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Developing new technologies to address neglected
diseases:

The role of Product Development Partnerships and
Advanced Market Commitments

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Acronyms

ACTs	Artemisinin-based combination therapy
ADIPs	Accelerated Development and Introduction Programme
AMC	Advanced Market Commitment
BMGF	Bill and Melinda Gates Foundation
BVGH	BIO Ventures for Global Health
CGD	Centre for Global Development
CIPHI	Commission for Intellectual Property, Innovation and Public Health
CRO	Contract Research Organisations
DALY	Disability-adjusted life years
DFID	Department for International Development
ESAC	Expert Scientific Advisory Committee
EU	European Union
GATB	Global Alliance for TB drug development
GAVI	Global Alliance for Vaccines and immunization
GFATM	Global Fund for AIDS, TB and malaria
GSK	Glaxo Smith-Kline
HIB	Haemophilus influenzae type b
IP	Intellectual Property
IPO	Initial Public Offering
LIC	Low Income Country
MMV	Medicines for Malaria Venture
MNCs	Multi-national companies
MVI	Malaria Vaccine Initiative
NCE	New Chemical Entity
NPV	Net Present Value
PDP	Product Development Partnership
PEPFAR	President's Emergency Plan for AIDS Relief
PPPs	Public-Private Partnership
PRPP	Pharmaceutical R&D Policy Project
R&D	Research and Development
U.K.	United Kingdom
U.S.	United States

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Background

This paper focuses on the complementary roles of Product Development Partnerships (PDPs)¹ and Advanced Market Commitments (AMCs), as mechanisms to incentivise industry towards the development of health technologies for neglected diseases. PDPs and AMCs are specific mechanisms under the more general categories of “push” and “pull” mechanisms, which seek to address the mismatch between need for health technologies to specifically meet developing country health needs and the commercial sector’s traditional lack of willingness to meet that need. The fact that only 16 of the 1,400 (or 1%) of new medicines developed between 1975 and 1999 were for neglected diseases is the result of this mismatch.

“Push” funding policies aim to incentivise industry via reducing industry’s costs during the research and development stages. Examples of push funding include direct research funding, tax breaks on R&D expenditure or fast track approvals. Here, we are focused only on the push mechanism of direct research funding, and specifically that which is channelled through PDPs in the neglected disease case. In contrast, “pull” mechanisms create incentives for private sector engagement by creating viable market demand – so pull is focused on the revenue side of the profit equation, rather than the cost side, like push.

An AMC would be a pull mechanism, aiming to create a market for future technologies of relevance to developing countries that is sufficiently large and credible to stimulate private investment into R&D and manufacturing capacity. The end-goal is to accelerate the introduction of technologies in developing countries. An AMC would require sponsors to make legally binding financial commitments to support a market of a pre-agreed value. The technology’s specifications – such as its efficacy, duration, target population and product presentation - are defined in advance, with the participation of developing country decision-makers. Companies participating in AMC agreements would commit to supply a successful technology at a pre-guaranteed price. Once the initial market value has been realised, and a reasonable return on investment made, companies would agree to ensure the supply of the technology to developing country markets at a pre-agreed lower long-term, the so-called ‘tail’ price. So the market price is guaranteed and the aggregate value or AMC sum is defined in advance, but the risk that remains is whether countries will order, and it is in this way that an AMC mimics how a normal market works. If the developing country does not order the product, the developer cannot start to draw down on the AMC value. This maintains the correct incentives for the product developer to bring to market the product specifications that the developing countries will order. It also ensures that, if a better product comes along, demand can shift to the new product, just as in a normal market.

AMCs are being considered only for vaccines at present. Vaccines may present specific characteristics that fit well with an AMC type incentive, although this is not to say that AMCs would not be effective for other technology types.

PDPs work by bringing together research partners from academia and the private pharmaceutical and biotechnology sector, along with public sector funding - acting as a sort of virtual non-profit pharmaceutical company. They leverage in technologies and in-kind contributions from the private sector and academia, and through channelling publicly provided direct research funding and brokering the pathway to market, they offset some of the costs and risks that prevent the private partner from engaging in the product’s development in the first place. PDPs are a relatively new

¹ Also called Product Development Public Private Partnerships, or PD PPPs

financing instrument for incentivising R&D, having been established during the past decade.

An important distinction between push and pull is who funds and who bears risk. In push, donors fund R&D through ex ante grants and bear the development risk, whilst in an AMC pull, industry would fund and bear the risk during development, with donors compensating industry ex post, upon successful development of the technology.

The June 2005 G8 Finance Ministers' conclusions on Development supported "scaling up support for vaccines and medicines research through the successful Public Private Partnership model". The July 2005 G8 Communiqué on Africa committed to "increasing direct investment and taking forward work on market incentives, through Public Private Partnerships (PPPs) and AMCs. At the December 2005 G7 meeting in London, Finance Ministers agreed to move forward in 2006 on a pilot Advance Market Commitment. GAVI and the World Bank were asked by G7 Deputies to provide a prioritised list of vaccine-preventable disease for the pilot, and to advise on how the AMC pilot should be developed. The technical and consultative work programme undertaken by GAVI and the World Bank included additional work to validate the AMC size and price per dose, as well as to estimate cost-effectiveness and other data. An advisory and expert committee were convened and consultations were held with developing country, industry and other key stakeholders to help develop the recommendation to the G7.

Most recently, some progress was made at the July St. Petersburg G8 Summit. The [G-8 statement on infectious diseases](#) lists the steps which individual countries committed to take. These include statements of support by Canada, Italy, UK, US and Russia for the launch of an AMC pilot in 2006. Canada and the UK have indicated support for an AMC pilot of the pneumococcal vaccine specifically, which both the US and Italy are also believed to support. Some of the G8 are also interested in exploring an AMC for malaria vaccines. The Canadians have pledged C\$100 million towards a pilot for the pneumococcal vaccine - the first specific offer of funds for an AMC. The next steps will be for those G8 countries who support a pilot AMC to establish a process in an existing institution - possibly GAVI - to take it forward, and for those countries to reach out to other possible donors, including countries outside the G8 and perhaps foundations, to participate in the program.

Consequent to these developments, DFID has required some analysis on the comparative advantages of push and AMC-type pull incentives and implications for how the two should be positioned along the R&D pipeline. This paper begins by highlighting some of the examples we do have of push and pull, across different sectors. However, it should be noted that there has been no systematic research on the effect of push and pull – only anecdotes and a few examples of more careful historical analysis, especially in the defence sector.

In the neglected disease sector, push of the PDP variety has only come into force in the past 6-8 years and pull of the strong incentive variety – ie AMCs – does not yet exist. Thus, we have limited empirical data to draw on.

This structure of this paper is centred around the following questions:

1. What historical examples do we have of "push" and "pull" effect on industry behaviour? (across industry examples)
2. What historical examples do we have of "push" and "pull" effect on pharmaceutical industry behaviour, outside as well as within the neglected disease sector?

3. Which differences between technologies are relevant to this push/pull discussion?
4. How might different types of investor - at least small biotechs versus big pharma - be expected to respond to the different incentives of PDP and AMC. What is the theory and what is the evidence?
5. How might push and pull incentives best fit within different stages in the R&D pipeline?
6. From a purely financial perspective, i.e. lowest net present value (NPV) to bring the product to market, which scenario is most efficient – paying for R&D through ex ante PDP grants, through ex post AMC payments or a combination of the two?
7. Taking two specific examples (pneumococcal vaccines and malaria vaccines), what push funds are needed, if AMCs are also present for these technologies?
8. What would be the likely economic consequences of overpaying, e.g. if push and pull funding duplicate each other and the company receives 'double payment' or if the AMC size is set too high?
 - a. Would it increase profits of pharma, or induce more investment/more players?
 - b. Even if you overpay, is it still a cost-effective investment?

1. Examples of “push” and “pull”

Across different sectors

The U.S. experience with integrated circuits provides a first example of push and pull.² A dozen push contracts were issued, initially failing to yield a successful technology. However, the mere fact that the Department of Defence had let the push contracts showed that there was interest in buying the technology. Two firms, Texas Instruments and Fairchild, believed that if they came up with the right invention, the Department of Defence would buy in substantial quantities (even though there were no guarantees). On a related point, each firm got strong patent rights on its unique features, which led to threats of patent litigation. To ensure that meeting its requirements would not be affected, the U.S. Department of Defence insisted that the companies form an open patent pool so that there would be no patent blocks.

The push itself did not result in the technology; rather it was the signal that the push sent (i.e. that there would be a pull forthcoming) that created the incentive. The lesson may be that push can be used to send signals about the product specification desired from a public health standpoint, but a pull might often be needed to enhance the value of the push and bring it to fruition.

A second example was the development of fissionable materials for the atomic bomb. The U.S. provided push funding to explore five different ways of doing it simultaneously, and this apparently was effective. Parallel paths of innovation, made possible by several different push contracts, was key to the eventual success in this example.

Another example is Bioshield I. Here, push funding via R&D tax breaks and a pull via “promise”³ to procure, did not bring about the desired industry investment. Based on industry feedback, Bioshield II legislation has more recently been proposed that would provide additional incentives including liability protection, expedited regulatory approvals, transferable patent extensions and stronger pull commitments. In the new legislation, the definition of applicability has been extended to include product development for infectious diseases of the developing world (not just countermeasures against bioweapons). Prospects for passage of this legislation are uncertain. However, if passed, it could test the impact of multiple interventions on the U.S. innovation system.⁴

These examples come from technology sectors where the eventual client would have the financial means to pay for the successful product, once developed. The defence sector also has a history of letting credible, long-term procurement contracts. We must therefore be cautious about the comparability and ability to extract meaningful lessons for neglected disease technology development. However, one obvious point emerges from the examples; that is *the usual presence of both push and pull incentives, whereby push is used to reduce costs and risks during development,*

² FM Scherer, example given during the UK-sponsored AMC Consultation meetings in November 2005:

³ The bioshield legislation included a \$6 billion procurement fund, which was not earmarked for specific products and had no volume or price commitment. The “needed products” were published and made clear via less direct routes and there were companies who responded in the expectation that they would earn a government contract for volumes sufficient to justify the R&D investments. One company developed a product that the pentagon had advocated for, and then was offered a procurement contract for less volume than would cover the cost of the manufacturing plant, let alone the R&D. This is an example of how a ‘pull’ policy, in the absence of volume commitments, can go wrong. (Hannah Kettler, personal communication)

⁴ Chad Gardner, personal communication

including brokering/ushering the technology through to market more quickly, and pull is used to add credibility to the eventual market incentive for the successful innovator.

In the pharmaceutical sector

As in the defence sector examples, push and pull within traditional pharmaceutical markets are usually acting synergistically, incentivising pharmaceutical firms to transfer basic research into useable products. On average, 44% of pharmaceutical R&D funding is provided by governments, via institutions such as the U.S. National Institutes of Health (NIH) and the U.K. Medical Research Council (MRC). Eight percent of the total funding is provided by non-profits and foundations and 48% of the total funding is provided by industry,⁵ with the expectation that it will be recouped through eventual sales in rich country markets (a natural 'pull').

The U.S. Orphan Drug Act of 1983 provides another specific example of push and pull working synergistically in the pharmaceutical sector. The Act provides a combination of pull - market exclusivity of 7 years – and push - tax breaks on R&D expenses and grant support - in order to stimulate R&D on products for diseases that are rare in the U.S. The E.U. adopted a similar act in 2000. The act has increased rare disease R&D; according to the FDA, more than 200 drugs and biological products for rare diseases have been brought to market since 1983, up from fewer than 10 in the previous decade.

