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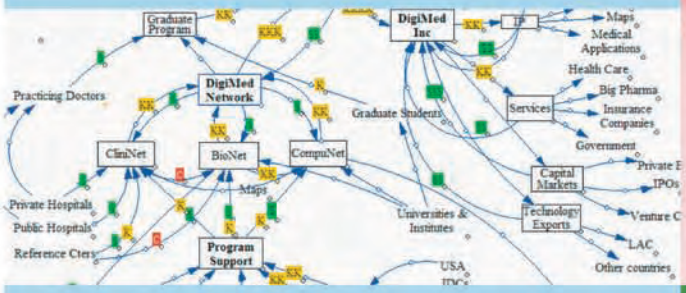

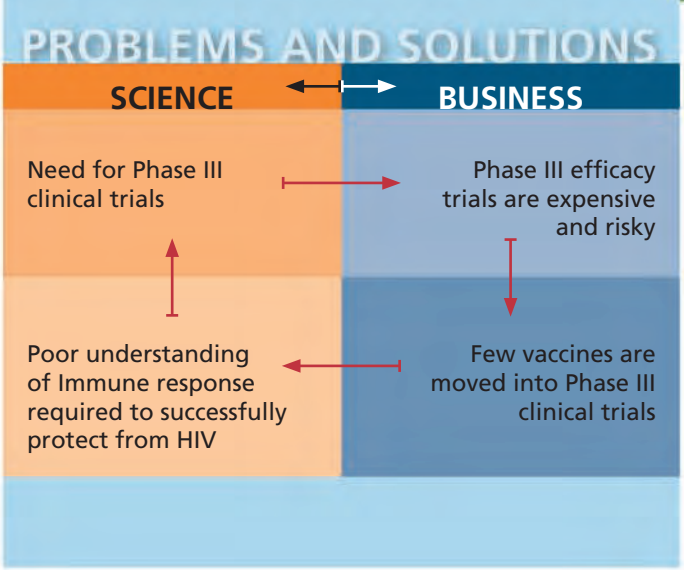

eJournal

An eJournal Sharing Creative and Innovative Ideas and Experiences about Global Issues in Agriculture, Health, and the Environment Facing Developing Countries

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The telescope shown on the cover and below is that used by Galileo Galilei to determine that the earth revolves around the sun. The drawings are representations by Leonardo da Vinci, among others of rounded mirrors, the basis of modern telescopes.

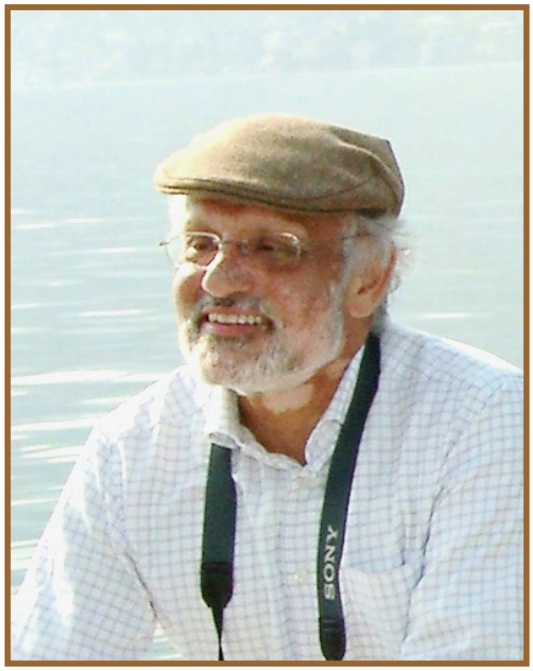
Both Galileo and da Vinci transcend their time because they broke with the disciplinary conventions of their days, pushed the boundaries of science, revolutionized our understanding of the world and our place in it, and shifted humanity's perspective up to the present day.

We hope this *e*Journal will contribute to new insights, knowledge and tools as authors share their creativity and original perspectives.

For Sanjaya Lall

We dedicate this volume of *Innovation Strategy Today* to the late Professor Sanjaya Lall of the University of Oxford, UK, who passed away at his home on June 18, 2005. He was a father and husband, friend and colleague, and most certainly a guiding light for many. We send our condolences and sympathy to his family and to the many friends, colleagues, and students who held him in high regard and loved him.

Sanjaya joined our editorial Board just this April during a meeting on *Health Innovation Systems and Diseases of the Poor in Developing Countries* that he elegantly co-chaired with Carlos Morel in Bellagio, Italy. In retrospect, one of the highlights of my encounter with Sanjaya was his interest in nature. He was fascinated by the blooming trees and flowers in the beautiful gardens of the Bellagio retreat center. On several occasions he would come back from a stroll in the gardens during a break, showing me his latest photographic "acquisitions" on the tiny screen of his camera, with almost child-like enthrallment and excitement. The pictures on the following page were taken by Sanjaya.



As Professor Lall, he was a world authority in the field of development economics, a creative, productive writer[1] and speaker[2] and a pioneering scientist in what is broadly called globalization. His work will live on because it has compellingly shaped our understanding of the world. Thomas L. Friedman contends that the defining economists during the cold war were Karl Marx and John Maynard Keynes, who each wanted to tame capitalism in their own way, whereas the defining economist of globalization was Joseph Alois Schumpeter. But as any reader of Sanjaya's vast publications[3] will be able to testify, he is the defining economist for our understanding of the integration of developing countries into the ever more interdependent and global economic system. Thanks to his analytical power, tremendous insights, and "simple" ways of explaining the complex issues that link developed and developing countries in an increasingly dynamic world, we can see that world more clearly and act in it more effectively.

It is therefore not only appropriate but also intellectually symbolic that we dedicate this volume to our memory of Sanjaya. The three papers in this issue are perhaps emblematic of his mind: first, the paper by *Richard Mahoney, Keun Lee, and Mikyung Yun* develops a theoretical framework to explain the growth of the biomedical industry that is applied to Korea's hepatitis B vaccine industry. The paper's extraordinary analytical power synthesizes the complex aspects of international vaccine development into a logical, rational framework. The second paper by *Rafael Rangel-Aldao* completely changes our perspective on innovation, complexity, networks, and health systems. Its challenging thought will broaden our conceptual horizons, and its concrete proposals to address unmet needs in developing countries through a change in our network and innovation system paradigms will give us new options for action. Finally, *Andrew Farlow* takes a focused, highly critical approach to a policy that asserts to stimulate innovation in global vaccine research and development, specifically 'advance purchase commitments' for vaccines. He firmly rebalances the policy—and debate—about 'advance purchase commitments' for vaccines. Among many other conclusions and recommendations, he proposes an 'Advanced Distribution Commitment' to fully fund the delivery mechanisms for HIV, malaria, and tuberculosis vaccines once developed. With the mounting global fiscal pressures we need to shift attitudes and have the G8 and other leaders put the money where their mouth

is and pay for vaccine work through effective collaborative and competitive systems.

View of the Villa Serbelloni's flowering gardens, Bellagio, by Sanjaya Lall, April 2005

These three papers represent in many ways not only Sanjaya's thinking but also the conclusions—and vision—of the Bellagio meeting he co-chaired and so powerfully influenced. One outcome of that April meeting was a paper that Sanjaya co-authored with many of us and which will be published in *Science* in mid-July (Morel *et al*). In that meeting we came to realize that although a large number of organizations and initiatives to bring improved health care to developing countries have made a rapid, exciting appearance, this has not been accompanied by a commensurate coordinating effort to ensure that all the parts work together, support each other, and lead to success. We concluded that such a concerted effort is needed to better understand—and perhaps even create—a *Global Health Innovation System,* coupled with its capacity to address health innovation for the poor. This does not mean creating a new organization or structure, but thinking more innovatively so that we can better understand, influence, and implement practices and policies that will maximize the system's ability to address the needs of the poor in developing countries.

On behalf of the entire editorial Board and of the authors of this volume, I express my deepest sorrow at the passing of Sanjaya. He was a humble and warm individual who simply had to be admired—and loved; his powerful intellect, penetrating insights, and humor made us respect and esteem him greatly. We shall all remember him as a tremendously skilled individual, with deep thoughtfulness and, above all, extraordinary humanity. And we shall miss Sanjaya's contributions in translating our vision—and inspiration—acquired in Bellagio into reality.

We entreat his spirit to guide us in our endeavors.

Anatole Krattiger
Editor-in-Chief, July 2005

Photo of Lago di Como as seen from the Villa Serbelloni, Italy, by Sanjaya Lall, April 2005

1 http://www.economics.ox.ac.uk/Members/sanjaya.lall/cv.htm lists his publications and CV.

2 For a video clip of a presentation at The World Bank, visit http://info.worldbank.org/etools/bspan/PresentationView.asp?PID=1254&EID=620

3 For example, Lall. 1999. *Promoting Industrial Competitiveness in Developing Countries: Lessons from Asia*. Commonwealth Economic Paper No. 39. Oxford: Queen Elizabeth House, or Lall. 1997. *Learning from the Asian Tigers: Studies in Technology and Industrial Policy*. Palgrave *Mac*millan.

Intellectual Property, Drug Regulation, and Building Product Innovation Capability in Biotechnology: The Case of Hepatitis B Vaccine in Korea

Richard Mahoney[1], Keun Lee[2] and Mikyung Yun[3]

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Executive Summary

This paper develops a theoretical Framework to explain the growth of the biomedical industry and applies it to Korea's hepatitis B vaccine industry. In the Framework and analysis, special emphasis was given to the roles of intellectual property (IP) and drug and vaccine regulations, which are what make this industry unique compared to other industries.

Our study shows that Korean vaccine manufacturers were not significantly inhibited by existing IP in developing their vaccines. These companies were able to obtain the requisite IP through joint ventures. The formation of these joint ventures was favored by the attractive domestic market for hepatitis B vaccine in Korea and the existence of technically capable scientists and engineers who could produce the vaccine. The successful development of the vaccines also reflects the government's improvement of the Korean Food and Drug Administration to more closely meet international standards. These stories of success and failure show how important it is for latecomer or catch-up firms to get access to foreign knowledge or IP, an outcome already suggested by other detailed case studies of seven industries.

According to the dynamic Framework, Korea passed through the first two Stages of the Framework roughly in 10-year steps through the 1980s and 1990s and is now in Stage 3. Today, Korean companies are seeking to develop original new vaccines. If they succeed, they will become full players in the international markets to develop and commercialize new vaccines. That means that the Korean bio-medical industry will move to the final development stage, namely full product innovation capability.

Other developing countries are progressing through the Four-Stage Framework to reach the status of Innovative Developing Countries (IDCs). To reach the status of an IDC (Stage 3), they need to give concerted attention to six determinants of product innovation:

- R&D in the public and private sectors
- Ability to manufacture new health technology products to high standards
- National distribution systems in both the public and private sectors
- International distribution systems including supply through international organizations such as UNICEF, the operation of global funds, and trade among countries
- Systems to manage IP for countries and organizations
- Systems for drug and vaccine regulation to achieve safety and efficacy

Other IDCs, as well as countries in Stages 1 and 2, can probably benefit from the lessons of Korea's experience. In addition, it is likely that one or more IDCs, such as India and China, will move to Stage 4 in the coming years, and it will be useful to study this transition.

Mahoney R, K Lee and M Yun. 2005. Intellectual Property, Drug Regulation, and Building Product Innovation Capability in Biotechnology: The Case of Hepatitis B Vaccine in Korea. *Innovation Strategy Today* 1(2):33-44. www.biodevelopments.org/innovation/index.htm

Introduction

New health technologies for the poor in developing countries urgently need to be developed. HIV, malaria, tuberculosis, diarrheal diseases, and respiratory infections disproportionately affect the poor in developing countries, but few vaccines and drugs exist for these diseases. While biotechnology research and development (R&D) is generating a large number of new technologies for the wealthy in developed countries, the poor are not similarly benefiting from the new science. One survey found that between 1975 and 1999, of 1,393 new-marketed pharmaceutical chemical entities only 16 were for tropical diseases or for tuberculosis.[1]

Several developing countries, including Brazil, China, India, and South Africa, are rapidly increasing funding for biotechnology. Some of their pharmaceutical companies have entered the international market with both generics and self-developed products. These countries and others are also improving their drug regulatory agencies and are adopting modern laws and regulations for intellectual property (IP) management. Rapid economic development is leading to expanded domestic markets, allowing for demand to grow for products addressing domestic diseases. We refer to this group of rapidly advancing developing countries as Innovative Developing Countries (IDCs).[2] Because diseases of the poor disproportionately affect their own population (and other developing countries), IDCs may become a major means for health product innovation for diseases of the poor.

It is important, therefore, to assess the changes taking place in IDCs and to seek to develop insights about how IDCs can best participate in and, in some instances, lead efforts to develop new health technologies for the poor in developing countries. Such an assessment should take into account changes in biotechnology manufacture, local demand for these products, potential for export, the nature and extent of public and private sector support for biotechnology research, and the changing environment of intellectual property rights and of drug and vaccine regulations. We will propose a Framework for analyzing these factors.

Using this Framework, we assess the development of health product innovation in Korea and, in particular, study the development and commercialization of hepatitis B vaccine. The major events that made Korea an important player in the supply of this vaccine for use in developing countries occurred from the early 1980s to the early 2000s. Today, Korea is a high middle-income country with membership in the OECD (Organization for Economic Cooperation and Development) and with a per capita GNP exceeding $10,000. Its development has been rapid—in 1954 it was one of the two poorest countries in the world. Since then, its economy on average has grown more rapidly than any other country in the world. Korea could therefore provide a model for other developing countries. In particular, we believe that Korea's experience can provide useful insights for understanding how product innovation capability in IDCs can contribute to the development of important health products for the poor. Because of the extensive controversy about the implications of IP rights for the availability of health products to the poor,[3,4] we have examined in-depth how IP evolved in Korea during this time and how this evolution affected the development of hepatitis B vaccine by Korean manufacturers. In particular, we look at the attitude taken by the Korean government and pharmaceutical companies toward TRIPS.

A Framework for Analyzing the Biomedical Industry

The Six Determinants

In this paper, we propose a theoretical Framework for analyzing the development of the biomedical industry in developing countries. Our Framework modifies work by Lee and Lim (2001) and Suh (1995).[5] We have adapted their Framework, which dealt with industries such as telecommunications, to apply to health product innovation.

Lee and Lim (2001) have introduced a framework to identify the determinants of technological and market catch-up by latecomer firms. In their model, technological regimes of industry, a concept developed by the Neo-Schumpeterians Nelson, Winter, Breschi and others, are considered as the determinants of the expected chance for product develop-

ment,[6] whereas such factors as cost edge, product differentiation, and first-mover advantages enter as determinants of the market success of the to-be-developed products. In addition, their model considers the importance of firms' strategies and the role of the government as additional determinants of catch-up by latecomer firms. These factors also affect both the chance for product development and market success.

The literature defines the technological regime of an industry by the combination of technological opportunities, appropriability of innovations, cumulativeness of technical advances, and the content of the knowledge base of a specific industry. As far as catching-up is concerned, not all of these factors are relevant. For example, for R&D activities by catching-up firms, appropriability of innovations would have less importance since, in most cases of catching-up, they are trying to emulate existing technologies. Lee and Lim, and Lee, Lim, and Song emphasize the importance of access to the external knowledge base (technology transfer) since it critically affects the latecomer's R&D prospect.[7] This access can come in diverse forms, including informal learning, licensing, foreign direct investment (FDI), strategic alliances, and co-development. The experiences with consumer electronics, PC, D-RAM, mobile phones, and, most recently, digital TV all indicate the importance of access to the external knowledge base, although the exact channels of access are diverse and depend upon the industry.

This issue of access to an external knowledge base now tends to be intertwined with the issue of IP; this is especially so for biotechnology. In the biotechnology industry, both explicit knowledge, which can be protected by patents, and know-how and trade secrets are important. Thus, for health products, access to knowledge often includes IP arrangements, and firms of advanced countries are reluctant to transfer technology when there is inadequate IP protection. Accordingly, we give special consideration to IP in our Framework and paper.

Another modification for biotechnology is the role the government plays when latecomers catch-up. In earlier evaluations of other industries, the role of the government would be discussed in terms of market protectionist measures for local producers, private-public collaboration in R&D, and/or R&D subsidies. While these are still relevant for the biotechnology industry, an additional role of the government is in the regulation of drugs and vaccines for health safety. Thus, we emphasize in our Framework and paper the drug and vaccine regulations of governments and international agencies.

In our Framework to analyze the biotechnology industry, there are six determinants of health product innovation:

- R&D in the public and private sectors
- Ability to manufacture new health technology products to high standards
- National distribution systems in both the public and private sectors
- International distribution systems including supply through international organizations such as UNICEF, the operation of global funds, and trade among countries
- Systems to manage IP for countries and organizations
- Systems for drug and vaccine regulation to achieve safety and efficacy

These six determinants can be grouped into four major categories: Manufacturing capability, R&D capability, National and International Distribution System Development, and Regulatory Environment (IP and drugs). This can be compared with Lall's suggestion of four determinants: Technological Activity, Competitive Industrial Performance, Technology Imports, and Skills and Infrastructure.[8] These four determinants span our determinants of Manufacturing capacity, R&D capacity, National and International Distribution System Development, and R&D Development. While Lall uses IP systems as an implicit determinant, because of our focus on biotechnology, we put explicit emphasis on IP and have added the sixth determinant of drug and vaccine regulation.

The determinants of the Framework are linked dynamically. Progress in one element requires progress in most—if not all—other determinants. It is difficult to progress in R&D capability without first increasing manufacturing capability or having a national or international (export) market (distribution system) to generate resources for investment in production facilities. One way that developing countries can access new technologies for local companies is to

enter into joint ventures with sophisticated firms in developed countries. But, as Lall points out, sophisticated foreign firms will decide to form joint ventures based on the value of the domestic market in the developing country, the capability of local R&D centers, and the expected level of IP protection. The interconnectedness of the six determinants is therefore very strong.

Because both IP and drug regulations are new elements in innovation theory, we provide an in-depth elaboration of them in our presentation of the Framework.

From Knowledge Access to the Role of IP

IP policy-making in developing countries has conflicting goals in terms of levels of protection. One goal is to encourage the influx of foreign technology. This can be achieved by providing an adequate level of protection for IP rights, which would enable foreign IP owners to pursue profits through licensing, marketing, and investment in the recipient country. This is especially the case when domestic R&D is mainly concerned with imitating or modifying foreign technology. On the other hand, developing countries have had access to foreign technology cheaply and have built up manufacturing capability more quickly when unfettered by IP rights. These advantages were incentives to provide a low level of IP protection, especially because there were few domestic innovators who could be harmed by such a regime. These insights lead to a dynamic perspective. In the early stage of catching up, conflicts with foreign IP holders are minimal because domestic capability is poor and no foreign firms are interested in bringing technologies to the country. As the country's technological capability improves, poor protection of foreigners' IP rights is likely to conflict with the further promotion of domestic capability. In the last stage, when local firms are able to generate their own IP, local demand for greater IP protection will increase, which will reduce conflicts with foreign IP holders.[9]

But this general picture of the dynamics of IP protection in developing countries does not apply to the pharmaceutical industry because of the special status of IP. In fact, the impact of IP on access to affordable medicines by poor developing countries was a major debate issue recently in the World Trade Organization (WTO). This debate focused largely on the rights of signatories of the TRIPS Agreement[10] to grant compulsory licenses and to engage in parallel trade. Some felt that unless developing countries had clear rights to these, then they would be unable to obtain needed drugs at affordable prices.[11] On the other hand, others felt that compulsory licenses and parallel trade attack the very foundations of the rationale for intellectual property rights, which they argue apply equally well in developed and developing countries.[12,13] The debate led to the Doha Declaration,[14]which re-affirmed the right of developing countries to protect the health of their people and noted that such protection might be achieved by compulsory licenses or parallel trade.

Although the implications of the Doha Declaration are by no means clear, the general long-term trend seems to be toward stronger IP protection. On January 1, 2005 most developing countries (excluding the least developed) that are members of the World Trade Organization and have signed the TRIPS Agreement will have to abide fully by the requirements of TRIPS. There are several implications for these countries, particularly with respect to pharmaceuticals, including vaccines. First, countries will have to issue or recognize patents for pharmaceuticals. Many countries, such as India, had excluded pharmaceuticals from patentability. They will have to award product patents instead of the common practice of awarding only process patents. The process-patent-only system has been one means by which developing countries have been able to copy patented drugs from developed countries. In addition, these developing countries will have to accord equal protection to patentees, regardless of whether they are citizens of the country or not. Some developing countries have tended to offer greater protection to patents by their own citizens to the detriment of foreign patentees. One means to accomplish this was to grant patents in narrow fields.[15] Further, developing countries will have to enforce patents issued by their patent offices, regardless of whether the intellectual property is used or not within the country. Local production will no longer be a requirement for a patent to retain validity. Each of these changes will inhibit practices that were originally established to stimulate local innovation and protect local industry. There is great controversy as to whether the disappearance of these practices will help or hurt the concerned countries.

Because of the extensive controversy surrounding the implications of IP rights for the availability of health products to the poor,[16,17] we have examined in-depth how IP evolved in Korea during the hepatitis B case study and how this evolution affected the development of hepatitis B vaccine by Korean manufacturers. In particular, we focus on the attitude taken by the Korean government and pharmaceutical companies toward TRIPS.

Market Success and the Special Role of Drug and Vaccine Regulation

One key difference between the pharmaceutical industry and most other industries, such as consumer electronics, is the role of the drug and vaccine regulatory system. The IP system and the regulatory system often progress in tandem.[18] In the early stage, there is little need for a well-developed national regulatory system. Most drugs and vaccines are imported from other countries, and it is assumed that the regulatory agencies of the producing countries take the necessary steps to ascertain safety and efficacy. Any local production is usually on contract to some foreign company, and the foreign company takes steps to ensure quality control to meet regulatory standards in their home country or other countries in which the products will be sold.

However, as local production of copied products intended for the domestic market becomes important, the need for local regulation emerges. The government now has an interest in checking the quality of the products. The main activities, however, are to check composition and review the production facilities. In the later stage, much more developed regulatory capability becomes necessary. Domestic companies want greater regulation for two reasons: they need an agency that can work with them to establish an approval process for newly developed products, and they need a fairly capable regulatory agency to support the development of export markets.

