_amount)
      project.add_capital(granted)
    end
  end

end
```

3.3. MODELLING AND SIMULATING INTERVENTION MECHANISMS

Next to simulating the current antibiotic R&D landscape, including the existing levels and forms of grants, the simulator mimics the effect of introducing two intervention mechanisms to stimulate R&D: (1) a *push* incentive, namely **increased and more focused grants**, and (2) a *pull* incentive, namely a **Market Entry Reward (MER)** which provides to developers a guaranteed and large payment upon approval, see Baraldi et al. (2016), Renwick et al. (2016), Mossialos et al. (2010). These two intervention mechanisms were selected for testing and simulation as they are two key interventions being discussed within the DRIVE-AB consortium.

Within the simulator, the increased and focused grants entail a larger pool of yearly funding that can cover partly or entirely the upcoming development stage's costs and hence influence the eNPV calculations for both SMEs and Big Pharma at the moment of *Deciding*, and also the *Fundraising* state of SMEs as they are funds made directly available to them. As MERs provide a certain level of payment, they impact the eNPV calculations for both SMEs and Big Pharma at the moment of *Deciding*, and also the external funders' (VCs and Big Pharma) evaluation of SMEs' projects at the moment of *Fundraising* by the latter. This certainty is especially relevant for projects with very low market sales projections.

The above are the primary channels through which the two tested mechanisms generate effects within the simulator, first on the decisions made by agents and then in terms of actual numbers of antibiotics being eventually approved over the 30 years span of our simulation. More precisely, the grant intervention mechanism operates by exposing the system to a single higher level of the yearly pool and a restriction as to which types of projects can access it. Instead, the MER incentive is tested by performing simulation runs with different values of the MER (between zero and 5 billion dollars) and subsequently considering which numbers of approved antibiotics are associated with the different values of MER.

Grants are modeled as free money that shows up as a supplementary from the perspective of agents. In other words, future potential grants are not included prospectively in eNPV calculations. Instead, grants that a project has received but not yet spent are considered a positive

cashflow appearing at time zero. In other words, grants are simply added to the calculated eNPV without discounting.

We model two types of MERs, a fully delinked and a partially delinked MER. As the name implies full delinkage delinks revenues from free market sales, while the partially delinked MER complements. An agent receiving a fully delinked MER may thus not sell the antibiotic in question on the free market which means that the agent gets the MER *instead of* the market sales. An agent receiving a partially delinked MER may however sell the antibiotic in question on the free market and thus gets the MER *in addition to* the market sales.

In effect this means that a fully delinked MER must compensate for the lack of projected free market sales and should thus, in theory, almost always have to be larger than a partially delinked MER (ceteris paribus) to achieve the same effect.

Importantly, agents in the simulation, as illustrated in the pseudo code examples, always choose between accepting or declining a pull intervention. More specifically, agents calculate the eNPV of accepting the intervention and the value of not, and then move forward based on whichever of the two has the highest value. This is a critical feature since many agents would otherwise be "punished" by a very small, fully delinked, mandatory MER as their market sales would be taken from them.

4. DATA

This section describes the input data used in the simulation and why this data is used. It will start with the data used for the agents (organizations) that represent the developers and financiers; then the entry rates for each of the different types of antibiotics; time, cost and the probability of success for each phase; market sizes and, finally, the data used for the different intervention mechanisms tested.

4.1. AGENTS AND ORGANIZATIONS

As mentioned earlier, the simulation is populated with agents that represent the different organizations Big Pharmas, SMEs and VCs. The number of Big Pharma that can populate the simulation is set to 10. This number was decided on during a one-day discussion with industry experts, representing both Big Pharma, SMEs and company valuators. Big Pharma have a "go" threshold to approve projects of $100 million. This threshold is based on Sertkaya et al. (2014) and has been discussed and agreed upon by expert groups in DRIVE-AB. It is worth noting that this threshold for a developer at the pre-clinical stage, and for later stages of drug development, levels of incentives might be different. The cost of Big Pharma capital is uniformly distributed between 8 and 11%. This has been agreed upon as industry standard within DRIVE-AB with input from EFPIA partners. The distribution captures yearly fluctuations in opportunity in the industry. The Big Pharma data is:

Big Pharma	
Number of companies with unlimited capital (BP)	10
BP Threshold (Million USD)	100
BP discount rate	8 - 11 %

We opted not to put a restriction on the number of SMEs entering the simulation but to "oblige" them to find funds for these projects (either "free money" in the form of grants or investors' money from VCs and Big Pharma). The simulator does not cover an SME's possible re-investments in new projects upon successful market entry. SMEs' eNPV threshold is set to 0 as SMEs typically continue development as long as they have enough capital to do so, and because they have limited opportunities to invest in other technologies. Reflecting these issues, the SME's discount rate is uniformly distributed between 5 and 8% (i.e., at lower levels than Big Pharma's). However, importantly SMEs do have to adopt the discount rate and eNPV threshold of their investor when they are funded with other means than grants. In other words they must acquire capital to develop, and that capital must be acquired at a much higher cost than their own discount rate. The SME data is:

SMEs	
SME Threshold (Million USD)	0
SME discount rate	5 - 8 % (following VC discount rate)

The simulation does not put any cap to the number of VC agents, assuming that as long as there are attractive investment opportunities capital from the VC sector will enter the simulation. Reflecting the fact that VCs typically apply the return on investment (ROI) calculation to make their decisions, they have no eNPV threshold in this simulation. Starting from the eNPV discount rates suggested by an expert in company valuation and SMEs shown below, we then verified if these discount rates provided sufficiently high levels of ROIs in each phase if compared to typical target ROI (also shown below):

	eNPV discount rates:	Target ROI (yearly)
Pre-clinical	18-20%	65%
Phase 1	15,5 – 17,5%	50%
Phase 2	13,5 – 16%	40%
Phase 3	8 – 15%	35% (our approximation)

Compared to the suggested discount rates, we reduced only the VC discount rate for the pre-clinical phase because those high levels made it impossible for *any* projects to reach positive eNPV even with very substantial incentives (over 5 billion dollars), so a calculation was made to see if those high discount rates were indeed needed to reach the required target ROI for preclinical phases. In short we used the total market sales level that is needed for ROI to reach the given level for each phase. Then the worst-case scenario market sales from Sertkaya et al. (2014) was given a factor to reach the same level as the needed ROI. The yearly market capture (ibid.) (see further down) have then been multiplied with the factor and the discount rate have then been adjusted to result in a eNPV of 0. The same was done for the best-case scenario to find the highest discount rate possible to have a positive eNPV. These calculations indicated that VC discount rates as high as 18-20% at Preclinical are indeed not needed to yield 65% yearly ROI, which is reached already with discount rates from 8%. Therefore, our adjusted VC discount rates for preclinical are 8 – 15%. This gives us the following data for VC:

Venture Capitalists	
VC Threshold in PC (Million USD)	0
VC Threshold in P1 (Million USD)	0
VC Threshold in P2 (Million USD)	0
VC Threshold in P3 (Million USD)	0
VC Discount Rate in PC	8 - 15 %
VC Discount Rate in P1	15.5 - 17.5 %

VC Discount Rate in P2	13.5 - 16 %
VC Discount Rate in P3	8 - 15 %

4.2. DISCOVERY RATES AND TYPOLOGY OF ANTIBIOTICS

The discovery rate was reverse engineered from the PEW pipeline[1] (May 2016). The number of phase 3 projects was counted, and using mean attrition rates from Sertkaya et al. (2014), the number of new antibiotics needed to enter the pre-clinical phase each year could be calculated to a mean of 198. This was then divided by the average time in phase 3 (27.8 months) which gives the average number of projects that need to enter the simulation each month in order to have a steady flow of projects throughout the simulation. However, in order to not be too static, the simulation instead uses ranges of entry rates for the various types of antibiotics. Lower entry rates indicate the rarity of that type of antibiotic, proxying the scientific and technical difficulty of discovering them. The discovery rate data and typology is:

Different Types of Antibiotics	Corresponding medical effect
Ab Type A	Gve- Novel class
Ab Type B	Gve-, Gve+ Novel class
Ab Type C	Gve+ or minor modifications
Ab Type A Entry Rate	0.05 - 2.5 in PC/month
Ab Type B Entry Rate	0.5 - 5 in PC/month
Ab Type C Entry Rate	2 - 7 in PC/month

4.3. COSTS, TIMES, AND PROBABILITIES OF SUCCESS

Data on cost, development time and probability of success are all based on Sertkaya et al. (2014). First, Sertkaya et al. (2014) present data for six different indications. Further, as we have a different typology, the mean of all indications was calculated for each phase (still with min, mean and max values). We have also added a transition time between each phase (3 month between pre-clinical and phase 1, 6 month between the rest of the phases). Note that we have included the cost for sample preparation (min = $2,4 million, mean = $2,7 million and max = $2,9 million distributed over all phases), process research/development (min = $18,7 millions, mean = $26,8 million and max = $34,8 million distributed over phase 1 and phase 2), plant design (min = $10,7 millions, mean = $13,4 million and max = $16,1 million distributed as 75% in phase 3 and 25% in NDA) and plant build (min = $69,6 millions, mean = $83 million and max = $96,3 million during NDA) (Sertkaya et al. 2014). The data used in the simulation are:

[1] http://www.pewtrusts.org/~/media/assets/2016/12/antibiotics_datatable_201605.pdf

Input Data Pre-Clinical	
PC Cost (Million USD)	20.14 - 22.366 - 24.592
PC Probability of success	0.175 - 0.352 - 0.69
PC Time to completion (Months)	55 - 69 - 75
Input Data Phase 1	
P1 Cost (Million USD)	18.5 - 25.4 - 32.2
P1 Probability of success	0.25 - 0.33 - 0.837
P1 Time to completion	15 - 16.5 - 27.6
Input Data Phase 2	
P2 Cost (Million USD)	18.3 - 26.0 - 39.3
P2 Probability of success	0.34 - 0.50 - 0.74
P2 Time to completion	15 - 19.3 - 36
Input Data Phase 3	
P3 Cost (Million USD)	39.6 - 66.4 - 142.8
P3 Probability of success	0.314 - 0.67 - 0.786
P3 Time to completion	16 - 27.8 - 53
Input Data Approval	
Approval Cost (Million USD)	50 - 79.3 - 108.5
Approval Probability of success	0.83 - 0.85 - 0.99
Approval Time to completion	12 - 15 - 18.5

4.4. MARKET SIZES

The market sizes and the yearly market share (i.e., which share of the potential market is actually captured by the specific molecule/project) are also taken from Sertkaya et al. (2014), but modified to account for inflation.

