**EXECUTIVE SUMMARY**
of
**"The Global HIV Vaccine Enterprise,**
**Malaria Vaccines, and Purchase Commitments:**
**What is the Fit?"**
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## A Short Prologue

This paper started life as an effort to put balance into the debate about 'advance purchase commitments' (APCs) for vaccines. However, it has come to explore a wider range of issues that impinge on vaccines in general. Particular attention is paid to HIV and malaria, mainly because these have recently been especially heavily promoted as candidates for APCs, though attention is also paid to a number of other vaccines, both past and present.

The term APC has come to have a range of meanings in the media, but is here defined generically as a pre-set foundation-financed or publicly-financed pool of subsidy to be distributed, after vaccine development, in a potentially complicated pattern across vaccine developers and countries and over time, and it refers also to the institutions, contracts, and monitoring mechanisms required to do this. In practice such a mechanism is going to be highly variable, according to the nature of the vaccine under consideration and the competences of the institutions involved, and clearly there is plenty of room for practice to vary greatly from theory.

The timing of this paper is prescient. APCs have suddenly become extremely topical, with the release in April 2005 of the report "Making Markets for Vaccines" by the Center for Global Development (CGD) in Washington, and its subsequent heavy promotion in the media and at a range of international institutions, including IAVI, the Gates Foundation, the World Bank, and this year's G8.

The emphasis of the "Making Markets" initiative has shifted over the last year or so from focusing on a range of underused and near-market late-stage vaccines, towards ever more emphasizing early-stage HIV, malaria, and tuberculosis vaccines, and especially the first two. Indeed, these early-stage vaccines were the headline targets in much of the CGD launch material in April 2005. The trigger for this shift was the announcement in November 2004 by the UK Finance Minister, Gordon Brown, of his intention to establish an APC for malaria. This created an unexpected window of opportunity to lobby hard for APCs for early-stage vaccines. At the same time, much of the 'policy space' for late-

stage and currently existing vaccines was being absorbed into the International Financing Facility for Immunizations, IFFIm.

This promotional effort seems to have necessitated the creation of a set of literature that severely downplays the problematic side of APCs for early-stage vaccines, and that instead paints a picture of a 'simple', 'straightforward', and 'powerful' new tool, even though APCs have never been used for anything before[1] – not even for the most trivial of cases – even as they are now being most heavily promoted for some of the most difficult of cases, and when the evidence of their 'power' is anecdotal at best.

The notion of APCs has been around for eight years or more – as has some understanding of the key problems[2] – though the terminology 'Advance Market' is more recent, dating only from about May 2004. Such newer terminology is not used in this paper very much since it constitutes a claim to truth and is not a fact in and of itself. It will become clear that APCs are not like standard markets with standard price signals, but are instead sets of institutions with rules and contracts based on sets of information that need to be defined in advance, and degrees of discretion to allow later flexibility in these rules and contracts. Price signals are replaced by committee decisions. Indeed, one of the main critiques here is that such instruments would struggle to replicate a number of important market features, especially the dynamic and 'quality' incentives inherent in markets over time, and that they continue to suffer from many of the risks that pharmaceutical firms regularly face such as 'dynamic inconsistency'.

This heavy promotion has been taking place against a backdrop of an intense, wide-ranging, and highly democratic investigation by the Commission on Intellectual Property Rights, Innovation and Public Health, at the WHO, set up by the World Health Assembly in 2003, looking into an extraordinarily wide panoply of approaches to tackling the problem of the diseases of the poor and the issue of IP. Before locking in APCs for HIV, and malaria (and maybe tuberculosis too) there is sense in seeing this larger process through to evaluate how APCs fare against, and indeed fit in with, other tools for tackling the problem. The best ideas should be the ones that survive such a process and are likely to work and not simply be the ones that happen to have been best financed and most heavily promoted. Indeed, with all this other thought-provoking activity going on, it is not even clear quite why those promoting APCs for HIV and malaria feel that they – above everyone else – should have 'their' idea acted upon by policymakers before the full benefit of this greater intellectual and evidence-based process has become clear. Given that an APC for HIV will have next to no impact for many years, and if set up wrongly would probably collapse anyway, it is even less clear why it would need to be quite so rushed. Given the years if would take to set up the institutional mechanism to support an APC for HIV and the strong global budgetary pressures to cut HIV vaccine research, the

[1] Not just vaccine, drugs, or medical devices, but no products or endeavors of any sort. The landing of rovers on Mars was not done via an APC, nor the creation of water treatment schemes in Africa, nor the establishment of democracy in Iraq, etc. (all 'simple' to define objectives).

