Firm Size Effects on Targeted Prizes to Incentivize Innovation in Neglected Tropical Diseases

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0   Abstract

The existing patent system has failed to incentivize innovation towards neglected tropical diseases, a family of diseases that disproportionately afflict the global poor. This paper proposes a targeted prize scheme as an alternative mechanism to induce R&D activities towards treatments for neglected tropical diseases. Through a case study estimating the cost of development for two drugs, we find evidence for firm size effects on the efficiency of pharmaceutical innovation, and posit that a prize system specifically targeting small firms may be indeed the most effective way to induce innovation in neglected tropical disease treatments.

1   Introduction

Neglected tropical diseases (NTDs) are a medically diverse group of 17 diseases that afflict over 1.4 billion people annually ("Neglected Tropical Diseases"). These chronic, infectious diseases are unique for their disproportionate presence among the world's poorest populations, and their long-term, long-range effects that pose a significant burden on the social, political, and economic welfare of developing countries (Hotez et al. 2009). The rampant presence of NTDs among the global poor reinforces the cycle of extreme poverty as the symptoms of these diseases—unlike acute infections like West Nile or Ebola—can persist for decades, reducing child survival, learning ability, and agricultural and economic productivity among the world's most impoverished and vulnerable populations (Nwaka and Ridley 2003, Hotez et al. 2007).

Despite the urgency and burden of these diseases, however, there exists a marked dearth in the development of treatments for NTDs, as existing incentive mechanisms—most significantly, the patent system—have failed to induce sufficient levels of R&D activity in these disease areas (Nwaka and Ridley 2003, Maurer et al. 2004). This paper seeks to address this gap in the literature by proposing an alternative incentive mechanism to induce R&D in NTD treatments in which a social planner rewards the small pharmaceutical firm who successfully innovates a therapeutic with a targeted research prize. We hypothesize that small firms are more responsive than large firms to fized prize rewards, and posit that targeted prizes for small firms to compete in drug invention may indeed be a suitable mechanism to induce innovation in NTDs

This paper progresses as follows: Section 2 is a literature review discussing existing and proposed mechanisms to incentivize innovation in NTD therapies. Section 3 presents and extends the baseline model, adapted from Shavell and van Ypersele's previous work (2001).

Section 4 presents a case study evaluating firm size effects on the development of two drugs. Section 5 discusses various reasons why small firms might ultimately be the best candidates for targeted prizes to incentivize NTD research, as well as the broader strengths and weaknesses of prize systems. Section 6 concludes.

2   Literature Review

2.1   NTD R&D Incentive Mechanisms

Broadly, mechanisms to incentivize R&D activity and innovation can be categorized as either "push" or "pull" mechanisms. Push mechanisms induce innovation by reducing the cost of R&D inputs prior to the development of the successful product, while pull mechanisms incentivize by rewarding already successful innovations after the R&D process has occurred (Mrazek and Mossialos 2001, Ravvin 2008, Morel and Mossialos 2010).

Several push mechanisms have been designed and implemented in response to the crisis in disease treatments for NTDs. Research grants are the most commonly used push mechanism in spurring research for NTDs, with targeted research grants provided by governments and nongovernmental organizations funding researchers at both public and private institutions (Ravvin 2008, Müller-Langer 2011). The Bill & Melinda Gates Foundation, one of the most prominent supporters of NTD R&D activity, committed over $500M in R&D grants in 2014 alone to various research and advocacy organizations ("Gates Foundation Commits More Than $500 Million To Tackle The Burden Of Infectious Disease in Developing Countries").

Private-public partnerships have been suggested as an alternative push mechanism to incentivize research activity in NTDs (Nwaka and Ridley 2003, Croft 2005). Under the private-public partnership scheme, private organizations are funded by public or nonprofit organizations,

with a predetermined contract that ensures that the resultant product, e.g. an African sleeping sickness vaccine or tuberculosis treatment, is provided to the target audience at affordable prices (Ravvin 2008). Targeted R&D tax credits—an additional push mechanism—further induce R&D activity towards NTD therapies by reducing R&D costs in designated areas (Müller-Langer 2008).

Because push mechanisms are applied prior to the development of the successful product, however, they are liable to a host of moral hazard and adverse selection problems (Müller-Langer 2008). As such, push mechanisms have been recognized as a suboptimal and inefficient solution to financing R&D for NTD treatments.

Pull programs, by contrast, are significant for their ability to induce R&D activity while eliminating moral hazard and adverse selection problems. The existing pharmaceutical patent system is one such pull mechanism and is the primary incentive, broadly speaking, for pharmaceutical R&D activity and innovation (Acemoglu 2003, Scotchmer 2004). Patents can be remarkably efficient at inducing R&D activity, particularly towards low-risk, high-reward therapies such as "copycat" drugs, extensions of existing drugs (e.g. extended-release formularies), and drugs for disease areas with well-established consumer markets (Dranove et al. 2004, Fisk and Atun 2008). Because patents incentivize R&D activity by reducing *ex ante* risk, however, there exists a fundamental market failure to induce innovation in comparably "risky" disease areas, including diseases with small or unprofitable markets (Kremer 2002).

This holds severe consequences for research in NTDs, as these diseases disproportionately afflict the global poor who cannot pay the monopoly prices required to effectively incentivize R&D under the existing patent regime (Kremer 2002, Maurer et al. 2004, Hotez et al. 2007). Adjustment policies have been suggested to rectify this market failure of the

patent system to induce R&D for NTDs. Most significantly, Kremer proposes a system of patent buyouts, in which a governing authority purchases relevant patents—e.g. the patent for a schistosomiasis treatment—and places the patent in the public domain to decouple research costs from the production and sales process which, in turn, ensures that distribution remains at efficient, competitive prices (1998).

Prizes[1] rewarded to a successful inventor also circumvent the issue of monopoly deadweight loss incurred under the patent system, as potential innovators are incentivized, but the successful innovation itself is made available in the public domain and can thus be made available to the population in need at affordable prices (Clancy and Moschini 2013, Grabowski et al. 2015). Unlike patent buyouts, however, targeted prizes are able to induce innovation in specific, pre-defined areas, as the reward's pre-established requirements can ensure that the final product is specifically tailored and useful to the population in need, e.g. is suitable for clinical usage in developing, low-resource settings. Empirical evidence additionally suggests that the establishment of a formal, centralized prize system to induce innovation in NTDs may be a viable alternative to the existing patent system, as prizes have already been shown to effectively and successfully incentivize R&D efforts and resultant innovations in technologies deemed of great social value or significance (Davis 2004).