The development of the Meningitis C vaccine in UK provides another example of push and pull working together. In 1994, officials in the U.K. Dept of Health noticed an increase in the notification and laboratory-confirmed cases of meningococcal disease. A vaccine for meningitis C was in the early stages of development at that time. In 1996, the UK 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. In 1999, the tender was issued, and three companies responded. The first to market was Wyeth in October 1999, with the two others coming to market in early 2000. Wyeth received a contract for 10 million doses, whilst Chiron was contracted to provide 5 million doses and Baxter 3 million doses. The combination of clinical trial support, and accelerated approval (push) and guaranteed purchase (pull) brought forward the development of the vaccine.⁶

Empirical evidence has shown that increasing the size of the pull affects pharmaceutical industry behaviour, at least in situations where some commercial market potential already exists to fuel the R&D pipeline. One study demonstrated that pharmaceutical R&D investment was strongly influenced by the size of the expected market; an increase of 1% in the potential market size for a new drug category led to a 4-6% increase in the number of new drugs in that category.⁷

In the neglected disease sector

Because there is lack of a viable commercial market, the private sector spends a miniscule amount of R&D time and money on diseases of the developing world. What is a little more surprising is the fact that public sector funding is also skewed

⁵ Page 4, Background Papers to Advanced Market Commitments for Vaccines: A new tool to fight against disease and poverty. Report to the G8 Finance Ministers, Giulio Tremonti, Dec 2, 2005. Download at:

<http://www.dt.tesoro.it/Aree-Docum/Relazioni-/Working-Pa/Background-papers-to-Advanced-Market.pdf#search=%22tremonti%20background%20papers%22>

⁶ Chapter 2, Making Markets for Vaccines, Ideas to Action. Centre for Global Development, Kremer, Barder, Levine, 2005.

⁷ Acemoglu D. and J. Linn. 2004. "Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry." Quarterly Journal of Economics 119 (3):1049-90.

away from neglected diseases. The UK's MRC spends just 6% of its total health R&D on research relevant to developing countries, and for the US NIH, it is only 4%. This is because public R&D funding is predominantly shaped by domestic priorities. Thus, the funding in developed countries has reflected domestic disease burden, and the result is that the global imbalance in publicly funded research in relation to the health needs of developing countries follows the same trends as the global imbalance in private funding driven by market forces.⁸

Although some neglected disease 'push' funding exists in the form of early research funded by NIH and the MRC, neglected disease 'push' funding is primarily channelled via PDPs, a model which has existed for around 6-8 years (with the exception of the International AIDS Vaccine Initiative, formed in 1996).

We are just starting to see empirical data on how push channelled via PDPs performs, at least for drugs⁹. First, we know that there is increased drug R&D activity as a result of PDPs. The Pharmaceutical R&D Policy Project (PRPP) identified 63 neglected disease drug projects underway at the end of 2004, three-quarters of which are being conducted by PDPs. At standard attrition rates, these projects would be expected to deliver 8 to 9 new neglected disease drugs within the next 5 years, which compares favourably with the 13 new drugs developed for neglected diseases in 25 year period from 1975 to 2000.¹⁰

Not only is there increased activity, but this activity has been shown to be resource efficient and well targeted to the needs of developing countries. Measurement of the various drug development approaches against metrics devised in the PRPP study showed that industry working alone and public groups working alone performed less well than PDPs for neglected disease drug development. Two of the performance metrics assessed, time to market and cost efficiency, are highlighted below.

As illustrated in the two figures below from the PRPP report, PDP drug development trajectories were significantly faster than public alone drug development times and they matched or exceeded industry standards for neglected disease research.

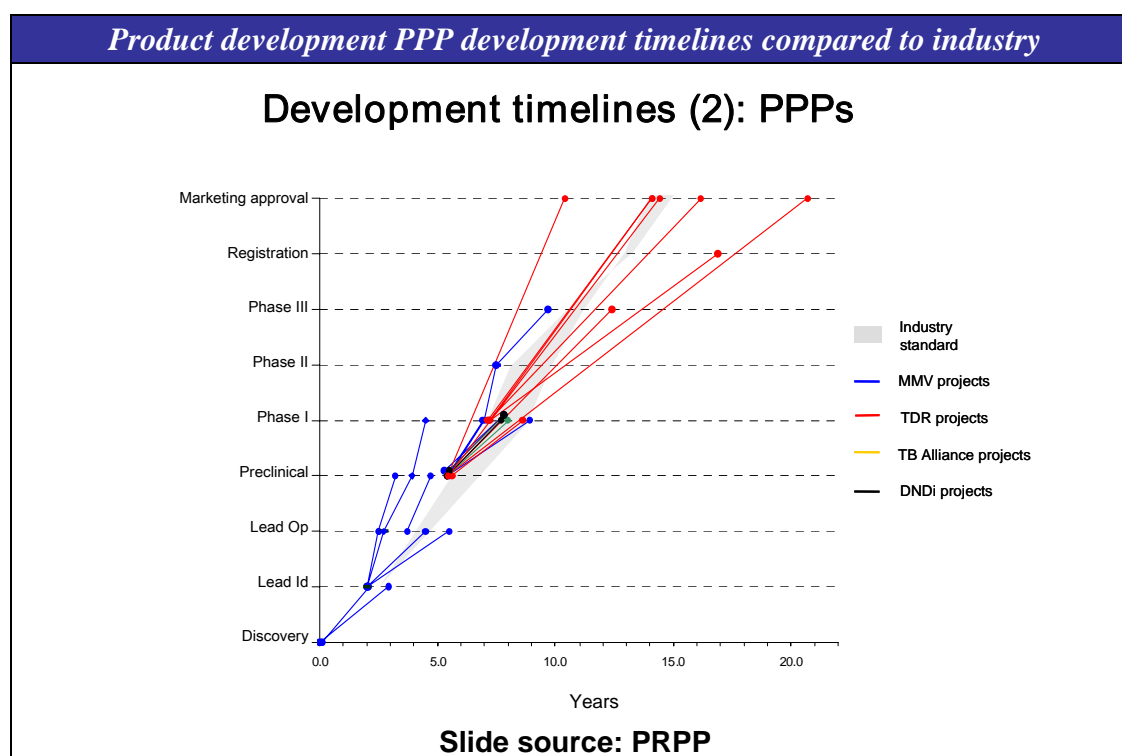
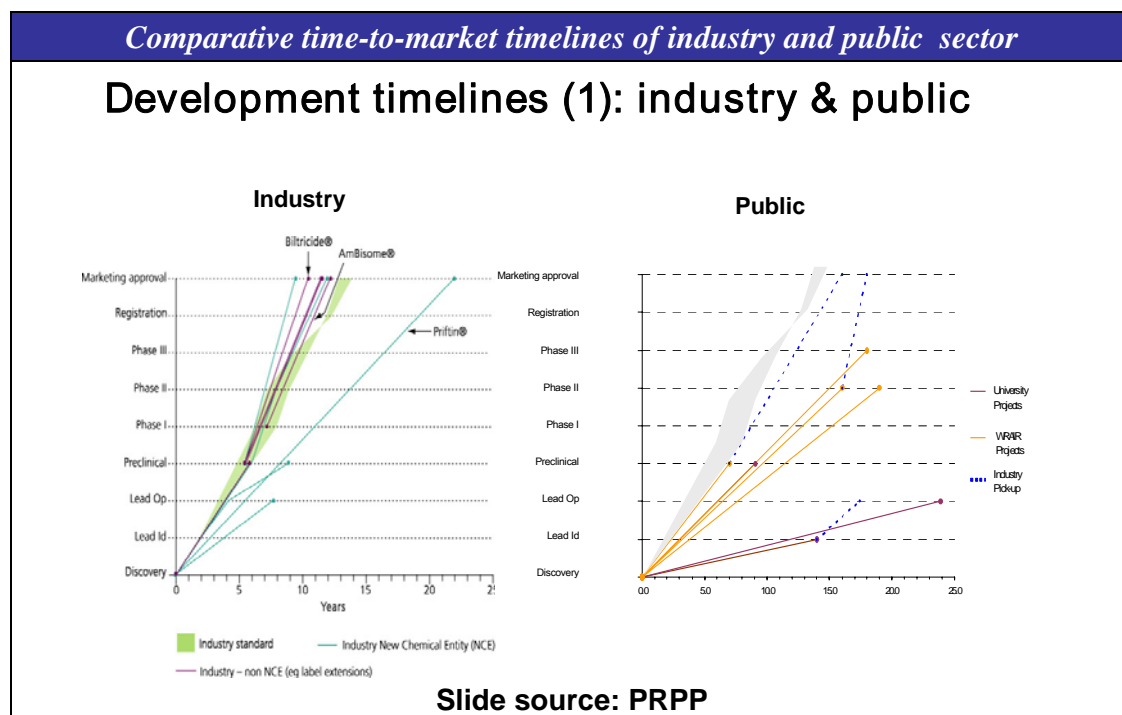
⁸ Page 59, Report of the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH). April 2006. <http://www.who.int/intellectualproperty/en/>

⁹ As discussed subsequently in this paper, drug R&D differs in several respects from vaccine R&D and therapeutic products also may differ from preventive

¹⁰ The New Landscape of Neglected Disease Drug Development, Moran et al.

Pharmaceutical R&D Policy Project (PRPP), September 2005.

<http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/documents/PRPP/TheNewLandscapeofNeglectedDiseaseDrugDevelopment.pdf>



In addition, the overall cost-efficiency of PDPs was judged to be superior to other approaches, partly due to their ability to leverage in-kind contributions from partners and partly due to the exclusion of capital costs¹¹. The total PDP drug development activity measured by PRPP from 2000 to 2004 was \$112 million including cost of failure for 40 projects. The industry cost for developing a new chemical drug entity for Western markets is substantially higher – estimated to be \$800 million including cost of capital and cost of failure in one study and \$400 million for out-of-pocket cost (including cost of failure but excluding cost of capital). The PRPP team concluded

¹¹ The validity of these arguments is discussed in further detail in Section 5.

that, even if the \$400 million is discounted for potential savings in conducting clinical trials in developing countries, it still seems that the PDP cost efficiency compares favourably. The table below, from the PRPP report, gives PDP development costs for selected projects.

Cost-efficiency of Product Development PPPs					
Project Name	Type of project	R&D costed	Indication	Cost * US \$million	Unquantified pro bono Input
ACTUAL COSTS					
FAS II	New chemical entity	Lead Identification	Malaria	2.7	Nil
PFT Inhibitors	New chemical entity	Lead Identification	Malaria	2.2	Some expert advice and data from BMS
Pyronaridine-artesunate	Fixed dose combination	Predclinical (+3 months Phase I)	Malaria	5.3	Shin Poong's Input (formulation chemistry)
PA-824	New chemical entity	Predclinical	Tuberculosis	4.5	Expert advice from ex-company employee
Synthetic Peroxide	New chemical entity	Discovery Lead Identification Lead optimisation Predclinical (+6 months Phase I)	Malaria	11.5	Expert advice from Roche
PROJECTED COSTS					
Pyronaridine-artesunate	Fixed dose combination	From predclinical up to registration	Malaria	15-20	
PA-824	New chemical entity	From predclinical up to end of phase III	Tuberculosis	86	

* We have used internal budgets, and added pro-rata'd indirect scientific costs.

