Comparative advantages of push and pull incentives for technology development: lessons for neglected disease technology development

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Only 10% of the total R&D spend worldwide is devoted to developing country needs, where 90% of the world’s population lives[2]. Not surprisingly then, only 16 of the 1400 (or 1%) of new medicines developed between 1975 and 1999 were for these neglected diseases[3].

However, this picture has begun to change during the past decade. Incentives for the development of neglected disease technologies have emerged, which can be categorized into “push” and “pull” categories. “Push” funding policies aim to incentivize industry via reducing industry’s costs during the research and development stages, whereas “pull” mechanisms create incentives for private sector engagement by creating viable market demand. Push mechanisms essentially pay for “effort” on the part of researchers, by underwriting the cost of that effort, while pull mechanisms pay for “results”.

In the “push” category, donors have begun supporting product development partnerships (PDPs) with direct research grants aimed at developing neglected disease technologies. And on the “pull” side, there have been large increases in development assistance for health, from US$ 5.6 billion in 1990 to US$ 21.8 billion in 2007[4]. Much of this has been routed through global health institutions such as the Global Alliance for Vaccines and Immunisation (GAVI), the Global Fund for AIDS, TB and Malaria, and UNITAID. It is estimated that about 40% of Global Fund grants are used for health commodity purchase and a much higher percentage of GAVI and UNITAID funds are directed towards commodity purchase. These funds send “pull” signals to industry that a credible market exists, though the strength of these signals is limited because the financial amount is not pre-defined well in advance, donors are not legally obligated to honour their funding commitments, and the products, volumes and purchase price are not committed in advance. Despite these shortcomings as a pull mechanism, the sheer size of these funds lends credibility to these markets for neglected disease and consequently, the number and diversity of suppliers targeting the corresponding product sectors has increased. An even stronger pull signal was sent when donors committed to the first Advanced Market Commitment (AMC), in which legally binding financial commitments to support a market of a pre-agreed total market value were made. Firms who develop a product meeting the pre-defined specification can tap into the AMC “market” as soon as the product is ordered by developing countries.

With the emergence of new push and pull mechanisms for neglected disease technology development during the past decade, stakeholders have been concerned about how pull and push relate – what evidence is there about how they might work together? Which is a more cost-effective way to incentivize research and development (R&D) on neglected disease technologies?

The respective roles of push and pull in bringing technologies to market

The evidence base for answering these questions is in fact limited and the “science” on the study of the entire spectrum of such incentive mechanisms is embryonic. Nonetheless, a few trends emerge upon review of push and pull incentives across sectors.

The use of prizes and grants as pull mechanisms was widespread in science historically[5]. For example, during the 19th century, prizes were offered for the study of yellow fever, improving the supply of quinine, and a cure for Asiatic cholera. Tuberculosis was the subject of prizes in France, the UK and the US. More recently, the XPrize Foundation and Innocentive are examples of organizations that offer rewards for inventions or solutions to specific problems in a number of scientific areas.

A key advantage of pull mechanisms is that the funder can draw on the expertise of a large and diffuse set of researchers, rather than identifying and funding a handful with the greatest potential. This advantage is especially important in cases where knowledge is spread throughout the world or experts are hard to identify. Brunt et al found that prizes offered by the Royal Agricultural Society of England increased

the number of inventors (competition) and the quality of their inventions[6]. Pull mechanisms of this sort may also induce competitive racing, with multiple parties vying for a prize. In theory, this may speed the rate of innovation, though it comes at a cost: racing may involve wasteful duplication of resources and effort, and racing does not promote the sharing of ideas, which may be vital in some areas of science. Finkelstein tested this theory empirically[7]. Examining the effect of policies that had the effect of pull mechanisms on vaccine markets in the US, she found that the expansion in market size and reduced liability induced innovation in the diseases affected by these policies, but noted that much of the innovation was socially wasteful business stealing and had little effect in early stages of vaccine development.