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[1] We distinguish between two types of prizes: so-called "blue sky" prizes that reward innovations without previously specifying the terms and requirements of the reward (e.g. the Nobel Prize in Medicine or Physiology, which is awarded to the researcher who makes a "discovery of major importance"), and targeted prizes, which reward innovations meeting a pre-specified set of criteria (e.g. the now-cancelled Archon Genomics XPRIZE, which promised $10M to the first team to "rapidly and accurately sequence 100 whole human genomes… at a cost of $10,000 or less per genome") (Scotchmer 2004, "Archon Genomics XPRIZE", "Nomination and Selection of Medicine Laureates").

This paper focuses solely on targeted prizes as a potential incentive mechanism for R&D in NTD therapies, as targeted prizes are, intuitively, more efficient than blue sky prizes at inducing innovation in specific research areas already deemed socially significant, like neglected tropical diseases.

3   Theory

3.1   *Baseline Model of the Prize System*

To evaluate the viability of prizes as an alternative mechanism to induce innovation in NTD drug development, we begin by considering the "reward versus rights" model described by Shavell and van Ypersele[2] of a profit-maximizing firm investing in R&D (2001). In accordance with Shavell and van Ypersele's model, drug development and innovation are defined by the following parameters:

- The unobservable research costs *c.* For simplicity, we treat the cost of R&D as a one-time-cost incurred by the innovator. Research costs include both the cost involved in the development of the successful drug, as well as the cost of failures.

- The probability of success *p*. The probability of successfully inventing a product increases with increasing research investment, and all inventors create equal, undifferentiated products. Moreover, $p'(c)>0$, and $p''(c)<0$.

Demand for the product is defined as:

- The demand parameter *t*,

- The quantity of the product *q,* and

- The demand curve for the product *d(q(t))*. The social planner does not know the true social value of the innovation, or the final quantities demanded and sold (e.g. the social planner does not know *t*). The innovator possesses perfect information about *t*, and so knows the true demand of the product.

Per Shavell and van Ypersele's analysis (2001), the innovator is incentivized under the patent system by $\pi(t)$, the marginal profit needed to break even during the monopoly period under the patent system. The innovator will then seek to maximize:

$$\pi(t)p(c)-c \qquad (1)$$

such that breakeven monopoly profits is achieved by the innovator.

Following the initial assumption of asymmetric information regarding true demand t, a social planner with unlimited funds is unable to set a reward R to induce the socially optimal level of firm investment for all levels of demand t, e.g. R is set by the social planner independent of true demand t. Thus, under the *ex post* prize scheme, the successful innovator receives a reward R from the social planner in a one-time event, where the reward amount R is a pre-determined, publicly known, and—most significantly—fixed quantity.

Upon receiving the reward, the innovator releases ownership of the invention into the public domain, and so the innovator makes zero profits from the subsequent production or distribution process. As such, the potential innovator is motivated only by the targeted reward R and will select investment spending level c to maximize

$$Rp(c)-c \qquad (2)$$

where R is equivalent to value of a successful drug to the innovator. Thus, the innovator will choose to invest $c(R)$ for any given level of pre-determined reward R (Shavell and van Ypersele 2001).

As discussed in Section 2, the existing patent system results in underinvestment in R&D towards neglected tropical disease treatments. Let the socially optimal level of surplus be $s^*(t)$, such that $s^*(t)$ is greater than monopoly breakeven profits $\pi(t)$ for all levels of demand. The optimal level of R&D investment at every level of demand t is then described as $c(s^*(t))$. And,

because the market experiences underinvestment in R&D, optimal investment $c(s^*(t))$ is by definition greater than patent investment $c(\pi(t))$ for all levels of demand t.

Shavell and van Ypersele (2001) propose an "optional reward regime" in which the successful innovator can choose between patenting the invention, or accepting the fixed reward R. Comparing (1) and (2) indicates that the successful innovator decision to select between the reward will vary based on their knowledge of true market demand t. The successful innovator will select the optional reward over patenting the invention for all values of demand t where $R>\pi(t)$. Intuitively, a firm will choose to invest in low-demand scenarios if and only if the end reward is sufficiently high—that is, the reward is greater than expected profits. When the social planner sets a reward R for a given $t_{threshold}$ such that $R=\pi(t_{threshold})$ exactly, the innovator is indifferent between the choice of the reward or the patent. Finally, when $R<\pi(t)$ due to sufficiently high demand t, the firm innovator will always choose to patent the invention over receiving a reward.

