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Supporting innovation against the threat of antibiotic resistance: Exploring the impact of public incentives on firm performance and entrepreneurial orientation

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ABSTRACT

Although there is an urgent need to find new antibiotics to fight growing antibiotic resistance, the development of antibiotics is at its lowest level ever. This innovation drought in the antibiotics industry is a challenge for managers, policy makers, and public health authorities. Currently, several strategies to incentivize antibiotic innovation are being considered, but their effects are unknown. Using the theoretical lens of the entrepreneurial orientation framework and Monte Carlo-based simulations on state-of-the-art pharmaceutical industry data, this study found that several incentives can increase the innovativeness of firms in this industry. However, the results show that these effects vary between incentives, between large and small firms, and across different research and development stages. This study analyzed these findings in the light of the entrepreneurial orientation framework and presents implications for theory, policy makers, and managers.

1. Introduction

Today several serious threats afflict humanity worldwide. One of the most severe threats is the rise in antibiotic resistance, where bacterial mutations decrease the efficacy of antibiotics (Laxminarayan et al., 2013). Antibiotic resistance is a growing threat that already causes more than 50,000 deaths per year in the EU and US alone (AMR Review, 2015), and several hundreds of thousands casualties are estimated in the rest of the world (The Economist, 2019). If new drugs are not developed to tackle antibiotic resistance, the death toll is projected to be between 10 and 50 million people globally (AMR Review, 2015). In such a scenario, the World's GDP is estimated to drop by as much as 3.8% (Adeyi, Baris, & Jonas, 2017). Therefore, new antibiotics are urgently needed. However, few companies have entered the antibiotics field during the past couple of decades, and many have abandoned it in recent years (Rex & Outterson, 2016). The global market for antibiotics is valued at approximately 45 billion USD (Grand View Research, 2018). However, this market includes mostly generics (i.e., old drugs such as penicillin) and is growing slowly. Innovation in antibiotics faces several challenges: high costs, high risk of failure, long development periods (10–15 years), and much lower returns on investments than other pharmaceuticals such as cancer drugs (Payne, Miller, Findlay, Anderson, & Marks, 2015; Spellberg, Bartlett, Wunderink, & Gilbert, 2015; Wright, 2015). Consequently, governments and international organizations are looking at ways to support innovation. These incentives should stimulate research and development of new antibiotics and support the industry's development (DRIVE-AB Report, 2018).

Therefore, managers and policy makers are facing the pressing challenge of how to best support innovation of a vital industry for society while pharmaceutical companies are increasingly deserting antibiotics research. Building on previous conceptual work (Ciabuschi & Lindahl, 2018) and the entrepreneurial orientation framework (e.g., Avlonitis & Salavou, 2007; Jiang, Liu, Fey, & Jiang, 2018; Lumpkin & Dess, 1996), this paper tests the potential effects of several public incentives aimed to develop innovativeness in the pharmaceutical industry, specifically innovations that encourage the development of antibiotics. Most suggested governmental innovation incentives encourage antibiotic innovation by making the introduction of new

Abbreviations: MER, market entry reward; rNPV, risk-adjusted net present value; M USD, million United States dollars; PoS, probability of success

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products more profitable (DRIVE-AB Report, 2018). Incentives can increase profits by providing higher revenues (including substituting sales) or by reducing development cost. However, whereas the influence of entrepreneurial orientation (i.e., innovativeness) on profitability is well established in the literature, the reversed influence of profitability on entrepreneurial orientation has been less studied. More specifically, while it is reasonable to think that increasing the profitability of innovation activities will lead to more innovations (i.e., new products), little is known about what circumstances make this possible. In other words, since the relationship between profits and innovativeness is highly contingent on contextual factors, we need to investigate the effects that several key variables, including company size and the characteristics of public interventions that stimulate profits, might have on this relationship.

Therefore, to fill these gaps and fulfill the aim of this study, we start by identifying the key variables that influence various public interventions on profitability as well as where along the innovation process these interventions are most able to support innovativeness and entrepreneurial activities. More specifically, we focus on both the receiving and the giving side of such interventions. As for the former, we consider the key characteristics of the innovation process (e.g., scientific challenges and stages in the pharmaceutical innovation process), of the developers (e.g., small and large pharmaceutical firms), and of the market for antibiotics (market sizes and potential returns). As for the latter, we consider the particular characteristics of the main types of public interventions aimed at supporting antibiotic innovation. Thus, our analysis relies on a series of known elements (i.e., parameters and characteristics that describe the stages of innovation, the developers, and the markets) and information to explore the potential effects of the new elements – i.e., the various public incentives. In fact, when trying to improve profitability and consequently stimulate innovativeness in the antibiotics industry, policy makers might use several kinds of incentives. Relying on these considerations, we formulated the following research question: *How and to what degree do innovation incentives designed to increase profitability influence innovativeness?*

To address this question, our paper uses a Monte Carlo simulation to compare the effects of three incentives designed to encourage innovativeness in the antibiotics industry. Furthermore, we use state-of-the-art industry data and consider the decision-making procedure of pharmaceutical firms in each step of drug development, which we identify below. The results highlight the potential of these innovation incentives to stimulate entrepreneurial activity in antibiotic development, the costs of deploying such incentives for public funders, and the trade-offs between the various incentives.

This study contributes to further developing the understanding of the relationship between innovativeness and profitability in the entrepreneurial orientation framework. Specifically, it empirically investigates this relationship and identifies the circumstances under which incentives targeted at increasing firm profitability also incentivize innovativeness most powerfully. In addition to its theoretical relevance for the innovation and entrepreneurial orientation literatures, this paper provides information relevant to public health as it should help policy makers evaluate incentives that governments across the world might implement. Finally, important managerial implications of our findings are also provided to clarify what firms can expect in terms of potential effects of incentives for antibiotic innovation.

The rest of this paper is structured as follows: First, we introduce the literature on the entrepreneurial orientation framework, the development of antibiotics, and policy incentives targeting antibiotic innovation. Second, we present the paper's methods and data, which is followed by the results and discussion. We conclude the paper by highlighting implications for theory as well as for policy and practice, and finally outline the paper's limitations and possibilities for future research.

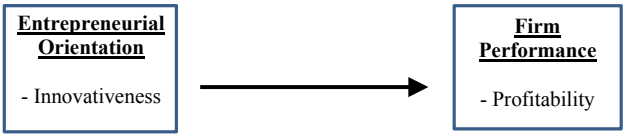

Fig. 1. The relationship between entrepreneurial orientation and firm performance. Simplified illustration of the main relationship between entrepreneurial orientation (innovativeness) and firm performance (profitability). Adapted from Lumpkin and Dess (1996)

2. Theoretical framing

2.1. Entrepreneurial orientation

To investigate the attempts to improve innovativeness in the antibiotic industry through innovation incentives, we apply the analytical lens of the entrepreneurial orientation framework. The entrepreneurship literature has established that firms vary in how entrepreneurially oriented they are and how this variation influences the performance of firms (e.g., Avlonitis & Salavou, 2007; Covin & Miller, 2014; Jiang et al., 2018; Lumpkin & Dess, 1996). In this paper, we base our analysis on the specific entrepreneurial orientation framework first introduced by Lumpkin and Dess (1996), which relates the entrepreneurial orientation of a firm to its performance (Fig. 1) (Brouthers, Nakos, & Dimitratos, 2015; Lee, Lee, & Pennings, 2001; Teng, 2007). Our discussion of the entrepreneurial orientation framework focuses explicitly on the relationship between profits (representing the framework's operationalization of performance) and innovativeness (representing the framework's operationalization of entrepreneurial orientation). Innovativeness reflects a firm's tendency to engage in and support new ideas, novelty, experimentation, and creative processes that might result in new products, services, or technological processes (Lumpkin & Dess, 1996). To study the relationship between entrepreneurial orientation and performance, we chose the variables profits and innovativeness as these variables are essential elements in the business logic and decision-making of leading research-focused pharmaceutical companies. Indeed, the competitive nature of these companies drives them to constantly develop new and innovative drugs as new drugs ensure the highest possible profits due to protections afforded by patents.

