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Neglected Infectious Diseases: Are Push and Pull Incentive Mechanisms Suitable for Promoting Research?

Frank Müller-Langer[*]

Abstract

Infectious diseases are among the main causes of death and disability in developing countries, and they are a major reason for the health disparity between rich and poor countries. One of the reasons for this public health tragedy is a lack of lifesaving essential medicines, which either do not exist or badly need improvements. In this article, we analyse which of the push and pull mechanisms proposed in the recent literature may serve to promote research into neglected infectious diseases. A combination of push programs that subsidise research inputs through direct funding and pull programs that reward research output rather than research input may be the appropriate strategy to stimulate research into neglected diseases. On the one hand, early-stage (basic) research should be supported through push mechanisms, such as research grants or publicly financed research institutions. On the other hand, pull mechanisms, such as prize funds that link reward payments to the health impacts of effective medicines, have the potential to stimulate research into neglected diseases.

I. Introduction

Infectious diseases are a major reason for the health disparity between rich and poor countries (Stiglitz and Jayadev, 2010). They kill 14 million people worldwide every year, predominantly affecting members of poor populations in developing countries

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(WHO, 2001). In fact, these countries make up 98 per cent of the global disease burden for infectious diseases, such as malaria, trachoma, lymphatic filariasis or schistosomiasis (WHO, 2008). One of the reasons for this public health tragedy is a lack of lifesaving essential medicines, which either do not exist or badly need improvement (Kremer and Williams, 2010; Mrazek and Mossialos, 2003). The pharmaceutical industry has little incentive to invest in research and development (R&D) for infectious diseases that predominantly plague poor nations, as medicines cannot be sold at a price that allows pharmaceutical firms to cover their high R&D costs (Buckup, 2008). There is a significant positive relationship between a pharmaceutical firm's expected returns and its R&D expenditures (Grabowski and Vernon, 2000). Furthermore, Acemoglu and Linn (2004) suggest that pharmaceutical R&D is directed towards more profitable markets. In fact, the pharmaceutical markets in the poorest countries are too small to trigger significant R&D for medicines for neglected infectious diseases that are prevalent in these countries (Maurer, 2005). Although a large number of consumers in the developing world lack effective medicines for such diseases, their purchasing power is too low to generate a sufficiently large market (Kremer, 2002). In these circumstances pharmaceutical companies decide that the return on R&D investment for neglected infectious diseases will be less than the return on an equivalent investment for medicines for the developed world (Webber and Kremer, 2001).[1] Although the infectious diseases that are the most prevalent in poor nations account for 11.4 per cent of the global disease burden, only 1 per cent of all pharmaceutical products marketed in the period from 1975 to 1999 were targeted at them (Trouiller et al., 2002). The introduction of patent protection in the developing world is not a sufficient solution to the problem

[1] One may argue that local R&D for medicines for neglected diseases prevalent in countries with emerging pharmaceutical industries, such as India or Brazil, may help to eradicate those diseases. However, Kettler and Modi (2001) find that Indian pharmaceutical companies are more likely to target diseases that are prevalent in industrialized countries, such as diabetes or cancer.

of underinvestment in R&D for neglected diseases (Kremer, 2002). Even if patent protection provided an adequate incentive mechanism to successfully stimulate R&D, patented medicines may still not be affordable for large groups of consumers in poor countries (Kremer and Glennerster, 2004). In this article, we analyse which incentive mechanisms mitigate the problem of underinvestment in R&D for medicines for neglected diseases.

The following section analyses push programs that subsidise research inputs through direct funding. The third section studies pull programs, such as prize funds and advanced purchase commitments. In the fourth section, we conclude and provide policy recommendations.

II. Are Push Programs Suitable for Promoting Research into Neglected Diseases?

Programs that subsidise research inputs through direct funding, such as research grants to universities and government laboratories or tax credits for R&D investment, are called push programs. Current push programs aimed at promoting R&D into malaria research are the Medicines for Malaria Venture and the Malaria Vaccine Initiative.

A. Publicly Funded Research Institutions

Large publicly funded research institutions, such as universities or the US National Institutes of Health (NIH), play a significant role in promoting basic research (Glennerster and Kremer, 2001). They help to create non-patentable fundamental scientific knowledge, which provides a base for the downstream discoveries of the profit-seeking pharmaceutical industry (Maurer, 2005). This

publicly available fundamental scientific knowledge generated by publicly funded research institutions reduces the research costs incurred by the pharmaceutical industry. It thereby potentially increases private incentives to invest in applied research (Webber and Kremer, 2001). However, negative experiences with publicly funded programs in financing the commercial R&D of marketable pharmaceutical products suggest that push programs are subject to difficulties resulting from information asymmetries between researchers and government research administrators (Kremer, 1998). Moral hazard problems may arise because government research administrators cannot perfectly monitor research activities (Kremer and Glennerster, 2004). Researchers, once they are funded, may have incentives to redirect their resources to non-core research activities, putting their efforts towards unrelated and more rewarding research projects or towards preparing the next grant application (Webber and Kremer, 2001). The effective management of the performance of researchers, together with reputation effects and the contingency of future funding on previous performance, may help to mitigate moral hazard problems (Gallini and Scotchmer, 2002).