Shavell and van Ypersele (2001) additionally consider the case of t^*, where t^* is the optimal level of demand. At t^*, the socially optimal surplus $s^*(t^*)$ is achieved by $c(s^*(t^*))$. The social planner will need to set an appropriate, optimal reward R^* that induces the optimal level of R&D investment. Specifically, the optimal reward R^* will necessarily equal the expected value of the social surplus, $E(s^*)$, to ensure that the associated level of reward-incentivized investment, $c(E(s^*))$, is equal to optimal investment $c(s^*(t^*))$. The optional reward system and this particular scenario in which the social planner has set the reward amount at the socially optimal level R^* is described in Figure 1.
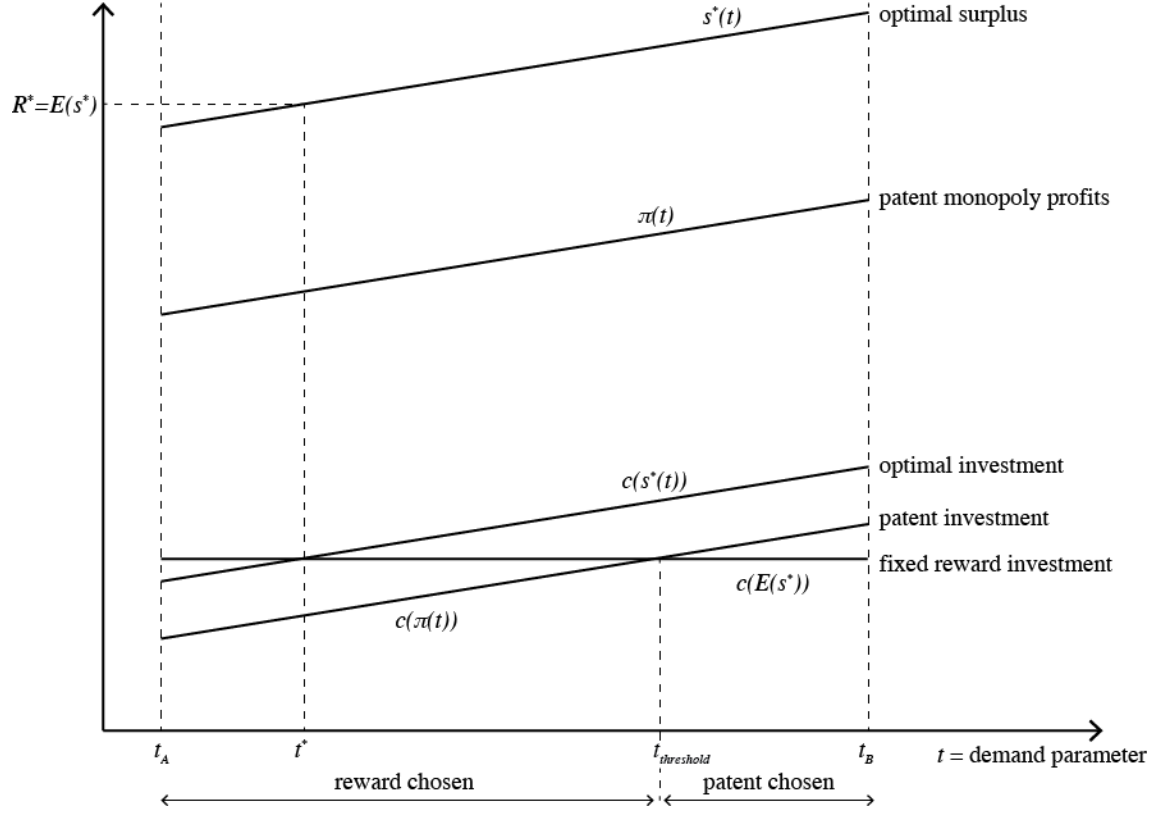
Figure 1. The baseline optional reward model.[3]

We consider Shavell and van Ypersele's (2001) welfare analysis of the patent system and the reward system, where they derive optimal social welfare over all levels of demand t as:

$$W^*(t) = p\big(c\big(s^*(t)\big)\big)s^*(t) - c\big(s^*(t)\big) \tag{3}$$

Shavell and van Ypersele (2001) extend their welfare analysis to the patent system: the innovator is incentivized by achieving monopoly breakeven profit, and so will choose investment spending such that (2) is maximized and $\pi(t)p'(\hat{c})=1$. Note that the monopoly quantity achieved $q_m(t)$ is necessarily smaller than $q(t)$ as monopoly patent spending $c(\pi(t))<c(s^*(t))$, and so there exists deadweight loss borne by consumers for all levels of demand. Deadweight loss $l(t)$ from monopoly pricing, then, is defined as:

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[3] Adapted from Figure 1 of Shavell and van Ypersele's work (2001).

$$l(t) = \int_{q_{m(t)}}^{q(t)} \left(d(q,t) - c \right) dq \tag{4}$$

Then, welfare loss under the patent system alone, can be defined as:

$$W^*(t) - W_P(t) = \left\{ \left[p\big(c\big(s^*(t)\big)\big) s^*(t) - c\big(s^*(t)\big) \right] - \left[p\big(c\big(\pi(t)\big)\big) s^*(t) - c\big(\pi(t)\big) \right] \right\}$$
$$+ p\big(c\big(\pi(t)\big)\big) l(t) \tag{5}$$

The first term, in curly brackets, is the welfare loss from R&D underinvestment, and the second

term is the welfare loss from deadweight loss due to the pricing under the monopoly system

(Shavell and van Ypersele 2001).

Under a pure reward system (e.g. the innovator is only able to receive a reward for the

invention, irrespective of demand t), the social planner does not know the true demand t and so

sets a reward R that is independent of t. Then, social welfare under the pure reward system is:

$$W_R(R) = p\big(c(R)\big) E\big(s^*\big) - c(R) \tag{6}$$

Using (3), we note that welfare loss from the pure reward system is:

$$W^*(t) - W_R(R) = p\big(c\big(s^*(t)\big)\big) s^*(t) - c\big(s^*(t)\big) - \left[p\big(c(R)\big) E\big(s^*\big) - c(R) \right] \tag{7}$$

Note that there is no welfare loss due to deadweight loss from monopoly pricing under the pure

reward system, as is present in the monopoly patent system; moreover, when reward R is set at

the socially optimal level, e.g. $R^* = E(s^*)$, there exists no welfare loss at all. There only exists

the problem of over or underinvestment in R&D when R is not set at the socially optimal level by

the social planner, due to asymmetry of information regarding demand between the social

planner and the inventor.

For the optional reward regime, welfare loss is dictated by demand level t known by the

innovator: for $t = (t_A, t_{threshold})$, the reward system welfare loss analysis in (7) applies, as the

successful innovator will choose the reward over receiving a patent, and so welfare loss is

generated when the social planner sets a suboptimal level of reward R. When $t = (t_{threshold}, t_B)$, the successful innovator will select the patent, and the welfare loss associated with the patent system in (5)—that is, the welfare loss from both R&D underinvestment and monopoly pricing—is present.