[2] The Sabin Vaccine Institute colloquium held at Cold Spring Harbor, New York, 5 – 7 December 1997 identified many of the issues and reservations still unresolved in the CGD's 2005 report (see Muraskin, W. "Vaccines for Developing Economies: Who will Pay?" Albert B. Sabin Vaccine Institute, New Canaan, CT, USA., 2001).

least delay in achieving an HIV vaccine would have been achieved by prioritizing the funding for the 'Global HIV Vaccine Enterprise' at this year's G8.

In spite of premature announcements of impending APCs for early-stage vaccines such as malaria – none of which, it is becoming increasingly clear, will look anything like the sort of APCs being promoted in the literature – it looks increasingly likely that the 2005 G8 will endorse a process of further analysis of APCs for these, and other, vaccines, of which the "Making Markets" report will be just the start. It would seem that a range of foundations, international organizations, and governments will commence commissions and investigations of various sorts and absorb a great deal of time on the issue. It is hoped that this paper will put back into the debate some of the balance that has been missing and will help policymakers to work out exactly when and how APCs might be useful policy instruments[3].

**PART 1** of the paper explores the nature of the underlying vaccine problem, which is found to be highly heterogeneous, ranging from the creation of complex and difficult *vaccines* – such as those for HIV, malaria, and tuberculosis for which many scientific difficulties still remain – through to the insufficient or non-use of already existing, sometimes very cheap, vaccines, such as those for yellow fever, hepatitis B, and haemophilus influenzae. The instruments needed for each – including the nature of 'purchase commitments' – differ greatly.

For currently existing and near-market vaccines, purchase commitments are all about creating stability of demand, incentives to invest in production capacity, the tailoring of an already existing product to new users, the creation of low product prices, and access to vaccines. This paper (especially Part 3) emphasizes these positive merits and strongly encourages these sorts of commitments. For non-existent vaccines such as those for HIV, malaria, and tuberculosis, purchase commitments, at least as so far promoted, are all about incentivizing R&D leading to the development of the vaccines in the first place. This paper (especially Part 2) finds this to be an entirely different problem and a great deal more problematic.

For ease of exposition the paper starts with the more difficult case of early-stage vaccines. Far more issues are raised for these vaccines than for late-stage vaccines, and it proves easier to explain things by working outwards from these vaccines. Part 1 therefore sets down a benchmark model for an APC as an R&D incentive for early-stage vaccines.

**PART 2** explores this benchmark in great detail. Indeed Part 2 takes up just under half the paper. It finds that APCs for early-stage vaccines are anything but simple and that there are very strong reasons to doubt their claimed strength, or, even, that they would have any current strength at all, especially for HIV. Perhaps before leaping in to set up such instruments and the layers of institutional structure to support them, policymakers should at least check this out more fully.

[3] This may all be premature. After these words were written, UK finance minister Gordon Brown announced that the UK would go ahead anyway with APCs regardless of the further analysis needed.

A number of observations about Part 2 are in order:

1) Part 2 is full of critical and 'problematic' observations. But this is largely because the supportive APC material for early-stage vaccines contains very little of this. If it had, there would be no need for this paper. Achieving balance may create the impression of imbalance. The reader is strongly urged to read the "Making Markets" report alongside this paper and to make up his or her own mind[4]. The second half of this paper tries to make up for this by being more constructive;
2) All tools for incentivizing R&D for vaccines are imperfect. One of the jobs of policymakers is to assess the *relative* imperfection and usefulness of each tool. This suggests that negative commentary about one tool – in this case APCs for early-stage vaccines – should be placed within a broader context including negative and positive commentary about other tools. This obviously cannot be achieved if the discussion of each tool only includes that tool's positive merits;
3) The efficiency of each tool varies greatly depending on the underlying problem at hand. The case for APCs for early-stage vaccines was not helped by the early decision to trivialize the science of HIV and malaria vaccine development to one that is 'linear', fixed, simple, and static, when for early-stage vaccines it is instead highly complex, and dependent on feedback loops, collaboration, and comparison of results and sharing of information, and with a mix of private and public-good features to the problem;
4) Some of the criticisms below are fundamental to the nature of APCs. Others pertain much more to particular designs of APCs, especially the ones currently being proposed for early-stage vaccines. Separating out the two is not always obvious and will be part of the exploration and the creation of a range of instruments, including suitably-modified APCs.