Adverse selection problems may occur in publicly funded push programs. Difficulties in determining the quality of research are likely to arise because these programs pay for research inputs on the basis of an *ex ante* evaluation of potential product delivery, not on the basis of successful product development (Maurer, 2005). Researchers have better information about the probability of success of a research program than do government research administrators (Kremer and Glennerster, 2004). They may, therefore, have incentives to act opportunistically by overestimating the probability of success of the research program in order to acquire the funding in the first place or to increase the amount awarded (Hollis, 2007). However, due to the lack of appropriate information, government research

administrators may be unable to determine which research projects should be funded or which diseases should be targeted (Kremer, 2002). Hence, asymmetric information with respect to the probability of success of research projects may result in the funding of projects that only have a small probability of success (Kremer and Glennerster, 2004). Even worse, government research administrators may decide not to fund a worthwhile research project with a high probability of success because they doubt that the project's probability of success is credible (Kremer, 2002). These problems can be diminished if a private pharmaceutical firm or research institution is only paid by a government agency after it has successfully developed a specific marketable pharmaceutical product. In this case, researchers will have strong incentives to evaluate the likelihood of success of their research projects more realistically and to focus on the development of the desired product (Kremer and Glennerster, 2004).

B. Targeted R&D Tax Credits

In contrast to publicly funded research institutions, targeted R&D tax credits are a direct contribution to pharmaceutical companies, designed to promote R&D into specific neglected diseases (Hall and van Reenen, 2000). R&D tax credits finance research inputs rather than research outputs (Kremer and Glennerster, 2004). In the USA, for instance, pharmaceutical companies are eligible for a 20 per cent R&D tax credit. Nevertheless, a bill introduced in the US Congress that proposed to increase the R&D tax credit for R&D into vaccines for HIV, tuberculosis and malaria to 30 per cent was never passed into law.[2] The private returns to R&D for neglected diseases are much lower than the social returns to R&D for these diseases (Lybecker and Freeman, 2007). This results in private firms investing less than is socially

[2] Vaccines for the New Millennium Act (US). H. R. 1504. 107th Congress, 1st Session, 4 April 2001.

optimal. R&D tax credits address this problem. However, as targeted R&D tax credits subsidise research inputs for a specific pharmaceutical product rather than rewarding successful product development, they are subject to monitoring problems similar to those for other push mechanisms (Kremer, 2001). Pharmaceutical companies may have incentives to use their superior knowledge relative to government agencies to maximise their claims through creative accounting (Kremer and Glennerster, 2004).

As for R&D for medicines for neglected diseases, eg., a malaria vaccine suitable for consumers in poor regions, R&D tax credits may present a number of issues (Mrazek and Mossialos, 2003). A targeted R&D tax credit could be claimed by a pharmaceutical company pursuing R&D for versions of the pharmaceutical product that are not appropriate for poor countries (Kremer and Glennerster, 2004). Suppose that a pharmaceutical company claims a targeted tax credit for R&D into a malaria vaccine. The health needs of residents in low-income countries with respect to a malaria vaccine significantly differ from the health needs of residents in high-income countries: A malaria vaccine appropriate for travellers or military personnel, who only spend a limited period of time in an endemic region, may have different characteristics than a malaria vaccine appropriate for residents, who live in those regions permanently (Kremer, 2002). Additionally, Kremer and Glennerster (2004) suggest that a malaria vaccine for consumers in high-income countries is more likely to focus on the early life-cycle sporozoite-stage of the malaria parasite when it is transmitted from an Anopheles mosquito to its human host. A malaria vaccine that focuses on the sporozoite-stage of malaria may only provide temporary protection and thus be inadequate for consumers in low-income countries (Kremer, 2002).

There is one final drawback associated with targeted R&D tax credits. They cannot mitigate the fact that residents in poor regions do not have access to affordable medicines (Kremer and Glennerster, 2004).

C. Conclusion to Push Programs

Given the dearth of R&D for medicines for neglected infectious diseases, direct public funding of basic research into these diseases could be an appropriate option to provide a base for downstream discoveries in the pharmaceutical sector. Moral hazard and adverse selection problems suggest that push programs may not be the optimal solution to finance the development of marketable pharmaceutical products. Push programs are, however, suitable to promote basic research and provide a basis for subsequent applied and commercially exploitable research. Additional mechanisms are necessary to encourage private pharmaceutical companies to develop medicines for neglected infectious diseases and to improve affordable access to those medicines for residents of low-income countries.

III. Are Pull Programs Suitable for Promoting Research into Neglected Diseases?

In contrast to push programs, pull programs such as prizes, advanced purchase commitments and patent buyouts reward research output rather than research input. A pull program rewards the actual creation of a desired medicine or vaccine but not the R&D input itself.