In this regard, we observe that drug-related regulations of international organizations, like WHO and UNICEF, also had a critical role in promoting the growth of vaccine producers in developing countries, like Korea. Indeed, the relationship between health product innovation and the role of regulatory agencies has significantly changed. During the 1960s and 1970s, regulation followed innovation. Scientists and manufacturers would design a new product and then request a regulatory agency to approve it for safety and efficacy. Today, increasingly stringent regulation drives innovation. Regulation affects virtually all aspects of product development. This includes laboratory procedures, equipment, and reagents. It also includes requirements for making prototypes and clinical evaluation lots. This dramatic change has been driven by regulatory authorities in Europe and the United States, primarily the U.S. Food and Drug Administration (FDA). Meeting regulatory requirements is the most significant component of the overall cost of drug and vaccine development, and these costs have risen dramatically in the last decade. The total cost of developing a new drug by firms in the U.S. has increased from $318 million according to a 1991 study to $802 million in a 2003 update of the same study.[19]

In the early 1990s, WHO recognized that these increasingly stringent regulations would have important implications for regulatory agencies in developing countries. As part of the Children's Vaccine Initiative, WHO examined the implications of these changes for the development, production, and distribution of vaccines. WHO adopted the view that there could not be two levels of regulatory requirements in the world, one for developed countries and one for developing countries. Instead, there should be a single standard. Therefore, WHO launched a program to provide technical assistance to national regulatory authorities in developing countries. An important reason for wanting to assist these regulatory authorities was to help national vaccine producers become suppliers to other developing countries. It was thought that producers in developing countries, like Korea, should be encouraged because they might be able to supply vaccines for less than producers in Europe and the United States.[20]

UNICEF is the principle procurer of vaccines in the public sector for supply to developing countries. Before UNICEF will purchase vaccine from a producer, the producer and the national regulatory agency must have been reviewed by WHO to receive "prequalification." As the Korean case suggests below, such procedures as on-site inspection and qualification also provide an excellent learning opportunity for developing countries.

Development of Hepatitis B Vaccine and Its Market in Korea

The Story

Two types of hepatitis B vaccine have been commercially produced: plasma-derived and recombinant DNA derived. Both vaccines consist of hepatitis B surface antigen (HBsAg) suspended in medium and adjuvant. Plasma-derived vaccine is made by separating the HBsAg from the plasma of individuals who previously were naturally infected with hepatitis B. Recombinant DNA vaccine is made by genetically modifying yeast cells so that they will manufacture HBsAg during fermentation. This vaccine is often referred to as rDNA hepatitis B vaccine. The plasma-derived vaccine was developed as early as 1974; the recombinant DNA vaccine was developed in the early 1980s. In general, in the early 1980s hepatitis vaccines became more widely available in the United States and Europe.

Small amounts of vaccine were also imported into Korea in the 1980s, but there was no local production capability and little research capability in vaccines. However, hepatitis B infection was a major health problem in Korea, and the imported vaccine was very expensive, limiting its use to only the wealthy. Thus there was a great deal of interest in the medical community and government circles to provide hepatitis B vaccine, and initiatives were launched to establish local production.

The Korean strategy was to get access to foreign know-how for vaccine production and to establish production facilities as soon as possible, hopefully before or around the time that product patents were allowed in 1987 in Korea. Two companies were involved with plasma-derived vaccines: Green Cross Corp. and Cheil Jedang Group (CJ). The former hired a Canadian (Korean-born) scientist to teach it how to make hepatitis B vaccine from plasma. This technology transfer did not infringe on any Korean patent. The latter obtained its technology by negotiating a license for a patent held by the New York Blood Center.

However, the late-developed rDNA vaccine soon took over the market from the plasma-derived vaccines because of concerns about making a vaccine from human blood. Thus, the Korean companies faced the new challenge of developing an rDNA vaccine too. Another company, LG Chem, also entered the industry to produce rDNA vaccine. Each company took a somewhat different route to develop the vaccine.

One incumbent firm, Green Cross, collaborated closely with a foreign source of knowledge and technology. It obtained patented technology from a German biotech company: RheinBiotech. The arrangement involved RheinBiotech taking a controlling interest in Green Cross. We note that the mode of cooperation changed from negotiating a license and/or hiring an expert consultant with the requisite knowledge in the case of plasma vaccine, to establishing a JV (joint venture) in the case of rDNA vaccine. The new-comer LG Chem decided to establish its own in-house R&D program to develop an rDNA hepatitis B vaccine. To accelerate this process, it formed a joint venture with a US biotechnology firm, Chiron Corp., that had access to the know-how for producing hepatitis B vaccine from yeast.

These two cases were successful. Both companies were able to launch their vaccines in the mid-1990s. By the late 1990s, the Korean companies were exporting recombinant DNA vaccine, and they led the way in driving down prices in the international market. Prices fell from as much as $30 per dose to less than $0.25 per dose by 2003. These two companies are the major players in the Korean markets as of 2004.

The route taken by the CJ Group did not lead quickly to success. Its idea was to develop an rDNA vaccine independently by using technology similar to that employed by LG Chem. Its methodology for production of the vaccine, however, was significantly different, namely a mouse cell line. This attempt did not succeed, partly because the Korean FDA refused to consider licensing a product using the mouse cell line.[21] Compared to the other two firms, CJ's development program took more time. While the first two already enjoy significant market sales, CJ still sells the older plasma-derived product and is only beginning in 2005 to produce an rDNA vaccine for commercial distribution from factories in Korea and Myanmar.

Roles of the Government and Drug Regulations

Once local production of hepatitis vaccine was in place, the government established a program of universal immunization for infants, thereby guaranteeing a profitable market for the producers. The government also played a critical role in enlarging the export market (international distribution system). It provided export encouragement that continues today. Through ODA (Official Development Aid), the Korean government supports a program for Korean companies to build vaccine factories in Myanmar and Vietnam.

Creating or guaranteeing an initial market has also been very important for other industries. In the case of CDMA mobile phone technology, the Korean market was established when the government declared CDMA as the exclusive national standard.[22] Similarly, for digital TV, the US markets were established when US standards were decided in favor of digital TV rather than analogue TV.[23] In the case of hepatitis vaccine, similar roles were played by government initiatives for universal immunization, export promotion, and, most recently, the ODA program.

We also note another important element of the initial market guarantee for vaccines. Without some prospects for market success, the foreign companies with IP and knowledge would not have interests in setting up a JV or licensing in Korea. In other words, developing an initial market (domestic or international) is important for inducing foreign companies to enter into joint ventures in a developing country.

Drug-related regulations and international organizations, like WHO and UNICEF, also had a critical role in promoting the growth of vaccine producers in Korea. Their role can be discussed in terms of both providing markets and implementing vaccine regulations and technical assistance.

As noted earlier, the relationship between health product innovation and the role of regulatory agencies has changed significantly. With ever-rising health standards, primarily led by the U.S. FDA, the cost of meeting regulatory requirements has risen dramatically in the last decade. In the early 1990s, WHO recognized this and, as part of the Children's Vaccine Initiative, launched a program to provide technical assistance to national regulatory authorities in developing countries. One important reason for such assistance was to help national vaccine producers become suppliers to other developing countries. It was thought that producers in developing countries should be encouraged because they might be able to supply vaccines at lower cost than producers in Europe and the United States.[24] UNICEF is the principle procurer of vaccines in the public sector for supply to developing countries. Before UNICEF will purchase vaccine from a producer, the producer and the national regulatory agency must have been reviewed by WHO to receive "pre-qualification." In the mid-1990s, a WHO team visited Korea and found that the producers could be pre-qualified but that the regulatory agency needed additional upgrading. WHO provided technical assistance, and eventually Korea satisfied WHO's requirements.[25] The Korean manufacturers are now major suppliers to UNICEF and have led the way in offering lower prices for hepatitis B vaccine. This is a clear illustration of the interconnectedness of regulation and markets.

Summary

We have examined the role that IP considerations played in the development and commercialization of recombinant DNA hepatitis B vaccine in Korea. Our study shows that in development of their vaccines Korean manufacturers were not significantly inhibited by existing IP. These companies were able to identify ways to obtain needed IP through joint ventures. The formation of these JVs was favored by the attractive domestic market for hepatitis B vaccine in Korea and by the existence of technically capable scientists and engineers who could produce the vaccine. This success in developing the vaccines also reflects the government's willingness to improve the Korean Food and Drug Administration so that it more closely meets international standards.[26]

We note that two successful cases with rDNA vaccine involved obtaining access to foreign knowledge through joint venture arrangements and thereby avoided possible IP problems. For rDNA vaccine, CJ Group tried (and failed) to develop a new method without pursuing either licensing or a joint venture. These stories of success and failure indicate how important it is to gain access to foreign knowledge or IP for developing country firms that are latecomers or catching-up. This is confirmed by detailed case studies of seven other industries.[27]

We note that Green Cross could be seen as an incumbent and LG Chem as a new entrant. Thus, according to the classification proposed in Lee and Lim's work, we can consider the Green Cross entry as a case of catch-up and LG Chem's as a path-following but stage-skipping catch-up.[28] LG Chem did not start from the first-generation plasma vaccine but jumped directly to the second-generation rDNA vaccine. The third example of CJ is an effort to catch-up by creating a new path, but it got delayed as it explored a new method for generating rDNA vaccine. We would not consider the CJ case a failure, not only because it is about to launch its own product, but also because it certainly accumulated lots of valuable tacit knowledge in its first effort.

IP and Growth of Biotechnology in Korea: A Dynamic Overview

A Dynamic Version of the Framework

The growth of biotechnology in Korea is a direct result of the high priority the government and industry has accorded to this field. Between 1981 and 2001, the Korean government investment in all R&D increased 40 times from $320 million (0.56% of GDP) to $12.2 billion (2.96% of GDP). By 2007, it is expected to reach 7% of GDP.[29] These growth figures are the highest in the world. The average annual growth rate in R&D funding per gross domestic product from 1981-1991 was 24.2%, compared to 22.3% in Singapore, 15.8% in Taiwan, and 7.4% in Japan.[30] To promote research, the government has launched special initiatives in ten fields, including biotechnology. This special initiative provides funding for up to ten years at an annual level of $800,000 to $900,000 for each Lead Project.[31]

The growth of biotechnology in Korea is illustrated by the following chart, which shows the patenting trends in Korea and the US for vaccines. The red bars indicate the number of Korean patents related to vaccines obtained by Korean inventors in Korea. The blue bars indicate the number of US patents related to vaccines obtained by Korean inventors. It is clear that Korean vaccine biotechnology evolved rapidly, especially beginning in the mid-1990s.

The growth of the biotechnology industry in Korea can be interpreted in terms of the six Framework determinants proposed in section 2. Here we propose a dynamic version of the Framework, one better suited to explain the industry's long-term evolution. It is presented in Table 1. While Linsu Kim and others have proposed a similar stage theory of technological development in developing countries, our contribution is to add the two elements of IP and drug regulations, which allows us to more effectively use the framework for the biotechnology industry.[32]

Korea was able to develop a vaccine industry very rapidly because it was able to address each of the determinants of the Framework:

- Manufacturing and IP: Get access to knowledge and technology (i.e., solve the IP and manufacturing challenges through joint ventures or license agreements with leading firms in the West). The Korean firms did not infringe patents. Also, in the 1970s and 1980s, Korea was not yet an attractive country for foreign companies to seek patents in. Korea was then still in Stages 1 and 2.
- National and International Distribution Systems: Reduce the risk of securing the initial market and lay the basis for accessing export markets. Rapidly growing international and national markets existed, and the Korean manufacturers' competitive advantages could be exploited owing to the low costs of production and the possibility of "process differentiation"[33] unique to vaccines.
- Drug regulation: Build up its drug regulatory capability. It did this partly by taking advantage of assistance from WHO and others.
- R&D capability: Provide generous support for human and institutional capacity development in health product innovation. This was accomplished through the large increases in Korea's R&D budget during this time.

Korea passed through the first two Stages of the Framework in roughly 10-year steps during the 1980s and 1990s. It is now in Stage 3. Other developing countries progress through a Framework with three Stages to reach the status of IDCs. To reach Stage 3, they need to give concerted attention to six determinants of product innovation. An extensive literature interpreting the technological development of Korea using a similar framework already exists. In what follows, therefore, we will focus on the IP aspect of the development by using the dynamic Framework.

Table 1: The Four Stages in the development of biotechnology

	Development of Manufacturing	Development of Distribution Systems		Development of R&D Capability		Development of Legal and Regulatory Systems	
		National	Int'l	Private Sector	Public Sector	IP	Drug and Vaccine Regulation
Stage 1 – Establishing the foundation	Importation of finished goods or assembly of finished products.	Small domestic market.	Very little except as toll manufacturer.	Very little.	Very little.	Initial development allowing patents for local inventors; foreign inventors not interested.	Very limited.
Stage 2 – Capacity building	Production on license or by copy.	Growing local market of increasing interest to foreign companies. Import substitution.	Growing. Companies learning how to establish export markets.	R&D to understand technology either to produce on license or to copy.	Development of university and independent research centers. Capacity building.	Foreign inventors getting interested, and local inventors starting to file more patents.	Limited services but without enforcement capabilities.
Stage 3 – Maturation IDCs	Manufacture of domestically developed high technology products.	Rapidly growing domestic market of interest to foreign companies.	Increasing exports that are becoming a significant contribution to GNP.	Small-scale advanced R&D effort capable of creating new products for domestic and export market.	Vast acceleration of funding for R&D. Development of major research centers. Linking with private sector.	Advanced IP system but not fully meeting TRIPS requirements because of lack of enforcement.	Advanced capabilities but not at highest level because of lack of enforcement capabilities.
Stage 4 The most-developed countries with a drug or vaccine industry	Highest capabilities to produce high technology drugs and vaccines.	Highly profitable market in both the public and private sectors, generating profits to support, in part, advanced research.	Global companies.	Generous support for health research from basic to applied. Large research investment by private companies including large pharmaceutical manufacturers and biotechnology companies.		A sophisticated system of IP management according to the requirements of the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS).	A sophisticated agency overseeing regulatory approvals of drugs and vaccines; the government also oversees clinical trials & production facilities and enforces rules/regulations.

Development of IP Systems in Korea

Korea is an interesting case study of a country that developed economically and, for the most part, independently enhanced IP protection without the requirements of TRIPS. Having joined the World Intellectual Property Organization in 1979, Korea acceded to the Paris Convention in 1980 and the PCT in 1984. It revised its laws in 1987 to allow product patents. Thus by the end of the 1980s, Korean laws and policies largely conformed to the requirements that TRIPS would eventually impose.

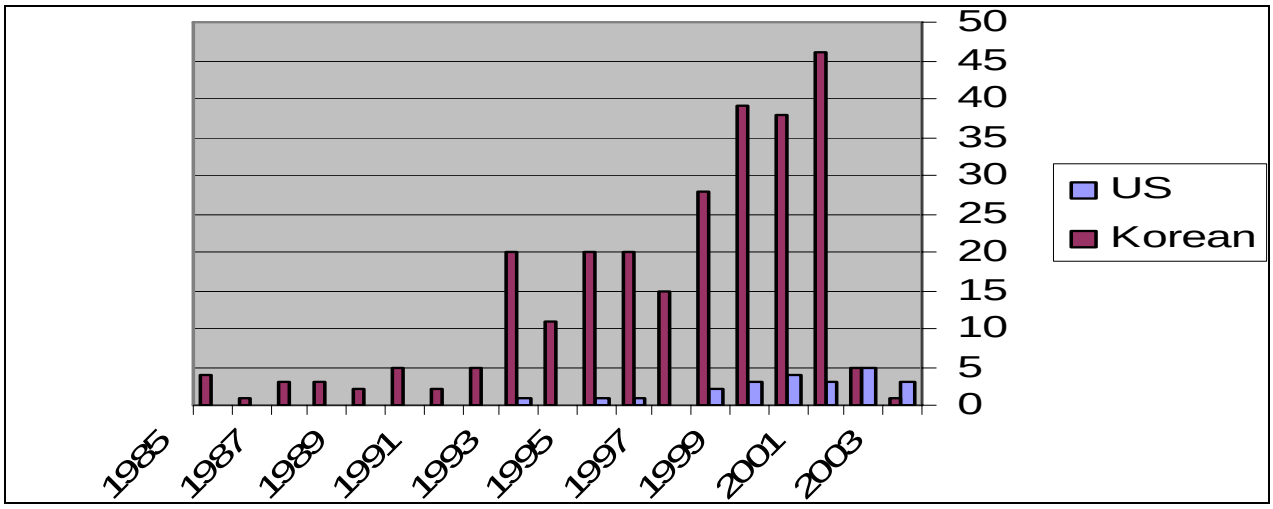
As with the development of biotechnology R&D capability, we suggest that Korea completed Stage 1 of its IP system in about 1990. Korea acceded to the TRIPS agreement in 1995, and further revised its IP laws in 1997-98 to reach full compliance with TRIPS. The World Trade Organization conducted a Trade Policy Review of Korea in 2000 and concluded that "protection of [intellectual property] rights has been strengthened by the signing of the new treaties, increased international cooperation, and stricter enforcement."[34] Based in part on the patent data in Figure 1, Korea seems to have completed Stage 2 of its IP system in about 2000, again in tandem with its progress in biotechnology R&D capability.

Like many other countries, Korea received great pressure from the US government to enhance its IP protection and enforcement. This pressure was particularly strong running up to the signing of the TRIPS Agreement because the US wanted to bring Korea out of the camp of developing countries, which were then strongly opposed to the TRIPS Agreement.[35] However, in the recent debate in the WTO on public health, Korea was able to hold its own position. This debate focused to a great extent on the rights of signatories of TRIPS to grant compulsory licenses and to engage in parallel trade. Actively participating in the debate, Korea took a middle ground, partly because its pharmaceutical industry is mainly concerned with producing generics for domestic consumption. It has few proprietary products in international commerce. Concerns, therefore, over whether developing countries might produce Korean proprietary products without license were muted.

The Role of Public Research Organizations in Biotechnology

How IP management in public research organizations is regulated is an important aspect of biotechnology innovation. Unlike the United States, Korean universities and research institutes were not major sources of technology for Korean industry during the 1980s and through most of the 1990s. Thus, most Korean companies wishing to obtain new technology had to look outside the country. In the United States, the Bayh-Dole legislation had gone into effect in 1980, and universities invested heavily in efforts to manage new IP that they developed. This included not only the out-licensing of patents for inventions made by research scientists, but also the creation of start-ups, which allowed a professor to set up a company for the specific purpose of developing an invention into a commercial product. Beginning in the late 1990s, Korea revolutionized its laws and regulations in respect to IP management by public institutions. Public universities were allowed to retain ownership of new IP and were encouraged to set up technology transfer offices. The *Technology Transfer Facilitation Law* was passed, mandating the establishment of technology transfer offices and setting guidelines for sharing licensing income with a specific allotment for the inventors.

Figure 1: US patents by Koreans related to vaccines *(Source: www.uspto.gov)*



In addition, Korea established the Korea Technology Trade Center (KTTC). The KTTC identifies particularly promising technologies, Korean or otherwise, and then works with potential partners to put together licensing arrangements. KTTC also has capabilities in market analysis and technology valuation. In the field of vaccines, KTTC played an important role in creating the joint venture, Celltrion, whose investors included private Korean parties and VaxGen, a U.S. based company concerned with vaccine development. Celltrion seeks to become a major international resource for the production of vaccines, monoclonal antibodies, and related products. Furthermore, to encourage technology transfer from public research organizations to venture firms, the *Special Measures on Venture Firms* was amended in 1998 to allow scientists in public research organizations to own equity and directly participate in venture businesses. With the permission of the research organization, staff scientists can hold joint positions in venture businesses or take temporary leave of absence.

In addition, under the *SME Start-Up Support Act*,[36] some fifty public research organizations are designated as venture incubation centers, providing technical and managerial assistance, and low cost R&D labs and other facilities for small start-ups. Many of these start-ups are spin-offs from the public research organizations. In 2001, the government took further action, unifying the policies and procedures for IP management by public research organizations. The impact of these changes in Korea has been dramatic: public research organizations have sharply increased activities in patenting, licensing, and the promotion of start-ups—particularly in biotechnology. In the United States, the areas around Cambridge, MA, and San Diego, CA, are recognized as focal points for biotechnology start-ups. They feed off the strong academic centers in their regions. Similarly in Korea, the Pohang University of Science and Technology (POSTECH) and the Korean Institute of Bioscience and Biotechnology (KRIBB) have become major sources of IP for start-ups and for existing commercial biotechnology firms in Korea.[37]

In sum, the development of IP systems in Korea has evolved in tandem with the evolution of biotechnology innovation capability, moving from Stage 1 to Stage 2 in about 1990 and moving into Stage 3 in about 2000.[38]

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Innovation, Complexity, Networks and Health

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Executive Summary

Innovation is here to stay; the term is everywhere. Many consider it the solution for almost any type of problem, whether academic, business, economic, social, or, more recently, the rapid development of low- and medium-income countries. Innovation, however, is rarely expressed properly. It is frequently confused with just anything novel, regardless of its usefulness or market impact. It is also closely associated with research and inventions, or more often simply with new commercial products. But none of the indices for either R&D or invention tell us much about what innovation really is and how it is produced—much less why it circulates and is widely diffused in certain countries but not in others. Moreover, some of the proponents of the innovation panacea often overlook the fact that innovation does not occur in a vacuum but is deeply rooted in uncertainty and complexity.

Innovation matters because it responds to the greater complexity caused by the ever-increasing uncertainty of systems far from equilibrium. This state of non-equilibrium appears in open systems, whether nations, companies, or communities, because they are permeable to external influence. Uncertainties are also expressed as "discontinuities" that drive and are driven by innovation. They may arise from many different sources, such as the disruptive technologies of biotechnology and nanotechnology. Disguised as market discontinuities, uncertainty produces complexity everywhere in many shapes and forms, but all focused on a sole objective: adapting to the continuous change of an ever-increasing magnitude. This adaptation, the satisfaction of unmet needs, is synonymous with innovation.

Complexity implies a high degree of differentiation and compartmentalization of function. This demands an even higher degree of connectivity and coordination among different parts of a system to assure effectiveness, efficiency, and direction of the whole. Nature deals with complexity by self-organization rather than by command and control, and this essay explains how a self-organizing system underlies most processes of innovation. Self-organization usually takes the form of scale-free networks with nodes and links distributed non-democratically. In other words, the better-connected nodes (hubs) are more likely to attract and form more links than poorly connected ones, so the rich nodes get richer, usually "at the expense of the poor."

Innovation is thus a part of the complexity of scale-free networks. Innovators are the hubs that connect to and lead others to follow their groundbreaking paths to fulfill market discontinuities, the unmet needs fed by uncertainty. How do these hubs lead to innovation? The "trick to innovation" is to match needs with solutions, but most needs are not articulated because they are based in tacit knowledge. What makes these unmet needs visible is the internal trade of tacit and explicit knowledge within human organizations. This is what paves the path to innovation for all communities, including corporate and academic ones. Internal trade is accomplished through groups and networks of practice that facilitate a high flow of both tacit and explicit knowledge among its members. The sources for identifying and solving unmet needs, therefore, reside in the right combinations of tacit and explicit knowledge. These forms of knowledge, in turn, only flow freely when more complexity is embedded in social interactions and networks.