Among many other conclusions, Part 2 finds:

● It is extremely difficult, even impossible in some cases, to set the 'size' of an APC so as to maximize the speed and efficiency of vaccine development. Setting 'size' too large or too small is wasteful for different reasons. This inability to set 'size' efficiently is reflected in a variety of past attempts to rationalize the 'size'. The current methodology – based on the average market size of new chemical entities developed for rich-country markets (about $3billion) and not on the potential costs of developing and manufacturing vaccines for HIV, malaria, and tuberculosis, as well as on a range of other factors – generates an essentially random size for early-stage vaccines[5]. Indeed, although this figure achieved a level of scientific certainty in other major reports and in the media[6], the

[4] A copy of "Making Markets for Vaccines" can be found at: www.cgdev.org/publications/vaccine.
[5] The fact that all three are set the same size when they must clearly have very different size requirements makes the point eloquently.
[6] The Commission for Africa, February 2005, citing the CGD, stated that: "For Malaria, the market size needed to deliver the malaria vaccine is $3 billion (CGD, 2004)." (http://commissionforafrica.org/english/report/thereport/cfafullreport_copy.pdf page 409, Chapter 6 Footnote 92). "Making Markets for Vaccines" Chapter 5 was even titled "$3bn per disease." The original press release (page 1) for the launch of the CGD report claimed that the report had "found that a market of

authors of the CGD report have now explained that the figure was for 'illustrative' purposes only[7]. Yet, having got the size wrong, we find severe limits to the ability to reset the 'size' later without negatively impacting incentives.

● It turns out to be very difficult to contrive product terms and payment rules to incentivize follow-on innovation by other developers (the 'making markets' part of the current proposal, in place of 'prize' thinking), and thus to encourage investment into a variety of vaccine approaches (it is made far too risky) and to drive the 'quality' of both the first as well as later products. In this sense, such programs – because of the fixed size of the pool of available subsidy, the role of a committee rather than of market signals in allocating the subsidy, and the risk that the pool is used up 'too soon' – will struggle to replicate standard market features. This is especially problematic for vaccines that are composite or potentially 'only' therapeutic, or for which the first products are very unlikely to be the best. The CGD report talks as if these incentives can be created but we find that it has nothing to say about *how* this would actually be achieved in practical situations, or, more importantly, how firms and investors would come to believe that this would be achieved.

Given the lack of any other way to drive investment decisions in the direction of 'quality' and follow-on innovation, APCs (as currently proposed) require a great deal of market risk be put back on to innovators – the opposite to the reasoning behind purchase commitments for existing and late-stage vaccines. Given the dysfunctional nature of many developing country health markets and the importance of competition and capacity for driving production costs lower, this impacts developers with much unnecessary risk and we find that it self-defeatingly undermines their incentive to do R&D in the first place. It also ensures that problems with production price and delays in access become part of the mechanism to incentivize the original R&D. This is not credible. This perceived need to put market risk back on to developers, even in situations of such well-known failure, is yet further evidence of the difficulties of using such programs to guide R&D for early-stage products.

This suggests that even under early-stage APCs the 'quality' of products, and the risks to developers, should be controlled more en route and not totally via a crude mechanism to disperse a fixed pool of subsidy at the end.

● Unlike late-stage or currently existing vaccines, we find that it proves very difficult to set minimum product specifications for an APC far in advance so as to avoid a great deal of discretion later, with consequent risk to developers. Setting the 'size' of each APC, the

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about $3 billion is needed." This was picked up in the media. The Washington Times, 7 April, claimed that "Under the proposal, rich countries would pledge to spend enough on vaccines for malaria, tuberculosis and HIV/AIDS to create a market of $3 billion", while ABC News, 7 April, stated that the report "recommends a $3 billion 'commitment' for each disease," and Voice of America, 8 April, stated: "The Center for Global Development estimates that an average commitment of $3 billion is required to create a market for each new vaccine."

[7] "Answering Concerns about Making Markets for Vaccines," Barder, O., Kremer, M., and Levine, R, 9 May 2005. Page 8 refers to the "the illustrative figure of $3 billion…intended to illustrate the concept, not fix a precise amount." www.cgdev.org/Publications/vaccine/_files/Response to Concerns.pdf.

rules for follow-on products, and the minimum product specifications all require, amongst other things, knowledge of expected R&D costs, the potential costs of manufacture and distribution, the future epidemiology, and even the future economic status of countries that may or may not be regarded as 'eligible' for the purposes of the program (i.e. knowledge of many factors, and not just of medical issues).

Since it is too risky for developers to face symmetric discretion that allows requirements to be raised as well as to be lowered, product requirements in the CGD contracts can only ever be lowered, and a bias is thereby imparted towards lower average quality of outcomes. Given future possible epidemiological and scientific developments this is not found to be particularly efficient (or ethical). This is just one example of multiple pressures towards 'lower quality' outcomes that the paper discovers. This is already showing in the case of malaria vaccines, where successive suggested product specifications for a malaria APC have been pitched ever lower – but it is a general problem. Such programs (as currently constituted) therefore risk actively discouraging the development of highly effective and safe vaccines.