A. Prizes

A targeted prize is a payment that is made to a researcher conditional on the achievement of a particular outcome, ie., a technical specification of a desired drug or vaccine (Maurer, 2005). Non-profit organisations have recently identified prize challenges as tools to create incentives that foster R&D in the pharmaceutical field. For instance, Prize4Life set up two challenges to promote R&D on Amyotrophic Lateral Sclerosis (ALS, also known as Lou Gehrig's disease). With respect to neglected infectious diseases, the X Prize Foundation and the Bill & Melinda Gates Foundation are currently developing an X Prize Challenge for the effective diagnosis of tuberculosis in the developing world, where the world's second most lethal infectious disease is most prevalent.

Love and Hubbard (2007) promote a radical rethinking in the field of pharmaceutical innovation policy, suggesting a mandatory prize mechanism as an alternative to the marketing monopolies constituted by patents. The basic idea of the 'Medical Innovation Prize Fund' is to 'divorce the incentive for innovation from the product's price to consumers' so that 'knowledge goods, including the R&D for a new medicine, can be placed in the public domain immediately' (Love and Hubbard, 2007, p. 1528). The reward shall only be given if an innovation has made a significant impact on public health. This would lead to 'open' innovations, yet still reward innovators financially (provided patients benefit from the new drug). An example of such a mechanism is the prize fund introduced by former US Representative B. Sanders, called the Medical Innovation Prize Act, based on proposals by Love and Hubbard.[3] The total size of the proposed fund was to be 0.5 per cent of the US gross domestic product. The prize fund would have been

[3] Medical Innovation Prize Act (US). H.R. 417. 109th Congress, 1st Session, 26 January 2005. An identical bill was reintroduced in 2007. Note that it never became law.

structured to target diseases that predominantly affect poor nations, with a minimum initial allocation of 4 per cent for globally neglected diseases.

Hollis and Pogge (2008) promote a voluntary prize fund named the 'Health Impact Fund' (HIF), which is designed as a supplement to the existing system of patent protection. In this optional pay-for-performance scheme for new medicines, pharmaceutical companies would be free to abandon monopoly pricing (but not their exclusivity right deriving from a patent) and instead participate by registering products with the HIF, which would reward them in proportion to the measurable net health impacts of their products. Rewards would be conditional on the products being priced (roughly) no higher than the average cost of production (Pogge, 2010). The scope of the HIF would be global. Participating states would act as funding partners. As for the nature of the payment, there are two design options. The first option is a fixed pool to be split among the innovators according to the product's health impact; the pool might be guaranteed for, say, fifteen years. This would make the cost of the HIF politically attractive and predictable for member states, but it would also place a burden on innovators resulting from uncertainty as to the exact rate of reward per Quality-Adjusted Life Year (QALY).[4] An alternative would be to offer innovators a fixed amount of money per QALY. This would remove uncertainty for innovators but impose uncertainty on member states regarding the annual cost of the HIF (Pogge, 2010). Unlike the mandatory prize fund proposed by Love and Hubbard, the voluntary HIF would be targeted at medicines for neglected infectious diseases in particular, while innovations with very high market value would still be distributed under the patent system (Hollis and Pogge, 2008).

[4] In this standardized measure of health benefit, a year in perfect health has the value of one, while a year in poorer health has a value between zero and one.

1. Advantages of Prizes

First, suppose that the creation of a new drug or vaccine is successfully stimulated through a prize and donated to the public or made available to the public at the cost of production. In this case, the drug or vaccine is not subject to the inefficient (monopoly) pricing associated with the market exclusivity provided by a patent. Second, in contrast to push programs, prizes are not likely to be subject to moral hazard problems. Because a researcher will only receive the prize once the desired drug or vaccine is successfully developed, incentives to stray from the task or shift research priorities to other projects are lower under a prize mechanism (Maurer, 2005). Third, the technical specification of a prize could be designed to spur the development of a drug or vaccine appropriate for use in low-income countries (Kremer and Glennerster, 2004). For instance, the prize for the development of a malaria vaccine may only be awarded if it fulfils specific requirements, eg., that the vaccine should prevent not less than 50 per cent of plasmodium falciparum malaria, which is the most dangerous type of malaria with the highest mortality rate (Maurer, 2005; WHO, 2005). Fourth, in contrast to patents, an innovator awarded a prize for successfully developing a specific drug does not have to fear profit-reducing infringement. He does not incur the high costs of litigation and identifying alleged patent infringers (Gallini and Scotchmer, 2002). As for prize funds such as the HIF or the Medical Innovation Prize Fund, there are further advantages. Because rewards would be linked to actual results in terms of incremental healthcare benefits, the pharmaceutical industry would not be inclined to manufacture inferior or unnecessary products but would be incentivised to make a measurable impact on global health. Consequently, competition for product quality and effectiveness would be created (Love and Hubbard, 2007). However, prices would remain low because pharmaceutical companies would have a great interest in making their product

available to the greatest number of people in order to achieve the greatest possible health impact (Pogge, 2010). Additionally, companies registered with a particular fund would be incentivised to do more than just sell the product. To make an optimal impact on public health, patients would need to be fully instructed on dosage and compliance. Because of the lack of a public health infrastructure in poor countries, patients often receive unsuitable products or suitable products that are not used in the right way (Mrazek and Mossialos, 2003). This 'last-mile problem' would be mitigated in a prize system in which companies would have an incentive to ensure that products are used properly by cooperating with governments and NGOs (Pogge, 2010).