The entrepreneurial orientation framework is well suited for understanding the problems faced by firms in the antibiotics industry as it focuses on the relationships between profits and product innovation (Covin & Miller, 2014; Lumpkin & Dess, 1996; Rosenbusch, Rauch, & Bausch, 2013; Wiklund & Shepherd, 2003). However, we use this framework to investigate how public incentives influence the relationship between entrepreneurial orientation (i.e., innovativeness) and performance (i.e., profitability) of firms that develop antibiotics. This relationship assumes that increased innovation efforts might lead to more profits and that more profits might lead to increased innovative efforts (e.g., Ciabuschi & Lindahl, 2018). That is, companies must expect a profit before they invest in innovation or re-invest profits in research and development (R&D) to sustain a long-term competitive advantage. As noted above, profits of pharmaceutical companies are contingent on a constant stream of new drugs that generate high revenues while under patent protection. Moreover, pharmaceutical companies typically reinvest much of their profits into R&D. Excluding generic drug companies (which do not conduct R&D), in 2018 pharmaceutical companies reinvested on average 20% of their revenues in innovation, as reported by the Association of British Pharmaceutical Industry. This is a very high percentage compared to the average for all industries, which is 1.3%. Because both the profit expectations and the profit re-investment assumptions are evident, innovation and profitability are very closely connected. Therefore, in pharmaceutical companies, innovation projects lead to more profits and more profits lead to more innovation projects.

Furthermore, the literature on entrepreneurial orientation highlights the influence of so-called 'contingencies' on the connection between innovativeness and firm performance (e.g., Lumpkin & Dess, 1996; Wales, Gupta, & Mousa, 2013). One such contingency is munificence, which concerns the industry's profitability and growth (Bourgeois, 1981; Lumpkin & Dess, 1996). The relationship between entrepreneurial orientation and performance is considered stronger for firms active in a munificent industry (Lumpkin & Dess, 1996) as there are more profits to be reaped. The greater profits made by firms in munificent industries are to a large extent re-invested in innovation (Bourgeois, 1981). Using this analytical lens, we view public innovation incentives as affecting the munificence of the industry; however, the related effect of variations in profits on innovativeness has received little attention from research concerning entrepreneurial orientation and even less attention has been directed at the effects that policy incentives might have on an industry's munificence.

One important argument, however, is that incentives provided by governments wishing to promote entrepreneurship should target truly advanced innovation efforts and consequently exclude replicative behaviors or minor innovative efforts (Mthanti & Ojah, 2017). More specifically, public incentives targeting innovation have the ability to impact innovativeness either directly by financing R&D expenditures or indirectly by increasing profit expectations. At the same time, these incentives will not influence actors who are not engaged in substantial innovation. However, innovation incentives can be designed in different ways and their effects on innovativeness and profitability are likely to vary, depending on the features of the recipients, which is the main focus of this study. In particular, we argue for the importance of contextualizing the effects of innovation incentives in a specific industry, which presents unique characteristics and practices, and the effects of the individual stages of an innovation process at a granular level, in this case R&D of antibiotics. Therefore, to situate the relationship between profits and innovativeness in the context of the antibiotics industry, we now turn our attention to the specificities of innovation and policies in this field.

2.2. Development of antibiotics

The development of antibiotics has many similarities to drug development in general, but also has many unique features. Below, we outline important aspects of innovation in the antibiotics field to better define the empirical context of our study.

Drug development is a highly regulated activity that has to be performed in several steps: Preclinical Development (including animal testing); Phase 1 Clinical Trials (testing on healthy humans to evaluate drug safety); Phase 2 Clinical Trials (testing on a small group of patients to assess drug efficacy and side effects); Phase 3 Clinical Trials (testing on a large group of patients to assess drug efficacy, compare effectiveness, and reassess safety); and Market Approval (including production start and release of the drug on the market). At each step, the drug being developed goes through closer scrutiny and can fail at any step, even the last one. However, as a drug moves down this so-called R&D pipeline, the likelihood of failing decreases while the cost of performing the steps increases. In all, very few drugs make it to Market Approval (less than 15% of antibiotics).

In the early stages, R&D work is typically done by start-ups and small companies. In the later stages, antibiotics development is taken over by large pharmaceutical firms (Big Pharmas) as these firms prefer projects that have progressed along the pipeline and therefore are less risky. Moreover, projects in later stages, such as a Phase 3 Clinical Trial, are very expensive, making this stage challenging for a small firm. However, for both large and small drug developers, bringing a new antibiotic onto the market entails considerable risks and challenges, such as very small and uncertain markets for new antibiotics (Payne et al., 2015), the high failure rate of antibiotics during development (Friedman & Alper, 2014), and the risk that antibiotic resistance will reduce the longevity and therefore sales of the new drug (Spellberg et al., 2015).

2.3. Public incentives to promote antibiotic innovation

Due to the threat of antibiotic resistance, governments and intergovernmental organizations such as the WHO, the UN, the G20, and the EU are designing several policy responses to this global threat (e.g., Laxminarayan et al., 2013; Årdal et al., 2017). These policy responses often come in the form of public incentives that promote innovation in antibiotics. These incentives can be grouped into two main categories: push incentives and pull incentives. Push incentives are interventions that aim to help firms move forward in the drug development pipeline by removing or reducing R&D costs. Pull incentives, on the other hand, represent some form of payment to developers who accomplish certain R&D outputs as a compensation for taking on the associated costs and risks. Current policy discussions on new incentives for antibiotic drug development revolve around a relatively small number of push and pull incentives, such as grants, Market Entry Rewards, and Phase 1 Entry Prizes. These three incentives are described below.

2.3.1. Grants

A grant is a push incentive that provides money to developers of antibiotics in the form of subsidies for the costs of R&D (DRIVE-AB Report, 2018). Grants do not restrict the drug developers in any way; they just pay for the costs of developing a promising antibiotic. Therefore, grants reduce or eliminate R&D costs for the recipient firm, which allows unprofitable projects to move forward, including the development of unprofitable drugs to treat rare diseases. That is, grants can allow firms to continue developing an antibiotic that otherwise would be terminated because of a lack of funds, the development project is seen as a high risk by private investors, or the market for the new drug would be too small to generate enough revenues to make a profit.