Slide source: PRPP

On the pull side, we do not yet have examples of the strong pull that AMCs would provide, so we have no empirical data with which to analyse AMC impact. However, we do have examples of relatively weak pull, in the form of GAVI and/or GFATM funding. GAVI financing of new vaccines is for 5 years and GFATM commitments are also for 5 years, albeit with some discretion to cease funding mid-way, dependent on country-level governance and performance with the initial grant money. The problem with these forms of finance is that the countries do not have sufficient security with which to introduce new technologies that are both expensive and long term, and therefore technology uptake/demand remains uncertain. Demand uncertainty can result in supply insecurity, since industry typically produces neglected disease products to conservative estimates of all possible demand projections in order to conserve capital and avoid wastage. This dynamic is accentuated in the vaccines field; for example, lack of finance security has been identified as a prime reason for low uptake of the expensive, GAVI-financed *Haemophilus influenzae* Type B (Hib) vaccine. This is due to the longer vaccine manufacturing lead times of 3 – 5 years, hence longer funding commitments and demand certainty are especially valuable here to incentivise investment in additional capacity and bring forth new supplier entry. Artemisinin-combination therapy (ACT) for malaria treatment also requires long lead times between investment and product availability, hence the vicious cycle of finance insecurity, demand uncertainty and supply uncertainty is resulting in slower than expected uptake with this technology as well.¹²

¹² Reference: See Grace, C. and Grupper, M. "Aligning ACT Supply and Demand: Short and Long Term Options", July 2005.
http://www.dfidhealthrc.org/what_new/Aligning%20ACT%20paper.pdf

Besides the relatively insecure financing, the Hib and ACT examples also have in common the lack of a strategic process for approaching the market with aligned supply and demand. GAVI has recently initiated the ADIPs (Accelerated Development and Introduction Programmes) for the pneumococcal, rotavirus and Hib vaccines, in recognition of this need to work with countries and suppliers, matching up demand and supply, and resolving other bottlenecks faced as new technologies are introduced in these settings.¹³ However, donor financing - a fundamental link in avoiding the vicious cycle - is only available for Hib, not for the rotavirus and pneumococcal vaccines at present. And although AMCs would provide the secure, predictable financing, demand volume is not guaranteed, so a risk remains that the vicious cycle would not be resolved. As PDP products come closer to market, some PDPs are taking on these ADIP-like roles and functions, compiling data required and forging institutional links necessary to facilitate speedy uptake to market. To ensure speedy uptake of new technologies, it would seem that both ADIP-like activities as well as secure, predictable financing (e.g. in the form of AMCs) would be the ideal combination.

In summary, mounting evidence shows the effectiveness and efficiency of push funding in the neglected disease sector. We do not yet have examples of strong 'pull' of the AMC variety; relatively weak 'pull', in the form of GAVI and GFATM funding, has resulted in patchy uptake of new technologies. Recent experiences of new technology introduction suggest that ADIP-like (or downstream 'access' promoting) functions will be needed to facilitate speedy uptake, whether development is funded by push or pull. PDPs are in a strong position to take on these ADIP-like functions, and indeed many are already forging ahead with downstream 'access' promoting activities.

2. Which differences in technologies are relevant to this push/pull discussion?

The data discussed above on PDP effectiveness and efficiency relates to drug PDPs, whereas AMCs are being considered for vaccines in the first instance. Therefore, we must consider whether there are any vaccine-specific issues that would change the analysis or the conclusions on push/pull complementarity.

First of all, market characteristics differ between vaccines and drugs. At \$6.9 billion (2001 figures), the market size for vaccines is a small proportion of the medicines market. The primary vaccine customer is the public sector, whereas drug sales are primarily to private sector consumers, even when distributed through public health sector channels.

On the cost and risk side, vaccines often require larger and more complex clinical trials and carry greater concern over liability.¹⁴ Unlike drugs, vaccines also require the proprietary manufacturing facility to be built in order to make the product for Phase III trials. Given the high capital and regulatory requirements, experience-based knowledge barriers for the applied development and production scale-up of biologics, and single product, single plant nature of vaccine production, the result is limited market entry and an increasingly consolidated industry. Many vaccine companies have been acquired by large pharmaceutical firms or have exited the

¹³ See Grace, C. Pages 30-36 of "Advanced Market Commitments for vaccines: A new tool in the fight against disease and poverty", Report to G8 Finance Ministers <http://blogs.cgdev.org/globalhealth/archive/BCKPapers.doc>

¹⁴ This is true of many other preventative as well as 'first in class' technologies (e.g. microbicides) as well.

business. Today there are only 12 licensed vaccine manufacturers in the U.S., down from 26 in 1967, with only four producing most of the products.¹⁵

High development costs, concentration of commercialisation expertise in a few large companies and longer investment lead times imply the need for large commercial partners to bring a mass production vaccine to market. The bespoke nature of large scale manufacturing facilities (and relative difficulty in refitting for alternative production) also makes companies less likely to invest unless there is a reasonable prospect that vaccines will be purchased and used. The overall summary of these differences is an exaggerated unattractiveness of the market for vaccines, and especially for neglected disease vaccines. The findings on PDP drug efficiency and effectiveness are likely to only be positively exaggerated in a situation whereby the market attractiveness is reduced. And the incentives required to motivate such firms are likely to be larger – given larger costs and risks – than for non-biological pharmaceutical products.

3. Push and pull response by firm type

In this section, we consider the theory and the evidence for how different types of investor - at least small biotechs versus large pharmaceutical companies - might be expected to respond to the different incentives of PDP push and AMC pull. Certainly, different types of firms operate with different strategies and constraints, and if the R&D incentive is constructed with the goal to attract different types of firms, then it must be appropriately designed to account for these different environments. Understanding the varying challenges and opportunities different types of firm face can help to guide proper structure of the incentives and synergy between incentives.

In the past 30 years the biotech industry has grown into a major industry of over 4,000 companies, ranging from small private companies to large, public companies with revenues of over \$1 billion. The majority of biotechs have limited capital resources when compared with large pharmaceutical companies, being funded by new equity investment and partnership funding from pharmaceutical companies, especially for later stage products. There are exceptions - biotechs which have been successful in raising capital and generating internal resources, approaching significant size, e.g. Chiron. Most biotechs are also willing to tackle smaller markets versus large pharmaceutical multinationals (MNCs). Biotechs will go for projects in the range of several hundred million, whereas big pharma targets “blockbuster” drugs with annual market potentials of at least \$500 million, preferably over a \$1 billion. Biotechs may be able to use publicly-supported grants to initiate an R&D programme, but their funding often runs out as products approach clinical development. Public grant support is not sufficient to support clinical development costs.

In contrast, large pharma companies have the capital and capabilities to commercialise candidates, often sourced from universities, public research institutes and biotech companies, through to licensure. New products launched by multinational firms are thus the result of 1) internal R&D projects, 2) acquisitions from or of smaller companies, or 3) partnerships with smaller companies. As much as 60 percent of the clinical-stage pipeline in large pharma companies today originated in biotech companies, being in-licensed or acquired to augment big pharma’s internally-generated pipelines. (reference later). Thus, large pharmaceutical companies have become the investment engine for much of the biotech sector, providing milestone payments to the smaller company as part of the deal terms when there is a large market to address. The exceptions (that is, where biotechs may not need to partner

¹⁵ Milstien, Batson, Wertheimer, Vaccines and Drugs; Characteristics of their use to meet public health goals. March 2005.

with big pharma) are products that can be developed through smaller clinical development programmes and marketed with a comparatively small, specialist sales force. Vaccines do not meet these requirements, being likely to require more extensive clinical development and larger distribution forces. Therefore, biotechs would need a funding mechanism –either big pharma or venture capitalists – to carry them through this expensive process.

In conclusion, biotechs have become increasingly responsible for much of the innovative activity in this sector and their participation in neglected disease technology development would be beneficial. However, we would theoretically expect AMCs to attract the attention of biotechs, only to the degree that biotechs can see a pathway through to interim capital access from other sources.

Industry consultations undertaken by BIO Ventures for Global Health (BVGH)¹⁶ confirmed this theory. Discussions were held on the AMC concept with more than 50 companies and more than 150 senior executives from a cross-section of the biotech and pharmaceutical sectors, as well as selected investors. Biotech executives surveyed were acutely concerned with the need for cash during development and the fact that AMCs do not address this. Milestone payments would be needed for those operating at earlier stages of the pipeline. Early-stage investors (particularly venture capitalists) look for a 5 to 7 year timeframe in which to make their returns. Venture capitalists will only become involved in early stage research if they can see an exit strategy within this timeframe, via sale of the young company, IPO or sale of the candidate to larger pharma. Industry consultations revealed a concern that it might take too long for big pharma to signal their interest in an AMC vaccine candidate, thereby leaving biotechs cash strapped and consequently limiting the impact of an AMC on biotechs. Biotechs would therefore need a mechanism that could bridge the gap between early development and proof of concept, or the point when they can team with large pharma. BVGH concluded that ‘AMCs at a minimum must be attractive to large biopharma companies to spur the interest of smaller biotechs and investors.’ BVGH also suggested that full engagement of the biotech sector would require some form of early payment (whether through traditional ‘push’ mechanisms or through milestones (interim ‘pull’) as supplements to AMCs.¹⁷

The PRPP survey of small firms active in drug PDPs yielded complementary insights. Small companies preferred:

- public support to neglected disease work in the form of ongoing capital during the R&D process rather than at the end of the pipeline;
- alternatives to conducting further R&D in-house, including licensing preclinical compounds to PDPs in return for up-front and milestone payments; or with further development to be conducted by another company under the auspices of the PDP;
- regulatory reliefs and assistance, including fee reliefs and fast-track registration;

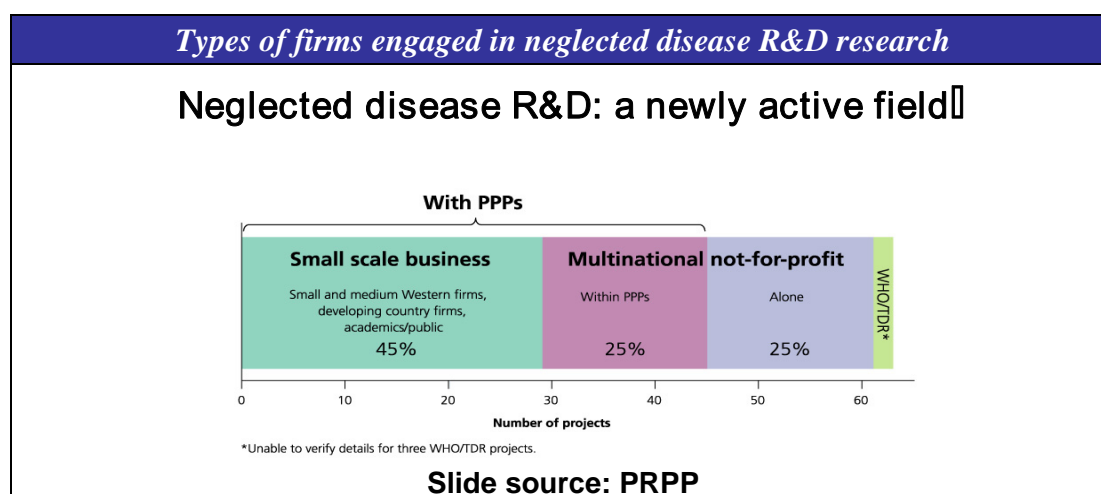
¹⁶Spun out of the Biotechnology Industry Organization (BIO), and supported by the Bill and Melinda Gates Foundation and the Rockefeller Foundation, the aim of BIO Ventures for Global Health is to harness the resources of the biotechnology industry to create new medicines for neglected diseases of the developing world.