Moreover, to expand the Sertkaya et al. (2014) to the global market as these covered only the US market (which is about 50% of the global market), we have consulted DRIVE-AB experts. The conclusion is to double the market sizes of Sertkaya et al. (2014) but simultaneously to reduce by half the yearly market shares, since penetrating a global market is considerably more difficult and slower than only the US market. We have also adjusted their figures to account for inflation. The resulting data used in the simulation for a product's yearly sales is:

Sales Revenues once on Market	Min, mean, max
Revenue Market Year 1 (Million USD)	0 - 22.4 - 67.2
Revenue Market Year 2 (Million USD)	0 - 41.4 - 116.6

Revenue Market Year 3 (Million USD)	0 - 74.7 - 211.9
Revenue Market Year 4 (Million USD)	0 - 122.2 - 346.8
Revenue Market Year 5 (Million USD)	0 - 186.3 - 527.5
Revenue Market Year 6 (Million USD)	0 - 275.1 - 779.7
Revenue Market Year 7 (Million USD)	0 - 357.5 - 1012.9
Revenue Market Year 8 (Million USD)	0 - 405.0 - 1147.9
Revenue Market Year 9 (Million USD)	0 - 480.3 - 1361.5
Revenue Market Year 10 (Million USD)	0 - 583.3 - 1653.4

4.5. INTERVENTION MECHANISMS

As mentioned, the two main intervention mechanisms tested in the simulation are MERs and grants. The value of the MER is set between 0 and $5 billion. This range is used to assess the effect of different levels of MER size also in comparison to no MER at all, while the max of $5 billion is based on Rex and Outterson (2016). Two types of MER are tested, one fully delinked from sales and one partially delinked. See section 3.2 for further description of the different kinds of MER. In the simulation runs presented in this report we tested both a so called "narrow MER", that is, only type A antibiotic projects are eligible for the MER, and a so called "broad MER", that is, both type A and type B antibiotics projects are eligible for the MER. The MER data imputed into the simulation is:

Market Entry Rewards	
MER Fully Delinked Size (Million USD)	0 – 5000
MER Fully Delinked Targeted Ab	Type A when narrow MER Type A and Type B when broad MER
MER Partially Delinked Size (Million USD)	0 – 5000
MER Partially Delinked Targeted Ab	Type A when narrow MER Type A and Type B when broad MER

Grants are given to developers in three phases: pre-clinical, phase 1 and phase 2. To each phase is distributed a total of $200 million, reaching a total for all phases of $600 million in grants. The grants are either *broad*, which means that they are given to type A, type B and type C, or *targeted* which means that only type A and type B can receive grants. Grant data is:

Current Grants	
Grants Current Targeted Ab	Type A, B, C
Grants Current PC Cost Reduction	200M, to cover 100 or 50% of cost
Grants Current P1 Cost Reduction	200M to cover 80, 50 or 30% of cost
Grants Current P2 Cost Reduction	200M to cover 70, 50 or 30% of cost

Current Grants + targeted Grants	

Extra focused Grants targeted Ab	Type A, B
Grants Current PC Cost Reduction	100M to cover 100 or 50% of cost
Grants Current P1 Cost Reduction	100M to cover 80, 50 or 30% of cost
Grants Current P2 Cost Reduction	100M to cover 70, 50 or 30% of cost

4.6. DATA DISCUSSION

Most of the input data come from Sertkaya et al. (2014) as this work is the most comprehensive and found to be accepted by the antibiotic community. However, there is generally a difficulty in finding exact and specific data on time, cost and attrition rates, due to confidentiality reasons. Departing from the work of DiMasi et al. (2004), Sertkaya et al. (2014) made further investigations to present more comprehensive, updated and, importantly, antibiotic-specific estimates on time, cost and attrition rates in antibiotic development.

In addition to this secondary source, a lot of discussions concerning the various data and input parameters have been had in the DRIVE-AB consortium. Many of the leading experts in the field are included in this consortium and they have thoroughly commented on the choice of data and inputs, as well as their ranges applied in this simulation.

5. EXPERIMENTS WITH INTERVENTION MECHANISMS

This section introduces the simulation results that have been produced by Task 9. The simulator initiates projects at the pre-clinical phase with a monthly frequency depending on entry rates per month (and type of antibiotic). Projects initially belong to SMEs. They are constantly looking for funding (grants or VC-based), exits or partnerships with large pharmaceutical companies. Hence they are 'interested' in mechanisms designed to support them. However, SMEs have limited funds and might have to hibernate a project until they find funds. SMEs base their decisions on eNPV calculations. An SME may find a VC that accepts to fund the SME's project if the project matches the VC's profitability requirements (based on its discount rate), but this funding covers only one phase at a time and needs to be found anew for the next R&D phase. If the SME forms a partnership with a Big Pharma then the subsequent stages will be funded and the eNPV value of their project will change based on the parameters of the partner. Alternatively, if an SME's project is bought up by a big pharmaceutical company, it will then be evaluated according to the new company's eNPV parameters. The simulator is highly stochastic in that many decisions are taken based on a distribution centered around a most likely mid-point. In this way we can observe a wide range of outcomes based on realistic ranges and likelihoods.

The simulator implements the logic described above. In this section, we described a number of experiments that we have conducted in order to test the intervention mechanisms proposed by the DRIVE-AB consortium.