2.3.2. Market entry rewards

A Market Entry Reward (MER) is a very large innovation prize awarded to developers who bring to market new antibiotics with a particular profile. A MER can follow different designs (AMR Review, 2015). In this study, we consider a so-called fully delinked MER (AMR Review, 2015), which is a pull incentive paid out incrementally and aims to fully substitute all future sales revenues of the antibiotic as the distribution of the drug is controlled by public agencies that delimit its use.

2.3.3. Phase 1 entry prizes

A Phase 1 Entry Prize is a particular form of milestone prize (Baraldi, Ciabuschi, Leach, Morel, & Waluszewski, 2016; Mossialos, Morel, Edwards, Berenson, Gemmill-Toyama, & Brogan, 2010); that is, it is a pull incentive that rewards an antibiotic developer for succeeding at a particular development stage. In particular, a Phase 1 Entry Prize, as the name suggests, pays developers who have successfully completed Preclinical trials and have a project ready to enter Phase 1. Whereas a MER is expected to have a long-term influence on firm innovation and might require more than a decade before being actually awarded as the new drug has to be approved to be awarded, a Phase 1 Entry Prize has an impact much earlier in the pipeline because reaching Phase 1 takes a much shorter time than completing the whole R&D process.

3. Methods and data

To investigate a situation that has not yet occurred, namely the effects of various potential incentives, we used computer-based simulations to create virtual projects based on the input parameters that characterize real antibiotic R&D projects. Our analysis focuses not only on the key characteristics of the innovation process (e.g., scientific challenges, costs, steps in the innovation process), the developers, and

the market for antibiotics but also on the characteristics of various potential public incentives aimed at supporting antibiotic innovation. Specifically, a Monte Carlo simulation was used to generate variations in the Risk-adjusted Net Present Values (rNPVs) of many virtual drug development projects. The rNPV is a key indicator of profitability widely used by pharmaceutical companies to decide whether to continue a drug development project. In our simulation, each virtual project was randomly assigned costs, development times, revenues, risks, and capital discount rates between a pre-defined range of values. The values of the parameters affecting rNPV and therefore profitability are based on public information about R&D for the entire antibiotics industry and on additional data collected by the authors.

Specifically, this simulation included 100,000 runs (i.e., virtual projects) to provide the necessary variation in R&D projects. These 100,000 virtual projects were exposed to three incentives that either pushed or pulled the R&D projects forward. In other words, each incentive changed the economic profile of all the simulated R&D projects – i.e., the projects' costs, development times, revenues, and risks of technical failure. In addition, we compared how each incentive affected the rNPV of each R&D stage. This comparison was performed to determine which stage in the R&D pipeline created the strongest effects in terms of profitability and innovativeness for each incentive.

3.1. Monte Carlo simulation

Assessing the effects of various innovation incentives on the R&D of antibiotics requires many scenarios, which are alternative realities for a given set of inputs performed during one run of the simulation. Moreover, many of the inputs to our simulation are ranges and include randomness. Incentives are introduced on an existing antibiotic landscape and with strict regulatory control. We also needed to combine the outcomes of various scenarios to assess each incentive, both individually and against each other. That is, we used computer-based simulations to investigate how each incentive performed.

More precisely, we used Monte Carlo simulations to investigate the performance of each incentive. Monte Carlo methods are a broad class of computational algorithms that rely on repeated random sampling to obtain numerical results (Metropolis et al., 1953). At their core, they use randomness to solve problems that *might* be deterministic. Consequently, Monte Carlo methods are used to model phenomena that have inputs with significant uncertainty; all the input parameters in our simulations, such as R&D costs and market sizes, were uncertain. Exploring the vast space of possible inputs and the ensuing outcomes allowed us to reason about the effects of policy interventions in multiple alternative realities. Hence, Monte Carlo simulations are useful when the inputs to a simulation are drawn from a probability distribution, each one unfolding during one run of the simulation (Fichthorn & Weinberg, 1991; Metropolis, 1987). A limitation of this methodology is that a simulation cannot model the intricacy of highly complex decision processes, such as those behind the choice to continue or to terminate an R&D project. Although this mathematical model only simplifies the reality of decision processes, it can provide a way to investigate the effects of many potential parameters, which can vary between predefined values.

3.2. Risk-adjusted net present values in antibiotics R&D

In this study, we have constructed a Monte Carlo simulation that explores the rNPVs of many antibiotics projects, from preclinical studies to market approval, with different innovation incentives and different initial conditions (e.g., technical probability of success, development costs, development times, expected revenues, and financial requirements of developers). The rNPV formula measures the profitability of an R&D project and is commonly used in the pharmaceutical industry to determine whether a R&D project is to continue to the next stage or to be terminated due to insufficient returns. Furthermore, companies in the industry as well as in our simulations apply certain thresholds to define the value that a project's rNPV needs to exceed for a developer to regard it as profitable. As a new decision to continue or terminate a project is made on the basis of the project's rNPV at the transition between each new R&D stage, the simulation makes it possible to assess the rNPV values of all projects in the different stages of the R&D pipeline, identifying their profitability profile and how this varies when different incentives are added to the simulation and at different R&D stages.

The probability of technical success of an antibiotic in each stage (i.e., of presenting satisfactory test results) is assumed to follow reported standard rates and is assigned to each project in a purely probabilistic manner using uniform distributions. We assume that developers and financiers decide whether to continue funding projects that have survived technical failures solely based on rNPV. This decision-making approach is widely applied to evaluate the profitability of major investments. Moreover, rNPV is a common evaluation tool used by large pharmaceutical companies and has previously been used to model decision-making in pharmaceutical organizations (Blau, Pekny, Varma, & Bunch, 2004; Okhravi, McKeever, Kronlid, Baraldi, Lindahl, & Ciabuschi, 2017). The simulator calculates rNPV using the following formula:

$$\boldsymbol{rNPV}\,{}^{N}_{r} = \sum_{n \in N} \frac{C_n\, P_0}{(1+r)^{T_n}\, P_n}$$

where N is the union of all R&D stages and years during which a product generates market revenues, r is the discount rate of the agent developing the specific antibiotic, $C_n$is the cash flow (revenue minus cost) of stage n, P_0 is the probability of reaching the market from the point at which rNPV is calculated, and P_n is the probability of reaching the market from the entry point of stage n. We assume that projects are evaluated on the basis of their rNPV only before transitioning to a new stage – i.e., a decision point.

3.3. Data

As mentioned, the development of antibiotics can be divided into five stages: Pre-Clinical, Phase 1 Clinical Trials (Phase 1), Phase 2 Clinical Trials (Phase 2), Phase 3 Clinical Trials (Phase 3), and Market Approval. These stages differ in terms of their duration, their cost, and the probability of projects successfully completing the stage. Upon creation of a project, the simulator draws random samples for all these parameters from uniformly distributed data based on empirically-derived data from a combination of two studies – Sertkaya, Eyraud, Birkenbach, Franz, Ackerley, Overton, and Outterson (2014) and Årdal et al. (2018). Additionally, all data from these two empirical studies have been reviewed and, where necessary, adjusted based on critical comments from experts and panels composed of representatives from academia, health authorities, and large and small pharmaceutical companies between 2016 and 2019 (in collaboration with the DRIVE-AB project consortium (DRIVE-AB Report, 2018) and with the Public Health Agency of Sweden). Data on expected net revenues (i.e., global sales minus costs) were sampled from a uniform distribution with lowest possible net revenues of 0 (representing antibiotics lacking a market at approval) and maximum net revenues of 1900 million US dollars (M USD). We assume that the market for any antibiotic increases linearly for ten years (which corresponds to the guaranteed exclusivity period or the average remaining patent life). According to recent sales figures and commentaries from experts in the field, this revenue distribution mimics a realistic scenario in which the average total revenues of a patented antibiotic is 950 M USD. Moreover, antibiotics with expected net revenues greater than 1900 M USD, being sufficiently profitable, would not require any innovation incentives and therefore are not considered in our study. The full set of input data is reported in Table 1.