3.2 Firm Size Effects

3.2.1 Review of Evidence for Firm Size Effects in High Tech Firms

Much of the literature in industrial organization is devoted to the study of firm size and its effects on innovation. A wealth of business and economic literature suggest that small, autonomous firms in specific industries tend to be more innovative than larger firms—significantly, in highly innovative, specialized, and R&D-oriented industries like engineering and biotechnology (Acs and Audretsch 1987, Zenger 1994, Zenger and Lazzarini 2004, Pla-Barber and Alegre 2006). Identified factors involved in size effects on firm innovation—specifically, in the phenomena of diseconomies of scale in engineering and biotechnology R&D and innovation—include the ability of small firms in high-tech sectors to attract more innovative individuals, to more effectively motivate and induce innovation from employees, and to adapt to and incorporate new scientific discoveries into R&D activities (Zenger 1994, Zenger and Lazzarini 2004, Pla-Barber and Alegre 2006).

The pharmaceutical industry has long been characterized as one such highly innovative, R&D-heavy industry, as "successful and continuous new drug introductions constitute the source of sustainable competitive advantage for firms in the industry" (Petrova 2014). Existing literature, however, appears to contradict whether or not smaller, more specialized

pharmaceutical firms possess an innovative advantage over larger, generalist firms (Petrova 2014).

To address the inconsistencies in empirical literature regarding the effect of firm size on pharmaceutical innovation, we consider the complex, multi-step nature of the drug development process itself, and regard drug R&D as two distinct stages: invention and commercialization (Budish et al. 2013). The invention of the drug consists of creating the new drug lead (i.e. the newly synthesized compound, biologic, etc.) and developing it to a patentable form. The commercialization of the drug is the process of bringing the drug lead to market through lead optimization, clinical trials, seeking regulatory approval, production, and marketing and advertising. Both stages are required to bring any drug to market, but the competencies required at each stage are vastly different: indeed, empirical evidence indicates that it is not uncommon for a small pharmaceutical firm to develop a candidate drug, and subsequently out-license the drug lead to a large pharmaceutical company or hire a contract research organization specializing in clinical trials for further drug development and human testing, as smaller firms often lack the expertise and funds necessary to carry out the capital-intensive process of drug testing and commercialization (Petrova 2014).

When considering the first stage of drug discovery in isolation, the workers and research activities conducted by a pharmaceutical company closely resemble those of a biotechnology firm. Both pharmaceutical and biotechnology firms employ individuals with similar academic backgrounds and experiences into very similar positions (e.g. molecular biologists and biochemists are recruited heavily into pharmaceutical and biotechnology firms as research scientists), and both conduct very similar types of technical research activities. Thus, we apply the empirical findings described above of smaller biotechnology companies possessing an

innovation advantage over larger firms into our analysis of small and large pharmaceutical companies, and continue our analysis of firm size effects considering only the invention stage of drug development.[4]

3.2.2 Firm Size Effects in the Optional Prize System

We proceed with the prize system model articulated in Section 3.1, and integrate the assumption detailed above that smaller pharmaceutical firms are indeed comparatively more innovative than larger firms due to empirically-observed diseconomies of scale present in high-technology research. There now exist two firms in this scenario: the small, specialist firm, and the large, generalist firm, where c_S is the research investment incurred by small firms, and c_L is the research cost borne by large firms. Because both firms experience diseconomies of scale in R&D, the large firm must pay a greater research c_L than the small firm's research cost c_S to attain the same expectation of success—that is, $c_L > c_S$ for research activities at every level of demand t. And, because firms experience diseconomies of scale, the marginal return on each additional dollar of R&D decreases for large firms, compared to smaller firms. This is modeled by an upward rotation in the optimal investment curve for large firms $c_L(s^*(t))$, such that $c_L(s^*(t)) - c_S(s^*(t))$ is increasing for all t. Note additionally that the probability of success P for large firms

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[4] As noted previously, both the invention and commercialization stages are necessary in drug development. We only consider the first stage of invention because many of the costs accrued during the commercialization stage—such as the cost of marketing and advertising to physicians and consumers, as is standard for commercialization of "first-world" pharmaceuticals—can be considered largely irrelevant in this specific case of NTD drugs. Pharmaceutical giant Valeant provides a particularly cogent example of commercialization spending in "first-world" region, when it paid $4.5M for a 30-second spot during the 2015 Super Bowl to advertise a treatment for fungal nail infections (Heine 2015).

Intuition dictates that such spending is clearly unnecessary to commercialize and advertise pharmaceuticals in developing regions and so, assuming clinical trial and regulatory approval costs remain effectively identical between drugs for so-called first-world diseases and NTDs, a firm would actually be comparatively more incentivized on the basis of lower costs alone to innovate in NTD therapies during drug commercialization. Because of this, we consider only the viability and necessity of a prize-based reward system in incentivizing innovation during the invention stage of drug development.

and small firms have now deviated: a small firm investing c has a greater probability of success than a large firm investing the same amount c in R&D, e.g. $p_S(c) > p_L(c)$.

The patent investment curve for the large firm rotates upward in accordance with the same logic—the large firm is now comparatively less efficient at R&D than the small firm, and so the large firm requires greater breakeven profits $\pi_L(t)$ to recuperate the increased R&D costs for every level of demand t. This upward rotation in monopoly profits for large firms in turn rotates the patent investment curve for large firms upwards, producing patent investment curves where $c_L(\pi(t)) > c_S(\pi(t))$, with $c_L(\pi(t)) - c_S(\pi(t))$ increasing for all levels of demand t, due to diseconomies of scale associated with R&D costs.