In many of the historical examples of push and pull across sectors, we find both push and pull working together synergistically. For example, about half of pharmaceutical R&D funding is provided by governments (push) through institutions such as the US National Institutes of Health and the UK Medical Research Council. The other half is provided by the pharmaceutical companies, with the expectation to recoup this investment through eventual sale (pull) in wealthy markets. The Orphan Drug Act in the United States also included both types of mechanisms (using R&D tax credits to push and extended market exclusivity to pull) in an effort to spur development of treatments for diseases that affect a small number of patients. Lichtenberg and Waldfogel showed that the Act appears to have induced a significant number of new drugs for orphan diseases, but it is impossible to identify the separate effects of the push and pull components[8].

The development of the meningitis C vaccine in UK provides another example of push and pull working together. When officials in the UK Department of Health recognized a growing public health problem of meningococcal disease, they announced that a tender would be issued for a meningitis conjugate vaccine. Push support was offered via clinical trial support, and fast-track regulatory support was offered as well. Although a vaccine for meningitis C was only in the early stages of development at the time of the 1996 announcement of these initiatives, three companies were able to respond to the tender by 1999. The combination of clinical trial support, accelerated approval (push) and guaranteed purchase (pull) brought forward the development of the vaccine[9].

Within the neglected disease sector

As experience with push and pull in the neglected disease sector is relatively new, there is little empirical evidence to demonstrate the impact of each mechanism. We can draw on theory when anticipating differences in response according to technology type, stage within the development pipeline, and firm type. However, there will still be micro-level differences in response according to each individual firm's strategic positioning, goals and portfolio opportunities.

The principal-agent model of economics suggests that pull mechanisms are superior when it is easy to specify the desired outcome, when agents are not capital constrained, and when the principal is risk-averse. In contrast, push mechanisms are expected to be superior when effort is easy to monitor and measure, and when the principle has a higher tolerance for risk. The problem is that PDP effort is not easily monitored; large information asymmetries exist between donors – usually not disease or drug development experts – and the PDPs. This makes the choice of which PDP to fund, and monitoring that PDP's use of the funds, more challenging and transaction-intensive. Information asymmetries can also exist between the PDP management and the firms, academics and laboratories with which they contract for expertise and drug development inputs, resulting in similar monitoring challenges. Further, donors who are less comfortable with risk, due to taxpayer accountability for instance, may be less comfortable with funding PDP push.

But there are potential problems with relying solely on "pull" mechanisms as well. Many of the organizations and firms from whom innovation might be expected in the neglected disease field – such as biotechs – may need push funding in order to access eventual pull funding. Being more capital-constrained than big pharmaceutical companies, biotechs do not typically take candidates to market; more often, they sell their candidates to big pharmaceutical companies before expensive clinical trials, in order to monetise their investment earlier in the process. We would expect this "normal pharmaceutical market" dynamic to be accentuated in the neglected disease field, where the eventual market is all the more insecure. Research from Bioventures for Global Health[10], which relied on consultations with industry, indeed concluded that the main respondents to AMCs would be large pharmaceutical companies.

However, we know that small organizations, including biotechs, do respond well to push incentives in neglected disease markets[11]. Certainly some small biotech firms with good financial connections and the right expertise might respond to pull incentives alone, but participation would be more assured if pull were accompanied by push incentives.

Within the R&D pipeline, the effect of push and pull will depend to some degree on the stage of the technology's development. Theoretically, we would expect PDPs to have greatest impact at earlier stages, where the variety of actors involved may not have ready access to finance and the scientific risk outweighs thinking about market potential. Conversely, the strongest response to an AMC would be expected once companies can see their way clear through the science to a plausible product, i.e. as one is about to enter animal or especially human tests, as this is the point where market calculations start to weigh in more heavily than scientific risk. However, in reality push is proving to be effective and efficient throughout the development pipeline within the neglected disease sector, not just in the earliest stages[12]. In the later development stages, push has been useful for facilitating technology uptake and links with other public institutions, as illustrated by product introduction of the Drugs for Neglected Disease Initiative PDP and the work of the pneumococcal "accelerated development and introduction plan".

