WP2: Antibiotic R&D pipeline simulation results.
Effects of different intervention mechanisms (Part 1)

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Introduction: A large-scale simulation comprising 90,000 runs has been designed to explore the effects of three prototypical interventions aimed to stimulate the global antibiotic R&D pipeline: Grants, Fully Delinked (FD) and Partially Delinked (PD) Market Entry Rewards investigated by DRIVE-AB. The simulation reflects key financial decision making processes that guide early stage development in small “biotech” firms (SMEs), often supported by venture capitalists (VCs), and projects acquisition by larger pharmaceutical companies (Big Pharma-BP) who bring the product to market. These results are intended to support policy decision by exploring the effects of various interventions on economically rational developers, aside from details of actual implementation.

Simulation Mechanism

The likelihood of an antibiotic reaching market approval is determined by the risk of technical failure and the financial decisions of developers (SMEs or BP), VCs, partners, and acquirers at the various R&D phases. The developer decides the “go/no-go” decision is based on antibiotic’s Expected Net Present Value (eNPV) which is calculated at each time step (month) t. Projects enter preclinical in FUNDRAISING through an SME developer and leave the simulation as either TERMINATED (eNPV is < the threshold of the actor(s) involved), FAILED (preclinically), or as COMPLETED (by reaching market approval). Securing funds (leading to DECIDING) can be achieved by either (i) grants; (ii) VC investments (funding limited to preclinical), (iii) exiting to, or (iv) partnering with BP (funding until market approval). eNPV in FUNDRAISING is calculated from the perspective of the acquiring actor, while in DECIDING from all involved parties. The project remains in DEVELOPING until it (i) exhausts all funds (~ FUNDRAISING), or (ii) reaches the next decision point (~ DECIDING). Failure in FUNDRAISING leads to HIBERNATING, where an exponentially increasing time penalty is incurred.

Sensitivity Analysis, key parameters explaining variance of market approval

Our sensitivity analysis show the variance of the mean likelihood of market approvals (number of antibodies that reached market divided by total number of antibodies entering preclinical) caused by antibiotic projected net revenues (A), R&D costs (B), technical probability of success (C), VC discount rates (D) and BP eNPV thresholds (E) alongside the offsetting effects of MERs of different sizes (from 0 to 3000M dollars, red to green).

General conclusions:

When the expected net revenues of an antibiotic are larger than 1.5B dollars, the marginal returns of increased MER sizes start to diminish. MERs should ideally be used to incentivize antibiotics with a “broken” market to avoid spending public money on financially profitable antibiotics.

In general, the reliance of our simulator on eNPV formulas as the key decision rule is certainly a limitation, as it neglects other decision logics (e.g. strategic choices on portfolio effects and non-financial logics entailed by corporate social responsibility). However our broad span of input parameter counterbalances the partial lack of detailed data and helps represent the heterogeneity of projects and developers in antibiotic R&D.
**FD & PD MER stimulate antibiotic development differently**

A Fully Delinked MER quickly exhibits positive effect over the status quo (mean likelihood of market approval = 0.86%), starting from roughly 21% increase with a MER size of 600M dollars up to a maximal percentage increase of 77% with 7500M dollars. With a Partially Delinked MER, we observed almost a 10% increase in market approval with baseline size of 200M, up to 200% increase with 1.25B MER.

**Balancing push and pull based policy intervention**

The additive effects given by various push (grants) and pull (MERs)/based incentives on mean likelihood of market approval (isolated cell values) are shown below. Additionally, an “optimal” level of public spending can be derived by balancing the size (million dollars) of push investment (number higher up in every cell) and pull investment (number lower down in every cell) per antibiotic entering preclinical.

**Effect of MERs on absolute number of approved antibiotics**

The effect of different sizes of FD or PD MERs is also shown as the change in absolute number of market approval for 3 hypothetical types of antibiotics (Type A, B, and C) with different artificially derived entry rates in preclinical. This way we can directly report the difference between a “normal” MER (exclusively targeting Type A antibiotics) and a “broad” MER targeting both Type A and Type B.

**Specific conclusions for incentives**

In brief, our results show that:

- A fully delinked (FD) MER doubles the likelihood of market approval at 800M dollars. It starts having an effect at 600M and reaches a plateau at around 1500-1750M dollars (~300% increase).
- A partially delinked (PD) MER doubles the likelihood of market approval at 600M dollars. It starts having an effect already at 200M dollars and reaches a plateau at around 1200M dollars (~300% increase).
- Grants alone (i.e., without MERs) increase the final likelihood of market approval by about 23.7% (0.2 percentage points).
- Grants alone increase the likelihood of entry into the various R&D phases as follows: 7.6% (3.5 percentage points) increase of entry into Phase 1; 19.2% (2.5 percentage points) for Phase 2; and 16.7% (1 percentage point) for Phase 3.
- Grants added to MERs can, depending on the sizes, increase the likelihood of market approval up to 42%, for MERs ≤ 1500M dollars.

**Information regarding results**

- The results:
  - are derived from a 90,000 simulation experiment with multiple projects per run.
  - are derived from the output of a particular sample of the antibiotic R&D landscape based on a selection of previously described parameters that are both realistic and makes the effect of pull and push incentives meaningful, and in which Big Pharma’s (BP’s) ENP thresholds are between 200M and 500M dollars; VC disinterest rates are between 18% and 30%.
  - are expressed in terms of (i) likelihood of market approval defined as the percentage of projects starting the preclinical stage which eventually are approved for market sales; or (ii) actual number of antibiotics reaching the market in 30 years, considering the three hypothetical antibiotics types: Type A antibiotics enter preclinical at a rate of 0.5% per month, Type B at a rate of 7.8% per month and Type C at a rate of 8.6% per month.
  - can reach a plateau level if almost all antibiotics surviving the attrition rates at the various R&D stages turn profitable by a given size of intervention, implying that the margin return in terms of added market approvals per additional investments, becomes extremely low beyond this level.

**Grants’ reinvigorating effect over the R&D pipeline**

Since market approvals are not as sensitive to total R&D cost (see Part 1), the isoloadeffect of grants is not as strong as the MERs: grants above 40% of total costs cure congestion the mean likelihood of market approvals only from 0.76% to 0.94% (25% increase). Grante influence the number of market approvals indirectly by increasing the number of antibiotics starting in Phase 1, Phase 2, and Phase 3 by 7.6%, 14.2%, and 16.7% respectively. However, early discovery grants (not included in the simulation) may also increase the number of antibiotics starting preclinical.