For a fixed prize R, both the large firm and small firm will choose to invest $c(r)$ to maximize (2). Note, however, that the upward rotation in the optimal investment curve for the large firm due to the larger firm's comparative inefficiency in R&D and innovation, results in R&D investment that meets a demand t_L, where t_L is smaller than t^* (where t^* is equivalent to t_S^*) for all levels of investment. Moreover, for the large firm to innovate at the optimal surplus level to meet demand t^*, the large firm must invest $c_L(s^*(t))$, where $c_L(s^*(t)) > c_S(s^*(t))$. Investment of $c_L(s^*(t))$ to meet t^* is unlikely, given that neither monopoly profits nor the reward amount will cover the costs the large firm incurs to meet demand t^*. Figure 2 describes the change in costs for large and small firms.
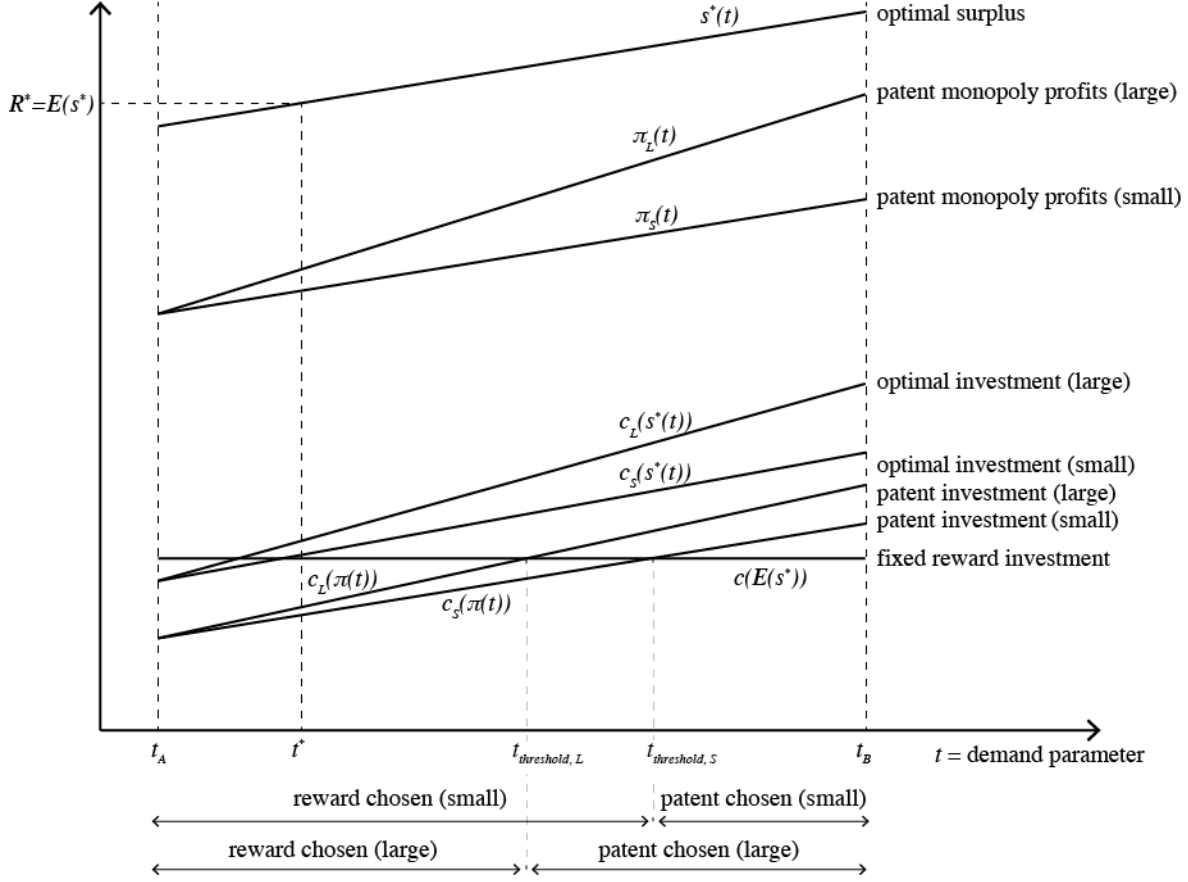
Figure 2. Firm size effects in the optional reward model.

As a result of these changes in the cost functions, we find that the threshold demand $t_{threshold}$ over which a firm chooses to patent the invention rather than accept the fixed reward has changed for large and small firms. The level of demand $t_{threshold, L}$ for the large firm when patent investment $c_L(\pi(t))$ exactly equals the fixed reward investment (e.g. the point at which the large firm becomes indifferent between selecting a fixed reward or patent) has decreased compared to to the threshold demand of the small firm $t_{threshold, S}$; intuitively, a large firm is now less willing to choose a fixed prize over receiving a patent. We revise the optional reward regime welfare loss analysis in Section 3.1 to account for these firm size effects on $t_{threshold, L}$ and $t_{threshold, S}$.

For all $t = (t_A, t_{threshold, L})$, the fixed reward R is greater than monopoly breakeven profits $\pi(t)$ for both small and large firms, and so the successful inventor—irrespective of firm size—

will always select the reward R. As was the case in (7), welfare loss within this reward-only region of market demand stems only from over or underinvestment due to an imperfectly set R, where $R \neq R^*$.

As stated above, the probability of success for small firms and large firms has changed such that $p_S(c) > p_L(c)$; moreover, the R&D costs for a large firm $c_L(s^*(t))$ to achieve the socially optimal surplus has increased relative to the small firm's R&D costs to achieve the same level of social surplus, $c_S(s^*(t))$. As a result of these changes in the cost functions of small and large firms, we find that the range of demand t over which the large firm chooses a reward over a patent for a successful drug has decreased, compared to that of the small firm. We revise the optional reward regime welfare loss analysis in Section 3.1 and find that because the willingness of the large firm to select the optional reward has decreased (e.g. the large firm has a lower threshold $t_{threshold, L}$ compared to the smaller firm, and so it will select the patent instead of the reward for more values of t), the large firm will tend to comparatively underinvest in drug R&D and additionally generate greater monopoly deadweight loss over all levels of demand t than the small firms.

We continue our analysis of firm size effects and relax the initial assumption that the social planner does not know the true quantity demanded of the innovation t. In most other sectors, the assumption that the innovator possesses superior information about product demand is valid. But, given the wealth of literature surrounding the need for neglected tropical diseases (e.g. researchers and organizations worldwide have provided—and will likely continue to provide—estimates of the burden of disease for and the need for neglected disease treatments[5]), we revise our initial assumptions regarding asymmetry of information between the inventor and

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[5] Among other organizations, the World Health Organization, Bill & Melinda Gates Foundation, Center for Disease Control, and World Bank regularly conduct research on and publish data regarding the burden and urgency of neglected tropical diseases.

the social planner, and proceed with the assumption that the social planner in the particular context of NTD R&D has a perfect understanding of true consumer demand t.

If the social planner knows the true social value of the innovation (following the revision of our initial assumption that the government now possesses perfect information about the quantities demanded by consumers, t), the reward R is no longer fixed or independent of t, and the social planner can select a reward $R(t)$ such that $R(t)$ is always greater than $\pi(t)$ to ensure that the potential innovator will always choose the socially optimal level of investment c^* for all levels of product demand t.