Higher development costs and longer investment lead times, combined with a concentrated purchasing base, exaggerates the unattractiveness of investment in vaccines, and especially for neglected disease vaccines

The type of technology under development will also affect the incentives required to have an impact on firms' investment decisions. Differences between vaccines and drugs are illustrative. Higher development costs and longer investment lead times, combined with a concentrated purchasing base, exaggerates the unattractiveness of investment in vaccines, and especially for neglected disease vaccines[13]. Consequently, the incentives required to motivate neglected disease vaccine developers are likely to be larger, and so it is not surprising that a vaccine has been chosen to serve as the technology pilot for the first AMC[14].

Comparing cost-effectiveness of push versus pull

Another angle from which to consider the question of optimal positioning of push and pull incentives is to ask the question from a cost-effectiveness perspective, i.e. given a finite amount of donor funds, how should these be allocated among push and pull incentives in order to achieve the greatest effect for the least cost?

Three types of costs

There are three types of relevant costs incurred in pharmaceutical R&D: out-of-pocket costs, costs of failure[15] and opportunity costs of capital[16]. In pharmaceutical R&D, these three different costs take on different levels of importance depending on the stage in the pipeline. Investments incurred earlier in the R&D pipeline are costlier from both a time-value-of-money and risk perspective, whereas out-of-pocket costs escalate as one advances into animal tests, then Phase I, then Phase II, and finally Phase III and the development of mass production methods.

Out-of-pocket costs

Kettler found that the cost of an NCE launched today can approach US$ 600 million[17], while a detailed review from DiMasi, Hansen and Grabowski estimates the cost of bringing a compound to market at US$ 802 million, including out-of-pocket costs, costs of failure and costs of capital[18].

Mahmoud et al hypothesize that neglected disease technology development costs might be lower than the US$ 802 million; this view has been cited elsewhere[19]. And recent studies by two drug PDPs provide evidence that the costs of their neglected disease drug development are much less than the DiMasi figures[20]. However, the cost savings for neglected disease research versus R&D for products aimed at wealthy markets would be realized whether the research were funded by push or pull. Out-of-pocket costs may be also be reduced when funded by push due to in-kind inputs from industry, although the total social cost of producing the product remains the same whether funded by private or public sector.

Cost of capital

Approximately half of the US$ 802 million estimate cited above arises from private industry's opportunity cost of capital, thus this cost parameter is a key one in the overall cost picture.

An important distinction between push and pull as incentives for technology development is who bears the risk. In push, donors fund R&D through grants and bear the development risk, whereas with pull, industry funds and bears the risk during development, with donors compensating industry upon successful development of the technology. Some have concluded that, when public sector carries the risk in “push”, overall costs are lower, reasoning that the public sector's cost of capital, or rate of return is lower[21]. This assumption arises from a simplistic observation that when governments borrow, the cost of government borrowing is usually low in comparison with the cost of private borrowing. But the government borrowing rate is low only because the national taxpayer provides the government with an implicit guarantee of its debt obligations. In addition, the opportunity cost of capital for public sector needs to reflect a social return in investment in schools, police etc, which elevates the required rate of return above solely the rate on borrowing[22].

In fact, the correct economic approach to calculating the opportunity cost of capital is to derive it from the project risk, and this comes from a comparison with investment in assets with similar risk profiles. Using this method, government and private industry should be applying the same discount rate, or opportunity cost of capital, to calculate the net present value of investment in neglected disease technology development, and consequently, there should be no difference between the cost of capital for public versus private sector when it comes to funding a specific project with a specific risk profile.