¹⁷ Advanced Market Commitments to Stimulate Industry Investment in Global Health Product Development, BIO Ventures for Global Health, Feb 16, 2006.
http://www.bvgh.org/documents/BVGH_AMCReport_Complete.pdf

- greater assistance with market entry, including possible centralised purchasing and easier access to public markets.¹⁸

Thus, we would expect the ability to respond to push contracts to be relatively more equalized across big and small biopharmaceutical companies, with biotechs readily interested in taking these on, as long as they have the relevant expertise. And where specific expertise gaps exist, PDPs have been known to facilitate and link expertise across different partners, including with developing country manufacturers. Biotechs would also obviously see value in early-pipeline R&D funding, where their activity is concentrated, on an ongoing or milestone basis, as well as technical partnering support for the late-pipeline, especially help with implementation, regulatory assistance and consolidated procurement.

There is some evidence of how small firms respond to push incentives as well as niche pull incentives combined with push. According to the PRPP study and illustrated in the figure below, 45% of the 63 neglected disease drug projects being conducted as of December 2004, were being conducted in partnership with small scale businesses, including small and medium sized western firms, developing country firms, and academic or public institutions, whilst 50% came from pharmaceutical MNCs, either working alone or in combination with a PDP.¹⁹



In addition, 70% of orphan drug designations went to small firms in the U.S. in 2001, while this figure reached 85% in the EU during the period 2000-2004.²⁰ The orphan drug example shows a response to push and pull working synergistically whilst the PRPP example shows a response to push alone.

In conclusion, we have evidence that small firms, including biotechs, respond well to push incentives and to pull incentives when accompanied by push. Although there would be many possible responses, depending upon the risk-taking proclivities of the firm and their access to sources of finance, in general we can assume that most biotechs could not fully engage with AMC pull type funding in the absence of push funding. AMCs may provide a weak incentive effect on low-cost thinking and lab experimentation within biotechs, but most biotechs would not be able to take up the development and testing challenge past initial human Phase I tests, and would either need push funding or a large pharma partner. We can therefore conclude that generally, the main respondents to AMC challenges would be big pharma

¹⁸ Pages 26 & 27 of the PRPP study

¹⁹ Page 7 of the PRPP study

²⁰ Page 9 of the PRPP study

companies, though some would not respond and some small biotech firms with good financial connections and the right expertise might respond.

4. Push and pull response by different stages in the R&D pipeline

“Basic” science was traditionally viewed as the main activity of the public or university sector and “applied” science, i.e. developing this research into technologies for commercial application, the activity of the private sector. Pharmaceutical firms were also traditionally vertically integrated, performing research, development and manufacture entirely ‘in-house’. However, this traditional picture is becoming increasingly outmoded. Large pharmaceutical companies are doing more basic research, at least compared to the 1960s and 1970s. And although large pharmaceutical companies continue to maintain activities in research, development and manufacture, new actors have entered the picture. The biotechnology industry has emerged as a major contributor to R&D, especially early research. And contract research organisations (CROs) now conduct 60% of all clinical trials²¹, rendering obsolete the view that such activity is only the foray of big pharma companies. Manufacturing is being increasingly out-sourced as well, although this is not necessarily the case in the vaccine field, where the vaccine itself or the technology platform may have proprietary value for wealthy markets.

In the U.S., several economic and legal developments facilitated a transition in the institutional arrangements for pharmaceutical R&D. These include the *Diamond v. Chakrabarty* Supreme Court case which confirmed that generic inventions were patentable, and the Bayh-Dole Act, which permitted Universities to take out patents based on inventions arising from public funded research. From these policy changes emerged universities as major players in patenting and licensing in biomedical R&D.²²

The result of these changes is that large pharmaceutical companies are in a weaker position in the innovation system, with a proliferation of new actors having increasingly important roles. Large pharmaceutical companies as well as PDPs therefore function largely as integrators of inputs of different parts of a more diverse industry, capitalising on the opportunities each offers.

Although more players are performing R&D functions, the financing picture remains largely consistent. Where a market exists, a large share of the basic scientific research is funded by the public sector, while the private sector concentrates on financing clinical testing and development, primarily developing products and turning promising candidates into drugs. As evidence, a study by the National Science Foundation found that 18% of the U.S. Pharmaceutical industry’s spending on R&D is devoted to basic research, whilst the other 82% goes towards applied research and product development.²³

In the context of these changes, where would PDPs be most effective? Theoretically, PDPs would fit most appropriately 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 vaccine, i.e. as one is about to enter animal or especially

²¹ Bloom et al, Chapter 4: “Priorities for Global Research and Development Interventions”, page 6. *Disease Control Priorities in Developing Countries*, a publication of The Disease Control Priorities Project (DCPP).

²² Report of the Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH). April 2006. <http://www.who.int/intellectualproperty/en/>

²³ Making Markets for Vaccines: Ideas to Actions, Centre for Global Development. page 18. <http://www.cgdev.org/content/publications/detail/2869>

human tests, as this is the point where market calculations start to weigh in more heavily than scientific risk.

However, the pattern of actual PDP activity in the drug sector seems to be different from what we would theoretically expect. According to the drug PDPs surveyed in the PRPP study, 80 per cent of the current multinational neglected disease projects are now in early pipeline R&D, i.e. discovery of new drugs up to the point of identification of a robust development candidate. The PRPP team consequently concludes that, in this sector, private companies are re-focusing in-house activity from late-stage clinical development to early pipeline R&D, which requires a significantly smaller out-of-pocket investment.²⁴ Companies focus on the early stage research in the expectation that the expensive clinical trials phase, and even some of the early stage research, may be subsidized by a PDP or other public or non-profit funding.²⁵ Companies surveyed in the PRPP study also valued PDP partnering during later stages of the R&D process because of PDP skills in facilitating the delivery of neglected disease drugs. Few companies surveyed had the in-house experience to do this alone, with most needing to secure public input in one way or another. This public input may be needed for:

- technical, scientific and clinical neglected disease expertise;
- access to facilities that MNCs no longer have (e.g. parasite houses, developing country clinical trial sites);
- knowledge of developing country product profiles and markets, and experience in developing country clinical trials and dealing with developing country regulatory and health authorities;
- brokering “guarantees” of public demand, with public involvement seen by all the companies surveyed as essential for developing country implementation and use of new products.²⁶

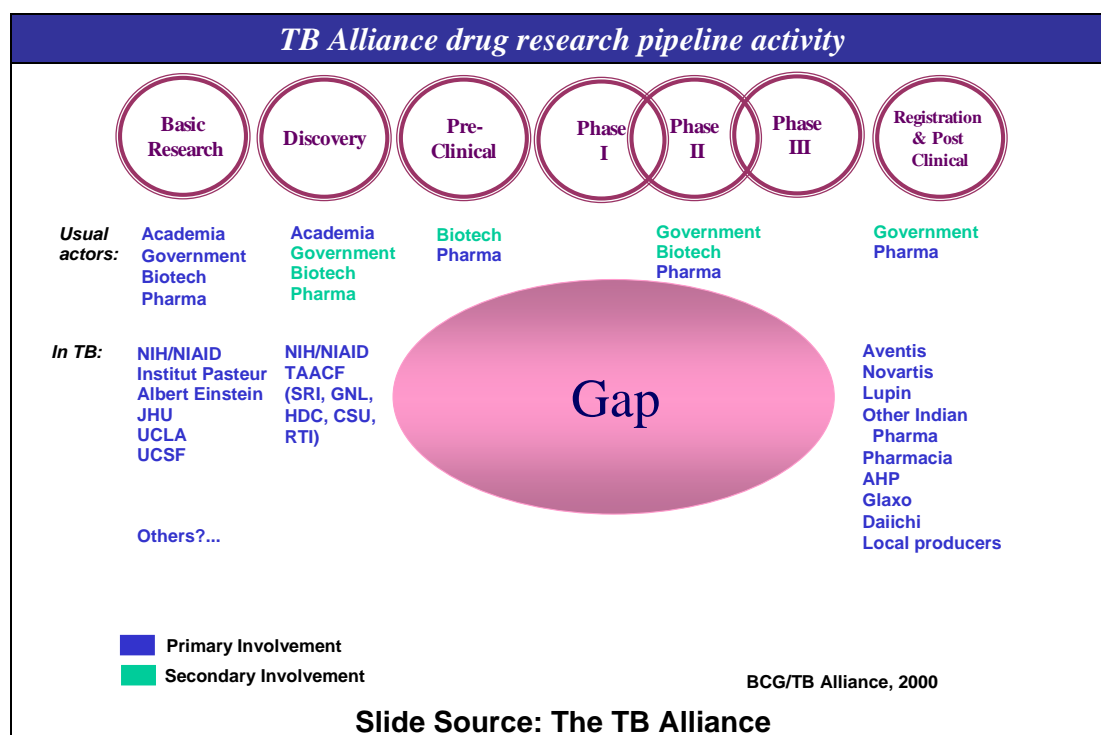
The TB Alliance supports the PRPP team’s conclusions of where the PDP’s can best contribute. The diagram below²⁷ shows the gap being filled by this drug PDP, which includes support of Phase III trials to licensure.

²⁴ Page 13 of PRPP study

²⁵ Page 89 of CIPIH Report

²⁶ Pages 13, 14, 17 of PRPP study

²⁷ Presented by Maria Freire, CEO of the TB Alliance at the UK cross-Whitehall TB meeting, June 7 2006



In the PRPP study, companies had varying preferences over when to partner with a PDP. GSK choose to partner from the earliest discovery stage, Sanofi-Aventis preferred to retain greater control over proprietary knowledge and partner only after Phase II, whilst Novartis was in-between. The approach on clinical trials was also mixed – some preferred to lead the clinical trials with the PDP only providing funding, whilst others envisioned co-conduct and still others would prefer the PDP to lead on trials, with the company providing only data management and regulatory support. All pharmaceutical MNCs surveyed planned to conduct manufacture and distribution of the final products, although some planned to do this in-house whilst others planned to license out to developing country generic firms.

The best position within the R&D pipeline for push and pull will depend to some degree on the specific technology and firms involved. It is usually assumed that push can have its greatest impact where there is high scientific risk. Section 5 looks at the quantitative aspects of this. On a more qualitative/organisational level, it is known to be difficult for scientists within a company to make a case that a vaccine that has stymied everyone else is possible to develop. Either a visionary leader or something to reduce the risk (like push funding) is needed. Once the scientific risk is reduced and the firm knows how to make a technology, the barriers become more market related. Even where there is a wealthy market to incentivise R&D of a technology suitable also for developing countries, push and/or pull funding is still needed in order to incentivise companies to adapt their formulations and/or test the product in developing country settings.

However, it also seems to be generally agreed that using PDPs for full-scale clinical trials should not be ruled out if highly promising candidates appear and no private entity is willing to take up the challenge.²⁸ In the late development stages, push can have effects that pull cannot have. Companies who have been active in global health (e.g. GSK, Sanofi) and who have done clinical trials in developing countries, may see the way to the pot of money, but other companies (those without ready access to

²⁸ Note that this is the case with microbicides and with HIV vaccines (at least for developing country trials).

capital markets or other forms of finance or those without previous global health experience in vaccines) may need a sherpa/broker to help them get to that pot of money. Push funding via PDPs can broker the way to licensure as well as help lay out the pathway to country decision making for uptake. For example, If GAVI had not already invested in the pneumoADIP and started to build up field sites to reduce the risk for companies, then the eventual AMC (if there is one) would have less impact or the impact would be more delayed. Even for the established global health players, they sometimes prefer a PDP to broker the conversations with institutions important to product uptake/introduction. The presence of PDPs, by virtue of their 'access' agreements with industry, can also allow influence over manufacturing strategies, pricing, distribution and marketing, whereas AMCs would only guarantee pricing.