Table 1
Overview of input data for Monte Carlo simulation.

SIMULATION INPUT DATA		Baseline	Grants	MER	Phase 1 Entry price
Preclinical	Duration (years)	***2–10***	2–10	2–10	2–10
	Costs (MUSD)	***2.1–17.5***	**0–14**	2.1–17.5	2.1–17.5
	PoS (%)	***18–69***	18–69	18–69	18–69
	Revenues (MUSD)	***0***	0	0	0
Phase 1	Duration (years)	***0.5–5***	0.5–5	0.5–5	0.5–5
	Costs (MUSD)	***1–15***	**0–12**	1–15	1–15
	PoS (%)	***25–84***	25–84	25–84	25–84
	Revenues/prizes (MUSD)	***0***	0	0	**29.4**
Phase 2	Duration (years)	***1–1.67***	1–1.67	1–1.67	1–1.67
	Costs (MUSD)	***1–30***	**0.2–24**	1–30	1–30
	PoS (%)	***35–74***	35–74	35–74	35–74
	Revenues (MUSD)	***0***	0	0	0
Phase 3	Duration (years)	***1.33–4.42***	1.33–4.42	1.33–4.42	1.33–4.42
	Costs (MUSD)	***16–115***	**3.2–92**	16–115	16–115
	PoS (%)	***31–79***	31–79	31–79	31–79
	Revenues (MUSD)	***0***	0	0	0
Approval	Duration (years)	***1–1.58***	1–1.58	1–1.58	1–1.58
	Costs (MUSD)	***40–88***	40–88	40–88	40–88
	PoS (%)	***83–99***	83–99	83–99	83–99
	Revenues (MUSD)	***0***	0	0	0
Sales period	Duration (years)	***10***	10	5	10
	Peak year sales	***10 linear***	10 linear	**1–5**	10 linear
	Revenues/prizes (MUSD)	***0–1900***	0–1900	**1100**	0–1900

The parameters and values used as input data in the simulations without incentives (baseline) or with incentives. For the different R&D stages, the years of development (duration), costs, probabilities of success (PoS in percentage), and net global revenues (during a 10-year sales period) are all uniformly distributed from the minimum and maximum values reported in the table.

Additionally, two types of agents representing small- and medium-sized enterprises (SMEs) and large pharmaceutical companies (Big Pharmas) have been simulated. SMEs and Big Pharmas have different attributes: different costs of capital that reflect the discount rates applied by actual investors and developers when evaluating projects at different R&D stages and different profit thresholds that a project must meet if the project is to continue. Specifically, we assume that Big Pharmas have unlimited funds available for their R&D projects (i.e., do not need to acquire them externally) that they invest strictly based on rNPV evaluations, which means that opportunity costs are considered. Conversely, we assume that for SMEs to progress their R&D projects need to acquire capital at interest rates ranging between 18% and 30%. The cost of capital reflects the discount rates applied by private investors when evaluating projects at different R&D stages. The discount rate for Big Pharmas is between 8% and 13%.

Lastly, agents use different profit thresholds that a project must meet if the project is to continue. These thresholds are manifested in the profit beyond a positive rNPV required by the agent. In our simulation, SMEs have no threshold, so we assume that they are only sensitive to relative and not absolute return on investment, whereas Big Pharmas use different profit thresholds at different R&D stages: 50 M USD for Preclinical; from 50 to 100 M USD for Phase 1; from 100 to 500 M USD for Phase 2; and from 200 to 500 M USD for both Phase 3 and for Market Approval.

3.4. Innovation incentives tested in the simulation

In addition to simulating the current antibiotics R&D landscape, the simulator mimics the effect of introducing three incentives to stimulate innovation: (1) a push incentive – grants; (2) a pull incentive – MERs, which provide developers a guaranteed and large payment upon approval; and (3) another pull incentive – Phase 1 Entry Prize, which is a payment upon completion of preclinical studies given to a developer that commits to entering Phase 1. As shown in the red bold figures in three rightmost columns in Table 1, the different incentives are simulated as follows:

- Grants are operationalized as a 20–100% reduction of Preclinical and Phase 1 costs and a 20–80% reduction of Phase 2, Phase 3, and Market Approval costs.
- MERs replace all revenues from market sales with a guaranteed fixed yearly payment of 220 M USD per five years, reaching a total size of 1100 M USD, which previous studies have shown to offer the optimal gains in incremental innovation (Okhravi et al., 2018).
- Phase 1 Entry Prize consists of fixed milestone prices provided at the entry of Phase 1 and corresponding to three times the average cost of Preclinical studies – i.e., 29.4 M USD. This value is considered to be a sufficiently attractive incentive by several international experts and pharmaceutical managers consulted during discussions and panels organized by the authors.

4. Results and discussion

The simulation shows that all three incentives can significantly improve the rNPV at different stages (Fig. 2).

However, the rNPV improvements from baseline significantly vary between the different R&D stages because each incentive acts more or less intensively at different stages of the R&D pipeline (Fig. 2). Confirming previous analyses (Okhravi et al., 2018; DRIVE-AB Report, 2018), our results show that a MER effectively increases the rNPV throughout all R&D stages. However, at the Preclinical stage, the rNPV improvement observed after introducing grants is on average relatively higher (~8.5 M USD) compared to the average improvement (~5 M USD) after introducing MER (Fig. 2). Additionally, for antibiotics entering Preclinical development, a Phase 1 Entry Prize of 29.4 M USD is enough to increase the rNPV by 5.1 M USD on average. The simulations with the lowest rNPVs (from –52 M USD to 81 M USD) in their Preclinical stage resulted in several termination decisions, but our results show that grants, MERs, and Phase 1 Entry Prizes can strongly enhance the financial prospects of antibiotics entering the Preclinical stage (Fig. 2). Additionally, the rNPVs are of highest importance when considering Preclinical projects, because they are evaluated at this early stage on the basis of all their future revenues, costs, and monetary incentives spread across the entire R&D pipeline.