Can innovation be cultured if we consider the existence of a system? That is to say, if we deconstruct innovation and study the connecting parts of the whole is it possible to understand how it works? And can we go even further and formulate policies that facilitate the functioning of the entire system? (For clarity, innovation is understood here in terms of novel solutions that favorably impact markets and

Rangel-Aldao R. 2005. Innovation, Complexity, Networks and Health. *Innovation Strategy Today* 1(2):45-65. www.biodevelopments.org/innovation/index.htm

users, not just the creation of novelty or technological prowess.) The answer to both questions is a cautious "yes" if we understand the whole as the result of a very complex and dynamic interplay of such components as institutions, culture, legal and regulatory frameworks, trade, and policies. Scale-free network theory, however, would then predict that very few of the parts or nodes would exert effective control over the entire system. That is, only a handful of universities, public institutions, hospitals, non-governmental organizations, private companies and individuals, and only a very few laws, regulations, and markets would function as dynamical attractors of this self-organizing system. We would understand why biotechnology is dominated by so few players from the numerous companies, universities, institutes, scientists, and venture capitalists that constitute the complexity of the whole.

For innovation to occur, creating interfaces or crossroads where different branches of science, technology, and markets all meet is key. This is now all happening at a global scale. The national realm is being replaced by single operating nodes of the so-called "space of flows" of the Internet, which is dominated by a few hubs of core competencies, such as knowledge production and high technology design. The global innovation system, then, operates as a spiral led by small interventions of all sorts. These trigger effective responses several orders of magnitude larger in scale and scope than the original stimuli, but only in those regions that favor high network connectivity (i.e., high income countries).

Most developing countries, including the most innovative, have yet to receive the full benefit of such major technological advances as biotechnology, genomics, proteomics, and molecular medicine. There are successes, of course, but these are mostly due to lax intellectual property laws, the production of low-cost generics, and vaccine production. These successes also result from government efforts that do little to prime the private sector to increase wealth and employment. A major obstacle to development is the lack of system integration of all components of the health system. Thus, the relative strength in scientific skill in some of these countries in no way guarantees their capability to create biotechnological and medical applications of economic value to their health systems.

Countries such as China, India, Brazil, and Korea, have an accelerated growth rate of patents in the last decade, but patents vary widely in their value as sources of innovation and therefore say little about their market impact when implemented. In addition, globally over 83% of the valuable patent families are concentrated in just five countries, closely corresponding with their economic competitiveness. Most low- and middle-income countries with a fast growth rate of patents have net individual contributions below 0.2% of the total.

To be successful innovators, low- and middle-income countries need to be connected much better into the global hubs of knowledge, which will effectively integrate their budding innovation systems. This is a great challenge but also a new opportunity to catch up with the discontinuities and disruptive technologies that are emerging today in modern health systems. One avenue to approach these connections is systems biology and its emerging digital medicine. This can be a powerful integrating tool for trained scientists and physicians on a global scale, including low- and middle-income countries. The multidisciplinary approach of systems biology offers ample opportunities to meet the unarticulated demand that is typical of low income countries, allowing for the integration at all levels of the innovation system.

The basic assumption of digital medicine is that risk and disease are closely linked to the malfunction of networks that somehow have lost key connections or hubs. This is the case for many genes and proteins related to cancer, obesity, diabetes, and aging. These networks could be jointly studied and visualized in the form of digital maps to help give doctors better preventive and diagnostic tools to improve the health system as a whole. This feat could be achieved by connecting scientists and physicians at the national level with their counterparts in the hubs of high-income countries where systems biology and molecular medicine are already taking place.

We present in this essay a business model that considers the formation of three interlinked networks of doctors, biologists, and computer scientists with global centers of basic and clinical research. Local scientists would become collective receptors of a plethora of knowledge produced mostly in global hubs, translating it into maps of clinical significance based on their joint studies of molecular networks. Doctors would then access these maps on-line to pinpoint traffic jams or perturbations of informational bimolecular networks, which may help them predict clinical manifestations before disease arises, as well as provide more accurate prognosis after treatment. The model accounts not only for current unmet needs for integrating the whole but also for its self-sustainability. It also considers how developing countries would benefit from paradigm changes in the supporting sciences of modern medicine, both physically and through the Internet's space of flows. Moreover, the business model has built-in flexibility and openness for the system to grow by self-organization after each turn of the innovation spiral.

Introduction

Innovation is here to stay; the term is everywhere. Many consider it the solution for almost any type of problem, whether academic, business, economic, social, or, more recently, the rapid development of low- and medium-income countries.[1] Innovation, however, is rarely expressed properly. It is frequently confused with just anything novel, regardless of its usefulness or market impact. It is also closely associated with research and inventions, or more often simply with new commercial products.[2] The ways that business and academia measure innovation contribute to this confusion because they gauge their innovative strength simply by the number of patents they churn out every year, whether or not these have applications, economic value, or are ever licensed to promote more innovations by third parties. Other widely used indicators are investment in research and development relative to GDP or population (regardless of competitive outcome), the percentage of sales of products invented in the preceding five years, and R&D expenditures with respect to gross sales.[3]

But none of the indices for either R&D or invention tell us much about what innovation really is and how it is produced—much less why it circulates and is widely diffused in certain countries but not in others. Moreover, some of the proponents of the innovation panacea often overlook the fact that innovation does not occur in a vacuum but is deeply rooted in uncertainty and complexity. It depends on the synergies created by other factors that are also most often set aside. Innovation is part of a system with moving parts, connections, and interactions that are seldom acknowledged by those same heralds of its magic.

Innovation is rarely the product of command and control—or even of policies that are believed to set novelties and solutions in motion. In other words, innovation cannot happen by decree or by enacting new laws; it is necessary for all the other parts of the system to be in place for innovation to occur. This is how it makes sense to talk about incentives. Unfortunately, when some political leaders talk about innovation the message is about a silver bullet that will somehow benefit us all. Instead, we must understand that innovation is the product of self-organizing forces managing an ever-increasing complexity.

We live in uncertain times manifesting continuous change. Ever present in our scientific knowledge and the technologies that shape our lives, this change is also a continuous source of innovation. Knowledge, technology, and need operate in a dynamic but not formless field. This essay attempts to address these issues in the context of the global relationships between haves and have-nots. It reviews the sources and paths to innovation, with its underlying system of many interactive forces. Most importantly, it considers how can we all benefit from a better understanding of innovation systems, especially in the context of the dramatic paradigm changes of the sciences and technologies that support healthcare today.

The Roots of Innovation

Why is innovation so important today for countries, companies, and all kinds of institutions? Innovation matters because, as pointed out by Prigogine, it is part of the response to the greater complexity that results from the ever-increasing uncertainty of systems far from equilibrium.[4] Prigogine extends the classical laws of physics to include instability and chaos:

> *When appropriate initial conditions are given, we can predict with certainty the future, or "retrodict" the past. Once instability is included, this is no longer the case, and the meaning of the laws of nature changes radically, for they now express possibilities or probabilities.*

We shall see that this type of stochastic course is present not only at the macroscopic level but also at the level of microscopic and "deterministic" processes such as DNA transcription and translation. Drawing from thermodynamics, the 1967 winner of the Nobel Prize in Chemistry also asserted that "a nonequibilibrium system may evolve spontaneously to a state of increased complexity [lower entropy and higher degree of order]. The ordering we observe is the out-

come of irreversible processes, and could not be achieved at equilibrium." Prigogine then points his argument to the origin of diversity in nature:

> *Near-equilibrium laws of nature are universal, but when they are far from equilibrium, they become mechanism dependent. We therefore begin to perceive the origin of variety in nature we observe around us. Matter acquires new properties when far from equilibrium in that fluctuations and instabilities are now the norm. Matter becomes more "active."*

Part of the reason for the non-equilibrium state comes from the fact that we all live in open systems, whether nations, companies, or communities, all of which are permeable to external influence, especially now that globalization sets interdependences that limit each systems ability to reach equilibrium. Another property of nonequilibrium systems has to do with bifurcations and dissipative structures of chemical reactions that tend to be self-organized:

> *When we push the system farther into nonequilibrium, new bifurcations typical of chaotic behavior may arise… In short, distance from equilibrium becomes an essential parameter in describing nature much like temperature in equilibrium thermodynamics… Once we have dissipative structures, we can speak of self-organization. Even if we know the initial values and boundary constraints, there are still many states available to the system among which it "chooses" as a result of fluctuations. Such conclusions are of interest beyond the realms of physics and chemistry. Indeed, bifurcations can be considered the source of diversification and innovation… We see that human creativity and innovation can be understood as the amplification of laws of nature already present in physics and chemistry.*

We can also look at uncertainty and complexity from a viewpoint other than that of the realm of physics and chemistry, namely the business world. In a recent *McKinsey & Company* study of the most successful companies in the US during a period of over thirty five years, Foster and Kaplan report that even the most advanced and efficient enterprises cannot sustain their outstanding performance for more than a decade or perhaps fifteen years.[5] The study also determined that the average company lifespan declined from over 75 years in the early part of the twentieth century (1928-1938) to less than 15 years in 1998, approaching what Peter Drucker once called the "Age of Discontinuity."[6] In another well-documented study, top executives from the oil company Shell tried to determine how centennial companies survive. The most approximate answer seemed to reside in the capacity of such corporations to reinvent themselves in a continuous form.[7] To put it in their own words, these companies "…change and adapt without compromising their cherished core ideals."

Uncertainty is thus expressed in the business world as "discontinuities," a term also widely used in academic circles. Discontinuities drive and are driven by innovation, and they may arise from many different sources, some from the so-called disruptive technologies,[8] (e.g., biotechnology and the pharmaceutical industry[9] or the diesel engine in the locomotive industry[10]). Markets are also discontinuous, and the most prominent reasons for disruption appear to be the acquisition of knowledge by consumers, the appearance of new paradigms of fashion and well-being, and the corresponding changes in the needs and habits of potential consumers and clients led by innovators.[11] In this respect, it is noteworthy that the current trend of preserving health and retarding aging is transforming a whole host of markets including foods, agriculture, medicine, fashion, sports, consumer goods, chemicals, pharmaceuticals, and biotechnology. Equally important is the knowledge coming into markets from new scientific disciplines such as Systems Biology. This knowledge is impacting industries and markets as different as Telecom/Media, Computing/Bioinformatics, Nanotechnology, and Biotechnology/Chemicals/Pharma.[12]

Disguised in the business world as market discontinuities, uncertainty produces complexity everywhere in many shapes and forms. All complexity focuses, however, on a sole objective: adaptation to continuous change of an ever-increasing magnitude. Such adaptation satisfies unmet needs and is synonymous with innovation. Complexity implies a high degree of differentiation and function compartmentalization, conditions that demand an even higher degree of connectivity and coordination among different parts of a system to assure effectiveness, efficiency, and direction of the whole.[13] As observed by former physicist Theodore Modis, "complexity compounds complexity," meaning that "complexity and change have grown at accelerating rates throughout history,"[14] a notion that agrees fairly well with the

high paced evolution of complex organisms after the Cambrian Explosion.[15]

Gene regulation in the evolutionary scale is another manifestation of the rapid acquisition of complexity and successful innovation in biological systems. John Mattick has recently explained how the appearances of introns, the splicesome, and non-coding RNA (micro RNA, RNAi) have all contributed to the enormous increase in the complexity of multicellular organisms by producing a digital system of gene expression. In his words, "This is essentially a feed-forward system of endogenous control, a programme that in theory could set developmental trajectories, guided by environmental signals to provide contextual cues and to correct stochastic noise in the endogenous programme."[16]

This raises a new question about how nature deals with complexity. Mattick's statement on the existence of digital biological systems anticipates the answer, but Prigogine provides a more down to earth and direct explanation in his book *The End of Certainty*:

> *The maintenance of organization in nature is not –and cannot be- achieved by central management; order can only be maintained by self-organization. Self-organizing systems allow adaptation to the prevailing environment, i.e. they react to changes in the environment with a thermodynamic response which makes the systems extraordinarily flexible and robust against perturbations from outside conditions. We want to point out the superiority of self-organizing systems over conventional human technology which carefully avoids complexity and hierarchically manages nearly all technical process… The superiority of self-organizing systems is illustrated by biological systems where complex products can be formed with unsurpassed accuracy, efficiency and speed!*[17]

Self-organizing systems and its underlying forces or "dynamical attractors" have been at the center of complexity theory, although a detailed discussion goes far beyond the scope of this essay. Stuart Kauffman, however, lucidly explains its essence:

> *First of all, contrary to our deepest intuitions, massively disordered systems can spontaneously "crystallize" a very high degree of order. Much of the order we see in organisms may be the direct result not of natural selection but of the natural order selection was privileged to act on. Second, selection achieves complex systems able to adapt: They achieve a "poised" state near the boundary between order and chaos, a state which optimizes the complexity of tasks the systems can perform and simultaneously optimizes evolvability.*[18]

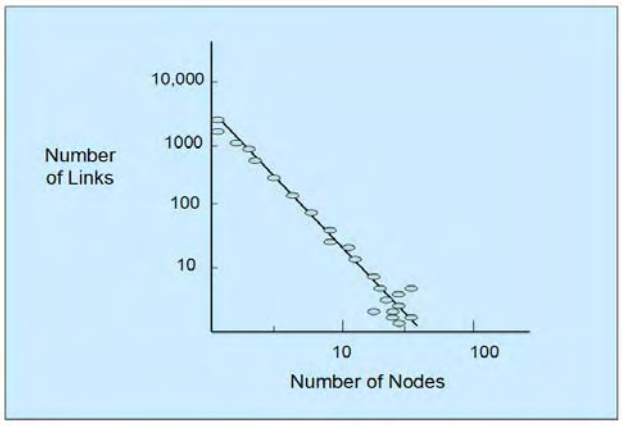
We will consider later how evolving self-organizing systems underlie most processes of innovation. For now, the next step in our road from complexity to innovation leads us to consider how self-organizing systems can be readily recognized by their association into so-called scale-free networks with nodes and connections (edges) that seem to follow a mathematical expression called a "power law." The physicist Albert-László Barabási, one of the main proponents and contributors of scale-free network theory, can guide us:

> *The theory of phase transitions told us loud and clear that the road from disorder to order is maintained by the powerful forces of self-organization and is paved by power laws. It told us that power laws are not just another way of characterizing a system's behavior. They are the signatures of self-organization in complex systems.*[19]

Barabási *et al.* demonstrated that self-organizing systems manifested as networks do not evolve at random; in other words, connections are not made independently of one another.[20] Nodes do not establish their links democratically, which would allow those with poor connections to eventually reach or be close to the average number of connections of most nodes (as a bell-shaped graph or *Poisson* distribution would express it). Instead, networks evolve such that better-connected nodes are more likely to attract and form more links than poorly connected ones. Accordingly, if we match connectivity to wealth or power in self-organizing networks, the rich always get richer and the powerful even more powerful—in most cases "at the expense of the poor."[21] The more links a node has the higher the probabilities that it will obtain more exponentially, thus creating a very unequal distribution that can be visually expressed as a log-log graph of nodes versus links with a decaying straight line (Fig. 1).

The result will be a clustering of very few, highly connected nodes in the network, hubs that are linked to the overwhelming majority of nodes, but which themselves do not possess such a high degree of connectivity. As Mark Buchanan, author of a popular book on network theory, explains:

Figure 1 *Power law distribution of internet nodes according to how many links they have*



Source: Adapted from Barabási[19]

> *In this network, in fact, just a few nodes have so many links that 80 to 90 percent of the network's total number of links feed into just a small fraction of the nodes. So the power-law pattern is the mathematical face of a special architecture, an architecture that is dominated by specially well-connected hubs.*[22]

This is what happens in real life social networks. Most people know or are known by very few, and only a selected minority knows almost everybody. Innovation can then be seen as part of the complexity of scale-free networks.[19] Innovators are the hubs that connect to and lead others to follow their groundbreaking path to fulfill market discontinuities, filling the unmet needs produced by uncertainty.

The Path to Innovation

How do these hubs lead to innovation in a health system? Let us consider innovation in the well-studied context of the business world, for there are many lessons here that can be applied to the public sector of low-income countries. Innovation in technology and services is usually achieved or triggered by those users or potential users who are closer to the market's specific desires, more specifically, to what Dorothy Leonard calls "unarticulated needs":

> *Understanding market needs is one of the most critical knowledge management tasks for developers of new products and services. Yet potential customers often cannot articulate the tacit dimension of their own knowledge and experience that drive preferences and needs. Moreover, developers may be unaware of how their existing knowledge assets can be shaped to accommodate market needs. Therefore, traditional market research tools, which rely heavily on explicit knowledge, are often inadequate to inform new product development –especially if the innovation is radical.*[23]

Market needs can be applied to almost any context, commercial or social, private or public. Leonard makes several points here that illustrate how difficult the path to innovation can be, but she also gives some hints about the kind of competitive advantages required for potential innovators. First of all, innovation leaders must identify specific needs and target them. Unfortunately, these are very hard to pin point because they are not explicit and thus elude conventional market studies. Second, consumers may only tacitly know significant needs and thus be unable to articulate them. To be sure, potential users do have certain preferences and needs, but these are hard to identify because they are context-dependent. They become evident only, or mostly, when confronted in their particular context (at home, work, play, etc.).

Accordingly, the third point is most important: radical innovation requires a set of unconventional tools to enable developers to capture tacit knowledge. The "trick to innovation," as Leonard points out, is "to match need with solution. Some new products or services are born because both need and solution exist within one brain." As an example, Leonard cites how Bill Hewlet developed the electronic calculator: he had in his head knowledge of both the need to transform the slide rule and a possible solution that could be reached by his own engineers. She cites many other examples, but the difficulties for future innovators are formidable:

> *But what if the need exists in one head and the potential solution in another? Even worse, what if neither need nor solution has ever been fully articulated? That is, the target user doesn't recognize the need and demand that it be satisfied and the target problem-solver doesn't realize that she has a solution buried in the capabilities of her organization that would enable her to meet that unarticulated need.*[22]

These questions anticipate some of the obstacles for our attempt to apply innovation systems theory to health care in Low-Income Countries (LICS). On the one hand, for example, physicians have an unarticulated need for a better understanding and command of modern techniques of genomics, pharmacogenomics, and proteomics—not just to know that such techniques can be applied to their patients but to be able to exploit them to their full potential and realize the benefit of their applications in diagnosis and therapy. Scientists, on the other hand, have the tacit need to build a better relationship, to integrate themselves within the social context of their countries without compromising what most concerns them: their capacity to produce scientific knowledge. Countries also need to bridge the gap between clinicians and researchers to improve their systems of health care, although meeting such a need is seldom present in their recipe of solutions for better health.

As Leonard indicates, the problem of recognizing non-articulated needs depends on managing its tacit dimension. Tacit knowledge, or the fact that *we can know more than we can tell* as Michael Polanyi states,[24] is a powerful tool used masterfully by the early nodes of innovation in their path to become hubs of scale-free networks. Here is the basic lesson:

> *Our body is the ultimate instrument of all our external knowledge, whether intellectual or practical. In all of our waking moments we are relying on our awareness of contacts of our body with things outside for attending to these things.*[24]

Polanyi deconstructed tacit knowledge into an elaborate stack of structures by which our body and senses first establish a functional relation with an object, a relation that will eventually allow us to recognize features, provide meaning, and understand context. Polanyi calls these the functional, phenomenal, semantic, and ontological aspects of tacit knowing. The important point to remember here, however, is that because we need our body to interiorize it, tacit knowledge cannot be easily articulated, codified or made explicit in texts or conventional market studies. In this respect Leonard adds:

> *To get somewhat closer to those tacit dimensions, we can set up usability laboratories, in which we scrutinize the behaviors or our customers as they interact with our products… More important, however, they see body language, which reflects tacit dimensions of knowledge –implicit reactions that the user may not be conscious of conveying… And researchers can intervene to make the tacit explicit through questions…*[23]

The internal trade of tacit and explicit knowledge within human organizations paves the path to innovation in corporate, academic, or any sort of community. In their studies of Japanese companies, Nonaka and Takeuchi distinguish four successive stages of a spiral to explain how tacit and explicit knowledge combine to generate a flow of knowing that feeds corporate innovation:

> *Organizational knowledge creation is a continuous and dynamic interaction between tacit and explicit knowledge. This interaction is shaped by shifts between different modes of knowledge conversion, which are in turn induced by several triggers. First, the socialization mode usually starts with building a "field" of interaction. This field facilitates the sharing of members´ experiences and mental models. Second, the externalization mode is triggered by meaningful "dialogue or collective reflection," in which using appropriate metaphor or analogy helps team members to articulate hidden tacit knowledge that is otherwise hard to communicate. Third, the combination mode is triggered by "networking" newly created knowledge and existing knowledge from other sections of the organization, thereby crystallizing them into a new product, service, or managerial system. Finally, "learning by doing" triggers internalization.*[25]

Learning is thus "a remarkable social process," and this fact led Lave and Wenger to introduce the concept of "communities of practice."[26] In other words, for an individual to interiorize knowledge it must be put it into action and practiced in the presence of groups that share "what they have learned through their mutual engagement in these activities."[27] Brown and Duguid went a bit farther, introducing the term "networks of practice" to emphasize the importance of virtual communities of "practice and knowledge in common," which either electronically or by direct social interactions communicate in real time.[28] The physical proximity of communities of practice, and the ease of communication of networks of practice facilitate a high flow of both tacit and explicit knowledge among its members, which explains, for example, the clustering of innovation hubs such as California's Silicon Valley and the Bay Area, New Mexico's Info Mesa, or the mega-centers of modern

medicine in Boston, New York, Bethesda, Houston, Dallas, and Rochester, among others.

We have thus come full circle in tracing the path to innovation from its roots. Networks, in this case, scale-free networks, explain how self-organization drives the complexity produced from the continuous uncertainty in systems far from equilibrium. Part of that complexity comes in the form of innovation, which consists of solutions to a changing context, to the market discontinuities that are often difficult to satisfy because they are unarticulated. To identify and find solutions to these new needs appears to require the right combinations of tacit and explicit knowledge. These combinations, in turn, only flow freely in an environment of greater complexity structured by social interactions and networks.

Innovation Systems

Can innovation be cultured if we consider it as a system? That is to say, if we deconstruct innovation and study the connecting parts of the whole can we understand how it works? It is possible to formulate policies to facilitate the functioning of the entire system? If we take into account the work of many scholars in the evolutionary theory of economic growth, and if the parts are institutions in the technology sector, then our answer is a cautious "Yes."[29]

We have seen that innovation is mostly a bottom-up process, one that emerges from those closer to either the knowledge frontier or to market needs that result from discontinuities that are not necessarily technology driven. For clarity's sake, innovation is understood here in terms of novel solutions that favorably impact markets and users—not just the creation of novelty or technological prowess.[30] Introducing new products and processes into markets says little about their ability to displace effectively other less advanced developments. Indeed, the benefit of considering the outcome of innovation is that it focuses on effectively achieving economically viable solutions to unmet needs.

We have also discussed how the moving parts of the whole are components of a self-organizing structure with the topology of scale-free networks. If we consider the realm of regions, countries, companies, or communities in terms of systems, a second question arises: how can we influence the arrangements and connections of the parts to make the whole more efficient? This question becomes more complicated when we consider that we all live in systems that are far from equilibrium, systems that are permeable to external influence and are not necessarily closed. To answer all of these questions let us briefly look at the so-called "National Systems of Innovation."