In practicality, the social planner can only set a single reward level for a targeted prize. If different reward amounts toward the same end product were publicly set, reverse price discrimination would exist, and both small and large firms would invest the R&D amount needed to attain the larger reward, irrespective of the government's original intentions to meet t^*.

The government can then choose to meet t^* by setting a single, market-wide reward function $R^*_L(t)$ such that the large firm is incentivized to invest $c_L(s^*(t))$, or $R^*_S(t)$ such that the small firm spends $c_S(s^*(t))$. In both cases, the optimal reward for one firm size is considered "imperfectly" set by the other. We consider the implications of this in the region of demand most applicable towards NTD research—demand $t = (t_A, t_{threshold})$ for which the small or large firm will always select a reward, because t is too low for firms to even consider innovating with a patent incentive.

A reward $R^*_L(t)$ is an unnecessarily high incentive for the small firm to reach t^*, and so the small firm will overinvest in R&D. (The large firm invests at the exact level $c_L(s^*(t))$ to meet demand t^*.) Conversely, $R^*_S(t)$ ensures that demand t^* is met only by the small firm's

investment level $c_S(R*_S(t))$, as $R*_S(t)$ is too low for the large firm to reach $t*$, and so the large firm will underinvest in R&D.

Note however, that in both cases optimal demand $t*$ is ultimately met—by either the small firm or large firm—and so from the consumer's viewpoint there exists no welfare loss from a dearth of product available in the marketplace, or from monopolistic pricing. If we revise the initial assumption of the social planner having unlimited funds, we find that the only the social planner bears any welfare loss associated with selecting a reward level optimizing R&D investments for either small or large firms. Because the social planner's only goal is to induce the invention of a specific product, and so is indifferent to the specific size characteristic of the inventing firm, reward $R*_L(t)$ generate greater welfare loss overall for the social planner, as it must pay a higher reward for the same end R&D activities. The difference in welfare loss borne by the social planner in setting either $R*_L(t)$ or $R*_S(t)$ is then:

$$\left[W^*(t) - W\left(R^*(t)\right)\right] - \left\{W^*(t) - W\left(R^*_{size}(t)\right)\right\} = R^*_{size}(t) - R^*(t) \qquad (8)$$

where $R*_{size}(t)$ is either $R*_L(t)$ or $R*_S(t)$. From (8), we see that the welfare loss incurred by the social planner in setting a reward amount determined by firm size is simply the difference between the selected reward level and the true optimal reward level. Note that because $R*_S(t)$ is the lowest reward amount needed to ensure optimal firm investment, $R*_S(t)$ is equal to $R*(t)$. Then, there exists welfare loss for the government in paying excess reward when the reward is set at $R*_L(t)$, but there is no welfare loss when the reward is set at $R*_S(t)$.

4   *Case Study*

To empirically evaluate firm size effects on the cost of drug discovery for treatments, we conduct a case study considering the cancer treatments Gleevec and Folotyn. Gleevec was

developed by Swiss pharmaceutical giant Novartis, and received FDA approval in 2001 for the treatment of chronic myeloid leukemia (CML), a rare form of leukemia that had a previously low life expectancy ("Gleevec", "Leukemia"). Since its release, Gleevec has become a global blockbuster drug, accruing over US$4.75 billion in global sales for Novartis in 2014 alone ("Product Sales"). Folotyn, by contrast, was developed by Allos Therapeutics, a small, US based biopharmaceutical firm that specialized in the development and commercialization of anti-cancer therapies. Approved by the FDA in 2009, Folotyn treats peripheral T-cell lymphoma (PTCL), an extremely rare and aggressive form of lymphoma ("Folotyn", Moskowitz et al. 2014). That Gleevec was developed by a large, generalist firm, and Folotyn by a small, specialist firm, along with the similarity and rarity of the diseases treated by each drug render these two therapeutics particularly useful for an evaluation of potential firm size effect on drug R&D costs.

4.1   R&D Cost Estimation

We first estimate the total addressable market in the US for each drug during its launch year, as determined by the prevalence of disease and the price of treatment in the launch year. Data on disease prevalence, drug pricing, and drug prescription behavior is gathered from the FDA, *The New York Times*, *Blood*, and *Leukemia*. Figures specific to each treatment's launch year are used to most accurately assess a firm's expectations of success and projections for a treatment's "true" potential earning power in recuperating R&D cost during the patent monopoly period and total addressable market.[6] The data available through these sources are rounded

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[6] Gleevec was unexpectedly and overwhelmingly successful in the years following its 2001 launch, which prompted Novartis to increase Gleevec's sticker price initial sticker price threefold over the next decade (Kantarjian et al. 2013). Such successes cannot be predicted, however, and so the launch year price and all related estimations are likely the most accurate signal of a firm's own estimation of a drug's R&D cost, and the firm's own estimation of expected revenue needed to recuperate those costs.

estimations, and so the resultant estimates derived from these figures are likely not exact. Table 1 summarizes the estimates.

Table 1. Total Addressable US Market for Gleevec and Folotyn in Launch Year		
	Gleevec (Novartis, 2001)	Folotyn (Allos Therapeutics, 2009)
[1] Prevalence of Disease in Launch Year	30,000	9,500
[2] Price of Treatment, Annual (US$)	30,000	70,000
[3] Total Lifetime Cost to Single Consumer (US$)	175,000	70,000
Total Addressable Market in Launch Year (US$)	900,000,000	665,000,000

[1] The total number of afflicted individuals in a given year. Complete market penetration is assumed, given the unfavorable prognosis of disease without these treatments, the absence of treatment substitutes, and the necessity of these medications in ensuring survivability. [2] Price of treatment per person is annualized based on price per month of treatment and median treatment duration. [3] Total lifetime cost to a single consumer is determined by the average duration of treatment and the launch price. See the Appendix for data sources.