● We find that APCs vary in their ability to create genuine *additions* to current markets and to current push incentives (including subsidies, tax-breaks, and PPP-funded efforts, etc.), and hence have varying ability to incentivize, and only pay for, genuinely 'additional' private investment. The problem intensifies, the more firms there are taking part in the mechanism. Part 2 describes many potential forms of this 'crowding out'. This is especially problematic for HIV for which there is already a highly variable current market that has somehow to be factored out[8], and a complicated interplay of other funding and research mechanisms. The original APC models[9] presumed this problem away by stripping out all other sources of funding and all other R&D activity when analyzing APCs. All of the cost effectiveness evidence (both the older evidence[10] and the more recent evidence[11]) also assumes that all of the value created by a vaccine can be ascribed to the APC alone[12]. While there is recent talk of APCs being complimentary with other approaches, all of the methodology is profoundly non-complimentary.

● 'Non-eligible' countries are found to be particularly difficulty to handle. It is not clear that these countries would act in ways to support an APC – like not using vaccines that fail the APC requirements – given that they are likely to pay much more for vaccines than eligible countries. We find various scenarios where their behavior risks destroying the dynamic incentives of the program.

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[8] This may not just refer to problems separating sales in the sales space, but to problems separating R&D incentivized by the program from that that is not.
[9] Such as Kremer Appendix 3, www.pm.gov.uk/files/pdf/Appendix%203.pdf.
[10] Found on the British Government's No 10 Policy Unit website, www.number-10.gov.uk.
[11] NBER Working Paper Series "Advanced Purchase Commitments for a Malaria Vaccine: Estimating Costs and Effectiveness" Berndt, E.R., Glennerster, R., Kremer, M.R., Lee, J., Levine, R., Weizsäcker, G., Williams, H. Working Paper 11288 www.nber.org/papers/w11288, April 2005.
[12] The latter study also allows for a range of malaria vaccine efficacy, and argues that "cost effectiveness is robust to variation in vaccine efficacy" (p13), but seems to ignore the fact that if a malaria vaccine is 'only' 40% effective and requires, say, up to three booster shots, then in resource-poor settings the cost of drugs and preventative treatments like bed-nets remains practically the same as before.

Neither is it clear that non-eligible countries (perhaps including Russia, China, and India) would contribute to expensive efforts, such as the 'Global HIV Vaccine Enterprise', if they know, or suspect, that they will then become non-eligible countries at the APC stage and face higher non-eligible prices for longer. This suggest that before they agree to fund or to take part in the 'Global HIV Vaccine Enterprise', their exact status vis a vis any future HIV APC will need to be resolved too.

If manufacturing capacity is limited – a highly likely scenario in the early days of a new vaccine – there are also dangers that incentives are created for companies to supply more lucrative markets first (including using research results for one HIV clade for another more lucrative clade first, should the science reveal this as possible) and only then the eligible markets after a delay. This is part of a more general risk, given that the APC is an 'option' to developers, that developers will not supply the APC program, or will only supply the program with delay, even when they have been incentivized in some way by the program.

Any product that will take a very long time to develop and such that the epidemiology and distribution over poor and more lucrative markets is likely to change greatly over time, are also likely to see increasing problems (and increasing complication and dispute). A medical condition that is exclusively attached to the poor is much easier to fit within such programs than one that also contains some more lucrative markets. This suggests that HIV is a much less appropriate application for an APC than malaria, though the increasing evidence of more widespread malaria casts doubt even on this.

● Meanwhile, countries eligible for vaccines under the APC are also found to behave in ways that potentially destroy the dynamic incentives of the program. They, in effect, have a veto over the program's success, and this leads to problems of long-term multi-institution and multi-country monitoring and policing of rent-seeking behavior on the part of both developers trying to secure the very high early subsides and those in political influence in such countries. Again, we are led to the conclusion that it remains problematic to have the subsidy for R&D paid via a large proportion of the high price of the first relatively small tranche of subsidy-favored vaccines.

● For currently existing vaccines and for late-stage vaccines, purchase commitments mostly take away risks. We find that APCs for early-stage vaccines come with a range of *new* risks attached, especially those of the mechanism itself – 'mechanism risk'. This is on top of the market risks already mentioned. Expected difficulties of operating the mechanism efficiently and fairly, the problems with 'credibility', the presence of even small elements of potential discretion but compounded over long horizons, and the risk of collapse of the program, are all hugely damaging to the value of an APC to private investors. No figures have been provided (though they have been requested) but it would not be surprising to find that that at 15-25 year horizons 80%, or likely a great deal more, of the current impact of an APC for HIV would be absorbed in capital costs, making an APC a very weak way to drive current R&D for an HIV vaccine.

We also find it instructive to view APCs just like any other financial instrument – capable of suffering the equivalent of 'financial crisis' and collapse. A section comparing APCs with government bonds proves instructive in this respect. Unlike government-backed bonds it is hard to see who, or how, such failure of an APC can be bailed out such as not to harm vaccine developers and the speed of discovery of vaccines. Given that an HIV APC would have no bite for many years, such a purchase commitment, if set soon, would, it is argued here, likely collapse years before it started to have any effect.