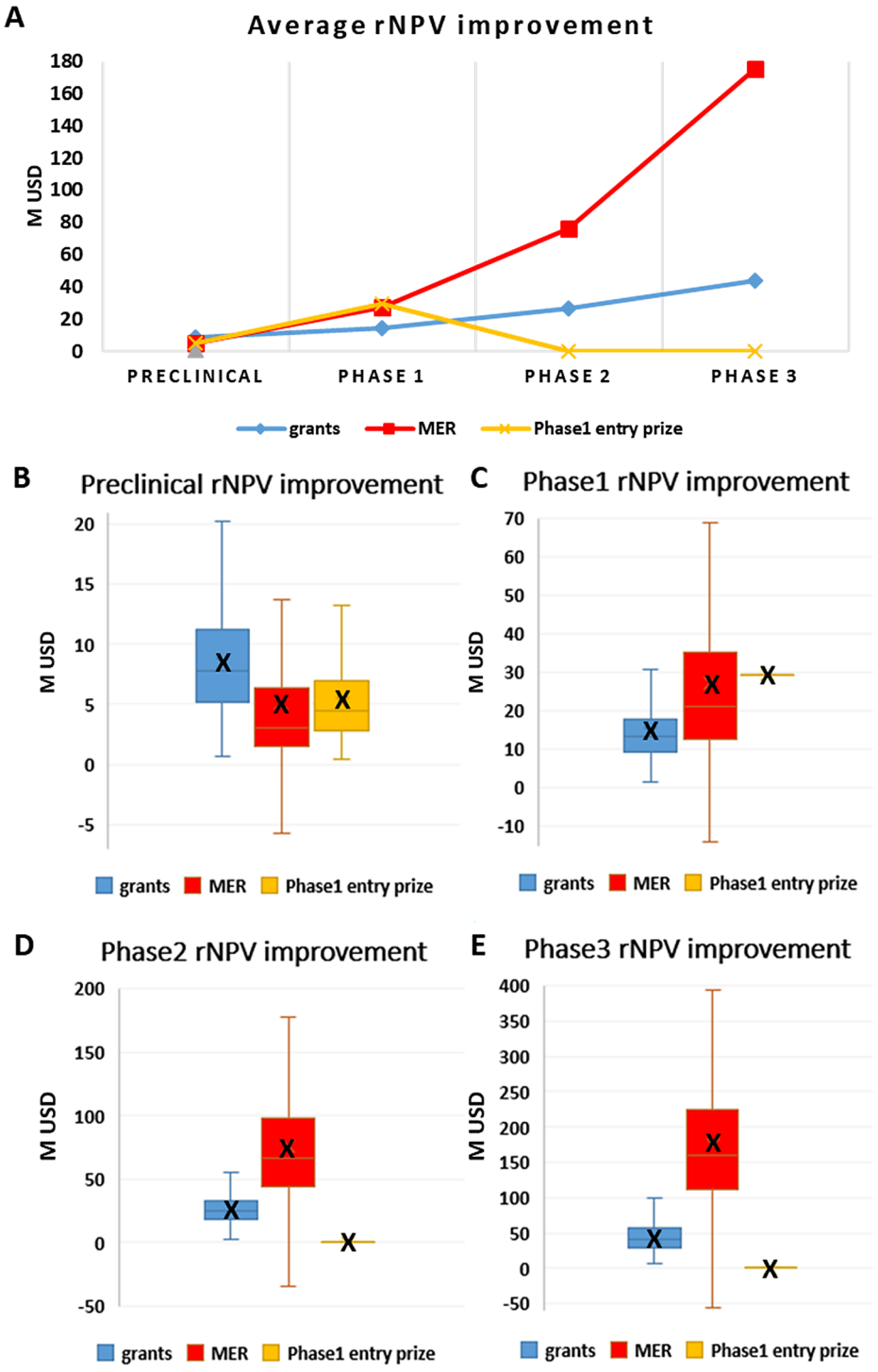

Fig. 2. rNPV improvements across R&D stages. The average rNPVs improvement across all R&D stages (A) and boxplot representations of rNPV improvements (expressed in M USD) in Preclinical (B), Phase 1 (C), Phase 2 (D), and Phase 3 (E) after the introduction of three incentives (grants – blue; MER – in red; and Phase1 Entry Prize – yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

For antibiotics entering Phase 1, a Phase 1 Entry Prize increases the rNPV by 29.4 M USD (i.e., the nominal value of the prize), while the introduction of grants at the same stage enhances rNPV on average ~14.3 M USD, and a MER provides on average a rNPV improvement of ~27.4 M USD. In Phase 2, reducing costs of more expensive R&D developmental stages through grants improves rNPV by ~26.8 M USD on average, while a MER results in a much stronger rNPV improvement of ~76.4 M USD for projects in the same phase. At later development stages, such as Phase 3, many antibiotics are financially profitable even without incentives, with an average rNPV of ~17 M USD, and introducing incentives such as grants and MER enhance these already positive rNPVs by ~43.7 M USD and ~175 M USD, respectively (Fig. 2).

These results suggest that in Preclinical stage grants have stronger effects on profitability compared to a Phase 1 Entry Prize or a MER. In Phase 1, the Phase 1 Entry Prize has the strongest effect, closely followed by the MER, but trailed by grants. Finally, in Phases 2 and 3, the MER shows the strongest results in improving profitability. These results suggest that the ability of various incentives to stimulate R&D in

Table 2
Costs and benefits of different economic incentives.

Incentives	Expected public expenditure per antibiotic entering the pipeline	Expected final public cost for each antibiotic reaching market	Number of profitable antibiotics reaching market approval			% improvement of number of antibiotics reaching market approval		
			Average	Big Pharmas	SMEs	Average	Big Pharmas	SMEs
Baseline	0	0	40	36	43	NA	NA	NA
Grants	16	230	1271	151	2391	2019%	306%	3731%
MER	71	1100	1057	378	1735	2237%	983%	3491%
Phase1 Entry prize	13	180	551	68	1034	822%	91%	1554%

Overview of the costs and benefits of different economic incentives: column 2 – the expected public expenditure in M USD per each stimulated antibiotic; column 3 – the expected total expenditure in M USD for each antibiotic that reaches the market; column 4 – the total number of financially profitable antibiotics from preclinical to the market (calculated as rNPV-based 'go' decision made by SMEs, Big Pharmas, or by an average of the two); and column 5 – the percentage improvement of the expected number of antibiotics (developed by SMEs, Big Pharmas, or by an average of the two) that will reach the market.

antibiotics vary considerably between different drug development stages. Moreover, as the Preclinical stage provides an outlook and profitability evaluation of the entire innovation process to follow, grants paid at this early stage are fundamental for pushing projects into the pipeline.

After introducing these public incentives, the rNPVs of all antibiotics in the simulations were used to estimate the relative increase in the number of antibiotics reaching market by combining the technical probabilities of failures with the financial profitability of each antibiotic. However, as mentioned in the methods section, not all developers have the same financial characteristics. Therefore, we analyzed the different evaluations of SMEs and Big Pharmas because these two actors use different discount rates and profit thresholds to decide whether a project will be approved at the next decision point. In fact, the number of consecutive 'go' decisions from the Preclinical stage to market launch defines all financially profitable projects that will be launched if they survive the risk of technical failure. The results of this analysis are shown in Table 2 and Fig. 3.

As shown in Table 2, a 1100 M USD MER is the strongest incentive with 1057 profitable antibiotics in all development stages and an expected 2237% percentage improvement of the number of antibiotics reaching the market on average compared to the baseline situation (i.e., no incentives). When considering possible differences between SMEs and Big Pharmas, a MER is still more effective if Big Pharmas are the developers, as it yields two to six times more profitable antibiotics (3 7 8) and three to ten times higher percentage improvement of antibiotics reaching the market (983%) compared to grants and a Phase 1 Entry Prize. However, if SMEs are the developers, grants are more powerful incentives than MERs. The introduction of grants resulted in 2391 financially profitable SME projects and on average a 3731% improvement of SMEs-developed antibiotics expected to reach market.