In the late nineteen-eighties, before the advent of the information society and rampant globalization, Chris Freeman,[31] Bengt-Ake Lundvall,[32] and Richard Nelson[33] independently championed the concept of National Systems of Innovation. This term, according to Lundvall et al,[34] has deep roots that go back to Adam Smith (1776), F. List, (1841) and Burestam Linder (1961), a former cabinet member of the Swedish government. The term was finally coined by Freeman in 1987.[35] Michael Porter,[36] however, disputed the importance of a national arena for innovation and focused instead on how the development of advanced technology clustered and flourished in rather limited sub-national regions, such as the Silicon Valley and the San Francisco Bay Area. The concept of a national system of innovation, however, remains important today because as Lundvall et al remarks:

> *As long a[s] nation states exist as political entities with their own agendas related to innovation, it is useful to work with national systems as analytical objects.*[34]

Without getting into the major details of the concept, perhaps the most important lesson that can be drawn from a National System of Innovation is an understanding of the whole as the result of a very complex, dynamic interplay of connecting parts that include institutions, culture, legal and regulatory frameworks, trade, and policies. We can therefore answer the first question posed above: it may be possible to improve the whole by identifying and understanding the inner interactions of the components.

Scale-free network theory, however, would then predict that very few of the parts or *nodes* would exert

effective control over the entire system. That is, only a handful of universities, private companies, and individuals, and only a very few laws, regulations, and markets would function as dynamic attractors in this self-organizing system. This explains, for instance, why biotechnology is dominated by so few players despite the numerous companies, universities, institutes, scientists, venture capitalists, and entrepreneurs that make up the interacting parts. It also explains how just one single law, the Bayh-Dole Act of 1980, could cause the innovative contribution of American universities to skyrocket by stream-lining their connections to the rest of the system.[37] By 2000, that single piece of legislation allowed universities to license more than 3,000 patents that generated over one billion dollars in revenues. The economic impact of Bayh-Dole for the whole country has been enormous, with more than $40 billion worth of new products and 270,000 jobs created since 2000. Consistent with the power of the few, one single patent assigned to Stanford University created biotechnology for years to come. It had two inventors, Stanley Cohen and Herbert Boyer, from Stanford and the University of California, respectively. A quick look at the marketplace will also inform us that of the top five biotechnology products for 2003, which have combined sales of $8.5 billion, four came from a single company: Amgen. It took 77% of the cake that year.

The answer to the second question is also a yes: we may be able to influence the arrangements and connections of the parts through indirect interventions in the system such as the Bayh-Dole Act, but bear in mind that the beneficiaries would be the very few, highly connected nodes. Other countries have followed suit with local adaptations of the Bayh-Dole Act in Japan,[38] Germany, UK, and other OECD countries. But the introduction of novel legislation by itself would not be a magic formula:

> *Recent initiatives by a number of OECD governments suggest considerable interest in emulating the Bayh-Dole Act of 1980, a piece of legislation that is widely credited with stimulating significant growth in university-industry technology transfer and research collaboration in the United States. I examine the effects of Bayh-Dole on university-industry collaboration and technology transfer in the United States, emphasizing the lengthy history of both activities prior to 1980 and noting the extent to which these activities are rooted in the incentives created by the unusual scale and structure (by comparison with Western Europe or Japan) of the U.S. higher education system. Efforts at "emulation" of the Bayh-Dole policy elsewhere in the OECD are likely to have modest success at best without greater attention to the underlying structural differences among the higher education systems of these nations.*[39]

Many Latin American countries, for instance, have tried other forms of indirect interventions that differ from those of intellectual property law. In general, they have implemented a two-pronged approach to influence their "national systems of innovation." This consists of 1) strengthening the knowledge-producing infrastructure, mainly the universities and public institutes, and 2) redirecting the scientific base to address local problems of global interest. Such is the case of Brazil and Chile. The former provided free electronic access to most scientific journals for all researchers in Brazil,[40] as well as duty exemptions to limited imports of scientific equipment and supplies.[41] Brazil has also directed its prowess in genomics to study microbes that affect crops of economic importance for the development of their country and also the world, such as citrus[42] and coffee.[43] As the second world exporter of salmon, Chile has focused their efforts on genetic vaccines to protect its cultures from microbial infection.[44]

Other types of interventions have to do with the Schumpeterian notion of *new combinations*,[45] that is, how to bring diversity together to establish functional relationships between fields, concepts, and technologies that are either distant or of no obvious proximity.[46] Creating interfaces or crossroads where different branches of science, technologies, and markets all meet is key for innovation to occur. The lack of it may explain, at least in part, why the Bayh-Dole Act may be of limited benefit to countries besides the United States. As envisioned by Vannevar Bush in the forties, there is an almost extreme degree of flexibility and freedom for all kinds of relationships of supply and demand for knowledge in the US, which provides a truly dynamic melting pot of people, universities, entrepreneurs, corporations, venture capital, government, and the market needs of society at large.[47] Frans Johansson explained this more recently in a very popular book:

> *Diversity in teams allows different viewpoints, approaches, and frames of mind to emerge. Diversity is also a proven way to increase the randomness of con-*

cept combinations. It is often said that one of the reasons for the United States´ unparalleled innovation rate is its very diverse population. People who have experienced the innovative power of diverse teams tend to do everything they can to encourage them. Whether we liked it or not, the process of innovation is dictated by random combinations of different concepts. Individuals and teams who often break new ground know this and therefore maximize their chances of finding intersectional ideas. They do it by introducing diversity into their occupations, teams, and encounters.[48]

Another point to consider for understanding the system has to do with the so-called "end of geography," or the *Internet Age*, as pointed out by Manuel Castells:

The Internet Age has been hailed as the end of geography. In fact, the Internet has a geography of its own, a geography made of networks and nodes that process information flows generated and managed from places. The unit is the network, so the architecture and dynamics of multiple networks are the sources of meaning and function of each place. The resulting space of flows is a new form of space, characteristic of the Information Age, but it is not place-less: it links places by telecommunicated computer networks and computerized transportation systems. It redefines distance but does not cancel geography. New territorial configurations emerge from simultaneous processes of spatial concentration, decentralization, and connection, relentlessly labored by the variable geometry of global information flows[49].

This space of flows, Castells explains elsewhere, consists of "trans-territorial complexes of activities," such as high technology corridors, finance circuits, and social networks, among others. These are made of specific geographic locations that are to a great extent independent of their immediate vicinities but very well connected across the world.[50] More importantly, Castells concludes that:

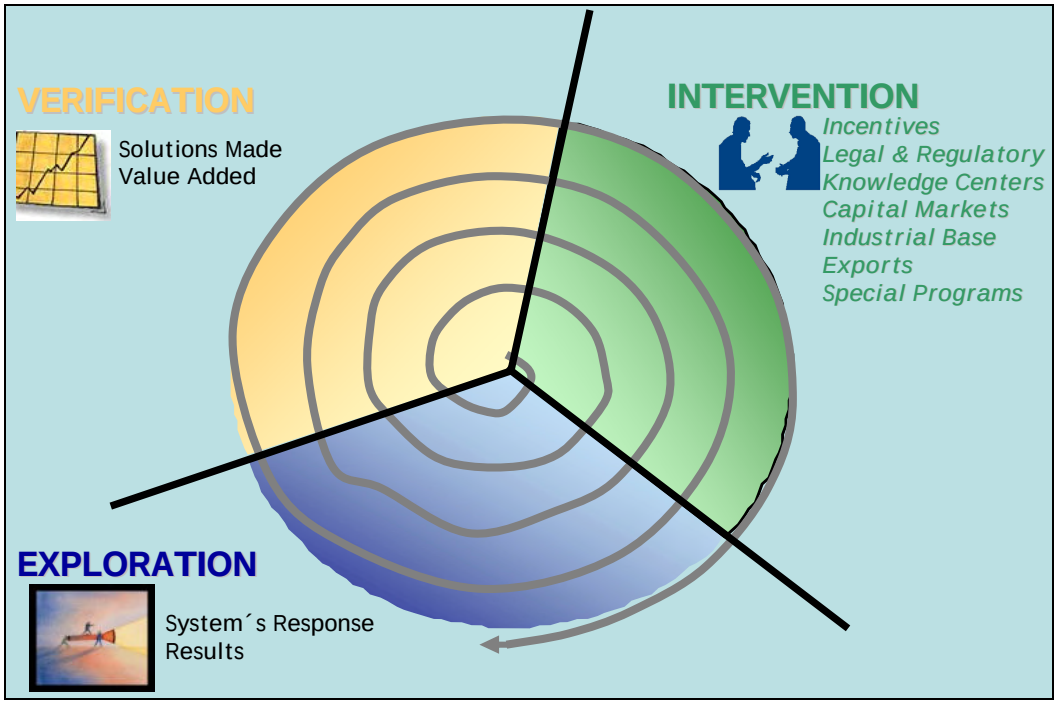
At any rate, the key distinction now is that we are not just organized around networks, but around information technology-powered networks, able to manage complexity, and to coordinate functions and perform tasks with networks of any size and complexity. The Internet accentuates this phenomenon [the space of flows]. We observe that the ability to reach out to the planet from a few locations concentrates on the core centers, the producers of innovation, and the knowledge elites.[51]

Castells' work reunites us with most of the concepts underlying innovation that we have considered so far: how to deal with the enormous complexity generated by continuous uncertainty coming from systems that are far from equilibrium, the importance of self-organization for this task, and the resulting power of scale-free networks. Let us end with an analysis of the flexibility and decentralization embedded in the space of flows. The leaders of innovation consider the system global. The national realm is thus substituted by single operating nodes of their universal space of flows, dominated by a few hubs of core competencies, such as knowledge production and high technology design. Centralization and decentralization in real time creates the right combination of control and flexibility to produce the Schumpeterian new combinations that emerge from an intelligent use of diversity, whether from centers of knowledge or from close links to markets worldwide. Again, those that are more highly connected and self-organized would be in a more favorable position to first identify and solve non-articulated needs and market discontinuities.

We can summarize the innovation system as a spiral with three successive stages (Fig. 2). First, there is the *Intervention* stage or initial stimuli. These may consist of a variety of measures, such as the Bayh-Dole Act, programs that mobilize a host of knowledge centers across the world like the Human Genome Project, or that bring these together into a single nation (e.g., *Onza* in Brazil,[42] or *BioRegio* in Germany[52]). There are many other types of incentives designed to promote innovation at the global, regional, or national level. Intervention will lead to an *Exploration* journey into the inner parts of the system to see how it responds and produces results with different degrees of effectiveness, results that depend on whether or not synergies were found within the system as whole. This will lead to the third stage, *Verification,* where knowledge is obtained about how the intervention caused innovation to occur after the first iteration.

Note also in Figure 2 that as the right solutions to discontinuities and unmet needs add value into the system, an implicit exponential relationship devel-

Figure 2: *Innovation spiral*



ops between the original stimuli and the successive outcomes of each iteration. In other words, the more we know about how the system works, the greater our ability to intervene at a larger scale and, of course, the better the final outcome. This would then help us to further understand why the Bayh-Dole Act has been so effective in the US but not in other developed countries. The parts of their respective systems may not be as well tuned for this type of intervention.

Innovation and Health Systems of Low and Middle-Income Countries

How do we apply these principles and concepts to health in LICs? Most developing countries, including the most innovative have yet to receive the full benefit of the major technological advances and innovations of the last twenty-five years. Biotechnology, and, more recently, genomics, proteomics, and molecular medicine have yet to make an impact. There are successes, of course, in such countries as Argentina, Brazil, Cuba, Chile, India, South Africa, and South Korea. But these countries based most of their strategy in lax intellectual property laws, the production of low-cost generics, and vaccine production. Their successes came mostly from government efforts, which do not prime the private sector to function as a mechanism to increase wealth production and employment. Accordingly, studies consider success in these countries in terms of products and services, and with few exceptions, their social and economic outcome (return on investment, market share, etc.).[53]

A major obstacle to developing biotechnology in LICs has little to do with education or the ability to learn. Indeed, the relative strength of trained personnel and laboratory facilities in some of these countries does not in any way guarantee the capability to successfully integrate biotechnological and medical applications of economic value into their health care systems.[54] Besides financing and long-term vision, the lack of system integration at all levels of the value chain of health care is a more significant impediment. In a health biotechnology program of Ibero-American countries (CYTED) that this author had the privilege to coordinate for a decade (1991-2001), the lack of system integration was clearly the major obstacle. It took

us over ten years to design,[55] produce,[56] field test,[57] and market[58] an instant diagnostic kit that required no special equipment or trained personnel to detect Chagas´ Disease in blood samples. The kit was later used by the Government of Honduras in their campaign to eradicate Chagas´ Disease from the country.[57]

If all of the investigators of Argentina, Brazil, Honduras, Spain, and Venezuela had been in a region with a more integrated health care system, the total time for this feat may have not exceeded two years, which is the time it takes to conduct epidemiological studies and field tests for an extended region. Among the many difficulties encountered by us in this very long journey to use recombinant DNA technology for the diagnosis of a debilitating disease with a high risk of transmission by blood transfusion in Central and South America,[59] were the lack of connections between hospitals, blood banks, basic research, and reference laboratories—not to mention the disparate sources of financing. We had to establish networks encompassing not only different fields of expertise that seldom interacted, such as epidemiology and molecular biology (again, the Schumpeterian new combinations), but also the boundaries between such distant countries as Brazil and Honduras, while also including Venezuela, Colombia, and many other Central American countries where blood transmission of Chagas is very important. When this study began in 1991, there were plenty of Latin American laboratories with personnel and facilities to perform sophisticated genetic engineering; indeed, by that time they had already cloned some of the necessary antigens of *Trypanosome cruzi*,[55] the parasite of Chagas´ Disease, to produce a diagnostic kit that performed similarly to ours 2003 kit. But the lack of systems integration delayed the introduction of advanced diagnostic technology into the market for ten more years.

Another difficulty was the lack of connections between academic institutions and private companies, scientists and entrepreneurs, laboratories, and manufacturing facilities. All of which were operating within a weakened framework of institutions that were supposed to protect the intellectual property of inventions and innovations.

Part of the answer to solving these obstacles that were preventing our invention from becoming a practical reality came from outside the region. We had informal contacts with an American biotechnology company, *Chembio*, or simply, *CDS*. This company had both the interest and capabilities to combine our confidential mixture of recombinant antigens with their proprietary ultra-rapid diagnostic technologies. Accomplishing this required overcoming a further hurdle by establishing a non-profit, private company in New York, which was the only commercial vehicle that we could find to reach the marketplace in our own region! The invention was never patented, however, and remains a trade secret today to avoid easy copying and asymmetrical competition in a region where patents are of little value due to the lack of enforcement of IP laws.

Another factor that plagues Latin America is that all kinds of local legislation lag well behind modern technological applications (e.g., biotechnology and genomics). This effectively stops system integration in health care. In Venezuela, for example, there is ample capability to use satellite DNA sequencing for forensic analysis,[60] but the only legally binding techniques are those of the old, laborious RFLPs. Our hospitals desperately need modern genomic medicine, but strict currency controls and import substitutions make it very hard to develop.

The same can be said applying biotechnology into food production and nutrition in many Latin American countries[61]. With few exceptions (Argentina, Costa Rica, and, more recently, Brazil[62] and Mexico[63]), most Latin American countries have not enacted legislation governing genetic engineering and the release to the environment of transgenic plants. Some are still immersed in the confusion generated in the late nineties by the Cartagena Protocol on Biosafety. [64] Brazil, incidentally, also approved legislation in March 2005 for stem cell research. [62]

There are signs of change, however, in this obscure and rather pessimistic panorama. A large multidisciplinary group of experts, including scientists, lawyers, and economists, and others, has recently asked the World Health Organization (WHO) commission on Intellectual Property, Innovation and Health (CIPH) to "evaluate a new treaty framework for medical R&D."[65] The proposed treaty includes several mechanisms to support medical research that, if implemented, may strengthen national innovation systems across the world, particularly those of LICS:

The treaty will provide:

i. Obligations for minimum levels of investment in medical research and development,
ii. Processes for priority setting,
iii. Obligations and incentives to support:
    a. Medical research and development, including priority research & development,
    b. Broader dissemination of scientific information and knowledge,
    c. Enhanced transfer of technology and capacity for research and development in developing countries, and
iv. Obligations and standards for transparency, including mechanisms to report, measure and understand the nature of the scientific, economic and social dimensions of investment flows in medical research and development. [66]

These measures and obligations, of course, will only produce effective results as they find synergies with other parts of the respective innovation systems for each country—if these exist at all. Otherwise, they become just another volume in the rather large library of wishful thinking to combat inequality in the world. But there are countries where significant innovation in medical research is already occurring: the "innovative developing countries," or IDCs. [67]

Countries such as China, India, Brazil, and Korea, for instance, have shown a strong potential for innovation, one expressed by an accelerated rate of the growth of patents in the last decade. [68] Patents, however, vary widely in their value as sources of innovation, and therefore say little about their market impact. For this reason, among others, the OECD has recently introduced the concept of "triadic patent families":

A patent family is defined as a set of patents (originating from the priority filing) taken into various countries (i.e. patent offices) to protect the same invention. The triadic patent families are defined by the OECD as a set of patents taken at the EPO, JPO, and USPTO that share one or more priorities (Dernis and Khan, 2004). The advantages of using the triadic patent families indicators for statistical analysis are:

- *They improve the international comparability of patent-based indicators. Only patents applied in the same set of countries are included in the "family", eliminating home advantage and the influence of geographical location.*
- *Patents in the family are high-value patents. The patentee will only take on the additional costs and delay related to the extension of the protection to other countries if it is deemed worthwhile.*

The criteria for counting the triadic patent families are the earliest priority date, the inventor's country of residence, and fractional counts. [68]

When world patent statistics are thus examined, we again observe the presence of a power law distribution for the most productive countries (or connected nodes, if triadic family patents are considered links). In 2000, over 83% of the triadic patent families were concentrated in just five countries, ranked in this order: United States, Japan, Germany, France, and the United Kingdom.

Korea, China, India, and Brazil did increase their rate of growth from 1991 to 2000, but with the exception of Korea, their individual contributions to the total were below 0.2%. After Korea (13th place), other countries in the top thirty-five were Chinese Taipei (21st), China (23rd), India (25th), Brazil (28th), and South Africa (31st).

Another interesting feature of this kind of analysis is the close correspondence of rapid patent growth with economic competitiveness. Not surprisingly, the most prominent increases in EPO applications corresponded with the economies of the top countries listed in the Global Competitiveness Report, such as Finland (1st), Sweden (3rd), the Netherlands (7th), and Canada (15th). [69] When normalized by GDP and population, the leading countries of growth in triadic patent families in 2000—besides the US—corresponded again to the most competitive economies: Finland, Sweden, Switzerland, and Japan.

Valuable patents, therefore, are just one part of the innovation systems of competitive economies. In the experience of this author as a co-inventor of several triadic patent families assigned to a large industrial corporation of Venezuela's food sector, we were able to extract value from inventions by licensing and sharing the technology with other qualified third parties of the European Union, with whom we already had close contacts and technological complementarities.[70]

Given the accelerated growth rate of patents in IDCs, we need now to explore how this indicator

relates to other components of the health care network, particularly those more closely associated with social and economical outcome rather than invention, science, and education. This will give us information about how to consider other nodes, such as entrepreneurial activities, flows of foreign capital and technology transfer, market capitalization of start-ups and spin-offs from universities and institutes, trade incentives, and the market share of indigenous products and services based on innovative technologies. Above all, it will help us to better understand the importance of transparent, stable legal and regulatory institutions. This is a task that needs immediate attention and intensive research.

The articulation of health care with a national innovation system requires the mobilization and close interaction of all its parts, not just those related to patents and inventions. Together with an intelligent use of the space flows of information society, a major paradigm change occurring today in regards to the practice of science and technology in most advanced countries my provide an opportunity for IDCs to accomplish this.[49]

Opportunities for IDCs: Networked Health Systems

The main lesson to be drawn regarding the status of IDCs as potential innovators in health systems is that neither their current scientific infrastructure and highly trained personnel in science and technology, nor their fast rate of patent growth are nearly enough to fill the gap of the endogenous capacity necessary to match a rapidly moving target: the effective integration of complex innovation systems in continuous change. We can summarize our own experience of many years in the Latin American region working on biotechnology applied to health, agriculture,[71] and food production, as follows:

- *Many developing countries in the Americas have yet to benefit from biotechnology. This is not because of inherent problems with either the science or technology, but rather because most nations lack a system for integrating the different participants in the research, development, and manufacturing chain. Thus, the relative strength in trained personnel and laboratory facilities in some countries in no way guarantees a successful capability for biotechnological applications of economic value or with an impact on development.*
- *NEW biotechnologies could have an impact on regional development, but only if regional scientific expertise were combined with clear business objectives addressed to national and international markets. This would create a demand for knowledge that would connect the human capital able to handle biotechnology's heavy intellectual requirements with others equally sophisticated in negotiating the kind of partnerships that actually bring benefit.*[54]

These are great challenges for the development of health systems in many low- and middle-income countries, including IDCs. But these may also be opportunities to catch up with the discontinuities and disruptive technologies that are emerging today in modern medicine, allowing for complexity to reach unprecedented levels. On the one hand, health related biotechnology is becoming a commodity: cloning, genome analysis, gene expression, and recombinant protein production can be contracted to third parties at reasonable costs.[72] The expiration of key patents will soon inundate the market with low-cost generics, and countries with lax patent laws will no longer enjoy the benefit of free imitations when Trade-Related Aspects of Intellectual Property Rights (TRIPS) becomes a reality this year.[73] Prowess in biotechnology, therefore, may cease to be a competitive advantage for many nations. On the other hand, the science and technology that supports medicine is also changing at a rapid and dramatic pace, from reductionism to synthesis, with a great fusion occurring today throughout the full spectrum of scientific knowledge and business. Again, biotechnology may soon be a matter of the past because it is being transformed from an essentially definable repertoire of technologies with applications in pharmaceuticals, agriculture, and industry to a diverse set of "platforms" with fuzzy boundaries. These make it difficult to distinguish the respective contributions of biology, information and computer sciences, mathematics, and engineering principles. Creative financing, managing, and marketing skills are combining these disciplines—with a political awareness of their social and environmental impact—to create a new synthesis in search of a name.

The completion of the Human Genome Project with its spin-offs (mouse, plants, microbes), the ongoing transformation of biology into another form of information science, and its emerging fusion with engineering principles to engender so-called "systems biology," all of these are changing substantially the scientific basis on which biotechnology initially rested. If we add to this the consolidation of the pharmaceutical industry into very large, integrated global conglomerates that have engulfed biotechnology, bioinformatics, and agrochemical companies,[12] then the conclusion is inescapable: the term biotechnology has blurred so much that it may soon become an anachronism.

Systems biology is, therefore, taking root as an integrating tool to comprehend how the genome and proteome respond to environmental changes through the cell's signal transduction machinery. These fields of research also represent a new avenue for innovation in health systems worldwide. Surprisingly enough, this is where trained scientists and physicians on a global scale, including LICS, could take advantage of the emerging plethora of biomedical knowledge related to the very roots of molecular medicine.[74] The main reason for this is that the multidisciplinary approach of systems biology offers ample opportunities to meet an unarticulated demand typical of LICS: the integration at all levels of the innovation system.