Given these newly-created risks, and the extremely complex process and expensive cost to develop vaccines for HIV, it is likely, in practice, that any practically useful APC for HIV would lock in at a very late date in vaccine development and would not do very much to repay the total R&D costs of developing the HIV vaccine(s). Due to the large costs of HIV vaccine development falling outside of the APC, it would also require a different set of IP arrangements over the created vaccine than those being proposed in the CGD report, which gives all rights to the last developer in the chain. HIV APCs would end up being all about scale and low production costs, the encouragement of multiple manufacturers, access to IP and know-how, and access to the vaccines. This is quite unlike those currently being proposed by the CGD report for HIV.

● Vaccine and drug development involves large sunk investments and, because of the inability to know many of the factors relevant to fixing the terms of APC contracts for early–stage vaccines far in advance, developers working under an APC will continue to expect the risk of dynamic inconsistency – the situation that arises when investment is irretrievably sunk and more favourable terms can thus be extracted from developers ex post, with the expectation of this feeding back to numb the incentive to do the investment in the first place. Firms will find that they compete twice – at the R&D stage, and at the APC stage through rent-seeking behavior. Even small risks of this arising will generate large needed extra risk premia. The body of the paper enumerates simple cases[13]. Getting rid of this risk requires credible contracts, yet achieving this credibility in any meaningful sense for early-stage vaccines is far more difficult than is currently intimated.

Dynamic inconsistency does not go away under an APC; we find that it simply metamorphosizes from a problem in the marketplace and with patents, into a problem with sponsors, their delegated APC institutions, and firms. The large (expected) gains to be made from rent-seeking the committee's decision also undermines the competitiveness of the program, especially deterring smaller, less powerful, players.

This suggests that paying a large amount of the R&D costs through large subsidies to the first 'few' vaccines of early 'winners' is still going to create a range of problems. Into the bargain, dominant and rent-seeking players face a great deal of 'reputation risk' that they might rather have avoided.

● A large chunk of the value of early-stage APCs rests on their supposed ability to create long-term supply and cheap products – say at $1 per course of treatment. The CGD

[13] See also the accompanying PowerPoint presentation, "Purchase Commitments for Vaccines: Their Uses and Their Limitations", available at www.economics.ox.ac.uk/members/andrew.farlow.

contracts call for determining, at the time of signing at the very start of the program, the 'guaranteed' long-term price or an ex ante methodology for determining it, and for the obligation of a company to supply *at that price* in the long-term – with penalties for not doing so – in return for having had the short-term advantage of initial sales at high, heavily subsidized, guaranteed prices. None of these parts of the mechanism are found to be viable. Indeed, failure on these points ultimately undermines R&D incentives. The CGD report bases its analysis on the unrealistic assumption that production costs will be as low as a dollar or so for both the first 200 million doses as well as for the long-term supply. A great deal more attention needs to be paid to the state of competition and the number of suppliers after the first 200 million-or-so treatments are gone as well as to the production cost of the first 200 million treatments.

● The paper discusses a range of current problems in the process of R&D for complicated early-stage vaccines, including: an overly-narrow research focus; cost of capital difficulties when the same few large firms research both the vaccines and drugs for the same conditions; and the problem of insufficient (and shrinking) global vaccine production capacity. The paper finds that APCs, as currently suggested at least, tend to reinforce many of these problems. It is also not clear that the underlying financial basis to the model – an emphasis on free cash flow with reward all at the end of the program – and the repeated practical biases towards large pharmaceutical players, does not instead aggravate these problems.

It might be possible that some of these problems could be corrected through push parts of the overall mechanism, especially problems relating to the breadth of vaccine leads investigated, but this needs to be more fully explored. Similarly, alternative forms of finance to expand the number of vaccine producers needs to be explored, but it is unclear whether this would be within or outside of an APC.

With the ever-increasing competition for the skills-base and resources caused by the expansion in research for bioterrorism, it may be more productive to target a wider range of ways to increase capacity, to provide wider forms of funding to a wider range of players, and to encourage technology transfer and similar measures – rather than emphasizing the response of the shrinking pool of current large pharmaceutical firms.

● We also conclude that APCs for early-stage vaccines place a disproportionate amount of their risk on to biotechs. 'Mechanism risk' and the risks of 'dynamic inconsistency' are especially high for such investors. And if the program collapses – indeed, biotech investor reactions to just such a possibility may make this largely self-fulfilling – it is biotechs and their investors, and not large pharmaceutical firms, who will pay the heaviest price. Ordinarily, large pharmaceutical firms would set milestone payments into contracts, given the expected market. However, because of the many risks of 'surrogate'-market mechanisms such as APCs, biotechs may wish (and, indeed, they have requested) to be protected from these risks by interim payments contained *within the program* itself. This creates a major headache for those organizing the program, and imposes large informational and monitoring demands upon them. It is hard to imagine that they could

structure such interim payments to be remotely efficient, given the extraordinarily complex distribution pattern of subsidy payment that it would entail overall.