2. Disadvantages of Prizes

First, if the sponsor of a prize does not have accurate information about the prospective benefits and costs of the innovation to be rewarded, the reward is likely to differ from the social value of the innovation, resulting in either underpayment or overpayment (Maurer, 2005). The core difficulty with respect to prizes is determining how large the prize should be. For instance, the prize fund mechanisms introduced above only reward manufacturers of products that have made a positive impact on public health. Calculating the incremental health impact of medicines, which is essential for the effective operation of the HIF, appears to be an extremely challenging task that could very well overburden agencies. Clinical trials do not give conclusive and accurate assessments of a drug's impact and are usually complicated by factors such as varying effects across different populations or the lack of suitable biomarkers (Liddell, 2010). Although these efforts could be supplemented by field trials, the huge expenditures of time and money demanded by such undertakings could easily prevent agencies from carrying them out in the first place (Liddell,

2010). Because the assessment of health impacts would rely in part on the number of units sold, fraud, aggressive marketing and advertising could become common practices among companies to exaggerate the benefits of their products (Liddell, 2010). As incremental health benefits are difficult to calculate, even *ex post*, decision makers could act at their own discretion. For instance, a new drug typically substitutes or complements an existing product. The new drug may also be (more) beneficial to certain patients and not beneficial to others (Kremer and Williams, 2010). Depending on the room for discretion left to a committee in charge of *ex post* assessment, prize funds may create the potential for static costs associated with rent-seeking and dynamic losses from inappropriate incentives (Kremer and Williams, 2010). A further problem with the assessment of new products arises if one considers complementary inventions. The exact distribution of the awards may be difficult because producers would have incentives to overstate the importance and the R&D costs of their respective inventions and thus mislead decision makers about the size of their share (Kremer and Williams, 2010). Additionally, sponsors have incentives to renege on their promise once the invention is finished, eg., by creating reasons that the invention is useless and not eligible for the prize (Maurer, 2005). It is, therefore, of critical importance that the rules of a prize, eg., the process for assessing the value of an innovation, are clearly specified in advance and enforceable by a court (Kremer and Glennerster, 2004). The sponsor must adopt a credible commitment strategy *ex ante* to reduce his ability to renege *ex post* to prevent the erosion of the incentives to innovate. This time-inconsistency problem may also be solved through a bonding mechanism, ie., a conflict resolution mechanism.

Second, Maurer (2005) suggests that publicly funded prizes are likely to be less favourable politically than patents because large lump-sum (governmental) prize

payments are more visible to voters than patent revenues spread out over a large number of doses.

Third, prizes may result in a wasteful prize race in which R&D investments are duplicated (Kremer and Glennerster, 2004). If prizes offer the full social value of an innovation, competing firms may allocate excessive resources to their research. Another disadvantage of prizes compared to patents stems from the fact that public or private sponsors are required to finance the prize (Maurer, 2005). If a prize is publicly financed, it may eliminate the deadweight loss associated with patents. However, public financing (ie., through taxation of other goods) creates its own welfare reducing distortions. Furthermore, if one considers a mandatory prize fund for the entire pharmaceutical market, it may be hazardous to make pharmaceutical R&D depend on the willingness of states to pay into the system, as unforeseen circumstances may cause them to commit to lower amounts of funding or prevent them from participating in the first place (Hollis and Pogge, 2008). Conversely, there is a certain danger that companies will simply ignore any voluntary mechanism if it generates lower profits than monopoly pricing. If, however, rewards from funds such as the HIF were great enough to increase existing profit margins in the pharmaceutical sector at the expense of the public purse, this aspect of public funding would arguably not be appealing to taxpayers (Liddell, 2010).

B. Patent Buyouts

Kremer (1998) examines the potential of patent buyouts to promote innovations and analyses the use of auctions to determine patent buyout prices. He suggests that the patent authority should offer to buy relevant patents at a price that is equal to its estimated private value plus a mark-up reflecting the ratio of the social to the private value of the invention. Under the assumption that the value of an invention is

observable to competitors of the patent-holding firm, the market value of the patent would be estimated through a sealed-bid second-price auction. The patent authority should place most of the patents it buys in the public domain so that the innovation can be produced and marketed at a competitive price. However, only a small fraction of the patents purchased would be sold to the firm with the highest bid to provide the auction participants with incentives to disclose their true expectations of the market value of the patent (Harhoff et al., 2003; Kremer, 1998). The patent authority would randomly choose which patent will eventually be sold to the high bidder and thus not be placed in the public domain.