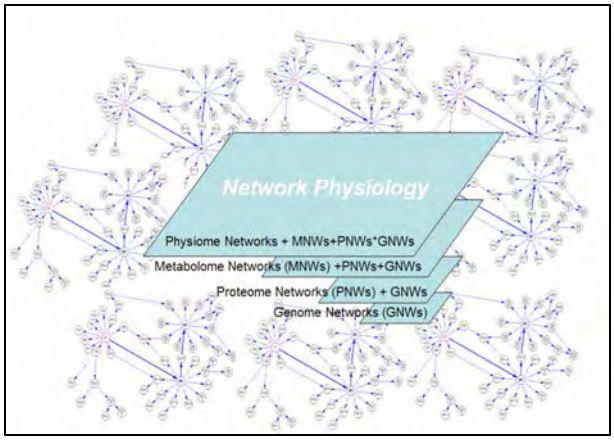
The molecular medicine emerging would be more likely to study the social life of biological information molecules in health and disease than just simply profile biomarkers associated with certain disease states.[75] Phair and Misteli have recently shown the molecular dynamics of such networking in vivo, and their results conclusively revealed that proteins, for example, associate and dissociate in a specific manner very rapidly (seconds) in the intracellular milieu.[76] It also seems that interactions of information molecules are organized in regulatory networks with the same type of "network motifs" that pertain to a wide range of other complex mechanisms that encompass ecological systems, neuronal synapses, electric circuits, and the Internet, among others.[77]

Besides the transcriptional network, the genome,[78] proteome,[79] metabolome,[80] and the physiome[81] all obey a power-law, which makes it likely that all the cellular signal transduction machinery that responds to the environment will follow suit and be amenable to study with the new bio-mathematical and computational tools of systems and digital biology. This interplay of pathways can be pictured as a connected stack of networks of increasing complexity, with feed-back loops that go across the entire chain of gene expression from deep in the genome up to the physiome as the external manifestation of body function and regulation. We would then talk about physiology as the final result of a web of interconnected networks (Fig. 3).

At each level of the stack we would expect to find very few informational molecules, hubs of each network of networks, such as genes, proteins, and key metabolites in charge of the regulation of overall physiological activity.

Digital Medicine would then arise with the aid of novel algorithms to visualize and measure the dynamics of these molecular networks, and pinpoint at each level of the stack possible traffic jams that may help to explain or prevent at the molecular level the clinical manifestation of disease. This is the basic assumption here: that risk and disease are closely linked to the malfunction of networks that somehow have lost key connections or hubs. That is the case of genes such as BRCA2, for example, which when mutated contributes to the abnormal formation of multiprotein complexes along the signal transduction machinery, resulting in an increased risk for many cancers.[82] The same can be said about aging in many types of organisms, from yeast to nematodes, where suppressed or mutated genes—very few in number—perturb the interactions of highly connected proteins or hubs associated either

Figure 3 *Stack of informational networks of biomolecules that feed Physiology*



with hormone receptors, such as the insulin/insulin-like growth factor (IGF-1), or other important functions, such as telomere maintenance and the oxidative stress response.[83]The perturbation of multiprotein complexes by the mutation of gene clusters encoding signal transduction has also been shown to pinpoint different etiologies of cardiovascular disease (dilated cardiomyopathy)[84] and even of infectious diseases at the level of "the inflammosome, resulting in inflammatory caspases,"[85] proteins that induce cell death by apoptosis.[86]

Genomics and proteomics are thus changing very rapidly from gene expression profiling[87] and the detection of biomarkers in a particular state of living cells,[88] to the quantitative study of gene and protein dynamic networks in healthy and diseased individuals. In proteomics, for instance, this is done by complementing mass-spectrometry with protein chips that enable protein self-assembly and determine the formation of multiprotein complexes.[89]

This is also being accomplished by real-time quantitative measurements of how these multiprotein complexes are triggered by phosphoproteins upon hormone stimulation.[90] Proteins can now also be studied in real-time in vivo with "paints" of quantum dots that signal their intracellular traffic in live neurons, or in lymph nodes of live animals during surgery.[91] More recently, the dynamics of gene expression and protein-protein interactions of the entire cell cycle were studied in yeast. One important discovery of this work was that just one hub (Cdc28p, cyclin-dependent kinase) displayed a profound effect on the entire network, giving further support to the assumption above about the importance of network hubs to study the social life of informational molecules:

> *We discovered that most complexes consist of both periodically and constitutively expressed subunits, which suggests that the former control complex activity by a mechanism of just-in-time assembly. Consistent with this, we show that additional regulation through targeted degradation and phosphorylation by Cdc28p (Cdk1) specifically affects the periodically expressed protein. With reliable time series of protein abundances, preferably in individual compartments, the resolution of this temporal network can be increased considerably, because even individual interactions over time could then be monitored. Moreover, the integrative approach presented here should be applicable to any biological system for which both interaction data and time series are available.*[92]

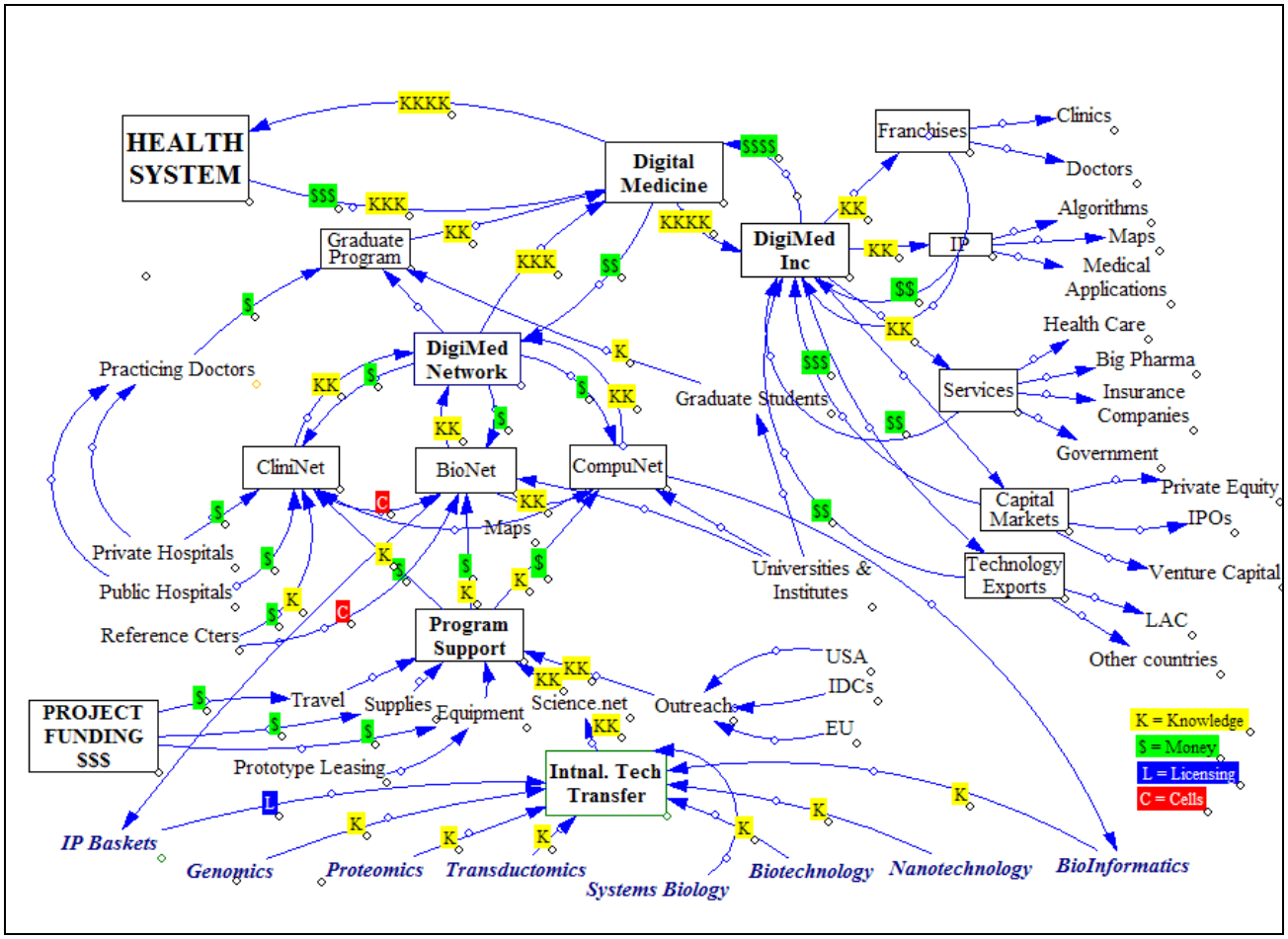
Digital Medicine in IDCs

How can IDCs implement this type of knowledge and capital-intensive approach to develop digital medicine as part of their health systems? A possible answer may be found in the form of a business model that considers not only system integration of digital medicine into health care, but also its financial and knowledge sustainability (Figure 4).

The business model in Figure 4 considers the formation of *DigiMed* as the main pillar of the R&D part of the system (shown to the left hand side as five boxes connected in a diamond-shaped form), a network of networks, consisting of the three essential components of a subsystem: practicing physicians of clinics and hospitals (*CliniNet*); molecular biologists with expertise in genomics, proteomics, and signal transduction (*BioNet*); and mathematicians, theoretical physicists, and computer scientists (*CompuNet*). All of them are to be chosen by their high degree of connectivity to colleagues in world class centers of excellence in the US, EU, and IDCs, as measured by their co-authorship on clinical and scientific journals of high impact (see later).

The main idea is to put together medicine and multidisciplinary science in such a way that, by working closely in such an unprecedented context for IDCs, doctors will be able to examine how signs and symptoms of disease may be related to perturbations of underlying networks of informational biomolecules, the dynamics of which could give them clues to better diagnosis, treatment, and prognosis. To achieve this, cells and clinical specimens from patients and reference centers will be forwarded from *CliniNet* doctors to *BioNet* molecular biologists (see flow of "C" in the diamond of Figure 3) to perform quantitative analysis at the hubs of signal transduction networks. Local scientists would become a collective receptor of a plethora of knowledge being produced mostly in the US about the cartography of these networks across the

Figure 4: *Insertion of Digital Medicine into the Health Care System of IDCs (Business Model)*



evolutionary scale, from yeasts,[93] Drosophila,[94] and nematodes,[95] to human cells in culture[88]. These interactions are likely to follow non-linear dynamics and stochasticity[96] that could be figured out in the form of equations and modeling by mathematicians and physicists from *CompuNet*. This, in turn, may facilitate the construction of the corresponding algorithms by computer scientists to produce dynamic maps of network function. Doctors of *CliniNet* would then access such maps on-line in an intranet, right at their offices, to pinpoint intracellular traffic jams or perturbations of informational biomolecule networks that may help them to predict clinical manifestations of disease and prognosis after treatment.

The three networks are fed by a Support Program that provides funds for facilities, equipment, supplies, and travel, as well as the necessary channels for knowledge exchange and technology transfer, both electronically (Internet2, Grid) and personally through frequent visits of local scientists to their foreign peers, as well as to develop hands on experience at their laboratory facilities of the technological areas listed at the bottom of Figure 3. This type of continuous exchange of knowledge and expertise assures an inexhaustible source of technology transfer from world-class healthcare research and development. It is an extremely cost-effective and efficient way for developing countries to benefit from the $46 billion a year spent by the best centers of excellence in the US, EU, and IDCs.[97] Moreover, the distribution of clinicians and scientists in separate but inter-connected networks keeps each of them doing what they do best, with no need to disguise either basic or clinical research with enticing wraps to assure funding.

Funds may come from a variety of sources, such as global or regional development banks, social entrepreneurs, and venture capital, either national or international. The diamond is completed with *DigiMed*

itself, consisting of a holding entity that: 1) sets focus and direction to the whole network, 2) assures the necessary links to the advanced education component (Graduate Program for future clinicians and scientists of digital medicine), and 3) packages knowledge to be funneled and/or commercialized through another body, The Digital Medicine Foundation. This can either make use of knowledge as a business in free-market oriented countries (right hand side of Figure 3) or deal with the public health care system (top left hand of Figure 3). The icons indicate the flows of knowledge (K), capital ($), licensing of IP (L), and living cells or clinical specimens (C) throughout the entire system and networks.

After project funds are exhausted in 3 to 5 years, the Support Program at the bottom of the diamond would be taken over by the Foundation of Digital Medicine (shown at the top of Figure 3). From a business standpoint, there will be several sources of revenue as the system reaches maturity and self-sustainability: 1) Services of advanced diagnostic and therapeutic tools, such as biomarker profiling and dynamic traffic maps of informational biomolecules, which indicate risk, disease, or prognosis at an individual scale; 2) Support to multinational pharmaceutical companies in their clinical trials of new types of medicines and drugs with local volunteers; 3) Services to insurance companies to assess the risk to key diseases of their affiliates and to help doctors diminish the morbidity and mortality of insured customers; 4) Support to governmental institutions to maintain healthiness and prevent disease in public servants; 5) Exploitation of intellectual property coming from the algorithms of the maps or their use as codified knowledge in the form of a franchise; and 6) Exports of the model to other IDCs or to the world at large.

The key factor to be considered for a program like this is something that most IDCs may have a lot of: qualified personnel in medicine, biotechnology, and most other branches of science and engineering required by systems biology, as shown by either their corresponding patent indicators[68], or by the recent study of biotechnology development in countries such as Brazil, China, Cuba, Egypt, India, South Africa, and South Korea.[98] In Venezuela, for instance, we researched all scientific and clinical publications (links) pertaining to the interest areas of each of the three networks during a five-year period (1996-2001). Not surprisingly, we found a power law distribution of authors (hubs) highly connected to both their peers and foreign centers of excellence, such as hospitals and scientific institutions in the most advanced countries of the world.[99]

Conclusions

In conclusion, we have combined most elements of innovation systems theory to develop a bottom-up approach that takes the form of a business model. It may have significant universal applications for improving health care in IDCs, or even in developed countries. The proposal takes into account not only current unmet needs to integrate the whole, but also shows how to benefit—both physically and through the space of flows of the Internet—from emerging disruptive technologies, market discontinuities, and the paradigm changes of the supporting sciences of modern medicine. Moreover, the business model has built-in flexibility and openness for the system to grow by self-organization after each turn of the innovation spiral.

Acknowledgements

This paper is dedicated to the memory of Sanjaya Lall.

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tion of what constitutes an innovation poses a number of definitional difficulties. Most products, and certainly the processes by which they are made, are complex systems. Change thus has to be defined in terms of: a) The attributes and performance characteristics of the product as a whole, and b) changes in components of the product which improve its efficiency, including the nature of the services which it delivers. Subsystem changes of this kind may be very small in scale but their cumulative impact can be considerable, and important from an analytical perspective. See OECD (1996) The Oslo Manual, Proposed guidelines for collecting and interpreting technological innovation data.

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Accelerating the Innovation of Vaccines:
Can the Global HIV Vaccine Enterprise, Malaria Vaccine Initiatives, and Purchase Commitments Deliver?

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Executive Summary

This paper seeks to rebalance the debate about 'advance purchase commitments' (APCs) for vaccines and analyzes a wider range of vaccine-related issues. HIV and malaria vaccines receive particular attention because they have been heavily promoted as candidates for APCs.

The vaccine 'problem' is highly heterogeneous, ranging from the creation of complex and scientifically difficult 'early-stage' vaccines–such as those for HIV, malaria, and tuberculosis–to the insufficient or non-use of already existing vaccines that are sometimes very cheap–such as those for yellow fever, hepatitis B, and haemophilus influenzae. Confusingly, the term 'APC' has come to cover all of these, despite their great differences.

In the case of HIV, malaria, and tuberculosis, an APC refers to a pre-set pool of R&D subsidy distributed by a committee long after investments have been made. The subsidy is awarded via a potentially complicated pattern of payments to vaccine developers and 'eligible' countries according to a system of pre-set contracts. APCs thus require extensive monitoring and IP mechanisms, as well as a bureaucratic structure that encompasses all of the required institutions.

The first half of the paper explores the many challenges faced by such early-stage APCs:

- It is impossible to set the 'size' of APCs so as to maximize the speed and efficiency of vaccine development.
- It is difficult to engineer product terms and payment rules to reward follow-on innovation and thereby encourage investment in a variety of vaccine approaches. Paying for R&D via big subsidies at the end of the entire process to the first 'few' winning vaccines undermines competitiveness and deters smaller, less powerful, players. Dominant players also face a great deal of 'reputation risk' that they might have avoided.
- It is difficult to guarantee long-term low prices and supply. Current proposals determine these in contracts set at the start of the R&D process—with penalties for failure—in return for the short-term advantage of initial sales at high, heavily subsidized prices. Unfortunately, such contracts are not credible. Moreover, if manufacturing capacity is initially very limited, companies might supply more lucrative markets before eligible markets (eg. using research results for one HIV clade for another more lucrative clade first). This is a general risk for APCs because developers and sponsors have little control over IP and 'know-how' than alternatives.
- To drive quality and follow-on innovation, APCs place considerable market risk on developers. This undermines incentives for R&D, especially given the dysfunctional nature of many 'eligible' health markets and the importance of scale in driving production costs lower.
- Bureaucratic structures must be complex and omniscient. Setting minimum product specifications and the rules for follow-on products requires knowledge of the expected technology and R&D costs, manufacture and distribution costs, future epidemiology, and even the future economic status of countries that may or may not be eligible for the program.
- Many institutional, legal, and IP issues still need to be resolved. Given the presence of many other R&D mechanisms (including Product Development

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Partnerships or PDPs) and the mix of eligible and non-eligible countries, APCs would potentially generate highly complicated IP, as well as institutional and legal tangles with very unclear jurisdiction. Resolving this piecemeal makes APCs more opaque, harder to evaluate operationally, and even less valuable as an incentive for private finance.

- Because APCs vary in their ability to create genuine *additions* to current markets and to 'push' incentives, their ability to create incentives for genuinely additional private investment also varies. This is especially problematic for HIV due to its rapidly changing market and epidemiological variables and the complicated interplay of other research and funding mechanisms.
- Developers face the risk of 'dynamic inconsistency' (when investment is irretrievably sunk and more favorable terms can be extracted from developers *ex post*). This generates large, extra risk premia on investments.

A range of other R&D problems are also discussed, all of which would be exacerbated by currently proposed APCs. These problems include overly-narrow research programs, large capital costs for a few large companies researching vaccines and drugs for the same conditions, and insufficient (and shrinking) global vaccine production capacity.

The paper also discusses the politics of APCs, warning against the danger of substituting public relations for rigorous economic analyses of early-stage APCs. It points to the use of highly selected evidence—even 'evidence' selectively created—to bolster the case for APCs for HIV, malaria, and tuberculosis. It finds that APC promoters are often too cavalier about costs: the costs of research failures, the real resource costs borne by pharmaceutical companies and their shareholders, and the costs to sponsors if they are partly responsible for failures. We must not forget that it is those who most need the vaccines who have the most to lose if an approach fails or if alternative approaches that might have succeeded are crowded out. The stakes are high, and so we must proceed urgently but not haphazardly.

In its analysis of an HIV APC, the paper reviews the many scientific difficulties facing HIV vaccine development and finds that they do not match well the economic models underlying APCs for HIV vaccine(s). It also notes formidable institutional obstacles. The current proposal calls for sponsor(s) to fully indemnify the committee running the program, with the eventual designated supplier(s) defending and indemnifying the sponsor and committee. This narrows potential participants to only the world's largest companies. It also heavily relies on third parties, such as the WHO, that are nevertheless expected to relinquish all decision-making powers to the controlling committee.

The paper analyzes malaria vaccines in light of the heavy interest shown by the British government in a potential GSK 'vaccine'. It argues that the scientific complexities and challenges are much greater than has been suggested and that current (UK and G8) policy pronouncements seem to consider an APC as a first-come, first-served 'prize' for 'a' vaccine. This ignores the necessary and more complicated endeavor of creating a range of vaccines over time. The paper also argues that a malaria APC would be an extremely complicated instrument that is unlikely to work in practice. In particular, investors are unlikely to *believe* it will work.

The paper contends that the terms of any malaria deal—and the mechanism in which it is embedded—have to be transparently set out along with a commitment and the resources to find better vaccine(s). The danger is that an early, partially efficacious vaccine will be much more politically salient than a lost, much more efficacious vaccine. Worse, the reaction to a non-efficacious vaccine may give one company too much influence over the larger outcome, stymieing other developers. Given the huge range of extremely positive activity going on—with up to fifteen PDP-backed candidate vaccines in clinical trials—it is not at all clear that an APC is the best way to fund all this activity. Indeed, GSK is negotiating another major injection of PDP funding, suggesting that the company is less convinced than politicians of the usefulness of APCs for vaccine R&D.

Not content to offer only criticism, the paper also considers what has been done right regarding late-stage and already existing vaccines. It considers a range of case-studies, including hepatitis B, haemophilus influenzae type B (Hib), smallpox, African trivalent meningitis vaccine, meningitis conjugate C, pneumococcus, and rotavirus. Their development routes do not remotely match the APCs being proposed for HIV, malaria, or tuberculosis.

For these vaccines, purchase commitments are all about stable demand (including improved demand forecasts), incentives to invest in production capacity, low product prices, the tailoring of an already existing product to new users, access to technology and know-how, and commitments to tackle market risk at many levels. Good information to set terms is available, and it is much easier to make purchase commitments 'additional' via competitive processes. There are 'relatively' low capital costs (e.g. compared to HIV vaccines) and much lower risks to biotechnology companies. Emerging country developers

and manufacturers play an increasingly important role, helped by improvements in their own regulatory infrastructures and wider sources of finance—and not just the 'deep pockets' finance of large pharmaceutical companies—for a wider set of players. A large number of these reasons are 'fungible' and apply to whoever carries out the research and whatever the funding source. Many of these 'purchase commitments' were *not* 'committee-driven' over long horizons. Indeed, pre-committed early-stage APCs would have conflicted with them. The paper strongly supports the former, and not the latter, type of purchase commitments.

The paper also tentatively suggests what the structure of a 'Global HIV Vaccine Enterprise' might look like, suggesting a combination of at least four *interlocking* components. These include a range of IP changes, more use of certain kinds of 'novel' IP and financial instruments that are connected to IP, an open collaborative information processing mechanism—including expanded, highly transparent clinical and preclinical trials and harmonized regulation—linked to IP and to the financial mechanism, and (for lack of a better phrase) 'contingent purchase commitments'. These would emphasize production and distribution, but by definition the terms could not be set in advance. Continuous, ongoing competition is stressed over one-time competition driven by a committee.