By performing 10 different experiments we tested the effect of two types of pull interventions, a fully delinked MER and a partially delinked MER including "narrow" MERs awarded only to projects of type A (with the lowest monthly entry rate) and "broad" MERs additionally targeting type B antibiotics (with a middle range entry rate). All these types of MERs were tested in isolation or in combination with two different push interventions, namely (1) the "current" grants corresponding to a yearly total sum of $600 million available for partially funding the cost of pre-clinical, phase 1 and phase 2 independently from the class of antibiotics in the system (current grants), or current with an additional sum of $300 million to exclusively fund the developmental stages of only type A and type B antibiotics (extra, targeted grants).

These experiments are named and listed as follow:

- Experiment #1: Fully delinked MER
- Experiment #2: Partially delinked MER
- Experiment #3: Fully delinked MER + current grants
- Experiment #4: Fully delinked MER + current grants + extra focused grants
- Experiment #5: Partially delinked MER + current grants
- Experiment #6: Partially delinked MER + current grants + extra focused grants
- Experiment #7: Fully delinked broad MER
- Experiment #8: Partially delinked broad MER

- Experiment #9: Fully delinked broad MER + current grants
- Experiment #10: Partially delinked broad MER + current grants

5.1. FULLY AND PARTIALLY DELINKED MER (EX 1-2)

The effect of a fully delinked MER on the hard to discover class of antibiotics (type A green in **Figure 2**) was assessed by introducing different sizes of interventions ranging from $0 to $5 billion. While the 3000 simulations runs show how on average less than two new type A antibiotics will be reach market in 30 years with no intervention, the introduction of a $500 million fully delinked MER already makes the market entries double in numbers, i.e., to about 4 on average.

For a partially delinked MER, the main difference compared to the fully delinked MER is that already starting from a MER of $100 million the number of new market entries doubles (from less than 2 to 4 on average), and then it linearly increases up to $750 million to a maximum of 12 antibiotics in 30 years (**Figure 2**). Interestingly, the number of new type A market entries reaches a "plateau" already around $1500 billion, which means that substantial increases in the size of the MER do not result into new type A market entries: this means that all type A projects still available (and surviving at the various R&D phases) become financially profitable with a MER around $1500 million.

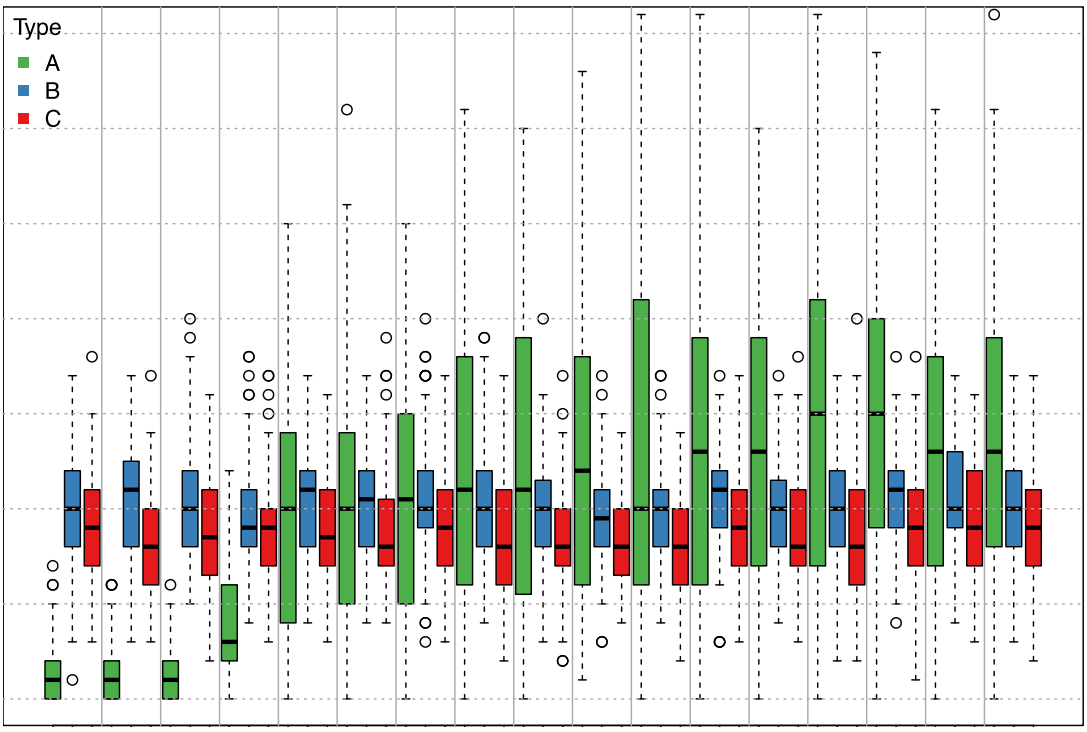


Figure 2. Boxplot representation of the total number of antibiotics reaching market within 30 years before (i.e., at MER = 0 on the X-axis) and after the introduction of different sizes of fully delinked MERs (from $0 to 5 billion) targeting type A antibiotics (in green), in comparison with the most highly occurring non-targeted type B and type C antibiotics (blue and red), whose market entries remain constant.