1. Advantages of Patent Buyouts

First, because the price the original developer of a patented innovation can realise from selling the patent to the patent authority typically exceeds the private value of the patent, patent buyouts are likely to increase private R&D incentives (Kremer, 1998). Thus, they may help to moderate the market failure that private returns on R&D are typically lower than social returns on R&D (Kremer and Glennerster, 2004). Second, as most of the patents purchased will enter the public domain so that the innovation can be produced and marketed at a competitive price, the deadweight losses due to inefficient monopoly pricing associated with patents will be eliminated. Kremer (1998) points out that the pharmaceutical sector would be a natural area to try the buyout scheme. When purchased patents are put in the public domain, pharmaceutical markets are likely to be relatively competitive, as compared to a patent-induced monopoly situation with large monopoly mark-ups. Moreover, considerable information about medical products is gathered during the patent approval procedure of a new medicine, eg., through the European Medicines Agency (EMA) in the EU or the Food and Drug Administration (FDA) in the US. Auction

participants could therefore use this information to make informed bids (Kremer, 1998). Finally, monopoly profits would be eliminated in those cases in which the patent purchased is put in the public domain. Patent buyouts thus potentially mitigate the problem that the original innovator's competitors are typically inclined to invest in wasteful duplicative research for substitute products in order to capture profits from the innovator (Kremer, 1998).

2. Disadvantages of Patent Buyouts

The second-price auction, which is of crucial importance to the effective operation of patent buyouts, is potentially vulnerable to collusive behaviour between the patent holder and auction participants (Kremer, 1998). Patent holders have incentives to pay auction participants to make a bid that is higher than their true valuation of the patent to increase buyout prices (Kremer, 2001). Most of the purchased patents are placed in the public domain, whereas only a small fraction of them would actually be sold to the highest bidders. Hence, on the one hand, the bribed bidders would face a low probability of having to pay the patent authority. On the other hand, the patent holders would be confident in getting an inflated price. However, Kremer (1998) points out several mechanisms for preventing collusive behaviour, eg., sealed bids, punishing colluding firms, or rewards for whistleblowers, among others.

Second, patent buyouts could aggravate the problem of patent races and wasteful duplication of R&D expenses, as the price the patent authority would pay for a patent is typically higher than its private (commercial) value (Gallini and Scotchmer, 2002). Additionally, patent buyouts are a visible lump-sum payment and thus are likely to be less politically attractive than the less visible patent revenues spread out over a large number of doses (Maurer, 2005).

C. Orphan Drugs

Huntington's disease, ALS and Tourette syndrome are referred to as rare diseases or conditions, as only a very small number of people suffer from them. Under normal market conditions, the prospective market for medicines for these rare diseases is too small to stimulate research by the private pharmaceutical sector (Villa et al., 2009). Drugs to cure these rare diseases are commonly referred to as 'orphan drugs'. Unlike neglected infectious diseases, these diseases are not necessarily diseases of poverty; however, they share the same core problem. Under normal market conditions, the pharmaceutical sector would be reluctant to develop new medicines to treat and cure these diseases. The main difference is that additional incentive programs to stimulate research into rare diseases have already been successfully established in industrialised countries.[5] The US Orphan Drug Act provides R&D incentives in the form of regulatory assistance, eg., fast-track regulatory approval, research grants and tax credits for clinical testing and R&D expenses incurred in connection with research into diseases that affect less than 200,000 persons in the US (Kremer and Glennerster, 2004).

From the pharmaceutical industry's perspective, the most important feature of the Orphan Drug Act is arguably the promise of seven years of market exclusivity from the date of approval.[6] Market exclusivity is achieved by prohibiting a regulatory agency from granting marketing authorisation to any similar medicine in the same therapeutic area (Villa et al., 2009). Market exclusivity is, in addition, granted independent from the existence of patent protection. In the pharmaceutical sector, developers of the initial product often face a risk that 'me-too' drugs may capture

[5] The US Orphan Drug Act became effective in 1983. Japan and Australia established orphan drug systems based on the US model in 1993 and 1998, respectively. The European Regulation on Orphan Medicinal Products was approved by the European Parliament in 1999.
[6] Section 527 of the Orphan Drug Act, 21 U.S.C. 360cc(a). See also Kremer and Glennerster (2004).

much of the initial product's market. This risk can even discourage R&D into the initial product in the first place, although patent protection would be available. The Orphan Drug Act's provision guaranteeing market exclusivity to the initial product aims to discourage the development of 'me-too' drugs in particular (Kremer and Glennerster, 2004). It is widely seen as a crucially important element of the act to stimulate research into orphan drugs (Shulman and Manocchia, 1997).