These findings suggest that a MER has a relatively much stronger effect in incentivizing Big Pharmas' innovativeness to develop antibiotics by improving these firms' profitability, but there is a comparatively weaker effect on SMEs. A Phase 1 Entry Prize has a stronger relative incentivizing effect on SMEs compared to Big Pharmas, and grants have even more of an incentivizing effect. These results indicate that different incentives vary in their effect on profitability and therefore innovativeness when it comes to different kinds of recipients in the antibiotic drug development landscape.

From our results, it is also possible to distinguish between the incentives' effects. Specifically, we can see which incentive could maximize the total number of projects moving forward as well as which incentives would require the least public spending to move a single R&D project into market. In other words, we can distinguish between the incentives' effectiveness (i.e., the incentive that generates the highest number of approved antibiotics) and efficiency (i.e., the cheapest incentive for a single antibiotic reaching the market). Our results show that the total public expenditures expected for a 29.4 M USD Phase 1 Entry Prize is lower than what is expected for grants and for a MER. Indeed, for each antibiotic in the pipeline, we expect to pay an average 13 M USD for a Phase 1 Prize, 16 M USD for grants, and 71 M USD for a MER (column 1 in Table 2). Moreover, the average cost to launch one antibiotic to market is equal to 180 M USD for a Phase 1 Entry Prize, 230 M USD for grants, and 1,100 M USD for a MER, making a Phase 1 Entry Prize the most efficient of the three investigated incentives (column 1 in Table 2).

Thus, the results show how the differences vary considerably in the public cost of incentivizing one antibiotic all the way to market launch (i.e., the efficiency of the incentives). Specifically, the findings suggest that the most efficient way of doing so is using Phase 1 Entry Prizes, followed by grants and then MERs.

Finally, as shown in Fig. 3, we have calculated the expected average number of antibiotics reaching the market in the next 30 years by combining the incentive-specific percentage improvements of the number of antibiotics reaching market approval reported in Table 2

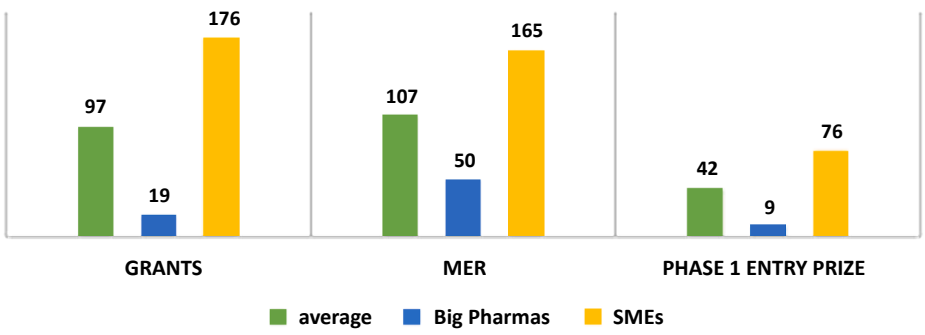

Fig. 3. Expected average number of antibiotics to market in 30 years. The average number of antibiotics that will reach the market with grants, MER, or Phase 1 Entry Prizes in 30 years. The results derive from different rNPV-based decisions made by SMEs, Big Pharmas, and by an average of the two (yellow, blue, and green, respectively). The absolute numbers reported in this figure were derived from the percentage improvements of the number of antibiotics reaching the market (Table 2) and a previously published simulation report in which less than five novel classes of antibiotics were shown to reach the market in the next 30 years without economic incentives (DRIVE-AB Report, 2018). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

(column 5) with the results of a previously published simulation report (DRIVE-AB Report, 2018). For both Big Pharmas and SMEs, this calculation reveals on average 107 new antibiotics will be supported by MERs, 97 by grants, and 42 by Phase 1 Entry Prizes. However, importantly, differences can be observed between SMEs' and Big Pharmas' projects and how they react to public incentives. For SMEs over the next 30 years, we expect 176 new antibiotics to reach the market when grants are used, 165 when MERs are used, and 76 when Phase 1 Entry Prizes are used. For Big Pharmas over the next 30 years, we expect in general many fewer antibiotics to reach the market with any incentive: 50 with MERs, 19 with grants, and 9 with Phase 1 Entry Prizes (Fig. 3).

Therefore, according to our simulations, the most effective innovation incentive for SMEs is grants and the most effective innovation incentive for Big Pharmas is a MER. Incentivized SMEs can eventually bring many more antibiotics to market than incentivized Big Pharmas. These findings indicate that various incentives can support the maximum number of antibiotics. MERs appear to be most effective, but only when considering both types of developers together. The more effective incentive for SMEs alone is grants. Grants and Phase 1 Entry Prizes are significantly less effective than MERs and grants stimulate innovation for both SMEs and Big Pharmas. Interestingly, the effectiveness of Phase 1 Entry Prizes awarded to SMEs in terms of new antibiotics reaching market in 30 years is larger (76 antibiotics) than that of MERs awarded to Big Pharmas (50 antibiotics). Moreover, such effects would be obtained at considerably lower public expenditure levels.

5. Conclusion

Building on previous developments of the entrepreneurial orientation framework by Lumpkin and Dess (1996), this paper set out to investigate empirically whether incentives aimed at increasing profitability also increase innovation. The findings in this study suggest several relevant insights regarding our research question: How and to what degree do innovation incentives designed to increase profitability influence innovativeness?

The findings reveal that incentives targeting profitability increase and sustain innovation in antibiotics. Moreover, the findings show that the influence of each type of incentive depends on which R&D stage is targeted and the type of firm (i.e., SME or Big Pharmas) that receives the incentive. The importance of considering the recipient's R&D stage provides an interesting distinction to the understanding of how innovation incentives influence the relationship between entrepreneurial orientation and profitability in the entrepreneurial orientation framework. Specifically, the findings of this study demonstrate how innovation incentives can improve profitability, which can improve innovativeness of firms. Moreover, as shown in Fig. 4, we provide a more nuanced picture of this relation by showing that (1) different incentives have different effects in terms of the number of innovations (new antibiotics) and public expenditures needed and that (2) both the effect of incentives on profitability and the effect of profitability on innovativeness vary depending on (2.a) the different R&D stages and (2.b) the different entrepreneurial orientations of the firms – i.e., small and large antibiotics developers (Fig. 4). These findings are new to research on innovation incentives and entrepreneurial orientation and are further elaborated on below.

5.1. Theoretical implications

This study contributes to the further development of the understanding of entrepreneurial orientation and specifically of the relationship between innovativeness and profitability. Our findings suggest that innovation incentives can reverse the relationship between innovation and profitability as indicated by Lumpkin and Dess (1996) and proposed by Ciabuschi and Lindahl (2018).