● We also find a large range of institutional, legal, and IPR issues that are still to be resolved. Given the presence of many other funding mechanisms and research interests (including PPPs), and the mix of eligible and non-eligible countries, APCs would generate a potentially highly complicated IP, institutional, and legal tangle with potentially very unclear jurisdiction. Some of these issues could be resolved in interesting ways – for example via technology/know-how transfer as part of an APC, or IP ownership in the hands of more than just the 'winner' after a certain point in time. However, resolving this in a piecemeal way simply makes APCs more opaque, harder to operationally evaluate, more difficult to use, and even less clear as an incentive signal to private finance.

● Liability issues impact at many levels, from those setting the APC terms right up to firms and regulatory institutions seeking to satisfy the terms. The current proposal is that the sponsor(s) fully indemnify the committee running the program – even as control over their funding is lost to a committee with discretion – with the eventual designated supplier to defend and indemnify the sponsor and members of the committee. As currently proposed, this therefore narrows down the potential participants to only the world's largest companies. There is also heavy reliance on third parties, such as the WHO, but they are nevertheless expected to relinquish all decision-making powers to the controlling committee.

It is not at all clear that this could work. If liability problems flow from a discretionary decision of the committee, could firms sue the committee and sponsors? What firm wants the PR disaster of suing the World Bank, the Gates Foundation, a PPP, or the WHO? Or indeed the CGD, if they are found not to have exercised 'due diligence' in setting up an APC program, and it collapses through no fault of those firms trusting in it to work, leaving them with heavy losses. To help achieve 'credibility' it would be desirable for APCs to be operationally independent of sponsoring institutions, but it is not clear that this could be so.

Since the final CGD report was released this attitude seems to have been modified somewhat, and issues of liability risk have been separated out, in discussion at least, from the actual program itself. It will be interesting to see how this develops.

**PART 3** reviews a range of past and future vaccines and elucidates what purchase commitments can and cannot achieve. Past cases analyzed include hepatitis B, haemophilus influenzae type B (Hib), smallpox, African trivalent meningitis vaccine, and meningitis conjugate C. The examples of current late-stage vaccines are pneumococcus, and rotavirus.

None of these case-studies remotely matches any APC being proposed for HIV, malaria, or tuberculosis. Many of the problems being resolved (and, in some cases, being created) by contracts are very different in these case-studies compared to early-stage vaccines. Many of the problems discussed above fall away the more late-stage a vaccine is.

Commitments become increasingly more efficient, and easier to set since good information to guide the setting of terms is increasingly available, including through standard competitive tenders and through access to scientific information. Commitments become much more easy to make 'additional', via procurement and other devices. There are 'relatively' low levels of capital costs (compared to, e.g. the case of HIV vaccines), and there are much lower risks to biotechs. Many of these reasons are 'fungible' – they apply whatever the source of funding and whoever carries out the research.

The case-studies illustrate a range of current faults in need of rectification. These include an over-reliance on short-run contracts, a range of current market-based risks such as poor demand forecasting, and the need for 'distribution commitments', 'vaccine/health infrastructure commitments', and commitments to tackle market risk at many levels. We already found that APCs (at least as currently designed) for early-stage vaccines even put market risk back on to developers!

In many practical case-studies, the breakthrough was through lowering production costs. This is a large emphasis of the current pneumococcus and rotavirus initiatives. The volume of current purchases is a key variable in this. Technology is important too. What are the incentives and sources of competition for this? Since technological shifts' and achieving multiple producers will depend on access to technology, IP, and know-how, especially at the manufacture and distribution stages, how is this achieved sufficiently early (bearing in mind the high fixed cost and long investment lags in vaccine production) and to ensure long-term supply at low price?

In the cases of vaccines for the poor, there has been an increasingly important role for developing/emerging country developers and manufacturers. For these countries, improvements in their own regulatory infrastructures were important in lowering costs, as were wider sources of finance – and not just the 'deep pockets' finance of big pharmaceutical companies – for a wider set of players. Many of these features are mutually reinforcing, with purchase commitments also having features of coordination devices for other parts of the overall solution. Yet, many of these purchase commitments are *not* 'committee-driven' over long horizons. Indeed, the precommitted APCs in the CGD literature would have conflicted with many of these purchase initiatives. This seems to have been recognized in the case of hepatitis B, a case-study that was dropped from the final CGD report.

If CGD were to have prioritized these late-stage and currently existing vaccines as learning experiences they would have come to realize some of the design faults in the early-stage APCs, and the conflicts these would have created. And this would have generated a more nuanced and sensible approach to the early-stage vaccines too.