In light of the recently concluded Gleneagles G8 Summit that identified health issues as a high priority, the paper ends by suggesting an order for future G8 priorities:

1. Fully funding the existing product procurement/donation mechanisms as a way to boost vaccine developers *now*.
2. Securing a seriously large injection of funding into existing global/regional consortia/PDP's and emerging vaccine enterprises, and increasing the accountability and quality of evaluation of these mechanisms.
3. 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 prices down, the creative use of IP and know-how, and the opening up of the market to more competition at late stages of development and procurement.
4. Putting in place an 'Advanced Distribution Commitment' to fully fund the delivery mechanisms for HIV, malaria, and tuberculosis vaccines once developed, including a commitment to remove the barriers to the provision of healthcare in developing economies themselves.
5. An attitude that bites the bullet about paying for vaccine work through much more collaborative, yet competitive, systems than we now have.

Though there has been much recent progress, for years too little emphasis was put on vaccine innovation and delivery. But there are danger signs in the shape of mounting global fiscal pressures coupled with a proliferation of challenges competing for the attention of global leaders, international institutions and the philanthropic community. Before it passes, this moment of intensified interest in vaccines should not be wasted but exploited to secure solid financial commitments, sound policies and proactive incentives for long-term vaccine solutions.

1. Introduction and a Benchmark Model

The General Policy Environment

Several thousand people in developing countries will die of infectious or parasitic diseases by the time you have finished reading this paper[1]. Many could have been saved by access to already developed vaccines and drugs, and much unnecessary pain and suffering avoided. In addition, barely more than one percent of total global spending on pharmaceuticals goes into the research and development of *new* products for diseases affecting 90% of the world's population[2]. It is a sign of hope, of frustration, of the craving for the human dignity and worth of others, that a variety of groups are currently engaged in a wide-ranging–and sometimes uncomfortable–debate about how to redress this imbalance.

Important strides have been made recently with the announcement of large fresh funds to purchase vaccines and to roll out immunization programs. The UK has promised $1.8bn (£960m) over 15 years, the Bill and Melinda Gates foundation a fresh $750m, and Norway $290m. One of the highlights of the UK's presidency of the G8 and the European Union this year could be significant progress on the vaccine front.

A highly heterogeneous problem

The vaccine problem is highly heterogeneous. It ranges from the low or non-use of many already existing, already cheap or even practically costless, vaccines[3], to the tantalizingly slow development of 'late-stage' vaccines–where most of the science is already known and a viable product is close to development –, to the dim and distant prospects of the development of 'early-stage' highly complex vaccines, such as those for HIV, malaria, and tuberculosis–where there are either no viable vaccines on the horizon or the current candidates fall well short of 100% effectiveness, and many of the scientific difficulties have yet to be resolved. In the media, this range of problems has tended to be lumped together, and the term 'advance purchase commitment'[4], APC, has also come to conflate them somewhat.

Recent confusions

This confusion has been reflected in recent policy pronouncements. In discussing the proposed new International Finance Facility for Immunization, IFFIm, the highly effective and hugely laudable use of funds to make current purchases of already existing, cheap, vaccines (for diseases such as measles, pertussis, tetanus, and for Hib-related diseases), to roll out major treatment programs, and to save millions of lives, has often been treated in the same breath as 'paying' for a long and expensive R&D process–through APCs–for currently non-existent and way-off HIV and malaria vaccines. Much of the recent body of work generated on 'pull' mechanisms has not helped either by constantly using late-stage language to discuss early-stage vaccines, suggesting that there are few, if any, distinctions, and ignoring many problems special to early-stage vaccines. Indeed, the core model used to describe HIV APCs by Kremer[5] makes no concession at all to it *not* being a late-stage vaccine.

The pull strength of APCs varies greatly, and it has not helped to constantly conflate potentially useful and comparatively straightforward uses with much weaker and much more problematic cases. Worse, it has lulled policymakers into a false sense of security. In many ways this paper is a call for balance in this debate, for better use of terminology, and for better assessment of the relative use of the various R&D instruments.

Redressing the balance

This paper may come across as lop-sided in its pursuit of the problematic in early-stage APCs, and some may also argue that too little attention has been paid to problems with *alternative* incentive mechanisms. However, given the relentlessly positive presentation of APCs for early-stage vaccines–from the heavily-biased cost-effectiveness estimates presented in the original UK No. 10 Policy Unit material, through a series of CGD reports and briefings that repeatedly leave out problematic details, to current APC cost-effectiveness papers[6] that ignore all costs of developing a vaccine *other than* the APC itself and are thus able to claim: "Three Billion Dollars Per Disease… At this price, the advance market commitment would be a bargain compared with many other development expenditures"[7]–this is to be expected in any effort to redress the balance.

Besides, there is a vigorous debate about the alternative incentive instruments, and one can hardly be criticized when filling out a niche in the debate that one is not adding to the already voluminous material on other incentive mechanisms[8]. Each mechanism must survive or fall based on its ability to survive critical evaluation. This paper seeks to contribute some of that evaluation. Others have to decide the outcome on the basis of this and that much greater body of other material.

Recent pull analysis

Recent influential work on 'pull' mechanisms has been produced by the Center for Global Development in Washington, D.C. with financial help from the Bill and Melinda Gates Foundation. This current paper analyses that work, especially 'Making Markets for Vaccines: A Practical Plan'[9] (henceforth referred to as 'Making Markets') and the book 'Strong Medicine'[10] (henceforth referred to as 'Strong Medicine'), and will make frequent references to these publications. Much of that work takes as given the large body of earlier work deposited at the UK's No. 10 Policy Unit website[11]–with its heavy bias towards early-stage vaccines–created almost entirely by one or two individuals who also wrote much of the later publications. For all the names attached to these files, surprisingly few are involved in any great capacity.

This earlier work raises many fundamental issues that require full and transparent discussion before large permanently-set, early-stage APCs could ever be enacted for complicated vaccines such as HIV, malaria, and tuberculosis. Yet neither the No. 10 Policy Unit nor the UK Treasury independently analyzed what they were given. An extensive previous paper[12] took a closer look at the No. 10 Policy Unit material and argued that the proposal raised many questions that still had not been answered. That paper was handed over and briefly discussed with a few key individuals at the Center for Global Development and elsewhere. However, and in spite of agreeing at the time with many of the unresolved issues, many of the issues remained unresolved more than a year later.

Some of those issues form part of the basis of what follows. One would expect for something that has to be *permanently and irretrievably fixed* to have any effectiveness[13], that teams of financial and industrial economists, and many more experts on the practical aspects of developing, distributing, and using vaccines, would have been set the task of 'stress testing' the framework against all eventualities. But this has not been the attitude. And one must wonder why not.

Indeed, many of these issues have been a source of concern for many years[14]. That they still persist more than eight years after the idea first surfaced (though only very recently taking on the guise of an 'Advance Market Commitment') and after a great deal of effort by a great number of individuals–not to mention a great deal of funding–says something about the underlying problems of relying on such programs to drive R&D for these vaccines.

A wide variety of individuals involved in pull analysis

Those involved in advising on 'pull' and other proposals are themselves a pretty heterogeneous group, with some indeed promoting the approach as a panacea for all vaccine R&D ills and hardly ever referring to anything else, and others having a much less exaggerated perspective, trying to see how the proposals might fit into a larger picture running from currently existing vaccines right through to early-stage vaccines[15]. There is a danger of reducing this wide and complex set of viewpoints to a caricature of the most blinkered, and this must be avoided. It would be wrong to suggest that some do not have their doubts about the greater journey ahead. And, in spite of sometimes strong differences of opinion, we should also not lose sight of the fact that *all* of those involved (including those that this author strongly disagrees with) are motivated at a very deep level by the need to tackle the suffering they see.

An 'Early-Stage' Vaccine Commitment is an Experiment

Until very recently it seemed that an approach to early-stage vaccine APCs was evolving, with awareness of the many potential difficulties and plenty of room for movement in thinking. However, with policymakers suddenly very interested in enacting *something*–maybe even *anything*–initial reservations have been cast aside, and the aim has shifted to getting policymakers to agree to large HIV and malaria APCs and to worry about the details later. Instead of critical and balanced analysis, there has been ever increasing positive and simplistic spin and the brushing aside of key 'problems'.

This is quite the wrong way to enact good economic policy, and even more so for an economic instrument that *has to be irreversibly fixed*[16] to even stand a chance of working, and that is also, by definition, an *experiment*. Since we cannot conduct experiments in real-life problems such as this, the only logical route open to us is to: i) stress-test in every way possible the concept of APCs, especially the financial and industrial sides to the modeling underlying them; ii) look at past examples and see what experience can be drawn from them; iii) experiment and build up from simpler to more difficult applications, and not jump to the more difficult applications first. The attitude has been to have none of this. Instead, we are supposed to just try the instrument and see what happens:

> "*If thirty years pass and no substantial progress has been made on the product of interest, a vaccine commitment may not be the most useful approach, and the policy would be worth reevaluating.*" [17]

So, it is fixed 'forever', and yet it is an experiment? If the reader has not started to worry by now, this alone should start the process. The current rush to fix large, irrevocable APCs for HIV and malaria, regardless of evidence of cost-effectiveness, or knowledge that they will work (and, indeed, that they will not simply 'get in the way'), is likely to be not just expensive but counterproductive, slowing down the speed

of vaccine development and the quality of vaccines, compared to alternative approaches for a given budget.

This paper argues the need for a more rational, open, and above all critical, discussion of this material, not just to work out where problems lie, but for the more positive purpose of working out exactly when such instruments are likely to be powerful, how they might be modified to actually work, and how they should be set vis-à-vis other instruments. In many ways this paper only goes over some of the ground the Center for Global Development Pull Working Group should have gone over in its deliberations. It lays down some of the awkward issues that those chairing that group should have laid before it for discussion[18].

The Idealised Benchmark 'Advance Purchase Commitment'

The phrase 'APCs' has come to have varying degrees of strictness in both interpretation and application. At one extreme it has been interpreted as just a generalized notion of 'willingness to pay' for vaccines. However, at the other extreme, there is a benchmark for when such devices are used to stimulate privately financed R&D, and it is worth setting that out exactly so that we can compare and contrast *that* with real-world enactments. No incentive instrument ever achieves an idealized enactment. The interest is in how easy it is to achieve an idealized application, and how far short applications fall. One of the presuppositions of much of the 'empirical' APC literature is that an idealized enactment is achieved each time. However, it is sobering to think that we have never had an APC meet conditions even remotely approaching the benchmark criteria for even the most simple drug or vaccine cases, nor, indeed, for any other product. And recent policy pronouncements for early-stage vaccines (malaria and HIV in particular) do not begin to approach the benchmark either. How far they fall short, and the implications of this for vaccine development, is an interesting policy issue in its own right[19]. Why policymakers would even consider starting with what must be some of the most complicated possible applications ever is quite beyond this author.

The idealized benchmark

APCs for vaccines are *legally binding* contracts (on only the funders in the case of early-stage vaccines[20]) that, to all intents and purposes from an economic perspective, *commit* '*forever*' a sum of money for the purchase of a vaccine or vaccines for a particular disease. According to the literature, this would be anything in the region of, say, $3bn-$10bn per major early-stage vaccine, though the eventual sum is not clear and could–and would–be a great deal higher. The suggested appropriate figure has kept falling and is now $3bn[21], though that is now described as only "illustrative"[22] and has gone back up to $4bn in recent policy pronouncements[23]. One would think that if there was anything scientific at all about the approach, a billion dollars here and there might matter. Again we get evidence that the figure is based, as a vaccine expert put it to the author, on no more than "kitchen table" calculations. Pitching to the lower end of the range (indeed pushing the lower range ever lower) has become popular just recently, but we will later see that this is very damaging behavior if the true requirement is much higher.

This is not the whole cost of developing a vaccine. The overall cost includes all public funding needed outside of the mechanism in order to make it work, as well as subsidies, tax-breaks, and other benefits private firms are granted for their research[24] (to the extent that a large *multiple* of these is not removed later from payments, as will be explained below).

The size of the fund (and its distribution over developers) must be set *precisely* high enough to re-create the *precise* size of *additional* market needed to encourage the entry of the *precise* amount of venture capital and stock market finance needed for the *remaining* research and development for producing a 'high quality' vaccine or series of vaccines (that will be needed over time, especially in the case of malaria and HIV). R&D costs would then be fully repaid through the purchase of a 'successful' vaccine or several 'successful' vaccines in a particular period of time (if there are several meeting eligibility conditions in any one period of time), or series of vaccines over time, and *only* the 'successful' vaccine(s) or series of vaccines. In this sense, the 'benchmark' idealized APC is a complex R&D subsidy program over multiple vaccine developers, with the allocation of a fixed overall amount of subsidy determined, in the absence of standard price signals, by a mixture of pre-set rules based on whatever information can be garnered at the start, and ex post discretion.

Payment would come from the taxpayers of richer countries, by foundations such as the Bill and Melinda Gates Foundation, and through co-payments made by developing countries tied, in advance, to the mechanism. The program is thus entirely foundation–and publicly-funded when it succeeds, and entirely financed by pharmaceutical firms if it fails.

Observe the multiple directions for decisions about eligible vaccines–across vaccines at a given point in time and across vaccines over time–with all expected decision rules set in the terms of the 'contract' at the start. In order to overcome any risks (as perceived by developers) that buyers will bid terms down after development, the funds are legally committed *in advance* to pay for those (and *only* those) vaccines generated in response to the mechanism on the basis of the pre-agreed rules. This is important, since one of the key justifications for the mechanism is to solve the 'time inconsistency' problem. This happens when firms have sunk their R&D costs and then buyers have the power to bid prices down to levels that do not fully cover those collective R&D costs. Knowing this in advance, no individual firm will therefore perform R&D in the first place. We will see that 'time inconsistency' continues to be an extremely difficult issue to get around under an APC. Indeed, it turns out to be intractable whatever the mechanism used to stimulate early-stage vaccine R&D, but especially so for those mechanisms concentrating payment in the end period. In addition, the more complex the science, the greater the ex post discretion will be, and the greater the time inconsistency. Time inconsistency can be reduced by stripping out all hints of scientific complexity, but this is hardly appropriate for these early-stage vaccines.

What the winner(s) get

The 'winning' vaccine developer or developers would be paid the value of *all* the privately-funded (and *only* the privately-funded) R&D costs (including *all* capital costs) of *all* firms (both the successful and the unsuccessful, and not just of itself) and *only* the private firms, who used such private funding on R&D towards the vaccine since the time the purchase commitment had been announced (and *only* since the announcement) and *only* for 'eligible' countries covered by the mechanism. The winner gets all the vaccine IP for both 'eligible' and 'non-eligible' markets–although this is very unclear if there are PDP aspects to the creation of vaccines.

A 'blockbuster'-style model[25]

For the time being we take at face value the presumption that there will be competition between developers, though we will find that it is increasingly less obvious that this will be the case. As with the 'blockbuster' drug-development model, an individual firm will therefore treat its vaccine R&D as a lottery with a very large 'prize' that just makes it a fair risk-adjusted gamble. Individual firms calculate the expected value of the 'prize' on the basis of the *privately-funded* R&D activity of all other private firms. If others, not firm *i*, do more R&D, then this will reduce the chance that firm *i* will win the contract and hence the expected value to firm *i* of its investment. 'Others' *should* refer only to other firms working under this funding mechanism, and not to any other researchers working under any other funding mechanism. We will see that achieving this 'separation' proves fiendishly difficult in areas of complex science involving the interplay of many different funding mechanisms and a complex mix of public and private researchers[26]. Worryingly for firm *i*, 'others' could refer to those being paid for under other funding mechanisms if these other mechanisms are not factored out of payments[27].

A first look at some very vague 'size' figures

To frame the thinking, it might help to have a quick overview of possible scenarios, though we also recognize that insufficient evidence has so far been presented to properly analyze early-stage vaccines, so that the figures are, of necessity, extremely rough and only 'illustrative'.

When it 'wins' the contract to supply the vaccines, it turns out that a firm's out-of-pocket costs are a tiny fraction of the contract size. For example, if 10 firms[28] put in equal effort on an early-stage HIV vaccine (again, maintaining the presumption of competition for now), and we presume that this is the optimal number of firms (we cannot), and that (because of all the risks and because of the high cost form of finance being used[29]) they face an expected 70% of capital costs[30] by the time a product is developed (and we ignore all crowding out for now), and we presume for the moment that only one firm wins (though, in most cases there would, supposedly, be a complicated split over time and across firms), then a $6.25bn APC will go to a firm having spent, in present discounted (2005) terms, less than $200m on private out-of-pocket research costs. This is the efficient and 'fair' outcome

and is not being critiqued here. It is in the nature of 'blockbuster' mechanisms that this is the outcome, though it does create problems for firms and for the committee running the program, as we will see below.

Incidentally, the response of one pharmaceutical executive when this was spelled out precisely was that winning such a contract for HIV would be just as much a "PR disaster" as developing an HIV vaccine under the current set-up. Throw in some of the discretionary elements (discussed below) that the firm would have to very publicly fight over in order to get a fair return in *the ex ante sense*, and it would be a "complete PR disaster", and much worse for such firms than some alternative approaches to funding.

In this case, if there were no 'crowding out' (explained in more detail below), the $6.25bn fund would pay for $1.875bn of out-of-pocket R&D costs across all firms and $4.375bn of capital costs. If there *is* crowding out and other inefficiencies, the ratio of 'payout' to the out-of-pocket private costs could be even more extreme. In this simple case, if there were 50% crowding out, the $6.25bn fund would pay for about $900m of new out-of-pocket research costs, or about 9 months' worth of what those working on the Global HIV Vaccine Enterprise argue is actually needed. The most likely short-run response of firms to such an incentive would be to not respond at all.

But for HIV it would need a mega-blockbuster commitment

Indeed, if it really is the case that HIV vaccines might take 15 years to develop and need $1.2bn per year of out-of-pocket research and trial costs, as those working on the Global HIV Vaccine Enterprise argue, then replacing this $1.2bn per-year flow for 15 years with venture-capital funded biotechnology firms and equity-financed large pharmaceutical firms and an APC at the end of the whole process, would, on not outrageous assumptions of required rates of return given all the risks discussed below–nominal required rates of return of 15% to 25% per year (real rates of 12% to 22%)–require an APC of about $65bn to $165bn[31].

Maybe this is why private firms spend so very little on HIV vaccine research? It is hard to believe that rich markets would not pay $25 or more per course of vaccine treatment, generating a multi-billion dollar market in such countries for an HIV vaccine. Maybe that is simply not large enough to cover all the risks faced by developers and the mega-blockbuster price tag they would need to justify the risks via the APC route? Maybe it also has something to do with the target being more than just creating a single vaccine? Maybe if those advocating for an HIV APC were to work out the potential size of *any* high-value market for HIV vaccines, and take one look at the pitifully low levels of private vaccine R&D funding for *that* market, they might come to a quite different conclusion to the simple 'lack of a market' argument?

Even simple math casts doubt on the notion that an APC "may provide the incentive that has been so desperately lacking"[32] and that if only we had one in place, all would be well. An HIV vaccine APC–if that is the route chosen–would, given all the risks, have to be a mega-blockbuster, and a great deal higher than anything currently being proposed. The best a $3bn APC would do in such a situation would be to allow one big, influential firm, at the end of the whole, expensive, largely publicly–and foundation-funded process to maneuver to claim all the IP. Even big firms might prefer some other approach to avoid being put in a position so potentially damaging to their reputation. This potential damage weighs heavily against the expected value of the APC compared to other approaches less risky to reputation.

For vaccine purchases of currently existing vaccines, these proportions would, naturally enough, be completely the converse, with low capital costs because of lower risk, no crowding out because of the ability to use competitive tenders, and much more easily set terms.

Specifying vaccine characteristics

Each purchase commitment would try to specify in advance–on the basis of expected science and the difficulty of development, costs of production and distribution, epidemiology, expected size of future eligible and non-eligible markets, etc.–the characteristics of a vaccine that would be acceptable for those eligible countries covered by the program[33]. In truth, this could not be remotely set in advance for conditions such as HIV, malaria, and tuberculosis. Observe how it is not just the characteristics of the medical condition alone that enter the decision process. There would therefore have to be a great deal of discretion left in the terms set. A contract might, for example, specify

250 million treatments for a malaria vaccine at $25 per course of treatment (making $6.25bn overall[34]), with distribution thereafter to those covered by the mechanism at cost-plus pricing.

There would be one, or supposedly several, big winners of the supply contract, with decisions about winners and losers and allocations made by a committee, based on a mix of rules and discretion. In the literature, this has come to be called an 'Independent Adjudication Committee', or 'IAC'. We use the same nomenclature here, but make no *a priori* presumption about its independence since this is highly unlikely to be the case, or, more importantly, highly unlikely to be *expected* by investors to be the case *at horizons of interest*.

In the above 'best-case' scenario (of no crowding out, though high capital costs), a vaccine costing $25 for the first 200 to 250 million treatments might compose $1-$2 for production and distribution, $6-$7 for out-of-pocket R&D costs of all firms (not just the winning firm), and $16-$18 for the cost of the finance (again of all firms). With 50% crowding out, only about $3 of the $25 would go towards fresh out-of-pocket R&D costs. Incidentally, it is not at all clear that the first few tens of millions of an HIV vaccine could be manufactured *that* cheaply (especially if there is no competition between manufacturers to drive production prices *that* low). We will discuss this in more detail in Section 2, when worries about this being the case would undermine incentives to do R&D in the first place.

Competition, supposedly

Freedom of entry and exit in the R&D process and competition to try to win the $6.25bn (now $3bn) contract will, we are told, lead to the 'optimal' number of firms working on vaccine trials and hence the optimal speed of development. However, 'competition' is essentially driven by the expected behavior of the committee, as well as expectations (and worries) about the behavior of other firms with respect to the committee. The number of firms in equilibrium is dictated by the initial size of the 'pot' of funds, so that having an optimal number of firms requires that the size of the 'pot' be chosen optimally at the start, which requires knowledge of both the science, likely costs of developing and producing a vaccine, epidemiology, etc. If the 'pot' is too small there will be too few firms and progress will be too slow and chances of discovery low. If the 'pot' is set 'too large' there will be 'too many' (showing up in overlap, waste, lack of cooperation, rent seeking behavior, efforts to capture the mechanisms, etc. with some of this harming other parts of an overall mechanism for discovering vaccines).

The underlying economic notion is that if, for any given 'pot' size, there are *too many* firms 'competing', then the chances of any individual firm winning the pot, or a part of the pot, are too low, the risk-adjusted rewards are too low, and firms will leave (or they will simply not enter in the first place). However, if there are *too few* firms, then the chances of being a winning firm are higher[35] and more firms will enter. In *both* cases, the laws of motion supposedly push in the direction of the optimal number of firms working on research leads in equilibrium[36]. For these laws of motion to work requires huge amounts of assumed competition. If terms could be permanently set in advance, firms would supposedly form their optimal strategies on the basis of their expectations of the strategies of other firms, and never on the behavior of the distributor of the 'pot'. When terms cannot be known in advance, ex ante competition between vaccine developers is policed via the expected ex post behavior of the committee (very unlike a standard competitive tendering).