5. Cost-efficiency and effectiveness perspective

Another angle from which to consider the question of optimal positioning of push and pull incentives is to ask the question from a purely financial perspective, i.e. given a finite amount of donor funds, how do you allocate these amongst push and pull incentives in order to achieve the greatest effect? If we assume that the public and private sector are equally efficient at managing the out-of-pocket costs incurred during the R&D process and managing failure risk - i.e. selecting and managing R&D investments in a way which makes those investments less risky, then the answer comes down to relative costs of capital, or more accurately, rates of return required between public and private sector funds. (As detailed in the Box below)

Financial cost-efficiency of push versus pull funding

Definitions:

F	Funds available for push funding (i.e. today)
y	Number of years before pull funding will be required
R_d	Donors' rate of return
R_i	Industry rate of return
n	Number of industry players
P	Probability of success expected by each firm (assuming all firms have similar capabilities)

Pull funding: If the donors reserve the funds **F** for later availability in **y** years, the funds available to donors for pull funding will be:

$$F(1+R_d)^y$$

Push funding: The number of industry players benefiting from push funding is **n**. An individual firm will receive:

$$\frac{F}{n}$$

The number of industry players who are expected to benefit from pull funding is **Pn**. If the funds will be made available in **y** years as pull financing, each firm would expect to receive the following in pull funding:

$$\frac{F(1+R_d)^y}{Pn}$$

However, the value of this expected financing today to a private firm should be discounted at its cost of capital (e.g. industry rate of return), and therefore it equals:

$$\frac{F(1+R_d)^y}{Pn(1+R_i)^y}$$

As an industry player expects to get this funding with probability **P**, the value of this funding to the industry player is:

$$\frac{F(1+R_d)^y}{n(1+R_i)^y}$$

So the question is, with a finite amount of donor funds, by which method of allocation does industry get the most value? In other words, which is greater:

$$\frac{F}{n} \quad \text{or} \quad \frac{F(1+R_d)^y}{n(1+R_i)^y}$$

Source: author's analysis

The above analysis shows that the question of which is more efficient - paying for R&D through ex ante PDP grants, or through ex post AMC payments - is mathematically equivalent to asking what is greater, R_i or R_d . If R_i is greater than R_d , then push funding is more financially efficient than pull. It is often assumed that industry's rate of return is higher than the public sector's,²⁹ however this is a mistaken assumption. It is true that the rate of interest paid in financial markets on public borrowing is lower than the interest rate paid by the private sector (i.e. the financial cost of capital is lower for public funds). However, 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."³⁰

So if R_i equals R_d , then there is no advantage to either push or pull, unless one or the other allows for better management of *risks* or achieves other (non cost of capital related) *cost* or *efficiency* gains. In fact it is commonly assumed that industry manages risks and costs better and is more effective, e.g. in getting quality products quickly to market. I will now go on to evaluate the validity of this assumption in relation to this sector.

"More effective" - Comparative development times

While it may be true that industry performs Phase III clinical trials quickly for products having robust markets, it is questionable whether the same is the case for neglected disease R&D. The PRPP data, described earlier, does not support the idea that industry's development times are quicker in the neglected disease sector. The qualitative unpicking in Section 4 of how push and pull fit within the neglected disease pipeline calls this assumption into question as well.

"More effective" – Comparative health value and innovative level

The PRPP study looked at the i) health value and ii) level of innovation of neglected disease products developed by industry alone, public groups working alone or public-private partnerships and the latter came out ahead on both counts. Of the 13 neglected disease products developed under the industry alone model, 12 had a low overall health value to developing country patients, whereas 3 of the 8 "partnered" products contributed significantly to reducing global health burdens.³¹ PDP-developed products³² have been responsible for:

- halving the global burden of onchocerciasis between 1990 and 2000 (ivermectin)
- schistosomiasis eradication in major parts of the world (praziquantel), and
- introduction of the first suitable new paediatric anti-malarial for decades (Coartem).

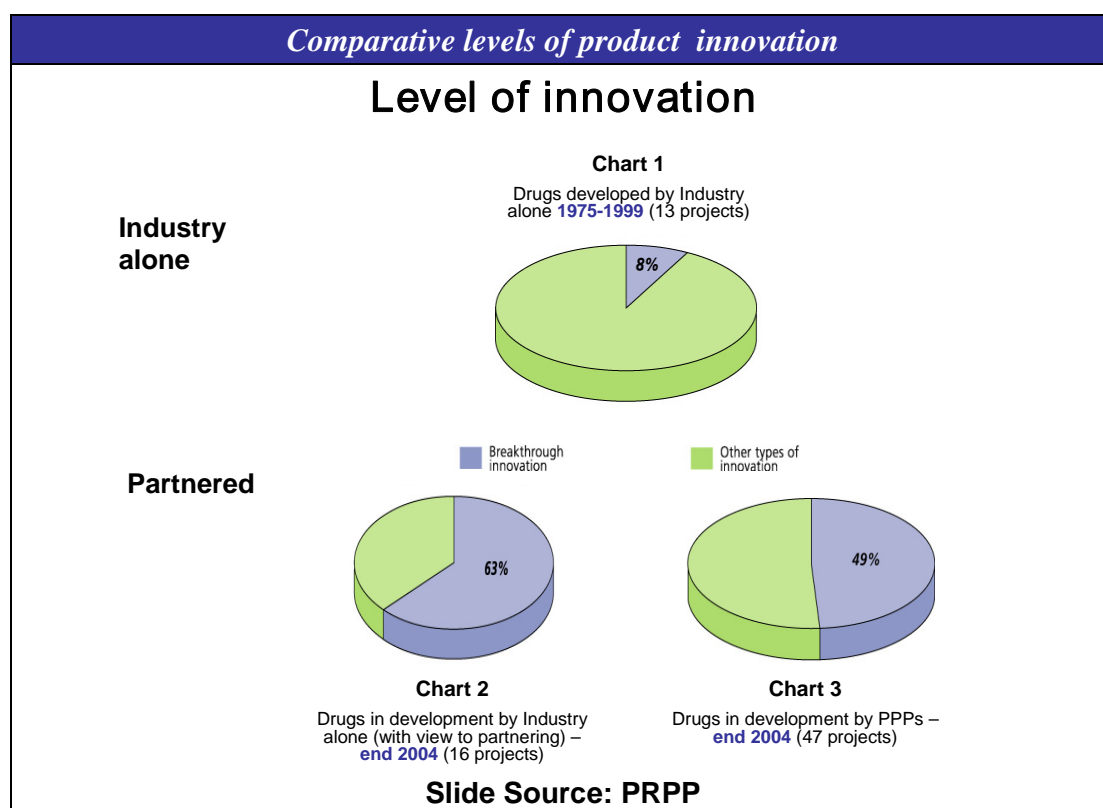
²⁹ See pages 35, 56, 57 and 79 of PRPP and page 141 of Mahmoud et al

³⁰ Owen Barder, Centre for Global Development, "Public funding, private funding and the cost of capital for R&D", unpublished mimeo

³¹ Which may be viewed as unsurprising since the objective of PDPs is to focus on high impact developing country diseases or those with limited existing therapeutic or preventive options

³² In combination with public-private-partnerships working on the product access/delivery end of the spectrum

Products developed through PDPs were also superior in terms of level of innovation. Whilst 49% of PDP products were what can be termed “breakthrough innovations”, this can be said of only 8% of the neglected disease products developed by industry alone.



“Less expensive” – Three types of comparative out-of-pocket costs

As far as comparative costs, there are three types of relevant costs incurred in pharmaceutical R&D: out-of-pocket costs, costs of failure³³ and opportunity costs of capital (already discussed in detail above).³⁴ 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. Thus, knowing how PDP push and AMC pull compare along these three cost parameters is important to determining where each best ‘fits’ from cost-reduction standpoint.

Out-of-pocket costs

Estimates of the average cost of development vary, and questions have been raised about the representativeness of the samples and therefore about the transferability of results. Kettler³⁵ found that the cost of an NCE launched today can approach \$600 million. The most detailed evidence on the cost of developing new drugs is from DiMasi, Hansen and Grabowski (2003), who estimate the cost of bringing a

³³ 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.

³⁴ 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.

³⁵ Kettler, HE. Updating the cost of a new chemical entity. London, Office of Health Economics, 1999.

compound to market at \$802 million in US dollars. This estimate is based on U.S. data of 10 major companies for 68 randomly selected compounds that came to market between 1990 and 2001, including primarily small molecule chemical entities (61) and only 1 vaccine. The cost includes out-of-pocket costs, costs of failure and costs of capital.

Mahmoud et al³⁶ hypothesize that LIC disease development costs might be lower than the \$802 million, due to a variety of factors.³⁷ The view that average costs of neglected disease product development would be lower than product development for 'normal' products has been cited elsewhere.³⁸ 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. GATB and MMV estimate the R&D out-of-pocket costs of approximately US\$150 million, or less than a quarter of DiMasi et al. Reasons for the difference include the fact that the GATB and MMV estimates include only out-of-pocket costs, with no allowance for the opportunity cost of capital. For comparison purposes, if we exclude costs of capital from the DiMasi figures, the total comes down to \$403 million. The remainder of the cost differential reflects two factors: i) fewer patients required for the trials (1,368 patients in GATB vs. 5,303 in the DiMasi et al study and ii) lower costs per patient of USD \$1,000 - \$3,000 for the GATB study in developing countries compared with USD average of \$23,500 per patient in the DiMasi et al study.³⁹ These savings could in principle apply to LIC drug development regardless of whether these drugs are developed by PDP or private sector alone.

Another factor contributing to the lower out of pocket costs reported by the MMV and GATB is that these PDPs benefit from in-kind contributions of personnel, technologies, and other resources supplied by their industry and academic partners. For example, PDPs can get access to industry libraries of commercial inhibitors (e.g. cysteine protease inhibitors for cancer/malaria), thereby 'piggybacking' public health work onto commercial work.⁴⁰ Synergies between the commercial and neglected disease portfolios may also sometimes be leveraged to reduce costs. MMV estimates these in-kind contributions as equivalent to its own incurred costs. If these in-kind costs are included, the full social cost for developing LIC drugs increases to US \$250-\$300 million per compound, or only 25-35% less than the DiMasi estimate of \$403 million. However, the actual budget cost to PDP funders is only US\$150 m to US \$178 m.

³⁶ Mahmoud, A., Danzon, P., Barton, J., and Mugerwa, R., "Product Development Priorities", Disease Control Priorities Project, The World Bank, Mahmoud, A., Danzon, P., Barton, J., and Mugerwa, R.

³⁷ Drugs for LICs may require fewer trials, fewer patents, or both per trial because of differences in drug types, trial objectives and different regulatory requirements. For example, drugs that are modifications of existing drugs will be able to draw on already available data. Drugs for LICs may also be tested for fewer indications, with less within-sample stratification and need to test for drug interactions. Clinical effects for parasitic or infectious diseases may also be more pronounced than for chronic diseases allowing smaller trial sizes. The cost of each trial may be lower due to lower costs of medical care personnel versus developed countries. Trial duration may be shortened because the target disease is acute rather than chronic. However, it cannot be assumed that it will always be cheaper to do a trial in LICs. For example, significant capacity building may be required to meet GLP/GCP standards or additional sites/countries required to guard against uncertainties (e.g. political instability).