Part 3 also reviews lessons to be drawn for the International Financing Facility for Immunizations, IFFIm.

**PART 4** reviews the many scientific difficulties of developing HIV vaccines. The scientific reality is not found to match particularly well that being presumed in the

economic models underlying APCs for HIV vaccine(s). Instead of the assumed simple, linear, unidirectional structure of discovery, the structure is found to be much more cumulative and reflexive, with knowledge links back and forth. Much HIV information discovery has large public-good features rather than the pure private-good nature presumed in the simple underlying models.

Part 4 also explores the complications and challenges posed by combination and therapeutic vaccines. How the structure of an APC of the sort being proposed could possibly reward such vaccine developments is not at all obvious. Indeed, APCs as currently proposed for HIV would tend to aggravate this endeavor. HIV especially illustrates the need for a broader research front, and, again, on its own, an APC would not obviously encourage this.

Some first thoughts on the nature of a 'Global HIV Vaccine Enterprise' are introduced. Several features are drawn out including the importance of continuous, ongoing competition, rather than competition through a committee at one point based on out-of date 'rules'. To achieve this it is not obviously clear that one would want to 'save up' the reward till the end, rather than distribute it over time. Neither is it clear that the notion of a 'Global HIV Vaccine Enterprise' is well captured in the dichotomous caricature of R&D as either push by 'subsidy' or pull by 'outcome'.

**PART 5** (extremely) tentatively suggests what the structure of such a 'Global HIV Vaccine Enterprise' might look like. It suggests a combination of at least four *interlocking* components. It argues that each is necessary; to have one component without the others is, in most cases, worse than not having it at all. These components include: a range of IP changes and more use of certain kinds of 'novel' IP instruments; financial instruments that are connected to IP; an open collaborative information processing mechanism linked to IP and the financial mechanism (including expanded highly transparent clinical and preclinical trials and harmonized regulation); and, for lack of a better phrase, 'contingent purchase commitment' contracts, with much more emphasis on production and distribution, and the terms of which could not be set in advance. Indeed if there had been less obsession with creating an instrument of value for one or two large pharmaceutical players, the CGD instruments would likely, it is argued here, have looked much more like these contingent contracts rather than the benchmark contracts described in Part 1.

**PART 6** looks at the case of malaria vaccines, in light of the recent interest in a potential vaccine being developed by GSK Biologicals in collaboration with the Centro de Investigação em Saude da Manhiça (CISM), with co-sponsorship from PATH's Malaria Vaccine Initiative (MVI), and the approval of Mozambique's Ministry of Health. Part 6 seeks to articulate the much greater complexity and challenge of the scientific problem than is often communicated in the media and, indeed, in the discussion about APCs for 'a' malaria vaccine. In particular, it argues that different vaccines will be needed, and that if an APC of the sort described in the literature is used and if incentives are not to be distorted, this will require the extremely complicated disbursement of APC funds across vaccines over time, even as the rules governing this disbursement must be credibly fixed

in advance based on knowledge of the future science and vaccine needs. Current (UK) policy pronouncements seem to be interpreting the notion of an APC as a first-come first-served 'prize', rather than the "Making Markets" interpretation.

Current signs are that the GSK biologicals case will look nothing like a benchmark APC. Indeed, GSK Biologicals is currently negotiating a further major injection of funding from the Gates Foundation into this particular malaria PPP, suggesting that GSK Biologicals are themselves less convinced of the power and usefulness of the benchmark APC route over the PPP route with procurement fund. Once this is accepted, it is here argued that this case looks to fit in more with the four component vaccine enterprise described above. The inefficiency of enacting just one component for the GSK Biologicals case is pointed out. The conclusion is that the terms of the current malaria deal, and the mechanism in which *it* is embedded, have to be set out (and, for the sake of efficiency, made public) along with a commitment, backed up by resources, to find the much 'better' vaccine[14], with this intent spelled out to GSK Biologicals and others from the start. Indeed this larger effort should be initiated *now*, so as *not* to make it less likely to happen, and should be part of the thinking about *this* case. The political danger is that the early, partially efficacious, vaccine is much more salient and politically valuable than the lost, much more efficacious, vaccine that is never seen or felt.

Part 6 discusses a range of APC issues that the malaria vaccine case illustrates well, including: the problems of interacting a benchmark APC with a complex PPP setting; the problems of generating ultimately 'better' vaccines, especially when there are at least three general approaches to malaria vaccine development with one currently much more explored than the others, and the risk that this poses to those working on current approaches; and the impact of the malaria genome – especially in creating risks for investors into current vaccine projects. It also discusses the importance and priority of a range of treatment and prevention initiatives, all of which are greatly underfunded.