Prices of vaccines to those not covered by the mechanism

Populations *not* covered by the mechanism (say Russians purchasing HIV vaccines for their non-eligible program, and plenty of other countries such as, perhaps, China, India, Brazil, etc.) would *somehow* (since it is difficult to see how it could be done) continue to pay non-eligible monopoly prices, since their markets would be treated as separate from the program. This is an important feature in the case of an HIV vaccine, but, given the recent evidence of the more widespread nature of malaria, it may also be an increasingly important feature in the case of malaria vaccines too. However, given the presence of the APC in poorer markets, this could mean that the prices faced by those not covered by the mechanism in 'richer' markets would be higher than they would have been without the contracts in place[37]. This may constrain the interest of non-eligible countries in supporting any HIV vaccine research, including the Global HIV Vaccine Enterprise, if it employs an APC at the end of the proc-

ess. It may also make such non-eligible countries a big threat to the workings of the program.

From now on, this is the benchmark R&D model against which all remarks in this paper will be directed. It will be argued below that advance contracting and commitments of various sorts are useful devices, and that late-stage vaccine work can be helped by contracts that commit funders to pay for 'performance'. But these have to be very clearly separated in the reader's mind from the notion being suggested (though none of the actual mechanism is laid down) in 'Making Markets' and 'Strong Medicine' for early-stage vaccines. The latter idea is based on the notion of recreating, from the very start of the process, a precisely sized *additional* blockbuster market and a precise set of rules (though still with large elements of discretion), based on the notion that this will drive a large amount of the development of vaccines. Clearly, purchasing commitments for currently available and cheap vaccines are a degenerate case of the above mechanism, since most of the features described above have collapsed to zero. Such contracts are not capable of telling us a great deal about the above mechanism.

2. The Difficulties of Early-Stage Advance Purchase Commitments for Vaccines

Drastic Simplifications

'Making Markets' is interested in both early-stage and late-stage vaccines, and recognizes that for the former vaccines "significant scientific barriers impede the development of vaccines for these diseases."[38] 'Strong Medicine', on the other hand, expends most of its firepower on early-stage vaccines for HIV, malaria, and tuberculosis[39] on the basis that this approach is the way to incentivize the discovery, development, and production of these particular vaccines.

For ease of exposition we look at the more complicated case of early-stage vaccines first. Far more issues are raised for these vaccines than for late-stage vaccines, and it proves easier to explain things by working outwards from the more difficult cases towards much simpler late-stage vaccines. 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[40]. 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, 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.

1. The science is fixed, simple, and static

To strengthen the case for complicated early-stage vaccines, the underlying modeling in all of the APC literature drastically simplifies the state of difficult, unpredictable, and dynamic science to one that it is *fixed* and known at both basic and applied levels, even for viruses as technologically challenging as HIV. Indeed early-stage vaccines are modeled *as if* they are late-stage vaccines. It is even pointed out in the literature describing the model that ultimately drives the

case for early-stage APCs that "this model is *best suited* for comparing different policies under *consistent assumptions about the state of technology*,"[41] (italics added). Linguistically, the phrase "consistent assumptions about the state of technology" means that the state of technology may be very inconsistent, but that the assumptions about it are consistent. Similarly the model is described as driven by "a consistent set of assumptions about the scientific difficulty"[42], which again means that the scientific difficulty can be very inconsistent, but that the assumptions about it are consistent.

But these phrases are misleading. For some reason, Kremer *never* uses the phrases "assumptions about the consistent state of technology" nor "a set of assumptions about the consistent scientific difficulty," even though that is *exactly* how the model is mathematically set up. This is at the heart of the misapplication of the approach to early-stage vaccines, and the exaggerated claims for the models 'strength'. It has been claimed that "[It] is wrong to say that the proposal depends on a particular model of scientific progress."[43] However, there is, in principle, a potentially infinite set of 'states of scientific difficulty', and the modeling device used selects only one 'state' from this set. When dealing with such difficult and complicated issues as HIV, malaria, and tuberculosis vaccine research, it is not particularly useful to have a model that is 'best suited' to a world that we do not have, and then get around this by *assuming* a world that 'suits' the model.

In addition to the presumed given state of science, the other chief simplifications are:

2. No patents on anything other than the end products themselves

Some will find this contentious. Others will find it simply 'odd', given the observation in 'Making Markets' that uncertainties around IP protection[44] are part of the problem . Although strong patents and strict secrecy requirements can diminish scientific discovery as well as enhance it[45] (and raise the costs of vaccine developers as well as lower them), patents are modeled as functioning perfectly, or some curious sort of 'open source' arrangement is being presumed. There are no financial constraints, investment hold-ups, strategic behaviors, constraints on flows of information, or concentrations of market power based on patent ownership. In fact, patents function so perfectly that they are simply *removed* on all but the end products. In real-world settings, however, intellectual property issues are shot through the entire R&D system. When the Malaria Vaccine Initiative (MVI) 'mapped' the patent status of the MSP-1 antigen, it found 39 different families of patents with monopoly scope impinging on it[46].

Because of the build-up of large private capital costs of those who invest in the hope of winning an APC, a core component holding a real-world early-stage APC (as opposed to an idealized one) together would be a chain of IP rights and/or secrecy. This would be very much so for very early researchers who would otherwise worry that they would not be able to internalize the value of their private R&D efforts, but equally or more so for those near to the end of the R&D process who find themselves with up to $6.25bn resting on their hold of IP. In the underlying model there is essentially no distinction between those doing early and those doing late stages of vaccine research since there is no sense of a 'process' over 'time'[47]. Research projects are also modeled as entirely independent of each other so the notion that the results of one project can be 'taken' by another project is stripped out of the reasoning. Unfortunately, none of this describes HIV, malaria, or tuberculosis vaccine research particularly well.

At the very least, the empirical basis for excluding patents on all intermediate products or processes in the modeling process should be presented. If part of the current problem with complicated vaccines like HIV is lack of information 'sharing', it is not obvious that imposing even less sharing and even more secrecy is the optimal way to proceed. If more collaboration and information sharing is to be encouraged under a Global HIV Vaccine Enterprise, it is not clear how repayment can be structured so as to fully internalize the benefit of a firm's own activities if repayment depends on a system based on secrecy and low information sharing. The results of the WHO Commission on Intellectual Property Rights, Innovation and Public Health[48], due in early 2006 (though much material is already becoming available), should give us some further pointers on this[49]. The Kremer modeling device short-circuits that debate, placing itself firmly at one end of the spectrum of views on the issue, pre-judging that there will be no IP problems of any sort from the start.

3. No benefits in sharing information across vaccine developers and no know-how monopoly

'Know-how' is especially important for vaccines–far more so than for drugs–and particularly so when some developers or potential developers are already at a technical or financial disadvantage. One obvious danger is that existing developed economy patent holders, facing a potentially emerging-economy competitor, will be able to exploit 'secret' know-how (as well as more general technical know-how and undisclosed test or other data)[50], including refusing to contract to transfer necessary know-how, thus creating a barrier to entry of the competitor. In such cases, compulsory licenses are much less useful than in the case of drugs; it is of little consequence to have such a threat if lack of know-how makes it non-credible. It is not clear how any current know-how gap might be exaggerated by a mechanism that emphasizes those with 'deep pockets' and free cash flows and (if not correctly screened out in payments) those with access to various other forms of subsidies.

4. No variation in the probabilities of discovery over the vaccine development process

There is therefore no problem in keeping cumulative R&D projects together, no risks to those making investments early in the development process, and no difficulty ensuring optimal intensity of R&D at *all* points in time[51].

Part of this varying probability is also a function of variation in the underlying push research and variation in the regulatory environment, such that fixing probabilities of discovery is tantamount to fixing push research and the regulatory environment.

5. No ways for technology to improve or deteriorate over time

There are no technology 'revolutions', such as the 1980s advances in molecular biology, nor technology 'shocks'. Neither do we have to worry about incentives to *improve* technology[52]. If such revolutions and shocks are possible, it then becomes a tradeoff between–on the one hand–'insuring' firms via a fixed payoff structure (with the contract sponsors facing the technological risk), which helps to keep firms' risks down and hence lowers the capital cost component of a purchase commitment, but gives them no incentives to improve technology, or–on the other hand–giving firms the incentive to improve technology through a variable contract (and observe how the committee running the program needs to know the potential technology in order to set the variable terms). But the latter contract faces firms with risk that also has to show up in a higher required APC.

Technology *does* change over time:

> "*The scientific basis for the development of new vaccines has accelerated greatly over the last 20 years. Major advances in the understanding of the pathophysiology of infectious diseases and a wealth of revolutionary technologies are expected to greatly enhance the feasibility of immunization against diseases for which vaccines do not currently exist.*"[53]

APCs either have to be set in expectation of this change and try to predict it, or they fall behind and need modifying[54]. Currently, the APC literature says that any improvement in technology that is *not* caused by the firm's efforts will not be offset by tougher terms. Imagine, for example, how terms of an early-stage APC would have been set *before* the success of the human genome project or the impact of the cracking of the malaria genome, and how an APC would have struggled to deal with this without wrecking its credibility. In both of these cases the bias is in the direction of this being a more costly–and never a cheaper–approach.

It might be very useful for those promoting the APC mechanism to ignore this issue, and to fix the underlying state of technology as for ever the same. Appendix 3 of the Number 10 Policy Unit submission does just this. But it removes a major driving force for improved vaccines and lower vaccine costs, and sweeps aside difficult problems when setting the terms of such commitments.

The removal of all variation in probability over time, all shocks, technological revolutions, and the ability to improve technology, is needed in order to remove all IP issues from discussion. It also greatly simplifies the decisions made in other parts of the research process not covered by APCs.

6. No build up of sunk costs

This might surprise those who work in pharma, but it helps to remove many potential distortions in the model[55]. Shortly, we will see that it is the source of many of the practical problems in using APCs.

7. Good understanding of the state of current and future science

The science is, after all, fixed in the models so that a reward system to incentivize vaccine 'quality' can be created. 'Making Markets' recognizes that price would have to vary to "take into account the *likely complexity* of identifying and producing a vaccine"[56] (italics added), but there is no convincing evidence that this could ever be done remotely correctly, especially for a complicated early-stage vaccine. The danger is that this subtlety is lost in practical applications, especially if policymakers have been persuaded that achieving success on early-stage vaccines requires essentially the same as achieving success on late-stage vaccines (ie. a 'pot' of money, and little else).

8. No large incumbent firms but, instead, perfect competition everywhere and always

This is needed to keep risk down, especially that of small firms, developing countries, and not-for-profit researchers[57]. This somewhat contradicts the stated intention of targeting large pharmaceutical firms: "A large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more."[58] In reality, entry and exit of the required number of firms cannot be presumed, given that there are only a few large firms being targeted by the mechanism, and the value to each of these firms of multiple vaccine leads is greatly reduced compared to more competitive scenarios. This is explained in more detail in Farlow 2004 Chap 10.

Lack of competition also creates problems targeting in the 'quality space' since there may be too few firms to generate quality-driving incentives[59].

9. No strategic behavior of any sort, and of any firm, based on sunk costs, patent ownership, finance, or any other real-world factor[60]

There has been such a growth in the number of patented inventions in biotechnology that issues about the strategic use of patents should not be overlooked (especially when considering the relative bargaining strength of large pharmaceutical firms versus biotechs, developed versus developing country firms, profit versus non-profit firms, etc.). Again, *expectations* about such behavior matter as much as the actual behavior itself.

Relevant examples to consider might include: products such as micro-organisms in a living but attenuated state, (recombinant) antigens and antibodies, an adjuvant or a vaccine delivery device; and processes, in particular relating to a method or steps in a method for producing a vaccine. Who has the balance of power in patent infringements in such cases for example? What if the IAC is biased, or just appears biased, in favor of large pharmaceutical firms in developed countries? The fact that next to no vaccine players from developing or emerging countries have been involved in the current discussion process for setting up APCs suggests that this is not a trivial worry. Kremer Appendix 3 essentially contains no interesting industrial structure, other than perfect competition everywhere and a level 'playing field', with no centers of regulatory power even in what is such a heavily regulated system.

10. No coordination problems across public and private sectors in their research decisions at a single point in time and over time

This may involve coordination of several layers of decision-makers. In reality there would be high and uncertain variability in the interaction between those parts of early-stage R&D on vaccines covered by an APC and those parts covered by mechanisms other than the commitment[61]. This would increase risk and hence capital costs for developers. Incidentally, most of this risk already exists and is part of the reason that private firms have low incentive to do R&D for 'neglected' vaccines.

As a concrete example, we will see later that the research leads for HIV vaccine trials that are currently being created are only in one area of potential research leads, and that there are several areas of 'neglected' leads. Were it to be set *now*, the size of the APC for an HIV vaccine would have be set *either* on the basis of the current limited set of research leads *or* on the basis of expected future research leads and future expected trial expenditures by IAVI and others. In the first case, if IAVI unexpectedly expands its own trials it would have to compensate firms working under the APC. The 'surprise' expansion of trials would reduce the chance of those working on the 'old' set of leads 'winning' an APC, and destroy the value of *their* already sunk investments. Advance knowledge of *this* possibility would deter investment under the APC. In the second case, the contract is inefficient in the short-run

and this distorts both short–and long-run outcomes. This problem never arises in a complete private sector system such as that described in the Appendix 3 model.

Clearly, setting terms a long time in advance of the clarification of these other factors will feed higher capital costs to private firms via the extra risks they face[62].

11. No coordination problems across public and private sectors and all countries in their vaccine purchase decisions and in their provision of vaccination delivery systems

This applies whether these sectors and countries are covered by the mechanism or not, and at a single point in time and over time. This is another result of trying to adjust quality ex post. Without this coordination, self-reinforcing choice of poor quality vaccines would be difficult to avoid[63]. It is impossible to coordinate these decisions in a way that is not risky for those operating under APCs.

This coordination is presumed efficiently achieved at all times in the modeling underlying 'Making Markets' and 'Strong Medicine' by a simple technical presumption: There is no sector other than the APC-motivated sector. Therefore there never is any interaction between sectors to worry about. In the Appendix 3 model, all other sectors, including the public sector, have been 'partial-ed' away; in effect, everything is *conditioned* on coordination somehow having already been achieved for all points in time and for all processes. Neither is there worry at any point in time about breakdown of coordination at any other point in time.

This is not just unrealistic, but very unfortunate given that this is one of the big problems that APCs are supposed to tackle. It hardly makes sense to presume it away. It might be an acceptable assumption in the case of bidding to manufacture already existing vaccines (using standard competitive tenders), but absolutely not so for early-stage vaccines such as those for HIV. Perhaps there are some–so far unmodeled–global treaties on R&D, global adjustments, and purchases of vaccines, that somehow efficiently insure against these coordination problems for those working under the influence of expected purchase commitments[64]?

There are large risks faced by private financiers if there is breakdown of this pre-agreed coordination, or, simply, difficulty in achieving precise coordination between the APCs and other layers of the research, development, and delivery process. Indeed, this is a fundamental problem that has always plagued those private investors in HIV, malaria, tuberculosis, and other vaccines–in the shape of insufficient levels of non-private research funding by governments and insufficient funds for vaccine distribution. As far as developers are concerned, perhaps 'advance push commitments' and 'advance distribution commitments' are missing as much as 'advanced pull commitments'? *All of these* missing commitments *have* to show up in extra costs for developers.

Putting too much emphasis on the pull commitment and not enough on the push commitments and distribution commitments is bad for the pull commitment. This problem is simply presumed away in much of the analysis (it is nowhere to be seen in the Appendix 3 paper). It is not clear, for example, that making eventual payments depend on the 'willingness' of developing countries to distribute the outcomes will ensure incentives towards 'highest' quality in such circumstances[65].

12. An idealized, non-cyclical, set of financial markets

In reality, moral hazard and adverse selection are not just faced by public funding bodies but also by private-sector managers and financial markets. By modeling on the basis of very simple underlying science, managers and financial markets never really have to struggle with many of these informational issues, are not harmed by secrecy, and end up performing a pretty trivial function[66]. Since a major driving force for the claimed effectiveness of APCs in achieving quality vaccines is through the power of stock-market based finance to perform much of the choice over research leads and 'quality', it does not help greatly to strip out most of the awkward features that make this choice challenging[67].

13. No pipelines of products, no problems with drug resistance, and no therapeutic vaccines

In truth, drugs and vaccines usually necessitate a continued pipeline of new products. This is both to improve quality (especially of therapeutic vaccines in cases when preventative vaccines are not possible)

and to keep on top of resistance in the case of drugs. This bites particularly sharply for the big killers of malaria and HIV, but also for tuberculosis. Early-stage APCs would struggle to achieve this[68]. This is similarly linked to the quality problem, since the optimal acceptable vaccine in an early period may have to be set higher than would be the case in a pure one-off vaccine creation. We will repeatedly see that tackling a whole range of 'quality' issues proves extremely difficult for APCs to achieve without a great deal of external control over quality and/or extremely heroic assumptions ex ante. Naturally, this defeats the notion that somehow early-stage APCs are non-interventionist, low on discretion, and avoid dynamic inconsistency problems.

This overly-simplifies the problem

Removing all of the complexity of points 1-12 greatly overly-simplifies the modeling of early-stage APCs. In particular, it drastically reduces the number of values such commitments might take and the number (and size) of degrees of discretion of the IAC and others. It also increases the ability of policymakers to set the size and distributions of allocations across vaccine players correctly and make APCs 'credible'. Credibility (and the complete legal bind of contracts from the start) is indispensable to the efficiency of such contracts and the reduction of capital costs. The best form of credibility is being able to fix an irrevocable payment. Having assumptions in place that practically guarantee this in an idealized model is extremely useful for this purpose–but it is not a good description of reality.

Every time one of these simplifications is breached, the extra cost imposed would have to be factored into the APC, otherwise the power of the contract to stimulate R&D is reduced. Each simplification touches on an important area in need of further analysis. Sweeping these problems under the carpet by simplifying them away is not bound to lead to good practical policymaking.

Difficulty in Efficiently Setting the Size

While it is "difficult to know how much a vaccine commitment would speed vaccine development,"[69] and although "there is no way of knowing in advance how big a return needs to be in order to induce an increased level of research and development,"[70] nevertheless policymakers must *somehow* be able to work out how large to set an APC. That policymakers can set the size perfectly (or, at least, well enough) is, after all, central to its supposed superior performance compared to alternatives. Indeed, the original cost-effectiveness figures deposited at the No. 10 Policy Unit presumed a perfectly set size every time, without even spelling out the problems of achieving this.

Wasteful if set too high

If the overall size[71] is set too high, there is waste (especially duplication, overlap, strategic rent-seeking, etc.) and reduced resources made available for other vaccines and health treatments, sanitation, nutrition, etc. Since the resources have to come from tax-payers or philanthropic foundations or facilities such as the International Finance Facility, IFF, there are all the extra deadweight losses of taxation and the opportunity costs of the other projects that foundations, governments, and the IFF are prevented from doing. If the IFF itself bares many risks, then overly large APCs add to that risk.

Wasteful if set too low

If the overall size is set too low (maybe because not all capital costs were correctly factored in or because it seemed politically expedient to set a low target), there will be too few active players, a sub-optimal level of vaccine R&D, and discovery is wastefully slow. But it is worse. Once set too low it is hard to rectify. The act of continuously revising upwards the size of the commitment acts like an extra discount factor raising the expected costs of those investing early; the *expected value* of a unit of investment is lower than for those who simply delay and get, in probabilistic sense, a higher price. This creates the perverse incentive to delay investment and discovery of the vaccine or vaccines[72], and the vaccines likely to be generated and paid for under the mechanism are lower quality on average.

Wasteful if R&D costs are highly uncertain

Maurer[73] points out the consequence when development costs are highly uncertain. Since CGD "after a long deliberation process did not narrow down beyond the range of $15-$25 per treatment,"–the upper bound being 167% of the lower bound–Maurer suggests it might be useful to explore what might happen if the wrong part of the range was chosen.

If the size of the APC starts, optimistically, at the bottom of the range when actual costs are at the top of

the range, and the interest rate is 10%, it takes 8 years till the APC has any effect (or it collapses first). If real R&D costs also grow at 5% per year, it takes 15 years to have any effect. This leads to delay, but also strong pressures towards 'poorer quality' (broadly defined) at any given APC size, since policymakers may feel pressure 'to get a result' whatever the cost in terms of 'quality'. Similarly, if sponsors chose the higher bound when the lower bound was a better reflection of R&D costs, they would expect to overpay by an average of thirty-four percent. Either way, the expected price-quality tradeoff is much poorer than it at first appears.

As Maurer points out, significantly "proponents do not promise to deliver more refined estimates in the future. They only argue that sponsors should choose a price based, *inter alia*, on 'the willingness of sponsors and recipient governments to pay.'"[74] Observe how these observations are based only on the R&D cost dimension of setting the APC size. We know that there are several other dimensions to the setting of optimal APC size and these can clearly only make this problem worse.

Not a good idea to set the basis of 'typical market size' for drugs

The current approach of the Center for Global Development is to base the size of the APC on some measure of the typical market size deemed necessary to stimulate the discovery of a developed-economy *drug*. *Implicitly* this means that the size of the APC is based on the typical costs of developing such drugs, since, in equilibrium, investment in drug development should be driven to the point where this is so[75].

The paradox is that–to the extent it is believed that privately-paid[76] R&D via an expensive APC is the route to developing complicated HIV, malaria, and tuberculosis vaccines–if it turns out that HIV, malaria, and tuberculosis are a great deal more difficult to develop than typical vaccines and drugs, then the size of the APC will turn out to be too low via this method, with very damaging consequences (including giving all the vaccine IP to a firm that has 'done very little' to justify it). This is not inconsistent with the notion that the instrument may grossly overestimate the (per unit) innovation costs likely incurred by developing and emerging country developers and suppliers, even while it may underestimate the costs of development of complicated early-stage vaccines by developed country developers. Yet, even in this case, for the sake of credibility and to prevent the dynamic breakdown of R&D incentives and loss of credibility, policymakers could *not* come along later and abolish the commitment or dramatically reset it.

It certainly seems very strange that while the Global HIV Vaccine Enterprise, in the face of strong budgetary pressures to cut HIV vaccine research, is arguing for global HIV vaccine research budgets to double to $1.2bn per year–by far and away the greatest research budget devoted to any vaccine in history–and leading vaccine experts are suggesting that this may have to be the level for the next fifteen years at least[77], nevertheless those advocating HIV APCs are basing all their calculations on recent market sizes of much simpler drugs and still nevertheless arguing that an HIV APC is the solution "that has been so desperately lacking"[78]. We toyed above with possible–and no doubt very wrong–figures for the needed APC to replace this stream of up-front payments for HIV and came up with $65bn to $165bn; nowhere near the amounts being suggested[79].

Either HIV is a fiendishly more difficult virus to create a vaccine for and will cost a great deal more to develop than probably any other vaccine in history, and the Kremer-inspired figures are simply and plainly wrong, or the figures are right and APCs operate at such a fantastically higher level of competence compared to all the alternatives that the Global HIV Vaccine Enterprise and other such approaches might as well be abandoned at birth. Going for lower-sounding figures might make an idea fly better with politicians, but it is extremely foolish–especially if one of the potential consequences is a collapse in HIV vaccine research.