Empirical evidence suggests that the combination of push mechanisms, such as grants or tax benefits, and pull mechanisms, such as the promise of market exclusivity as provided by the Orphan Drug Act, successfully stimulates the development of medicines for rare diseases (Lichtenberg and Waldfogel, 2003). As of 4 October 2007, the total number of orphan drugs approved since 1983 is 315 (Ricklin and Lambris, 2007). In contrast, fewer than 10 such medicinal products for rare diseases were marketed in the decade prior to the Orphan Drug Act (Berndt et al., 2007). As to the underinvestment in R&D for neglected infectious diseases, the Orphan Drug Act may serve as a successful and tested model of a combination of push incentives, such as tax credits and grants, and pull incentives, such as the promise of market exclusivity over a certain period (Lichtenberg and Waldfogel, 2003).

D. Advanced Purchase Commitments

Advanced purchase commitments (APCs) are *ex ante* commitments by national governments, international organisations or private foundations to purchase a certain quantity of a drug or vaccine that has yet to be invented at a certain price (Kremer and Glennerster, 2000). A government, for instance, could sign a contract to buy a prospective malaria vaccine suitable for use in low-income countries from a pharmaceutical company. The vaccine would be required to meet certain technical

criteria such as safety, efficacy and usability and pass a market-test regarding its suitability for use in low-income recipient countries (Kremer, 2001; Kremer and Glennerster, 2000). If the vaccine is successfully invented, the government would then make the vaccine available to countries in need at a price that is lower than the monopoly price (Kremer and Glennerster, 2004). The main purpose of an APC is to create a sufficiently large expected market for medicines for neglected infectious diseases so that pharmaceutical companies find an investment in R&D worthwhile. Berndt et al. (2007) have investigated how large a purchase commitment would need to be to give developers incentives comparable to product markets for diseases prevalent in rich countries. Their results suggest that a $3.1 billion commitment in the net present value of sales would be comparable to the value of the sales earned by an average of a sample of recently launched commercial products.

1. Advantages of Advanced Purchase Commitments

First, the most attractive features of a suitably designed APC are arguably that it reduces market uncertainty and increases the expected market for a desired drug or vaccine, as it specifies a guaranteed price and the quantity to be purchased in advance (Webber and Kremer, 2001).

Second, in contrast to push mechanisms, APCs reward successful research output rather than research input (Kremer and Glennerster, 2004). They are consequently less vulnerable to moral hazard problems than push programs. The developer of a malaria vaccine will only sell a certain quantity of a vaccine at a certain price if the vaccine is successfully developed, fulfils all technical criteria, and passes the market-test for suitability in low-income countries. His incentives to stray from the task are thus lower under an APC than under a push mechanism (Glennerster and Kremer, 2001).

Third, Kremer and Glennerster (2004) suppose that the sponsor is less than totally confident about the scientific prospects for the successful development of a malaria vaccine due to huge scientific challenges. On the one hand, a sponsor may not be inclined to provide direct push support to finance research into a malaria vaccine because he may not be willing to bear the risk of financing a project that eventually fails. On the other hand, he might be more willing to make an APC, even when scientific prospects for success are not entirely clear (Kremer and Glennerster, 2004).

Nevertheless, pharmaceutical companies supposedly have better information than sponsors or buyers about the feasibility of scientific research. Hence, under an APC, those pharmaceutical companies that find that the development of a malaria vaccine is scientifically feasible and commercially attractive will pursue research into the vaccine (Kremer and Glennerster, 2004). By creating incentives for pharmaceutical companies to follow those research strategies that they think will result in marketable pharmaceutical products, APCs imitate the R&D incentives a market typically provides (Webber and Kremer, 2001).

Fourth, suppose that the buyer of a vaccine or drug promoted through an APC makes the medicines available to consumers in least developed countries either for free or at a relatively low price. In this case, APCs would help to mitigate both of the central problems related to neglected infectious diseases: the underinvestment of R&D into those diseases and the lack of access to affordable drugs and vaccines in least developed countries (Kremer, 2002).

Fifth, an analysis of the costs and effectiveness of APCs conducted by Berndt et al. (2007) revealed that APCs can have a substantial stimulating effect on the R&D for a specific vaccine and still be cost-effective.

2. Disadvantages of Advanced Purchase Commitments

APCs are, like prizes, subject to a time-inconsistency problem (Kremer and Glennerster, 2004). Prior to the development of a desired drug or vaccine, buyers, such as governments or private foundations, have incentives to promise a guaranteed price that allows the innovating firm to cover its R&D costs at a given specified quantity. Innovators, however, remain in a position of considerable economic dependence because they have made large investments relying upon the purchase commitment of (typically) a single party on the demand side. In this situation, buyers can make use of a vast bargaining power. They have incentives to renege on their promise *ex post* when the R&D investment is sunk, to obtain the drug or vaccine at the lowest possible price (Webber and Kremer, 2001). Potential innovators will anticipate this situation and be reluctant to invest in risky and expensive R&D in the first place, or they may charge a premium before they take part in this type of a pull program (Maurer, 2005). Consequently, to prevent a hold-up situation, an explicit long-term commitment with clear, judicially enforceable rules is of crucial importance. One way to address this is the establishment of an adjudication committee independent from the sponsor or buyer (Kremer, 2002). The main purpose of this committee would be to evaluate whether a vaccine or drug promoted through a purchase commitment satisfies the eligibility requirements (Kremer and Glennerster, 2004).