The effect of a partially delinked MER was similarly tested with the introduction of a $0 to 5 billion pull intervention awarded to type A antibiotics only (**Figure 3**). The main difference compared to the fully delinked MER is that already starting from a MER of $100 million the number of new market entries doubles (from less than 2 to 4 on average), and then it linearly increases up to $750 million to a maximum of 12 antibiotics in 30 years (**Figure 3**). These results indicate that the "plateau", already identified for the fully delinked MER at $1500 million, now occurs for the partially delinked MER at a much lower, indeed half, level of MER, This means that with a MER size of $750 million all projects remaining in the simulation (i.e., not failed due

to scientific reasons) start to become financially profitable, making the effect of a larger MER irrelevant.

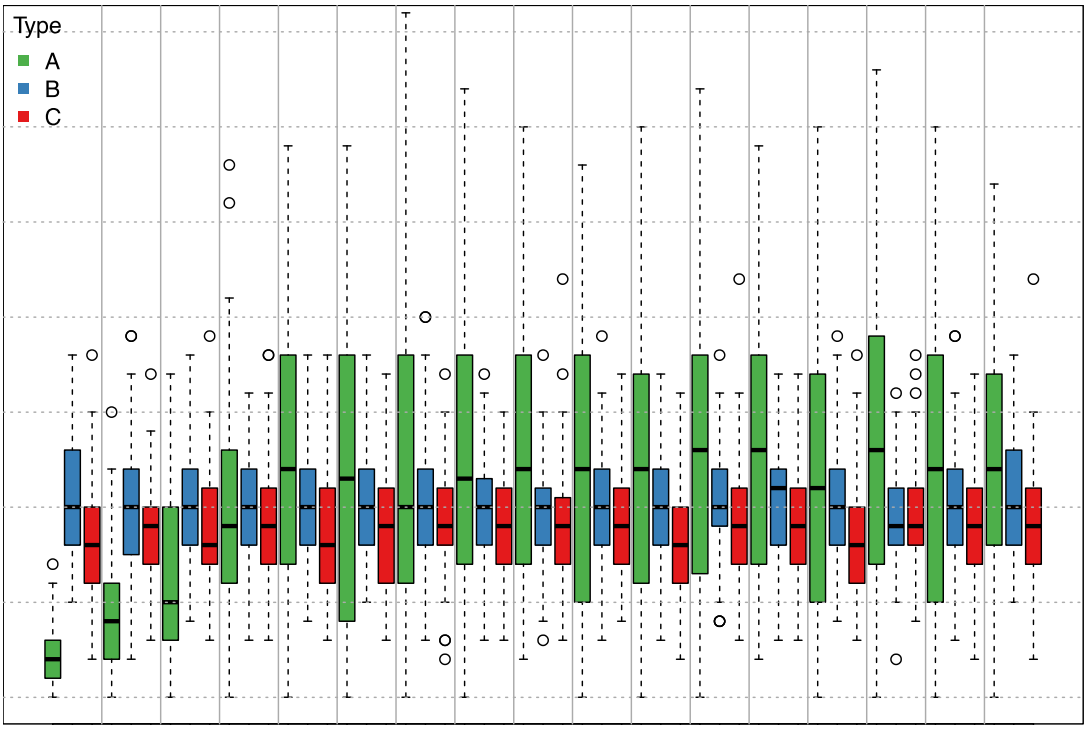


Figure 3. Boxplot representation of the total number of antibiotics reaching market within 30 years before (i.e., at MER = 0 on the X-axis) and after the introduction of different sizes of partially delinked MERs (from $0 to 5 billions) targeting type A antibiotics (in green) in comparison with the most highly occurring non-targeted type B and type C antibiotics (blue and red), whose market entries remain constant.

Thus, an important difference can be observed by comparing the effects that the two type of interventions (fully delinked MERs and partially delinked MERs) had in pulling to market the most wanted and hard to discover class of antibiotics (type A). In particular, the full effect of the pull intervention in partially delinked MERs is achieved at lower sizes (approximately $750 million) compared to the fully delinked MERs ($1500 million). Additionally, in order to double from an intervention-free scenario the market entries of type A antibiotics, a $100 million are

sufficient in the partially delinked MER, while $500 million are needed in the fully delinked MER to achieve the same doubling. However, it is only the direct costs that are compared. The indirect costs of a partially delinked MER is to a large extent financed through sales, and thereby by tax payers' or health insurance customers.

5.2. FULLY AND PARTIALLY DELINKED MER WITH GRANTS (EX 3-6)

In experiments 3 to 6 we tested the effect of two forms of grants: (1) the current level of grants and (2) and extra focused grants corresponding to current grants with an addition of $300 million yearly and targeted specifically to only type A and type B projects. Additionally, these grants were tested in combinations with the two types of pull incentives as described in previous section (fully and partially delinked MERs).

The current level of grants which allocates $600 million per year to partially cover the cost of development up to phase 2 for all antibiotics in the pipeline, could double, without any MER, the total number of type A antibiotics' market entries in 30 years (from less than 2 to almost 4 on average: see the zero-MER level red line in figure 4A).

Additionally, more focused extra grants of $300 million yearly awarded to type A and type B only molecules result in a further increase of approximately 50% in the number of type A antibiotics entering market, that is, about 6 new type A (compare the red zero-MER level line in figure 5A and figure 5B).

In figure 4 and figure 5 we also show the effect of these push mechanisms in combination with the previously described MER mechanisms.