Moreover, when considering the effect of interventions aimed at supporting innovativeness by enhancing profitability within an industry, we see how different incentives create different effects and each incentive causes different responses from different types of firms. Specifically, we found that incentives have different effects on SMEs and Big Pharmas. This difference echoes previous research on small firms and entrepreneurial orientation (e.g., Avlonitis & Salavou, 2007), but our findings add an important detail: they highlight how the different characteristics of firms make their entrepreneurial orientation more or less sensitive to incentives and the possibility of reaping profits. That is, compared to Big Pharmas, SMEs seem to be more easily influenced by incentives. From a theoretical point of view, this result suggests that SME and Big Pharmas have diverging entrepreneurial orientations, with small companies more willing than larger companies to take risks and pursue innovative development opportunities. In this regard, Big Pharmas' historically high profitability and high opportunity costs (due to the many alternatives open for their investments) hinder rather than stimulate innovation; that is, Big Pharmas less readily continue an R&D project at key decision points.

Moreover, since innovation incentives influence a firm's profitability and capacity to innovate, depending on the R&D stage, companies pursuing drug development might display important differences in their entrepreneurial orientation depending on which specific R&D stage they operate in, and they might even change their own entrepreneurial orientation as they pass from one R&D stage to another. This result provides a more nuanced view of entrepreneurial orientation

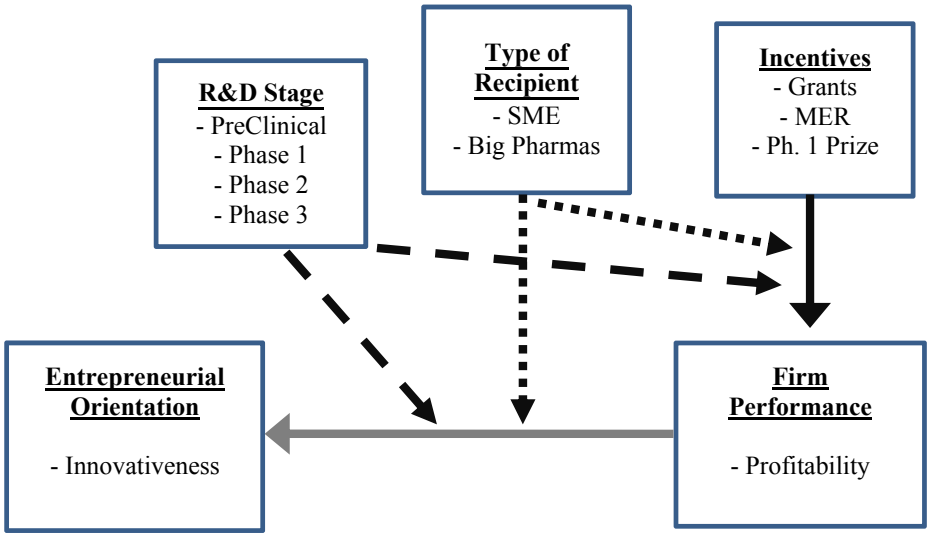

Fig. 4. Illustration of the influences of different incentives. Summary of discussion illustrating how the effect of incentives on increasing profitability (vertical black arrow) and how profitability increases innovativeness (horizontal grey arrow) and vary between incentives. However, it also shows how both these effects differ depending on (1) the type of recipient of the incentive (dotted arrows) and (2) what R&D stage the recipient is in (dashed arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

than previously suggested in the literature: entrepreneurial orientation is not a static characteristic but varies depending on the kind of innovation and development activities firms are specifically dealing with. Although this result is related to the pharmaceutical industry, it might also be true for other industries characterized by long, stage-wise, heavily regulated, and expensive R&D processes.

5.2. Implications for policy and practice

In discussing how to revive innovation in the antibiotics industry, this paper has important implications for managers and policy makers because it evaluates several incentives currently considered for implementation by governments across the world.

Specifically, since SMEs seem easier to incentivize to pursue antibiotic R&D projects, they constitute a simpler target for future incentives to sustain antibiotics innovation. However, although Big Pharmas are more difficult to influence, these large companies hold the key to global distribution of new drugs, which is an issue that needs to be considered for the eventual success of any innovation. Additionally, as the efficiency of innovation incentives varies considerably, the findings have clear implications for policy makers with respect to which stage of the R&D pipeline is easier (and cheaper) or harder (and more expensive) to incentivize innovation with comparable means as well as what incentives might be the most efficient – i.e., yield the greatest incentivizing output per dollar spent. Lastly, to effectively and efficiently support innovation in the antibiotics field, policymakers need to simultaneously consider the kind of recipients (i.e., SMEs and Big Pharmas) and the R&D stage of the projects they aim to incentivize.

5.3. Limitations and future research

All the simulations performed in this study simplified highly complex behaviors and decision processes and considered only quantifiable and objective inputs, which constitutes limitation of this study. Future research might therefore use agent-based simulations capable of capturing more complex behaviors by actors, including portfolio-based decisions and interactions between organizations. In addition, future research might investigate synergistic effects derived from combining the various push and pull incentives as well as study the actual effects of any of the incentives discussed here once they are applied in practice. Lastly, future research could use surveys to better capture the details of the decision-making and behavior of the different developers of antibiotics.

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Data Statement

The data associated with the paper are strictly confidential and bound to non-disclosure agreements signed by the authors with various industry partners. As a consequence, the authors are unfortunately unable to make this data available.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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References

Adeyi, O. O. B., Baris, E., Jonas, O. B., et al. (2017). Drug-resistant infections: A threat to our economic future (vol 2): final report (English). Retrieved from the World Bank Group webpage: http://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future Accessed December 9th 2019.

Årdal, C., Baraldi, E., Ciabuschi, F., Outterson, K., Rex, J. H., Piddock, L. J., et al. (2017). To the G20: Incentivising antibacterial research and development. *The Lancet Infectious Diseases, 17*(8), 799–801. https://doi.org/10.1016/S1473-3099(17)30404-8.

Årdal, C., Baraldi, E., Theuretzbacher, U., Outterson, K., Plahte, J., Ciabuschi, F., et al. (2018). Insights into early stage of antibiotic development in small-and medium-sized enterprises: A survey of targets, costs, and durations. *Journal of Pharmaceutical Policy and Practice, 11*(1), 8. https://doi.org/10.1186/s40545-018-0135-0.

Avlonitis, G. J., & Salavou, H. E. (2007). Entrepreneurial orientation of SMEs, product innovativeness, and performance. *Journal of Business Research, 60*(5), 566–575. https://doi.org/10.1016/j.jbusres.2007.01.001.

Baraldi, E., Ciabuschi, F., Leach, R., Morel, C., & Waluszewski, A. (2016). Exploring the obstacles to implementing new economic mechanisms addressing antibiotic resistance: A multi-actor and system-level analysis. *American Journal of Law & Medicine, 42*(2–3), 451–486. https://doi.org/10.1177/0098858816658276.

Blau, G. E., Pekny, J. F., Varma, V. A., & Bunch, P. R. (2004). Managing a portfolio of interdependent new product candidates in the pharmaceutical industry. *Journal of Product Innovation Management, 21*(4), 227–245. https://doi.org/10.1111/j.0737-6782.2004.00075.x.

Bourgeois, L. J. (1981). On the measurement of organizational slack. *Academy of Management Review, 6*, 29–39. https://doi.org/10.5465/amr.1981.4287985.