³⁸ DiMasi, J.A., Hansen, R.W., Ronald, W. and Grabowski, Henry G. (2004): "Assessing Claims about the Cost of New Drug Development: A Critique of the Public Citizen and TB Alliance Reports". Available at: http://csdd.tufts.edu/documents/www/Doc_231_45_735.pdf

³⁹ Page 4 of Mahmoud et al

⁴⁰ Page 59 of PRPP

Failure rates/managing risk

Cost estimates are also affected by failure rates. GATB and MMV show overall project failure rates similar to those of DiMasi 2003. However, it should be noted that PDPs also reduce risk and cost through portfolio synergy effects. 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.⁴¹ The way this candidate 'culling' is managed may differ between private pharma and PDPs. Private pharmaceutical companies usually manage a portfolio of products aimed at many different diseases, making choices based on potential profitability across the entire disease range, whereas PDPs have a more focused portfolio and may follow more leads in a particular field..

Other advantages PDP push can bring⁴²

Other possible PDP benefits that could be factored in include:

- helping to design product features for developing country use from the outset, e.g. help with target product profiling to ensure that the product's presentation and other features are designed for maximum acceptability and feasibility in the developing country context
- ensuring access conditionalities are incorporated from the outset (e.g. price agreements or licensing arrangements that may allow a range of different manufacturing strategies to be implemented)
- allowing a portfolio approach within a disease area, which may provide greater opportunity for combination approaches to be developed and tested (as opposed to purely private sector development, whereby competing companies may own the relevant technologies needed for combinations)
- PDP possible greater commitment to building developing country research capacity
- PDP advocacy impact in raising the profile of neglected disease research

In conclusion, the R&D cost components to consider when comparing push and pull are comparative out-of-pocket costs, comparative failure rates and comparative cost of capital.

Comparative costs of capital are a key cost driver, which can double the total costs of conducting R&D. Many studies fail to properly account for the donor/public opportunity cost of capital, consequently claiming that privately financed R&D is more expensive than publicly financed R&D (the corollary being that AMCs would cost more than if the same research is funded via "push"/donor funds.) However, such a view contravenes basic economic principles. The private sector cost of capital should be included in the estimate of the necessary size of an AMC and the social cost of tying up public resources in R&D in the expectation of future benefits should be included in the costs of publicly funded research. In a proper comparison of the two, there is no significant difference in the cost of capital. Thus, the choice between paying for R&D through PDP grants or through AMC should instead be based on their comparative R&D effectiveness and efficiency in managing the other cost components as well as risk of failure.

Whilst out-of-pocket costs may be lower with neglected disease research versus R&D for products aimed at rich-country markets, this is due to the differences in inputs, not necessarily due to the greater skill PDPs have in managing costs versus

⁴¹ Page 59 of PRPP

⁴² Saul Walker, personal communication

industry. Out-of-pocket costs may also be reduced for a PDP who benefits from in-kind inputs from industry, although the total social cost of producing the product remains the same whether funded by private or public sector.

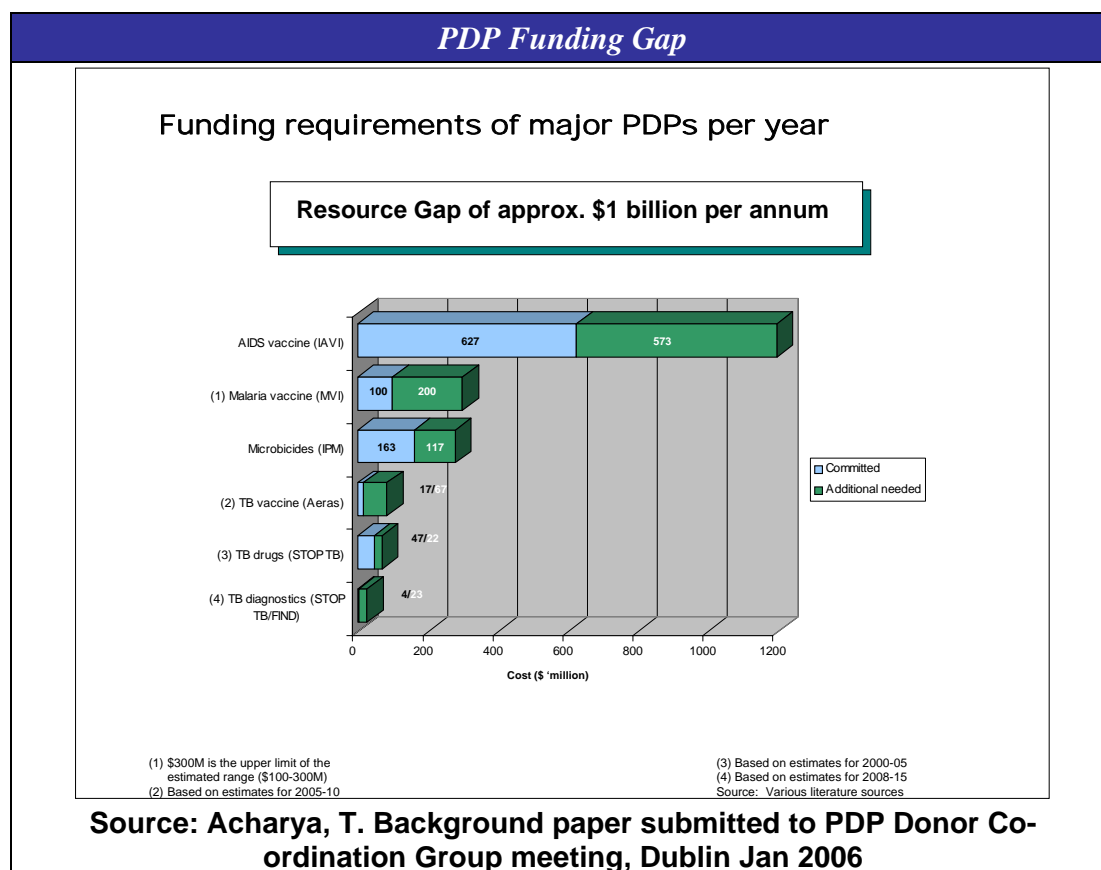
PDPs and industry show similar overall project failure rates, however, PDPs should be expected to have greater ability to reduce risk and cost through portfolio synergy effects.

In terms of R&D effectiveness, the PRPP study revealed that drug PDPs were superior in terms of time to market, health value and innovative level of the products, when compared with industry-alone neglected disease development.

Other qualitative benefits to having PDP push funding in the mix include: bringing together the best mix of technical, scientific and clinical neglected disease expertise; enabling access to facilities that MNCs may no longer have (e.g. parasite houses, developing country clinical trial sites); knowledge of developing country product profiles and markets, and experience in developing country clinical trials and dealing with developing country regulatory and health authorities; brokering “guarantees” of public demand; helping to design product features for developing country use from the outset; ensuring access conditionalities are incorporated from the outset; allowing a portfolio approach within a disease area; possible greater commitment to building developing country research capacity; and advocacy impact in raising the profile of neglected disease research.

6. What level of push funds are needed in an AMC era?

We can start answering this question by looking at PDP funding needs, assuming no AMC exists. The current funding gap for all PDPs is estimated to be about \$1 billion per year. This number represents PDP estimates of *additional* resources needed, beyond those currently provided, in order to fund the portfolio of products existing in the current PDP landscape.



There is disagreement amongst analysts as to whether AMCs should result in increased or decreased push funding for the vaccine technology chosen as the AMC pilot. Some argue that donors must avoid overpaying - i.e. to prevent industry from 'double-dipping'. According to this view, donors must reduce push or pull to account for the presence of the other. However, other analysts have shown that even if you 'overpay' industry - providing push funding but not adjusting the AMC downward - you still come out with a favourable cost per DALY because of the very low relative cost per DALY that you get with vaccines anyway. Proponents of this view opine that lack of information would make fiddling around with AMC reductions in the presence of push mechanisms too transaction-cost intensive.

Yet another perspective is that push funding should actually be increased in an era of pull. The argument here goes that the presence of adequate pull funding would actually enhance the value of push funding, because it increases chances that candidates will be taken to market rather than abandoned when and if donor interest shifts. Therefore the presence of AMCs makes donor investment in PDPs all the more viable and likely to result in a product being developed and taken up in developing countries.

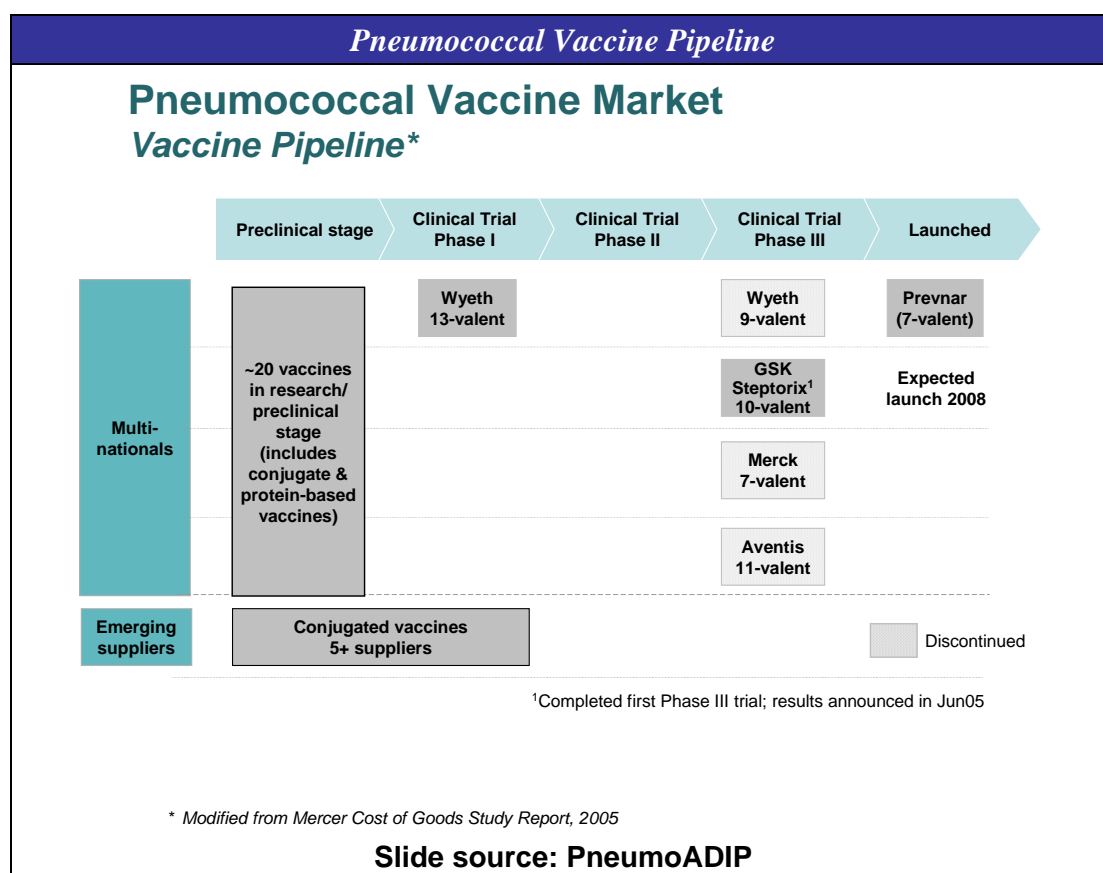
Getting down to practicalities and specifics, we can look at the two technologies which are most likely to be chosen for the AMC – the pneumococcal and malaria

vaccines - and look at what push funding will still be needed within these sectors, if an AMC goes forward.