Note that Gleevec's sticker price is lower than Folotyn's for a year's treatment course. However, adjustments must be made to account for differences in the physician prescription behaviors and prognoses after treatment for each medication, both of which were factors likely included in a determination of launch year pricing. Gleevec is prescribed for a median of 70 months, and has transformed CML from a disease with a low survival rate to a chronic, manageable disease (Huang et al. 2012). To contrast, physicians prescribe Folotyn for 70 days on average, and PTCL remains a disease with a very poor five-year survival rate (Pollack 2009). The higher, unadjusted sticker price of Folotyn, then, likely accounts for the treatment's significantly lower expected total lifetime cost to consumers due to PTCL's lower prevalence and smaller total addressable market.

Numerous factors go into the determination of a new drug's price for the duration of its patent monopoly period, including customer and insurance company willingness to pay, the availability of substitute therapies, and the firm's need to recuperate R&D costs at a specific discount rate. At the launch times for Gleevec and Folotyn, both treatments were considered the

first truly targeted therapies for their respective cancer subtypes, resulting in what was largely inelastic demand for the treatments (Pollack 2009, Kantarjian 2013). Given the inelasticity of consumer demand for these products, it is likely that Novartis and Allos Therapeutics set the monopoly prices for these treatments at levels necessary to recuperate the R&D costs associated for each therapeutic as quickly as possible.

With this assumption of pricing being only dependent on R&D costs, we use net present value to estimate the maximum level of R&D investment given an expected total addressable market, assuming the firm wants to recuperate the costs as quickly as possible (e.g. over a single period). The estimates are summarized in Table 2.

Table 2. Estimated Maximum R&D Investment for Gleevec and Folotyn		
	Gleevec (Novartis, 2001)	Folotyn (Allos Therapeutics, 2009)
[1] Maximum Initial R&D Investment (US$)	811,000,000	599,100,000

[1] Initial investment is determined using estimates of Total Addressable Market (Table 1), and DiMasi et al.'s estimation of a pharmaceutical company's discount rate in valuing future expected earnings over a single period (e.g. to recuperate R&D costs) at 11% (2003).

One commonly cited estimation of a successful drug's total R&D costs (including the cost of failure of other products) is US$802 million (DiMasi et al. 2003). Comparing the costs in Table 2 with this figure suggest that the Gleevec and Folotyn estimates are within an acceptable range. Moreover, the R&D cost estimates indicate that Novartis spent 1.4 times the amount that Allos Therapeutics did on a cancer therapeutic, suggesting a comparative advantage for Allos Therapeutics over Novartis, given the firm's small size and specialization in oncology treatments.

4.2   Optional Reward Regime Estimation

Returning to the initial proposition of an optional reward regime, we estimate the welfare losses associated with firm size in drug development. The incidence and prevalence of different cancers—like that of neglected tropical diseases—are well-studied, reported, and aggregated through government organizations such as the National Cancer Institute, and so it can be assumed that the US government has full knowledge of national demand for treatments addressing specific cancers, and is able to set an optimal reward necessary to induce investment to meet market demand. The welfare analysis in Section 3.2 then holds.

We use the R&D cost estimates in Table 2 as a baseline to determine the reward level necessary to incentivize a small firm or a large firm. (If a firm expects to invest US$1 billion for R&D, then a reward must be greater than that value, e.g. at least one additional dollar.) (8) estimates the welfare loss associated with a reward set to optimize Novartis's R&D investment, or a reward set to optimize Allos Therapeutics' R&D investment, where the difference between the optimal reward level and each respective firm's cost is assumed to be equal. Table 3 displays the welfare loss estimates for rewards set at either R^*_L or R^*_S, as determined by (8):

Table 3. Estimated Welfare Losses Borne by Government		
	Optimal Reward for Large Firm	Optimal Reward for Small Firm
[1] Welfare Loss (US$)	235,000,000	0

[1] Determined by taking the difference between the discounted reward and the discounted estimated R&D cost (Table 2; see also equation (8)), using DiMasi et al.'s pharmaceutical investment discount rate of 11% to discount the initial investment cost (2003).

The estimated welfare loss borne by the government in choosing to set an R^*_L rather than R^*_S is not insignificant, suggesting that setting rewards that specifically seek to target small

firms—rather than firms that target the general population of innovators—may be more prudent for a social planner seeking to incentivize targeted R&D efforts.

5   Discussion

As demonstrated by Shavell and van Ypersele's prior work (2001), an optional prize system is a robust, viable alternative to the existing patent system in incentivizing drug R&D for NTDs; we extended this theoretical framework to posit that smaller firms would be comparably more efficient in response to a fixed prize reward at all levels of demand for a specific product than a large firm.

Estimations of the costs of development and associated welfare losses for Gleevec and Folotyn corroborate this hypothesis of small firms being better targets for prizes posted *ex ante* to induce innovation in low-demand research areas. Revisiting the theoretical assumption detailed in the optional reward of pharmaceutical firms experiencing diseconomies of scale in research would be prudent, however, as the assumption is based on existing research specific only to the biotechnology and engineering sectors. Additional study estimating the costs involved in drug development from a significantly wider sample of pharmaceutical companies is necessary to more robustly validate this assumption and the initial findings of this case study.

There do exist some inherent drawbacks to a reward system. The success of a reward in incentivizing optimal investment to meet market demand is contingent upon setting the correct reward amount. Many of the theoretical assumptions built into the cost estimates in Section 4— e.g. that the launch price is set to exactly recuperate all R&D costs within the first year—are dramatic oversimplifications of the true drug development and pricing process. To more accurately estimate a specific drug's costs, it is necessary to more thoroughly evaluate other

factors involved in the drug development process, including the role of other research groups or laboratories in the development of the drug, as pharmaceutical and clinical biology research is heavily reliant upon prior advances and discoveries made in basic science. The development of a drug never truly starts at a proverbial square one; there is likely already an existing body of knowledge surrounding that disease area. Additionally, it is not uncommon (as stated above in Section 3.2.2) for pharmaceutical companies to buy licenses of promising compounds for further testing and development. The costs or cost reductions associated with the availability and incorporation of that preexisting knowledge into the drug development process should be considered in a more thorough cost estimation.