Adding the current level of grants ($600 million yearly) to a fully delinked MER enables a MER of $1250 million to be sufficient to make all type A antibiotics profitable (as visible in the convergence of all MER-level lines in figure 3A on the $1250 million level). In relation to the previous discussion on the plateau reached by the MER, this results indicate that the "current level" grants reduce by about $250 million the MER level at which the plateau of Figure 2 is reached. The additive effect of the extra ($300 million/year) and targeted grants (totaling at $900 million) is to further reduce to around $1000 million the level of the fully delinked MER which makes all type A antibiotics become profitable and reach the plateau of Figure 2 (see the convergence of all MER-level lines in figure 4B on the $1000 million level).

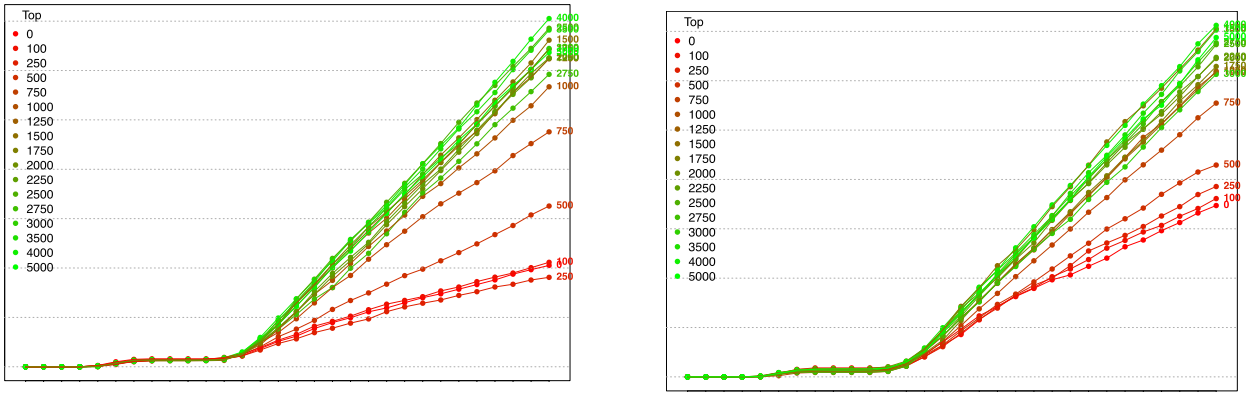


Figure 4. Line plots showing the mean cumulative market entries for project type A in 30 years under different sizes of single fully delinked MERs (from $0 to 5 billions) on 3000 simulation runs. The MERs were introduced in addition to $600 million in yearly grants (**A**) or to grants of $600 million plus $300 million targeted exclusively to type A and type B antibiotics (**B**).

Similar, although not as strong, results emerge when a partially delinked MER is combined with grants. As for combining it with "current grants", a MER of $750 million is sufficient to bring to market more than ~12 type A antibiotics in 30 years (see the convergence of all MER-level lines around the $750 million value in figure 5A); while the extra and targeted grants (totaling at $900 million yearly) enable $500 million partially delinked MERs to make all molecules in the pipeline profitable (see the convergence of MER lines around the $500 million level on figure 5B). Therefore, the introduction especially of extra and targeted grants allows reducing the level of partially delinked MERs that reach the antibiotic plateau by $250 million from the value of $750 million of Figure 3.

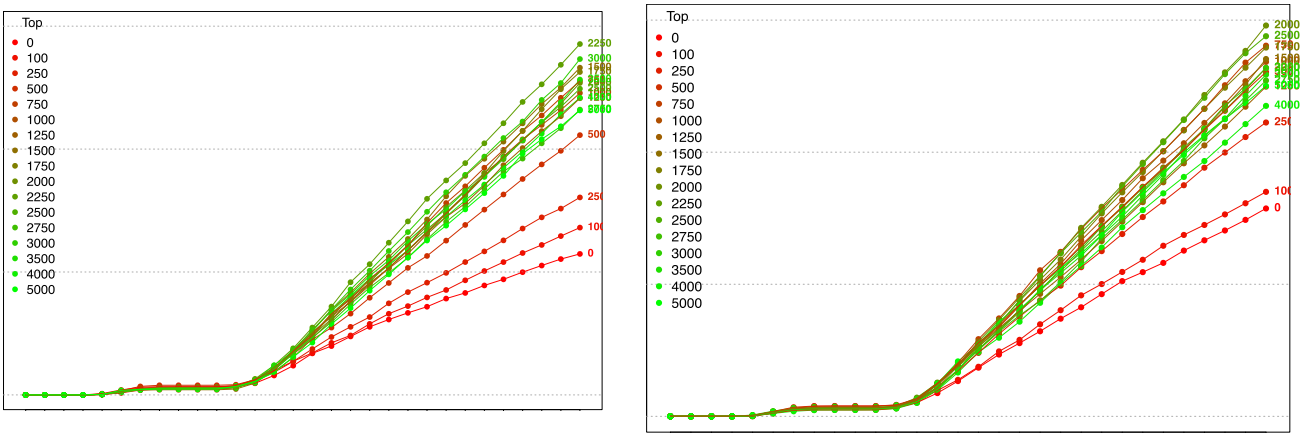


Figure 5. Line plots showing the mean cumulative market entries for project type A in 30 years under different sizes of single partially delinked MERs (from $0 to 5 billions) on 3000 simulation runs. The MERs were introduced in addition to $600 million in yearly grants (**A**) or to grants of $600 million plus $300 million targeted exclusively to type A and type B antibiotics (**B**).