Pneumococcal Vaccine

A 7-valent pneumo vaccine already exists, but this misses 2 important serotypes for developing countries. Therefore the AMC expert committee recommended that the AMC be designed to provide incentives for firms to invest in the accelerated development and production scale-up of any of the 20 or so vaccine candidates within the pipeline that would represent improvements on the existing vaccine.

The size of the AMC was calculated using a model estimating the risk-adjusted return to firms based on the specifics of the pneumococcal market, demand forecast, product pipeline and the amount of incremental private sector investments required to serve the developing world. A pneumococcal vaccine AMC size of \$1.5 billion (nominal) was recommended, to specifically pull three additional vaccines to market, which would contain important serotypes for developing countries. It is expected that the AMC will target, or 'pull', the 10 and 13 valent pneumo vaccines to market, expected to be licensed in 2008 and 2010 respectively, as well as one additional vaccine earlier back in the pipeline. The AMC is expected to last for 9-10 years given assumptions in the model. The \$1.5 billion has been calculated assuming that it would provide a sufficient financial return to these three firms for the incremental investment they will have made towards use of these products in developing countries. This includes investment in late stage clinical trials to prove efficacy in developing countries, plant capacity to supply these countries, resurrecting 'discontinued' vaccine development programmes, developing second generation technologies (e.g. protein vaccines), and providing long-term, sustainable and predictable prices.



Slide source: PneumoADIP presentation "Concept Proposal for an Advance Market Commitment to Accelerate Pneumococcal Vaccine Use in Developing Countries", 23 September 2005.

The BMGF has just announced \$75 million in 'push' funding to PATH, intended to fund early clinical development of the next generation pneumo vaccines, hopefully bringing a handful of these into clinical trials. This push funding should accelerate the path of 3rd generation vaccines, superior to the 10 and 13 valent vaccines, into AMC eligibility. Companies developing 3rd generation protein-based vaccines include Sanofi-Pasteur, Chiron and GSK/ID Biomedical. Four of the conjugate vaccines in pre-clinical development are being developed by emerging market based manufacturers from India, China and elsewhere.⁴³

Although the BMGF funding is expected to have some impact on accelerating the 3rd generation vaccine to market, there may still be a funding gap. This is because \$75 million will fund a substantial amount of early research, and even early clinical development (since Phase I and Phase II trials are relatively inexpensive). However, Phase III trials are estimated to be in the range of \$150 million per candidate. So if a handful of these early-stage candidates need to get through Phase III trials, and the AMC is sized to pull only three candidates (two close to market and one early stage), then more than \$75 million may eventually be needed to push improved pneumococcal vaccines to market.

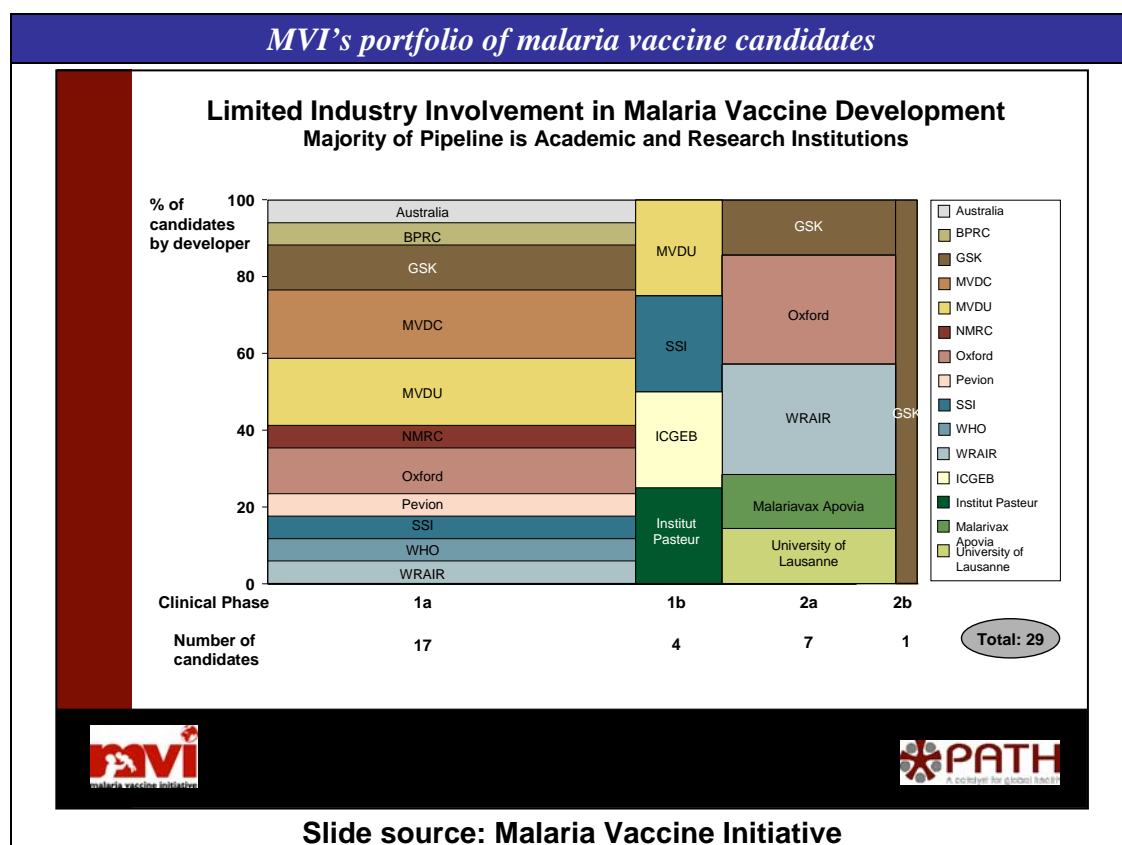
Malaria Vaccine

The first malaria vaccine to come to market will likely be the GSK candidate, which is showing partial efficacy in clinical trials. This technology is expected to come to market by 2011 and is fully push funded by Gates through to licensure. Because developing country consultations have revealed a strong preference for a malaria vaccine which is at least 80% effective, the AMC expert committee recommended that the AMC be structured to pull forward the next generation of vaccines. (Please refer to the figure below, illustrating the pipeline status MVI's portfolio of candidates.) The malaria vaccine has been sized at US \$2.3 billion, with intention to "provide incentives for firms to invest in taking forward the most promising of the 100⁴⁴ candidates in the pipeline", and/or potentially motivating firms to develop new, more promising candidates. The AMC is expected to begin by 2016-2018 and last for 11 years.

The AMC is sized to support two products successfully meeting AMC standards. It is also sized assuming that these two vaccines will be 50% push funded either via PDPs or through other research channels, esp., governments or the Gates Foundation. So at a minimum, these two malaria vaccine candidates alone will need 50% push funding in order for the AMC economics to create the right incentive.

⁴³ Orin Levine, personal communication

⁴⁴ According to WHO, as of mid-2005, almost 70 out of more than 100 vaccine candidates are in research or have not yet entered clinical trials. 18 candidates are in the earliest Phase I trials and nine have entered Phase II trials. Many of these 'candidates' are actually vaccine constructs, or pieces of vaccines.



In conclusion, the AMC calculations of size needed to 'pull' neglected disease technologies to market have already accounted for and assumed specified levels of push funding. So at a minimum, the assumed levels of push funding would need to be provided in order for the AMC economics to incentivise industry. However, it should be noted that the AMC, if accepted by the G8 and implemented, will be piloted in only one disease area initially, leaving many other research sectors with the large funding gap highlighted earlier. More push funding even within the sector chosen as an AMC pilot may increase the speed and overall effectiveness of the two mechanisms working together.

7. The likely economic consequences of “overpaying”

One of the issues about the relationship between push and pull is the concern that the combination of AMC plus PDP could lead to double-dipping, creating windfall profits for industry. In the technical work led by GAVI and the World Bank, two solutions were offered to remedy this potential situation. The AMC “market size”/total sum could be adjusted for any push funding received. Alternatively, push funders could ask for compensation on any push funding received, for those who are successful in securing AMC returns. Various options were proposed for the latter, but all of these options would be complicated to administer. Instead, the total AMC sum recommended to the G8 has been adjusted downward for an assumed level of push funding, the level of which was suggested by expert committee.

A similar concern has been voiced about the potential for the AMC to be set too high, again creating windfall profits for industry that would not be an efficient use of donor funds. One response to this concern has been to point to fact that commercial investment in R&D is strongly influenced by the size of the expected market, from which one may conclude that if you set the AMC too high, you will simply get more investment and get more producers of better products more quickly. In this virtuous competitive rent-seeking model -- one would expect firms to “swarm” (Schumpeter's term) in to exploit the combined opportunity so as, at least on average, to incur costs that virtually exhaust the rents available from the combined PDPs and AMC, or AMC alone, if that is all that exists. However, whether this theory would be true in a particular AMC sector would depend upon the already existing market structure, and in particular, whether there are lots of firms with the necessary expertise plus interest to enter that sector. With relatively few plausible participants, it is quite possible that there would be sufficient reticence to enter, with the result that a considerable pot of money is left on the winners' table and not offset by the unsuccessful firms' costs. Again, the key is the size of the company pool from which one draws. Given the consolidation and exit in the vaccine industry in recent years, the pool of companies doing full-scale development and vaccine testing is small. High capital entry costs to vaccine development and manufacturing plus limited and concentrated expertise in crucial areas – such as large scale manufacturing process development, reflects a degree of specialisation which makes flexible movement into vaccines ex ante less feasible.

However, a degree of ‘overpaying’ in the vaccines sector may still result in a cost-effective investment. This is because vaccines are typically a very cost-effective investment anyway, usually at under \$30 per DALY saved, relative to other health interventions. Therefore any potential ‘windfall profits’ could be small relative to public benefits. Berndt et al.⁴⁵ demonstrate that the AMC investment remains cost-effective within a large range of AMC sizes. With an AMC size of \$3.2 billion for a malaria vaccine, comprised of a \$15 treatment price for 200 million treatments, the result is \$15 per DALY saved, including vaccine purchase and delivery costs. If the treatment cost is increased to \$25 per person for 250 million treatments, the result is a cost per DALY of \$26.46 As a benchmark, the cost of purchasing and delivering anti-viral drugs for AIDS in low-income countries is estimated to cost at least \$613 per year of treatment, and a cost of \$100 per DALY saved is generally considered to

⁴⁵ Berndt E, Glennerster R, Kremer M, Lee J, Levine R, Weisacker G, Williams H “Advance purchase commitments for a malaria vaccine: Estimating costs and effectiveness,” National Bureau of Economic Research (NBER) working paper #11288, 2005.

⁴⁶ Note that the latter scenario assumes that the increased AMC size results in more R&D activity and as a result, an advancement in three years of development and adoption, thereby increasing the speed of uptake and consequently, lives saved.

be highly cost-effective in poor countries. So whether a malaria vaccine costs \$15 or \$26, both would be very cost-effective investments.

8. Summary

Although comparable empirical evidence is scarce, a review of push and pull incentives across sectors reveals the usual presence of both push and pull incentives, whereby push is used to reduce costs and risks during development, including brokering/ushering the technology through to market more quickly, and pull is used to add credibility to the eventual market incentive for the successful.