Another disadvantage of APCs stems from the fact that sponsors must specify the desired innovation to be promoted through the purchase commitment beforehand (Villa et al., 2009). APCs may therefore be an inappropriate mechanism to promote basic research, as it is typically difficult to specify the output of basic research and appropriate eligibility requirements in advance (Kremer and Glennerster, 2004). In contrast to basic research, it is easier to specify what is meant by an efficacious and

safe drug or vaccine. Institutions, such as the EMA or the FDA, are already specialised in making such specifications (Kremer and Glennerster, 2004). In addition, similar to the problem of setting an adequate reward for prizes, it may be difficult to set an adequate guaranteed purchasing price in advance to spur research because expected R&D expenses are variable and difficult to estimate (DiMasi et al., 2003). Thus, Maurer (2005) suggests that APCs could result in either underpayment or overpayment. On the one hand, given a certain quantity, if the buyer sets the guaranteed price too low, the APC fails to stimulate R&D. On the other hand, if the buyer sets the price for a certain quantity too high, the additional benefit may cause a suboptimally high level of research efforts by competing firms.

Finally, like patent buyouts and prizes, APCs might be less politically attractive than patents because revenues spread out over a large number of doses are less noticed by voters than (government) payments (Maurer, 2005).

E. Conclusion to Pull Programs

The core benefit of pull programs is that the sponsors of the program only have to pay when an innovation is successfully developed (Kremer and Glennerster, 2004). By linking payments to successful development, pull programs decrease shirking of researchers and increase their incentives to concentrate their research efforts on marketable innovations (Kremer, 2002). The US Orphan Drug Act provides a tested benchmark of how research into diseases with a small expected market can be stimulated successfully through a combination of push and pull mechanisms. As for neglected infectious diseases, pull programs such as the advanced vaccine purchase commitment brought forward by Kremer and Glennerster (2000) have the potential to increase the incentives for pharmaceutical companies to develop medicines for neglected diseases through a market-oriented and transparent approach. The main

difficulty with targeted prizes is the advanced specification of the desired innovation (Glennerster and Kremer, 2001). However, prizes are less vulnerable to moral hazard and adverse selection problems than push mechanisms and therefore appear to be an appropriate incentive mechanism to promote basic research where monitoring is typically difficult. Prize fund mechanisms such as the HIF appear to be adequate to promote research into neglected infectious diseases, as they link reward payments to both the successful development of effective medicines and the incremental health impact of registered medicines (Hollis and Pogge, 2008). Registered pharmaceutical companies would have significant interest in selling effective medicines at low prices and mitigating the 'last mile problem'.

Nonetheless, patent buyouts also work in cases where the desired innovation cannot be specified in advance (Kremer, 1998). APCs and patent buyouts are market-based and link payments to the successful development of a desired product. A crucially important feature of both is the potential for the establishment of access to affordable medicines in low-income countries (Kremer and Glennerster, 2004). In a patent buyout scheme, purchased patents are normally placed in the public domain so that innovations can be produced and marketed at a competitive price, which is typically lower than the monopoly price (Kremer, 1998). Patent holders are likely to benefit from participating in the buyout mechanism, as they would enjoy a price that is typically significantly higher than the private value of the patent. Buyers of vaccines or drugs for neglected infectious diseases promoted through an APC would typically make the medicines available to patients in least developed countries either for free or for a low co-payment (Kremer and Glennerster, 2004). Nevertheless, it is of crucial importance that the advanced commitment is legally binding and enforceable to mitigate the hold-up problem once the innovation is made (Hollis,

2007).[7] As for patent buyouts, the auction mechanism used to determine the buyout price in a buyout scheme must be safeguarded against collusive behaviour between auction participants and the patent holder (Kremer, 1998).

However, there are also some practical differences between APCs and patent buyouts. First, APCs only work if the sponsor determines specific details of the desired innovation beforehand, whereas the buyout scheme requires no such determination (Kremer, 2002). Second, APCs are less vulnerable to problems associated with the discovery of harmful side effects after the development and regulatory approval of a medicinal product (Kremer and Glennerster, 2004). For instance, suppose that unacceptable harmful side effects occur subsequent to a patent buyout. In this case, Kremer and Glennerster (2004) argue that the patent authority may have to engage in a potentially wasteful fight with the innovators to recover the buyout money. In contrast to patent buyouts, a sponsor participating in an APC could relatively easily suspend the purchase of a drug or vaccine as soon as unacceptable harmful side effects are discovered (Kremer and Glennerster, 2004). Additionally, APCs are likely to generate less public resentment than patent buyouts because the purchase payments are successively spread out over a large number of doses (Maurer, 2005). For pharmaceutical products such as vaccines that could relatively easily be specified in advance by governmental agencies, an APC is likely to be as effective as patent buyouts in terms of stimulating research into medicines for neglected diseases (Kremer, 2001). APCs are, however, likely to be politically more attractive than patent buyouts and less vulnerable to collusive behaviour (Maurer, 2005).