From a practical standpoint, setting this optimal reward to induce innovation would require a task force dedicated to the role of accurately estimating the initial R&D costs involved in the production of a not-yet-invented drug. The R&D investment estimations in Section 4 highlight the difficulties in verifying (short of simply benchmarking off historical data as a sanity check) the accuracy of cost estimates for a single drug. Moreover, Section 4 applies a retrospective approach in estimating R&D costs for a given drug based off of available, existing pricing data. A forward-looking approach to estimating the R&D costs of a not-yet-invented drug (including the cost of failure) is significantly more tenuous and, given the unpredictable, heterogeneous nature of the scientific invention process, can be considered largely impossible.

Moreover, the sizes of the rewards needed to incentivize optimal levels of investment are not trivial. To effectively incentivize the invention of Folotyn based on the discounted cost estimates in Table 2, the reward quantity would need to exceed Allos Therapeutic's expected total addressable market of US$665,000,000, all of which (assuming the reward is government funded), would be covered by taxpayer money. Given the complexity and range of political

opinion on American humanitarian efforts and foreign aid, it would likely be difficult to produce that level of funding towards a reward that incentivizes innovation for even a single NTD, let alone all 17 NTDs. Rewards funded by nongovernmental organizations and other independent entities like the Bill & Melinda Gates Foundation are likely the optimal choice to ensure that the prizes are adequately funded. Funding of prizes from such organizations would remove the financial burden of paying for NTD R&D from taxpayers, and instead shift the responsibility to individuals interested in the cause.

Additionally, targeted prizes do not reward or incentivize follow-up or sequential innovations. Indeed, the first dengue vaccine is not necessarily (nor is it likely) the best possible dengue vaccine. But, unless the social planner actively initiates additional innovation in dengue vaccine technology by releasing a second reward after the first has already been claimed, there exists no market incentive for firms to continue innovating in that particular field. Though the reward system spurns some initial innovation that otherwise would not have been present under the patent system, it can also stifle additional improvements in the field.

To that end, a reward that spurns some research towards developing treatments for NTDs—even if that research is not representative of the best work possible—is still better than the existing patent system's market failure to incentivize any research at all. Given that the reward system is likely capable of inducing at least some innovation in therapeutics for NTDs, it is important to note some key advantages of the reward system and, more specifically, the possible advantages of a reward system that focuses primarily on establishing targeted prizes for small firms as a way to most effectively induce innovation while reducing social planner-borne welfare loss.

First, a fixed prize provides greater incentives to small firms because the reward money is split among fewer workers in a small firm—that is, the prize is less dilute—than in a large firm. A large firm requires a larger reward R for each person to receive the same lump sum award, and so workers in a large firm would be even less inclined to participate in a contest for any given reward level R than a small firm.

Small firms may additionally exhibit greater sensitivity to reputation effects, due to their greater degree of specialization in a specific therapeutic area. Large pharmaceutical companies often have a whole suite of products available—Novartis, for example, produces pharmaceuticals treating osteoporosis, hypertension, ADHD, and Hepatitis B, all of which are essentially unrelated conditions—and so are likely less concerned with winning a prize specific to NTDs because they capable of deriving profits from other disease areas. It follows that a large company would then be additionally less concerned with receiving the requisite media attention within the NTD research space that follows the reception of such a prize, as they can generate positive media attention in a variety of disease areas. Small companies, by contrast, are necessarily more specialized, and so the small firm that receives a targeted prize will value more highly the NTD-specific media attention than a large firm, as the increased media attention can bring increased funding for closely related R&D activities, and as the small firm lacks other avenues for generating positive media buzz.

Moreover, small firms may place more value on the welfare of local populations than large firms, thereby increasing small firms' comparative effectiveness in a contest for a targeted prize. Sinovac is a particularly cogent example of geographic effects on small firms' willingness to invest in comparatively more "local" problems. Sinovac, a small Beijing-based biopharmaceutical firm, was the first group to successfully develop and launch an H1N1 vaccine

during the swine flu pandemic of 2009—an outbreak that disproportionately affected East and Southeast Asia ("China set to provide first swine flu vaccines", Knox 2013). Indeed, Sinovac's core company mission is to develop novel vaccines specifically for severe, emerging infectious diseases like hand foot and mouth disease that heavily afflict China and other Asian countries, but that remain largely absent in more lucrative, western markets, indicating that a firm's incentive to innovate can be locally generated ("Sinovac R&D Strategy", Solomon et al. 2010, Wong 2011). That smaller firms are likely more grounded and invested in the social welfare of local populations beyond just economic profit, then suggests that a prize specific to small pharmaceutical firms within a given local context may be a useful program in inducing NTD drug research. Further study evaluating geographic effects on firm willingness to participate in a targeted research scheme could prove interesting as part of a broader attempt to incentivize research in NTDs.

6   Conclusion

The urgency and necessity of treatments for NTDs has been widely recognized as being extremely detrimental to the social, economic, and political growth of developing regions. Developing countries faced this burden uniquely, and so there is a pronounced market failure to conduct R&D activities towards NTD therapeutics as the drug development process is currently incentivized by the patent system, which relies solely on sufficiently high market demand and consumer ability to pay to drive innovation.

This paper proposes a targeted, optional prize scheme as an alternative incentive mechanism to induce pharmaceutical innovation in NTD therapeutics, and evaluates theoretical and empirical firm size effects in drug development. The case study evaluating two drugs, each

from a small or large firm, respectively, suggests that small pharmaceutical firms may indeed by more efficient at pharmaceutical innovation, and thus be more suited for targeted prizes. Additional study to more broadly characterize potential firm size effects on innovation efficiency and reward responsiveness may prove fruitful in evaluating, designing, and implementing a targeted prize scheme as a viable alternative to the existing patent system.

7   Works Cited

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8 Appendix – Data Sources

Data Sources	
Gleevec	
Prevalence of Disease in Launch Year	Kantarjian et al. (2013), *Blood*
Price of Treatment, Annual (US$)	Kantarjian et al. (2013), *Blood*
Average Duration of Treatment	Hocchaus et al. (2009), *Leukemia*
Folotyn	
Prevalence of Disease in Launch Year	Malik (2009), FDA
Price of Treatment, Annual (US$)	Pollack (2009), *The New York Times*
Average Duration of Treatment	Pollack (2009), *The New York Times*