5.3. BROAD TARGETING FULLY AND PARTIALLY DELINKED MER (EX 7-10)

In order to assess the role of different pull mechanism for a broader group of antibiotics in the pipeline, including also type B antibiotics with monthly entry rates ranging from 0.5 to 5 in pre-clinical development, we performed 4 additional experiments.

The broad fully delinked and partially delinked MER (whose effects are displayed on figure 6 and figure 7) were tested in combination with current levels of grants (figure 8A and figure 8B). As described for the narrow MERs (which targeted only type A projects), we observed a similar difference between fully and partially delinked MERs, which are however now affecting also type B antibiotics, in terms of the levels of the two kinds of MER which enable all projects (type A and B) to become profitable: fully delinked MERs reach a plateau for type B at about $1500 million (the same as for narrow MERs for only type A), while partially delinked MERs reach such a plateau for type B at about $1000 million (higher than the $750 million for type B)

Adding current grants to the two kinds of MER produces then the effect of reducing by about $250 million the level of both kinds for MER which reach the plateau: to $1250 million for fully delinked MER and $750 million for partially delinked MER (see the convergent lines in Figure 7A and B).

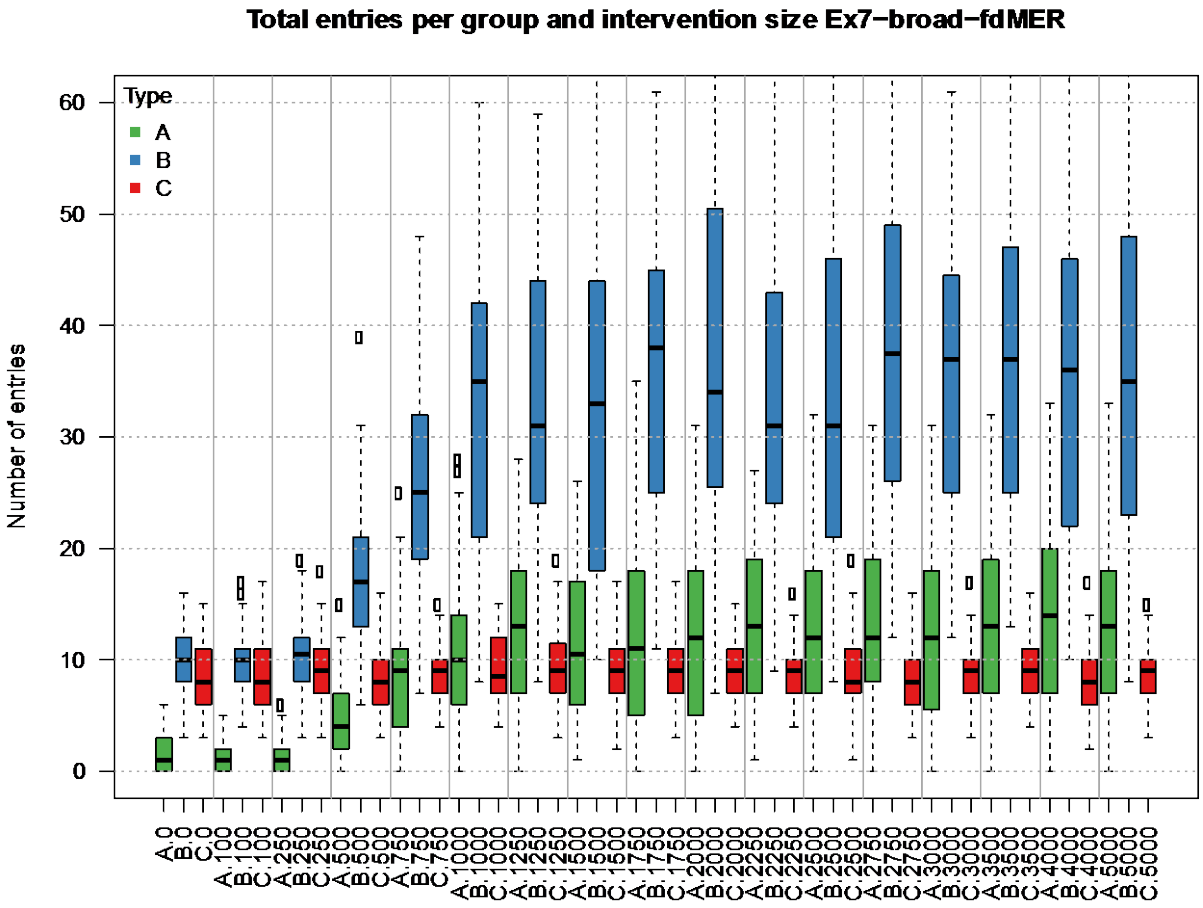


Figure 6. Boxplot representation of the total number of antibiotics reaching market within 30 years before and after the introduction of different sizes of fully delinked broad MERs (from $0 to 5 billions) targeting type A and type B antibiotics.