From a comparison of the mandatory prize mechanism (applied in the Medical Innovation Prize Act) and APCs, Love and Hubbard (2007) conclude that APCs

[7] See also Layne-Farrar and Schmidt (2010) for a thorough analysis of the hold-up problem in the context of complementary patents.

require a huge degree of *ex ante* specification before financial support is provided, whereas the prize fund model offers flexibility by linking the reward solely to an *ex post* assessment of health results for the patients. Additionally, the evaluation of therapeutic benefits after the development of a therapy stimulated by optional reward systems, such as the HIF, may be less difficult than the specification of pharmacological characteristics beforehand, as is required in APCs (Kremer and Glennerster, 2004). Nevertheless, Hollis and Pogge (2008, p. 7) point out that the HIF is a comprehensive approach applying to 'all kinds of pharmaceutical products that improve human health and not just a particular specified vaccine for a neglected disease'. By linking rewards to actual health benefits rather than 'subsidizing sales', the HIF system fosters innovation and improves accessibility in a comprehensive way to improve global health. Kremer and Williams (2010) appear to be generally open-minded towards the prize mechanisms, but they favour a voluntary mechanism, such as the HIF, as opposed to Love and Hubbard's mandatory approach. By implementing a mandatory prize fund mechanism, the pharmaceutical industry's expected return on investment could be reduced, as no adequate alternative incentive mechanism to reward R&D would substitute for this mechanism if it failed (Kremer and Williams, 2010). Experimenting with voluntary mechanisms would lower this risk. It therefore seems advisable to first experiment with voluntary mechanisms in order to learn more about the most effective designs and also, arguably, to draw conclusions as to the effective designs for mandatory mechanisms.

IV. Conclusion and Policy Recommendations

Empirical evidence suggests that the incentives from patents in the developing world are not sufficient to promote research into neglected infectious diseases that is adequate to the social and economic costs of those diseases. We have, therefore,

analysed several push and pull incentive mechanisms proposed in the literature, with respect to the question of whether they mitigate the problem of underinvestment in R&D for neglected infectious diseases.

Push mechanisms, such as research grants and publicly financed research institutions, appear to be more suitable than pull mechanisms, such as APCs, to promote basic research. Absent any subsidisation of research inputs, private incentives to invest in basic research are suboptimal because basic innovations may neither be patentable nor commercially exploitable. The results of basic research are typically not specifiable in advance so that basic research usually cannot be stimulated through an APC (Kremer and Glennerster, 2004). Nevertheless, basic research discoveries provide the basis for subsequent applied research that is patentable and commercially exploitable (Maurer, 2005). Push mechanisms are, however, vulnerable to moral hazard and adverse selection problems, due to information asymmetries between researchers and research administrators (Webber and Kremer, 2001).

As to prize fund mechanisms, a voluntary mechanism is preferable to the more radical mandatory approach. We recommend experimentation with voluntary mechanisms that focus on a specific product, eg. X Prizes, which could then be improved and applied to a broader range of settings if they succeed. Experimentation and trial and error with voluntary mechanisms may also help to refine proposals for mandatory programs such as the Medical Innovation Prize Fund. As to patent buyouts, the buyout price would typically be at least twice as large as the private value of the patent and thus potentially increase R&D incentives (Kremer, 1998). Purchased patents would typically be placed in the public domain so that an innovation could be produced and marketed at a competitive price. This would

mitigate the problem of access to affordable medicines when manufacturers of pharmaceuticals charge monopoly prices.

Legally binding and enforceable APCs are also likely to promote pharmaceutical research into neglected infectious diseases through a transparent, market-oriented approach (Kremer, 2002). Sponsors involved in an APC would typically provide consumers in low-income countries with medicines at zero cost or for modest co-payment. However, APCs appear to be more appropriate than patent buyouts, as they are likely to be at least as effective as patent buyouts in terms of stimulating research but more politically appealing and less vulnerable to collusive behaviour (Kremer and Glennerster, 2004).

In conclusion, a combination of push and pull programs appears to be an appropriate strategy for stimulating research into neglected infectious diseases. On the one hand, early-stage (basic) research should be supported through push mechanisms, eg. research grants or publicly financed research institutions. On the other hand, pull mechanisms, such as legally binding and enforceable purchase commitments or prize fund mechanisms, have the potential to stimulate research into neglected infectious diseases and help solve the problem that consumers in low-income countries lack affordable access to essential medicines.

V. References

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