In the neglected disease sector, mounting evidence shows the effectiveness and efficiency of push funding. We do not yet have examples of strong 'pull' of the AMC variety, however recent experiences of new technology introduction suggest that the AMC (market pull) alone will not be enough to facilitate speedy uptake in these settings. Push funding as well as PDP brokerage functions and other expertise will likely be needed as the products approach introduction. However, it is also obvious that generalising is difficult, as there will be differences by technology type, disease type, market attractiveness (i.e. neglected disease vs. those with some degree of commercial interest). The costs of entry, distribution of expertise and development challenges differ considerably across disease and technology; the same incentives may therefore have different impacts in different fields (and be more or less efficient).

This individuality of response to push and pull is true also if we look at response by firm type and by stage in the development pipeline. By firm type, we have evidence that small firms, including biotechs, can and do respond well to push incentives and to pull incentives when accompanied by push. Generally, we would expect the main respondents to an AMC for vaccines to be large pharmaceutical companies⁴⁷, though some would not respond and some small biotech firms with good financial connections and the right expertise might respond. Even for similar firm types, responses will likely differ by individual firms given the variety of strategic objectives and product portfolio opportunities of each firm.

Within the R&D pipeline, the best positioning for push and pull will again depend to some degree on the specific technology and firms involved. It is theoretically plausible that push can have its greatest impact where there is high scientific risk. However, in reality push is proving to be effective and efficient throughout the development pipeline. Thus, using PDPs for full-scale clinical trials should not be ruled out if highly promising candidates appear and no private entity is willing to take up the challenge. Even in late development stages, PDP push can have effects that pull may not have, for example, facilitating technology uptake and links with other public institutions.

When looking at the optimal positioning of push and pull funds from a cost-efficiency perspective, i.e. whether to pay for R&D through ex ante PDP grants or through ex post AMC payments, the relevant parameters to examine are comparative effectiveness, costs of capital, out-of-pocket costs, and risk management.

Comparative costs of capital are a key cost driver, which can double the total costs of conducting R&D. The idea that costs of capital are reduced or non-existent for public versus private sector is mistaken. In a proper comparison of the two, there is no significant difference in the cost of capital. Thus, the choice between paying for R&D through PDP grants or through AMCs should instead be based on their comparative R&D effectiveness and efficiency in managing the other cost components as well as risk of failure. Out-of-pocket costs may be lower for neglected disease research versus R&D for products aimed at wealthy markets, but this is true whether funded

⁴⁷ At least in the vaccines field; large pharma companies may not be active in other fields where AMCs could be piloted in the future, e.g. microbicides or diagnostics

by push or pull. Out-of-pocket costs may 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. PDPs with push funding may have an advantage in risk reduction, due to having a portfolio of neglected disease candidates from which to select. When comparing R&D effectiveness of push versus pull along the development pathway, PDPs have proven to be superior in terms of time to market, health value and innovative level of the products, when compared with industry-alone neglected disease development. There are a variety of other inputs that PDPs uniquely provide that can be expected to yield better overall results for product efficacy, access, and acceptability. This suggests that public-alone and industry-alone neglected disease R&D is sub-optimal and pull should ideally be combined with PDP push.

As for how push and pull funding should be adapted to account for the presence of the other, the AMC calculations of size needed to 'pull' neglected disease technologies to market have already accounted for and assumed specified levels of push funding. So at a minimum, the assumed levels of push funding (e.g. 50% of total costs for a second generation malaria vaccine) would need to be provided in order for the AMC economics to incentivise industry. However, it should be noted that the AMC, if accepted by the G8 and implemented, will be piloted for only for a vaccine in one disease area initially, leaving many other disease and technology sectors with a large funding gap. It may also be true that more push funding even within the sector chosen as an AMC pilot would likely increase the speed and overall effectiveness of getting a product to market, that is assuming there is a fairly robust field of firms from which to draw R&D interest.

9. Further Work

There are several issues relating to the AMC's interface with push mechanisms, currently only on the horizon for vaccines, that have not been examined here, but which warrant consideration. The first of these is the issue of how to co-ordinate push and AMC impact within a sector, so that they add to, rather than detract from, the credibility and effectiveness of the other. For example, once push and pull funding is already in place, what criteria and institutional process should be used to determine whether additional or altered push and pull can be agreed? Considerations here include potential effect on first-to-market as well as second generation innovators and retaining the credibility of each mechanism. AMCs must be flexible enough to cope with the change in industry microeconomics and what this would mean for pay-back and/or overcompensation to each player. One could envision a scenario whereby AMCs are set up in order to "pull" specific candidates to market, assuming a certain number would launch products at certain intervals, implying certain pay-offs, and then the whole situation changes due to substantial new push funding either providing advantage to one player over another or bringing a whole host of new candidates to market so that no single player receives adequate R&D compensation.

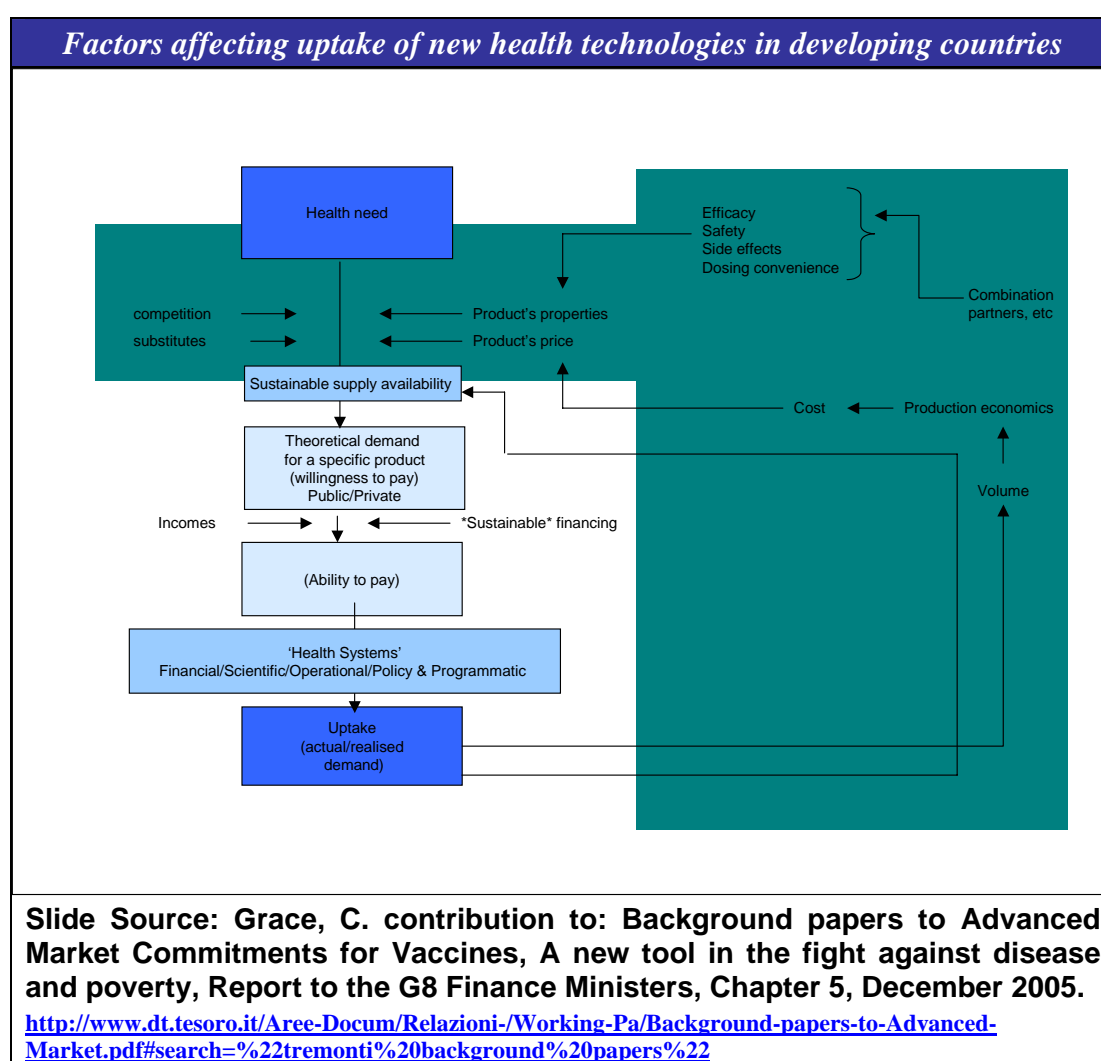
Another area for further work centres on the issue of technology uptake. The introduction of artemisinin-based combination therapies (ACTs) for malaria provides an illustration of what can go wrong in new technology introduction processes.⁴⁸ Even though many countries have secured full 3 year, and potentially 5-year, GFATM financing of ACTs, orders are well below WHO projections and even below what countries had proposed to order in their own GFATM bids. The problems stem from

⁴⁸ See Grace, C. and Grupper, M. "Aligning ACT Supply and Demand: Short and Long Term Options", July 2005. http://www.dfidhealthrc.org/what_new/Aligning%20ACT%20paper.pdf

a vicious cycle of shortage of drugs, high prices, and questions around sustainability of finance. But underpinning these problems are institutional co-ordination and technical issues that seem to plague nearly all new health technology introductions, the alleviation of which would help prevent this vicious cycle from developing in the first place.

Understanding how to improve and facilitate speedy uptake will be central to the health impact of what is produced whether by push and pull. A range of complex issues must be accounted for in this decision-making process, including the financial sustainability and affordability of existing and new products; the expected costs and benefits compared with other competing priorities; scientific and regulatory concerns; as well as policy, programming and operational issues.⁴⁹

The diagram below presents a visual depiction of the complexity of all the factors that need to fall into place in order to facilitate uptake.



Although this paper is focused on the push/pull role primarily in incentivising research and development of new technologies, it must not be forgotten that patient access is the ultimate goal, and that the largest challenges often begin after licensure. Clearly,

⁴⁹See Grace, C. Pages 30-36 of "Advanced Market Commitments for vaccines: A new tool in the fight against disease and poverty", Report to G8 Finance Ministers.
<http://blogs.cgdev.org/globalhealth/archive/BCKPapers.doc>

innovation is needed not only on the R&D side, but also in bringing together all the processes/actors/systems that will facilitate getting the technology to the patient. There needs to be alignment of the financing with the demand, an understanding of how the supply chain works, and a mechanism for bringing the necessary actors and institutions together. There is also the consideration that vertical 'push' of technologies may not necessarily be the most efficient nor effective way to facilitate uptake. It may be better to focus on enhancing each country's capacity, within and across disease areas, to make evidence-based, objective decisions about technology uptake, including how to prioritise which new technologies should be introduced in what timeframes.

A third area for further work stems from the idea that the push/pull dichotomy may in fact be an incomplete lens through which to look at questions of how to get improved products meeting developing country health needs to market more quickly. Health innovation systems have many interlinked components; these may include public R&D funding (through PDPs or otherwise), tax breaks for R&D, double-bottom-line venture capital, liability protection, new approaches to intellectual property (e.g., patent pooling, open source, and technology management capacity building), expedited regulatory approvals, transferable patent extensions, publicly funded market analyses and partnering assistance, global procurement funds (e.g., GAVI, GFATM and PEPFAR) and AMCs.⁵⁰ Many of the same questions that we are now asking about the push/pull interface (i.e. which of these are most cost-effective, which aspects are synergistic, which may be duplicative?) exist also when looking at the entire system.

⁵⁰ Chad Gardner, personal communication. For a more complete treatment of these mechanisms, see the Report of the Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH). April 2006. <http://www.who.int/intellectualproperty/en/>