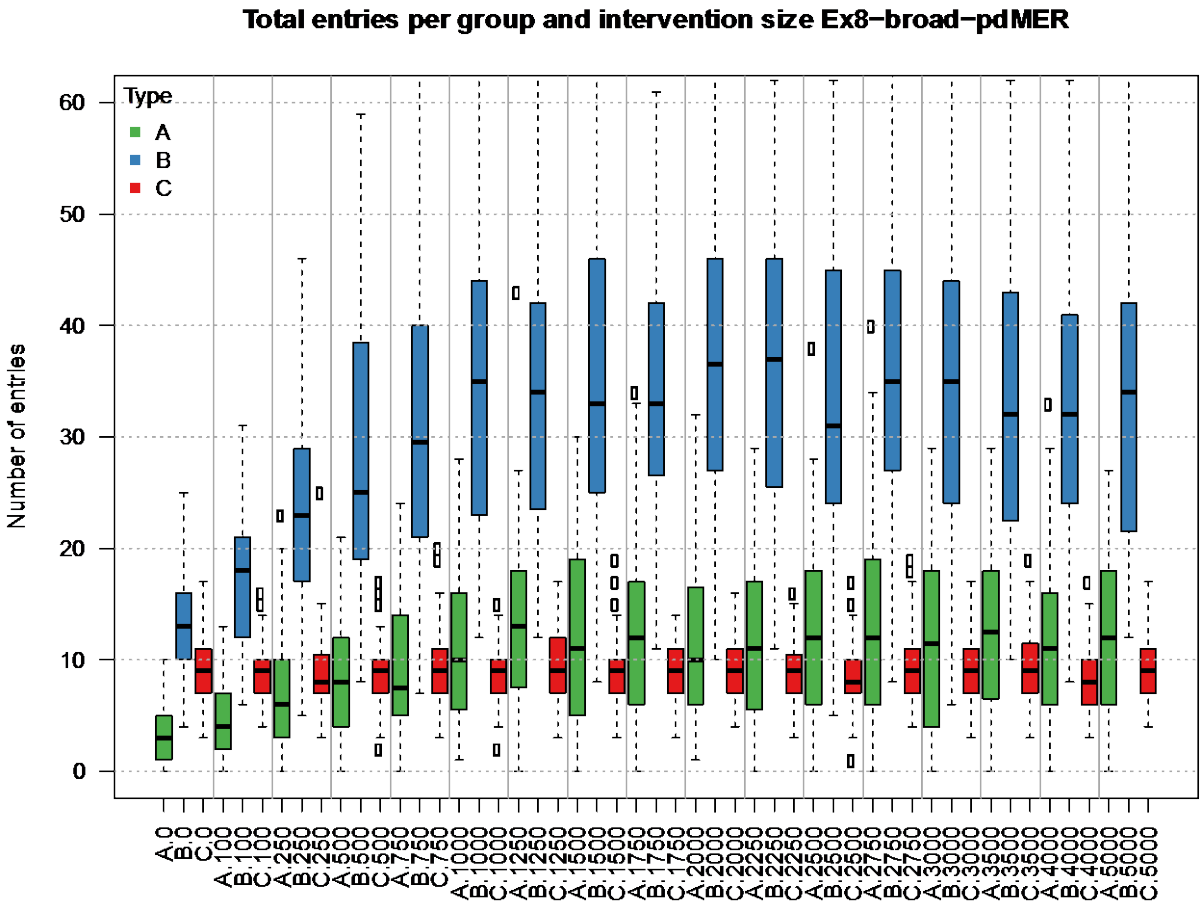


Figure 7. Boxplot representation of the total number of antibiotics reaching market within 30 years before and after the introduction of different sizes of partially delinked broad MERs (from $0 to 5 billions) targeting type A and type B antibiotics.

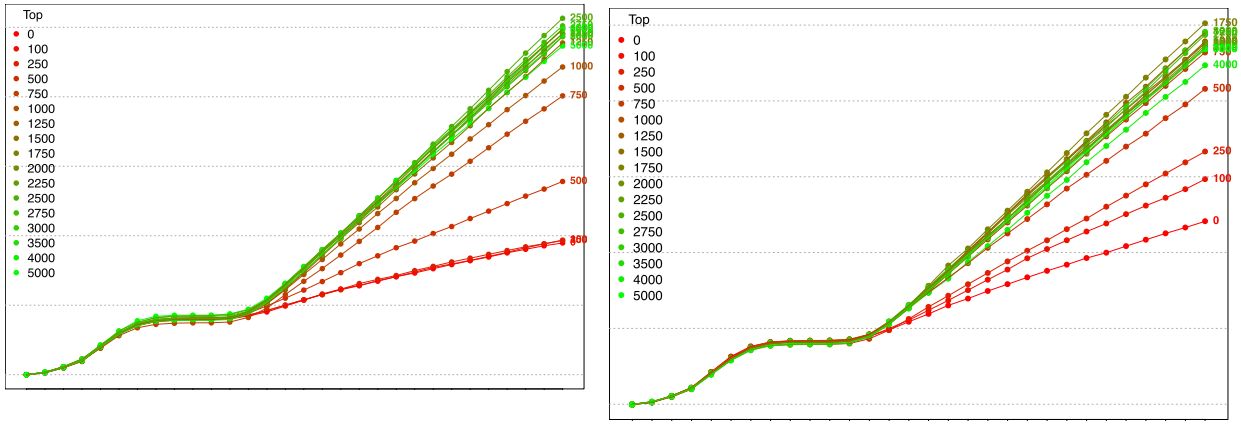


Figure 8. Line plots showing the mean cumulative market entries for project type A and type B in 30 years under different sizes of single fully delinked MERs (**A**) and partially delinked MERs (**B**) on 3000 simulation runs. The MERs were introduced in addition to $600 million in yearly "current" grants.

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