**PART 7** concludes the paper with a discussion of, essentially, the politics of APCs. It warns against a PR-based approach taking over from an approach based on rigorous and critical economic and financial analysis of early-stage APCs, and against the use of evidence that has been heavily selected, and even selectively created, to bolster a case for APCs for HIV, malaria, and tuberculosis. It is also argued that promoters of the APC route for these cases are often too off-hand in their treatment of failure of the approach. There *are* costs to failure: the real resource costs have to be borne by pharmaceutical firms and their shareholders; it is not clear that the program organizers would not *themselves* face costs and litigation if part of the fault lies with them; and the real losers are those who do not get vaccines if the approach fails or if alternative approaches that might have succeeded have lost out to this approach.

Part 7 argues that APC advocates, inadvertently perhaps, also run the risk of providing intellectual succor and reassurance to those thinking of cutting back vaccine research, especially for HIV, in the face of tightening budgetary pressures, and that, indeed, this

[14] This is proxy language for a 'set of vaccines'.

risks deterring private investors – whose projects feed off this research. At the very least APCs should be better tested before risking funding cuts.

The sensible approach in the light of the inherently experimental, speculative, nature of such instruments, the dangers of further delay, the dangers of losing IP rights, and given that we have never *tried* such instruments on *anything*, is to cross-examine – 'stress test' – every aspect of the proposal, and to appeal to independent empirical evidence. It is argued that enacting APCs for HIV, malaria or tuberculosis without learning a great deal first through practical application to other cases runs a series of large risks.

Part 7 suggests an order of G8 priorities:

● First, fully funding the existing product procurement/donation mechanisms run by foundations, companies, non-governmental organizations, and international bodies. This will do most to boost vaccine developers *now*.

● Second, securing a seriously large injection of funding into existing global/regional consortia/PPP's and emerging vaccine enterprises – for HIV alone this would have to be in the order of $12-$18billion over ten to fiteen years – rather than issuing huge way-off financial promises and setting up yet another complex institutional mechanism that will simply act as a drain on current institutions and the 'systems capacity' of GAVI, the Vaccine Fund and others, and exhaust too much political capital;

● Third, making a combination of more targeted funding and, where applicable, purchase commitments for all of the late-stage products in which they are likely to have at least some strength, with the emphasis on getting product price down, the creative use of IP and know-how, and the opening up of the market to competition at late stages of development and procurement;

● Fourth, putting in place an 'Advanced Distribution Commitment' commiting to fully funding the delivery mechanisms for HIV, malaria, and TB vaccines once developed, and including a commitment to remove the barriers to the provision of healthcare in developing economies themselves, especially the tax and regulatory barriers that often prevent the poor from obtaining essential medicines, and a commitment to tackle institutional failure and corruption that holds back provision of healthcare and access to medicines;

● Fifth, downplaying early-stage APCs and – instead of falsely raising policy-makers hopes – concentrate on convincing policy-makers that they need to bite the bullet about paying for up-front HIV vaccine work through a much more collaborative system than we now have, and by fully backing the 'Global HIV Vaccine Enterprise' and other vaccine enterprises. Part 7 argues that such vaccine enterprises should have complete control over whether or not they choose to set up purchase commitments and should not have a large separate APC mechanism imposed from outside in advance, given that this (especially the IP implications) risks aggravating the problems of such enterprises. Such

APCs would have little impact for many years yet be an irrevocable, but badly fixed, experiment that would aggravate more collaborative approaches.

The paper finishes by analyzing the likely outcomes of the 2004-6 G8 Summits. It concludes that policy-makers have been distracted in 2005 from taking real action on early-stage vaccines. It shows how many of the proposals for the 2005 G8 are struggling and how the 'Global HIV Vaccine Enterprise' and other early-stage initiatives could have been much more strategically promoted – as one of the few things that might have achieved G8 agreement and success. The Enterprise approach has the great benefit, compared to many other items on the agenda, of already having the commitment of the US with President Bush's announcement of support at the 2004 G8 Summit. Furthermore, the next G8 holder, Russia, has *more than any other country to gain from a 'Global HIV Vaccine Enterprise'* and could be a great deal more willing to take the baton than currently seems the case. From Russia's perspective, an HIV APC is the least desirable outcome, since by being a likely non-eligible country it would face much higher prices than for vaccines generated under a 'Global HIV Vaccine Enterprise'. Passing an emerging 'Global HIV Vaccine Enterprise' from the USA 2004 G8 agenda onto the Russia 2006 G8 agenda would have the double impact of helping Russia and others to face up to their impending crises too. Given the increasing budgetary pressures both in the US, the UK, and elsewhere, now is a better time than later to be doing something to push the initiative forward and to lock in funding. This would be no mean achievement, whatever else comes out of this year's G8 summit. Instead of wasting energy and political capital trying to set, permanently, a large, currently ineffectual, HIV APC of the sort being proposed in the literature, this strategic opportunity is being squandered.