Failure rates/managing risk

Cost estimates are also affected by failure rates. With a portfolio management approach, candidates from multiple sources are compared to each other for their comparative advantage including cost, efficacy and potential for resistance. The role of the PDP's Expert Scientific Advisory Committee (ESAC) is to cull the weaker candidates, relative to other technologies intended for the same disease area[23]. The way this candidate “culling” is managed may differ between private pharmaceutical companies and PDPs. Private pharmaceutical companies usually manage a portfolio of

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products aimed at many different diseases, making choices based on potential profitability across a range of diseases[24], whereas PDPs have a more focused portfolio and may follow more leads in a particular field. Although theoretically the disease-niche portfolio approach of PDPs should reduce failure risk, PDPs are showing overall project failure rates similar to those of DiMasi[25].

Thus, there would appear to be no out-of-pocket, risk reduction or cost of capital cost advantage to either push or pull within the neglected disease sector. The key comparative issue consequently becomes whether one mechanism or the other, or some combination, is more effective at neglected disease technology development.

Which is more effective – paying for R&D through “push” grants or through “pull” payments?

We are just starting to see empirical data on how push funding channelled via PDPs performs, at least for drugs[26]. First, we know that there is increased drug R&D activity as a result of PDPs. Research also suggests that PDPs are proving superior in terms of time to market, cost-efficiency, health value and innovative level of the products, when compared with industry-alone neglected disease development in the absence of a pull incentive. Further research is needed in this area, although experience so far suggests that development of some technologies would be facilitated by the presence of push incentives, regardless of whether a pull incentive exists for the technology. ❑

Key messages

- In many of the historical examples of “push” and “pull” incentives for technology development across sectors, we find both push and pull working together synergistically, whereby push is used to attract partners to engage in the work during development, and pull is used to add credibility to the eventual market incentive for the successful candidate.
- Pull mechanisms may be a superior incentive mechanism when it is easy to specify the desired outcome, when agents are not capital constrained, and when the principal is risk-averse. Push mechanisms are expected to be superior when effort is easy to monitor and measure and when the principle has a higher tolerance for risk.
- There would appear to be no cost advantage to either push or pull within the neglected disease sector, so the choice between the two incentives, or how to combine them, should instead be based on their comparative R&D effectiveness for development of the technology in question.

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13. The vaccine market is smaller than the drug market and the primary vaccine customer is the public sector. On the cost and risk side, vaccines often require larger and more complex clinical trials and carry greater concern over liability. This is true of many preventative as well as “first in class” technologies, such as microbicides. Unlike drugs, vaccines also require a proprietary manufacturing facility to be built in order to make the product for Phase III trials.
14. Advance Market Commitments for Vaccines, http://www.vaccineamc.org/ (accessed 10 August 2009).
15. In the US, the FDA approves only one in five compounds that enter human clinical trials. The costs incurred for the four failed candidates must be included in the costs of bringing the fifth, successful candidate to market. These costs are calculated into the NPV model as a failure rate discount on the numerator.
16. The opportunity cost, i.e. time value of money, of not employing the cash in alternative uses, calculated into the NPV model as a decreasing (over time) rate in the denominator.
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21. See pages 35, 56, 57 and 79 of PRPP and page 141 Mahmoud et al. Product development priorities, disease control priorities project. The World Bank.
22. As explained by a principal architect of the AMC concept, “The financial cost of capital to the public sector understates the social cost of capital to the public sector, because it ignores the implicit cost to taxpayers of underwriting those investments. Taxpayers face a non-zero expected cost of having to bail out the government by paying higher taxes; and that expected cost is broadly equal to the difference between the market cost of capital for the public and private sectors. When appraising expenditure options, governments should (and do) take account of the overall social costs and benefits, including the social time preference rate, and not merely the financial costs reflected in market interest rates.” Owen Barder, Centre for Global Development, *Public funding, private funding and the cost of capital for R&D*, unpublished mimeo.
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26. As discussed elsewhere in this paper, drug R&D differs in several respects from vaccine R&D and therapeutic products also may differ from preventive.