Brouthers, K. D., Nakos, G., & Dimitratos, P. (2015). SME entrepreneurial orientation, international performance, and the moderating role of strategic alliances. *Entrepreneurship Theory and Practice, 39*(5), 1161–1187. https://doi.org/10.1111/etap.12101.

Ciabuschi, F., & Lindahl, O. (2018). The decline of innovation in the antibiotics industry and the global threat of antibiotic resistance: When entrepreneurial efforts are not enough. In S. Cubico, G. Favretto, J. Leitão, & U. Cantner (Eds.). *Entrepreneurship and the Industry Life Cycle* (pp. 205–229). Springer International Publishing.

Covin, J. G., & Miller, D. (2014). International entrepreneurial orientation: Conceptual considerations, research themes, measurement issues, and future research directions. *Entrepreneurship Theory & Practice, 38*(1), 11–44. https://doi.org/10.1111/etap.12027.

DRIVE-AB Consortium. Report: Revitalizing the antibiotic pipeline Stimulating innovation while driving sustainable use and global access 2018 http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf [accessed 1 December 2019].

The Economist, leaders, (2019, May 4th). Drug Resistance: Netflix and Pills. The Economist, pp. 12.

Fichthorn, K. A., & Weinberg, W. H. (1991). Theoretical foundations of dynamical Monte Carlo simulations. *The Journal of Chemical Physics, 95*(2), 1090–1096. https://doi.org/10.1063/1.461138.

Friedman, D., & Alper, J. (2014). *Technological challenges in antibiotic discovery and development: A workshop summary. Chemical Sciences Roundtable; Board on Chemical Sciences and Technology; Division on Earth and Life Studies*. National Research Council.

Grand View Research, (2018). Antibiotics market size, share & trends analysis report. https://www.grandviewresearch.com/industry-analysis/antibiotic-market Accessed December 9th 2019.

Jiang, X., Liu, H., Fey, C., & Jiang, F. (2018). Entrepreneurial orientation, network resource acquisition, and firm performance: A network approach. *Journal of Business Research, 87*, 46–57. https://doi.org/10.1016/j.jbusres.2018.02.021.

Laxminarayan, R., Duse, A., Wattal, C., Zaidi, A. K., Wertheim, H. F., Sumpradit, N., et al. (2013). Antibiotic resistance—the need for global solutions. *The Lancet infectious diseases, 13*(12), 1057–1098. https://doi.org/10.1016/S1473-3099(13)70318-9.

Lee, C., Lee, K., & Pennings, J. M. (2001). Internal capabilities, external networks, and performance: A study of technology bases ventures. *Strategic Management Journal, 22*(6–7), 615–640. https://doi.org/10.1002/smj.181.

Lumpkin, G. T., & Dess, G. G. (1996). Clarifying the entrepreneurial orientation construct and linking it to performance. *Academy of Management Review, 21*(1), 135–172. https://doi.org/10.5465/amr.1996.9602161568.

Metropolis, N. (1987). The beginning of the Monte Carlo method. *Los Alamos Science, 15*(584), 125–130.

Metropolis, N., Rosenbluth, A. W., Rosenbluth, M. N., Teller, A. H., & Teller, E. (1953). Equation of state calculations by fast computing machines. *The Journal of Chemical Physics, 21*(6), 1087–1092. https://doi.org/10.1063/1.1699114.

Mossialos, E., Morel, C., Edwards, S., Berenson, J., Gemmill-Toyama, M., & Brogan, D. (2010). Policies and incentives for promoting innovation in antibiotic research. World Health Organization. Regional Office for Europe.

Mthanti, T., & Ojah, K. (2017). Entrepreneurial orientation (EO): Measurement and policy

implications of entrepreneurship at the macroeconomic level. *Research Policy, 46*(4), 724–739. https://doi.org/10.1016/j.respol.2017.01.012.
Okhravi, C., Callegari, S., McKeever, S., Kronlid, C., Baraldi, E., Lindahl, O., et al. (2018). Simulating market entry rewards for antibiotics development. *Journal of Law, Medicine & Ethics, 46*(2), 32–42. https://doi.org/10.1177/1073110518782913.
Okhravi, C., McKeever, S., Kronlid, C., Baraldi, E., Lindahl, O., & Ciabuschi, F. (2017, April). Simulating market-oriented policy interventions for stimulating antibiotics development. In Proceedings of the 50th Annual Simulation Symposium (p. 2). Society for Computer Simulation International.
Payne, D. J., Miller, L. F., Findlay, D., Anderson, J., & Marks, L. (2015). Time for a change: Addressing R&D and commercialization challenges for antibacterials. *Philosophical Transactions of the Royal Society B: Biological Sciences, 370*(1670), 20140086. https://doi.org/10.1098/rstb.2014.0086.
AMR Review (2015). Securing new drugs for future generations: the pipeline of antibiotics. Retrieved from the Review on Antimicrobial Resistance website: https://amr-review.org/sites/default/files/SECURING%20NEW%20DRUGS%20FOR%20FUTURE%20GENERATIONS%20FINAL%20WEB_0.pdf Accessed December 9th 2019.
Rex, J. H., & Outterson, K. (2016). Antibiotic reimbursement in a model delinked from sales: A benchmark-based worldwide approach. *The Lancet Infectious Diseases, 16*(4), 500–505. https://doi.org/10.1016/S1473-3099(15)00500-9.
Rosenbusch, N., Rauch, A., & Bausch, A. (2013). The mediating role of entrepreneurial orientation in the task environment–performance relationship: A meta-analysis. *Journal of Management, 39*(3), 633–659. https://doi.org/10.1177/0149206311425612.
Sertkaya, A., Eyraud, J. T., Birkenbach, A., Franz, C., Ackerley, N., Overton, V., & Outterson, K. (2014). Analytical framework for examining the value of antibacterial products. https://aspe.hhs.gov/system/files/pdf/76891/rpt_antibacterials.pdf Accessed December 9th 2019.
Spellberg, B., Bartlett, J., Wunderink, R., & Gilbert, D. N. (2015). Novel approaches are needed to develop tomorrow's antibacterial therapies. *American Journal of Respiratory and Critical Care Medicine, 191*(2), 135–140. https://doi.org/10.1164/rccm.201410-1894OE.
Teng, B. S. (2007). Corporate entrepreneurship activities through strategic alliances: A resource-based approach toward competitive advantage. *Journal of Management studies, 44*(1), 119–142. https://doi.org/10.1111/j.1467-6486.2006.00645.x.
Wales, W. J., Gupta, V. K., & Mousa, F. T. (2013). Empirical research on entrepreneurial orientation: An assessment and suggestions for future research. *International Small Business Journal, 31*(4), 357–383. https://doi.org/10.1177/0266242611418261.
Wiklund, J., & Shepherd, D. (2003). Knowledge-based resources, entrepreneurial orientation, and the performance of small and medium-sized businesses. *Strategic Management Journal, 24*(13), 1307–1314. https://doi.org/10.1002/smj.360.
Wright, G. D. (2015). Solving the antibiotic crisis. *ACS Infectious Diseases, 1*(2), 80–84. https://doi.org/10.1021/id500052s.

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