The economic logic should be that each APC is set at a level commensurate with the difficulty of the underlying science and the cost of R&D of developing the product at hand. The only reason it seems that one would use 'typical market size' for drugs at all in calculations for conditions as scientifically difficult as HIV is to window-dress the idea for public consumption and avoid having to discuss the costs of vaccine development or any of the underlying science. Why else would one use an approach that is bound to generate a completely wrong figure every time[80]?

Auction theory is no help for early-stage vaccines, so lots of monitoring

No evidence is provided that size could *ever* be set remotely correctly for early-stage HIV, malaria, or tuberculosis vaccines. An auction is mentioned[81] as a way to set size, but like the original cost-effectiveness figures before it, this is another part of the argument that was once heavily promoted but has now been largely abandoned. In particular, since raising the size of an APC in an auction acts like an extra discount factor–making early investment even more expensive and incentivizing firms to delay investment–size can therefore only be raised at the rate of the interest rate, but *no faster*. But the rules about how to do this are difficult to set.

How is the start 'size' chosen? How is the speed of rise set? Are politicians willing to sign on to such open-ended programs? Will developers believe that an ever-exploding APC size is credible? How is judgment made that not enough investment has taken place, necessitating further rise, if monitoring is weak and given that the result on which to base this judgment is only ever provided at the end of the process by the generation of the vaccine? The current CGD thinking is that this is too difficult (or politically unacceptable) and is not being planned (or CGD are not yet saying how this later re-adjustment will happen).

Optimal R&D *intensity*, and therefore the size of a vaccine APC, could *not* be based on the information only provided by the actual development of the vaccine itself[82]. The chicken cannot come before the egg.

The solution, 'Strong Medicine' *now* suggests, is to pay great attention to the egg. This comes in the shape of further institutional layers and a "system of monitoring how much research was being undertaken on a vaccine"[83] at *all* stages of development inside *every* company that remotely hoped to eventually apply for an APC (or even might apply but just doesn't know it yet), with purchase prices and quantities updated in light of this information. This means, usually, a rise, since there is a bias in the mechanism towards raising but never lowering the size of the commitment. If some of the figures above are even remotely correct (with only a fraction of the 'pot' of funds capable of actually going to early-stage out-of-pocket research), there would be large risks of seriously large future rises in the size of the HIV pot (if not abandonment before). It is hardly likely that this open-ended contract would be set up. And it would be wasteful anyway.

Would firms be so free and easy with their information?

All firms, it is claimed, would be able to trust that their highly sensitive information would be kept 'confidential' even if the committee handling it to set size and terms included others from the industry. To enforce truthfulness, failure to hand over all information would, it is claimed, lead to firms losing eligibility and having to write off all research costs so far incurred (though it is very unclear how firms could be barred from using any of their results in later activity, either inside or outside of the mechanism; for example, on a competing non-mechanism HIV vaccine and in non-eligible countries). This monitoring contradicts the claim made in 'Strong Medicine' and elsewhere[84] that policymakers do not need to know much about what firms are doing under the mechanism or have to police them. It also contradicts the claim that the reliance of other R&D approaches on the truthfulness of firms is fatefully flawed[85]. It also contradicts the line taken in 'Making Markets' that "requirements on the developers would be minimal, consisting of only light reporting obligations."[86]

The previous concern about running an auction was justified

One would think that the strong emphasis on an auction in previous versions of the APC proposal might suggest a very real worry that terms could not be set efficiently. The fact the auction proposal has now been abandoned does rather suggest that all the recent spin about the terms of HIV and malaria APCs being efficiently set should be replaced by more sober reflection. Even more so when one realizes that the replacement mechanism for the auction ends up relying on an incredible degree of monitoring and intervention, something that was flatly castigated as something to be avoided by those now relying upon it. We observe how, under the auction mechanism, price should *not* be a great deal higher than that originally fixed. This is because the act of continuously revising upwards the size of the fund creates the perverse incentive to delay discovery of the vaccine, raising the expected cost and making it ever harder to monitor the level of activity going on and the level of required activity[87].

How likely is it that firms will reveal this information? Or that some (large pharmaceutical firms) will find it easier to hide such information than others (biotechs)? As Graham Dukes points out:

> *"Any government considering entering into such an arrangement will demand an extremely thorough and audited breakdown of the costs of research, development and production of the product in question, in order to ensure that the price being asked is fair. It is here that any specific agreement might run aground, since firms have as a rule been extremely reluctant to provide detailed and audited data to justify their prices."*[88]

According to 'Strong Medicine', all this information would have been handed willingly to the authorities on a plate.

Clearly the best-case scenario has it that the size of the fund is set correctly at the start, with monitoring totally dispensed with, and the many and various necessary ex post adjustments guided essentially information-free. This is the way things are done in the key Appendix 3 model.

Recently, any notion of setting the size correctly at the start has been abandoned anyway. All this talk of auctions and monitoring and firms giving information to help set the terms efficiently and so forth is obsolete. The current $3bn (or $4bn or $6bn?) APC for HIV, malaria, and tuberculosis is set with no reference to HIV, malaria or tuberculosis at all, but relative to the "typical market size deemed necessary to stimulate the discovery of a developed-economy drug", which, from the perspective of the underlying science and cost of developing an HIV vaccine, effectively means that the APC for HIV is completely random. Since the winning firm gets all the HIV vaccine IP–after a long and expensive public–and foundation-funded process–this is a spectacularly inefficient way to do things.

Difficulty in Efficiently Distributing the Subsidy to Incentivize 'Quality' and Follow-on Innovation

It is not just overall size that matters. This mechanism has a variable subsidy at its heart. There is a multidimensional 'quality' problem to contend with–a quality 'surface' across products and across time, all hugely aggravated by the fact that the 'quality', science, and costs are all highly uncertain. This problem has probably never been anywhere near as acute with previous vaccines as it is with HIV, malaria and tuberculosis, for which there is no such thing as '*the* vaccine' but instead a set of 'multiple and diverse vaccines' to be discovered over time. Farlow 2004 section 7.8 reviews the many facets to this 'quality' issue, and the rest of chapter 7 of that paper gives more details on some of the problems. Many of the problems highlighted in that chapter and this section are going to be present under all kinds of incentive mechanisms. The critique in this section is not to be read as indicating that the problem goes away under other approaches.

The CGD model calls for the setting of minimum requirements for a vaccine at the start, and a small committee with the power to lower those standards yet further when determining how to distribute the funds–but never, under any circumstances, to raise standards. However, predicting an efficient technical specification resembling the ultimately useful vaccine–or, indeed, the series of ever-improving vaccines to reward a series of developers–would be impossible to set years in advance for HIV, malaria, and tuberculosis. The CGD Working Group was advised of this difficulty. If one knew everything of interest for all time, and there were no sunk costs[89], one might just be able to set one target for all time and dispense with rules and discretion (the approach taken in Appendix 3). Otherwise, it is not particularly helpful to ignore these problems. Similarly:

> *"Advance purchase commitments may also stifle incremental innovation. Because they create a 'winner takes all' solution, it would be difficult for incremental, follow-on competitors to emerge, thus dulling the benefits of competition on cost and improvements. The innovation that wins will crowd out competing inventions because it is being given away free by the public sector. This 'crowding out' effect means that no improvements will be made to the winning formulation, and this may have negative consequences for resistance and effectiveness in subpopulations."*[90]

When the author discussed these issues in April 2004 at the Centre for Global Development it was clear that most of this problem had not been tackled. The idea of 'Making a Market', rather than what was essentially at the time a prize, is a much later innovation in thinking, and is reflected in allusions to quality and redistributions of the fund, etc. The whole point of the observation, however, was that the needed hotpotch of rules and discretion would be impossible to set up

in advance in order that innovation over time would not be stifled. One can write warm-sounding allusions to such rules but that is very different from actually *creating* and *using* such rules. HIV, malaria, and tuberculosis probably challenge us more on these issues than just about any other diseases. It really is quite surprising to see the problem being treated so lightly.

Some thoughts on the 'quality space'

Crucially, it is *expectations* of how this problem will be dealt with that feed investors' behavior, with the risk that if the issue is handled badly it makes less-than-optimal vaccines self-fulfilling[91]. As Kremer puts it: "mis-specifying eligibility and pricing rules could misdirect research incentives away from appropriate vaccines."[92] We also know that it is not just the attributes of the medical condition that matter: "The type of technology in question will influence the formation of eligibility and pricing rules."[93] This is a tall order.

To try to encourage work on 'higher-quality' vaccines, rather than 'lower-quality' vaccines, and in an attempt to reduce the risks of those who finance this activity, there would need to be a set of potentially *very* complicated rules about qualities of acceptable vaccines–and variation in allocations and prices of vaccine purchases across multiple developers and purchasers–over time and division of the fixed pot of subsidy. We say 'try to encourage', because it turns out to be hugely difficult–and probably even impossible–to use contracts to create the credible set of beliefs that enable the control of 'quality' through ex post adjustments after investment costs have already been sunk.

Intuitively, 'quality' varies over the 'technology space' (interpreted as distributions over research leads). The job of the commitment setter is to set the rules so that 'effort' towards the more difficult and expensive parts of the space–where the 'quality' lies–is relatively more rewarded. If the IAC knew the technology space *exactly* (which includes knowing firms' costs and the scientific difficulties) they could set a precise rule with larger rewards the more difficult it was to get to a particular part of the space[94]. If they do not know the space exactly, they can only create a highly imperfect rule, taking great care over where in the technology space rewards are placed in case they cause distortion. Policymakers are reduced to more average rewards everywhere, and, indeed will *never* achieve the highest quality results. Hence, on average, achieving 'quality' is more expensive.

In addition, because of all the uncertainty to players, the APC cannot simply pick out the highest quality area (even if the setter knew where it was) with a huge payment compared to the rest of the space (which might seem the most logical thing to do), since this would face players with huge risks should they fall onto other parts of the space where the payments are tiny. This is central to the argument that APCs should not be set up to just reward one firm. So the rule over 'how much the quality rule varies' itself requires knowledge about the characteristics of firms, such as their access to finance, degree of risk aversion, etc.

Removing the quantity guarantee

By removing the 'quantity guarantee'[95] the intent is to remove the risk that the sponsor will end up funding a non-used product and harming those working on more useable products. The foreknowledge of this, *so long as it is credibly believed*, will incentivize firms to work on products that are suitable for developing country settings.

This is also supposed to incentivize follow-on innovations, something especially important in the cases of HIV, malaria, and tuberculosis, where the first vaccines are not necessarily going to be the best (more so if they are only therapeutic rather than preventative vaccines). Supposedly, by optimally 'holding back' on the distribution of the (fixed) 'pot' of funds, resources are left over for follow-on, improved, vaccines (including therapeutic vaccines), and incentives are created for *their* R&D[96]. But how much to 'optimally hold back'? Notice the way that the special needs for monitoring in the case of therapeutic vaccines–and the need to create incentives to replace *such vaccines*–should form a big part of thinking about the overall 'holding back' strategy. This is not easy to set up ex ante before much of the science is known.

'Me toos', 'me similars', and vaccine replacement

It is argued that: "Subsequent vaccine suppliers [will] be allowed to *share the market* as designated suppliers, provided their products are deemed (by the Independent Adjudication Committee) to be *material improvements* on the first designated supplier" (italics added)[97]. Similarly: "If a firm developed a subsequent,

superior vaccine (as agreed by the IAC), that product would *also* be eligible for the price guarantee (the price guarantee would apply to the first 200 million treatments, *shared* among the eligible products *according to demand*)"(italics added)[98]. This was clarified recently as follows:

> "*The sponsors guarantee to pay the developer a predetermined price for the vaccines they buy, but they do not guarantee how many they will buy. The sponsors commit to topping up token co-payments by developing countries. So while Vaccine 1 is the only vaccine available, it will sell well, and Company 1 can expect good revenues. But when Vaccine 2 is approved, and* ***if it is a substantive improvement*** *over Vaccine 1, then it too is eligible for the guaranteed price… a firm can expect to sell their product at a reasonable price, but there is no guarantee that a better product won't come along and* ***cut into the market share***" (emphasis added)[99].

None of this makes any economic, never mind ethical, sense. The 60% or 70% efficacious HIV vaccine should *immediately* replace the 50% efficacious HIV vaccine and take all of its sales. How would, and why should, any developing country be forced to continue taking the 50% efficacious vaccine? Especially given: i) There is only a token level of co-payments (that the country may not itself be paying anyway); ii) The huge costs of treatment (and economic losses) and suffering for those who go on to get the disease on account of taking the 'weaker' vaccine; iii) The large costs of a vaccine program that are in addition to the costs of the vaccines themselves; iv) The political cost to leaders; v) The general suspicion there may be concerning the motives of pharmaceutical companies and the use of inferior products on the poor.

International trials need developing country trust

Any international trials program will be utterly dependent on the trust of developing countries, something that should not be risked by keeping poor quality vaccines on the market (and trying to conceal this fact). Given the ongoing controversies over clinical studies for nevirapine[100], it is inconceivable that developing countries could have the less efficacious vaccines forced on them. Indeed, pharmaceutical firms themselves would not want to risk the reputational and financial hit across their portfolio of products by keeping such vaccines on the market. And why would any developed country ever devote its development budget (and political capital) to vaccines known to be of lower quality? In addition, if there was an intent to set up further APCs for other products, why would policymakers not be mindful of reputational hazards for those later commitments?

Sharing a market is reasonable if the second product is in some sense a useful 'me-too', or perhaps more precisely a 'me-similar', vaccine. This is not to be ruled out, especially when many factors impact on the effectiveness of vaccines, and there may be a lack of clarity about long-term effectiveness anyway, and hence room for similar vaccines[101]. Furthermore, if a vaccine is closely similar to another, the capacity that has been put in place to produce it might as well be used, especially if manufacturing capacity and supply is heavily constrained (which is a very real possibility in vaccine production given the long lead-times needed for investments in capacity)[102].

Generally though, if the later vaccine is better, the firm should not have to compete with, but, instead, simply replace an incumbent producer's product.

The problems of allowing total replacement

Indeed, it should *always* be a fully credible possibility for a vaccine to be totally replaced by the superior vaccine of a competitor. This would be potentially expensive for the first firm, unless somehow they had been sufficiently insured by up-front payment. But then, paradoxically, it would be especially difficult to achieve replacement if most of the fund had already gone on the first vaccine. Clearly, the two requirements conflict. The issue then is to what degree and how this is be factored into total payment schemes given this fundamental conflict.

Observe that when replacement comes about, the firm being replaced may, in the eyes of the public, have already received more than adequate returns for its investment (the public only see things in the ex post sense, and not in the ex ante sense required for the investment). What rules and institutional set-up could possibly credibly commit to replacement based only on ex ante criteria?

Observe also that since replacement is only a statistical possibility, the APC will have to be set high enough to allow for this outcome even if, on average, some of the APC fund is 'left over' unused. The only alternative to this is for firms to understand that: i)

either governments and taxpayers will step in ex post to ensure full replacement (but then we are back to the problem we have today, though after having already spent a great deal of money), or, ii) incentives will have to be created that make replacement less likely in the first place. This is where a truly independent IAC comes in, since it has to be prepared to enforce something extremely expensive and (to the firms) possibly controversial. For example, it has to be prepared to totally replace the vaccine product of a developed economy firm with that of a developing- or emerging-economy firm.

It may well be that, whatever way is used to motivate research, being totally replaced is a large, but necessary, risk for developers of vaccines for complicated and evolving viruses. And this risk also has to be priced into private capital costs. It could even be that this risk is much higher in the case of such vaccines than in the case of drugs. In particular, complex biological products such as vaccines are sensitive to the production process generating them and are much less likely than drugs (though, maybe, not the newer 'biotech' drugs) to be able to rely on bio-equivalence comparisons, so that each vaccine is much more likely to have to undergo clinical trials and seek licensure on the basis of its own unique data. This generates a great deal of sunk capacity that has no use if the vaccine is replaced. This raises a further issue: If a product is clearly better and should replace all previous supplies, what incentives are there to expediently create the manufacturing capacity to do so?[103] Again, this suggests that directing quality of complicated vaccines like HIV through sales of vaccines may be more difficult than is sometimes made out.

The dangers that poor vaccines drive out better vaccines

There is of course a simple way to avoid ever having to face this conflict: set one payment, put little else of the framework in place to adjust for quality or to encourage replacement, and ensure that the 'better' products never arise in the first place to challenge the products that would otherwise likely be replaced. The dynamics of the mechanism, in practice, also help to insure that the replacement situation would not arise in the first place, since–for all its talk of competition–the capture of the mechanism would (by the late stage of the process) ensure that the number of large pharmaceutical firms active on a vaccine would be very limited anyway. The number of potential vaccines would therefore be insufficient to pose a threat to those already holding contracts[104]. The exact workings of such commitments need to be set very carefully to avoid poorer quality vaccines driving out potentially better quality vaccines, and large 'deep pocket' firms driving out smaller, financially constrained, firms.

Composite vaccines

As a very practical example of all this, suppose various companies are working together to try to develop a composite HIV vaccine. The last thing they would want to face is a reward system that only pays for their additional therapeutic value on top of some other less composite (or even non-composite) vaccine that might arrive more quickly[105]. Indeed, it would be a disaster to arrive on the market *after* the first 200 million vaccines had been produced, the quantity cap breached, and most of the fund already gone (no doubt also gone to the 'easier' portions of the market). The expectation that *all* of the value of the composite vaccine[106] will not be extracted, will disincentivize it from the start. Yet, this problem is only captured in a footnote: "The Working Group intends that terms should distinguish between those developers who are second because they are simply copying the first developer's vaccine and those who are second simply because their independent research program happened to take longer."[107] But this is a wish only; no details are provided as to how it would, or could, in practice be achieved. Clearly one would *not* want to incentivize away from more complicated composite vaccines in rules set up many years in advance.

Market risk and risk to developers

What does "*according to demand"* mean anyway? Such phrases only make sense if developing countries have the resources and know-how not only to work out the nature of vaccines currently available (a therapeutic vaccine for HIV for example), but–given the need to create dynamic incentives for vaccine R&D–the nature of *potential* future vaccines too. The danger is that the 'market test' puts a huge amount of risk onto the shoulders of companies. After all: these are resource-poor markets; most buyers are relatively uninformed; there is no marketing as such, though there are plenty of ways to encourage decision-makers to take one firm's product over another firm's product (more so if the 'other firm's' product does not even exist yet[108]); vaccine usage needs a good distribution system, with

such systems generally *not* under the control of vaccine companies; there are heavy knock-on costs to purchase decisions; there are multiple organizational problems; there is a severe lack of qualified personnel on the ground; there are multiple political interests; there are cultural barriers; and there are strong 'self-fulfilling' pressures driving towards lower-quality outcomes in the co-payment mechanism used by eligible countries to pay for vaccines under the program.

Given the historic record of good-quality and cheap vaccines being underused, it is not immediately obvious that the expectation of investors would be that 'good'-quality products automatically would get used while 'bad'-quality products would not. This, ex ante, feeds investor expectations and R&D incentives towards the 'lower-quality' outcomes.

The irony of facing firms with demand risk

It seems very odd to face firms with the very thing–demand risk–that is at fault in the current system. And it is ironic that late-stage vaccine funding commitments work largely by removing demand risk, only then to see early-stage vaccine APCs relying on demand risk to generate incentives.

The only reason we are forced to do this is because quality is not being controlled *en route*, so the APC approach has to feed demand risk on to developers at the end.

It is not clear that firms themselves would not just rather there be some guarantee of revenue even if the quantity take-up is low because of faults in the distribution system, with policymakers and other institutions responsible for ensuring that the distribution system works. Otherwise, this adds another decision-maker, and further increases uncertainty about whether a product will get used, generating yet higher capital costs, which only feeds into yet higher vaccine prices anyway. More on this later.

A basic economic principle is that to incentivize firms, they should only face risks generated by factors over which they have control and that matter for the objective of interest. They should not be forced to face risk, including demand risk, that has nothing to do with their own acts. Exactly how much firms should be insured and how much risk they should face is still a mute point in this literature.

Pricing rules to generate a split

In recognition of this problem, it is suggested that the "pricing structure *can be designed* to provide substantial insurance against demand risk for prospective vaccine developers so as to yield a net present value of revenue *comparable to commercial products even under pessimistic uptake scenarios*" (italics added)[109]. But this simply indicates the complicated tradeoff that needs to take place, not that it *would* take place or ever *could* take place.

It suggests that there must be sufficiently up-front payment to insure against the 'market risk'–including the risk that generics, 'me-toos', and others take market share, but also the risk of vaccine health infrastructure failure, and a range of other risks. But there also has to be a sufficiently low level of payment up-front to gives firms the incentive (because they are not insured) to develop a distributable product, whilst also leaving 'enough' resources over (in just the 'right amounts' too) for later developers. However, there is no way of knowing *in advance* how the degree of 'up-front-ness' should be set if the split of funds is to be fixed and not to rely on discretion, unless we know from the start the exact nature of the expected underlying technology and, indeed, the expected 'uptake scenario', 'market risk' and a host of other risks that are outside of the vaccine firm's control (including the risk that earlier vaccine developers who have already sold their 'allowance' will still try to take the market of later vaccine developers–a logical act if capacity is already in place). Observe that, again, this comes about because quality is not being guided *en route* to development but instead by firms' expectations of the IAC's behavior after development.

An alternative approach might be to allow the IAC to be much more involved in clarifying quality issues at much earlier stages of development than the APC literature currently suggests. But, if so, this intervention runs the danger of all the faults that the mechanism was supposed to be removing from policymakers' hands. In addition, if members of the IAC are drawn from a subsection of the industry, it risks deterring some vaccine developers if they perceive that their power to influence decisions will be much weaker than that of other much larger players (at 10-20 year investment horizons this is a big risk). Again, we find that the approach is becoming just as interventionary and full of monitoring as the push ap-

proaches it was supposed to be replacing, with the added complication that all the intervention takes place after heavy sunk and privately paid for investments are in place.

The sums do not add up anyway

The sums do not add up either. If even after "pessimistic uptake scenarios", revenue streams "*comparable to commercial products"* have nevertheless been handed over, the cost of actually getting a viable vaccine will have risen even higher. Yet again we have to remind ourselves that the 'commercial return' refers to the *ex ante* $6.25bn and not the much smaller, but still seemingly profitable, *ex post* return. If a commercial return is deemed to be $6.25bn, and the scenario dictates that this has to be given, then once this has gone, resources have to be *expected* by other developers to be provided from *somewhere else* to pay for their products. Once the $6.25bn has gone, it has gone! And worries about this fact will destroy incentives to explore better vaccines unless somehow payments can be made much more open-ended. But the latter open-endedness destroys the point of the mechanism.

Knowing when to stop 'holding back'

The 'holding back' of payments described above is only optimal to the extent that improved vaccines are to be expected and to the *degree* they are to be expected. As an extreme example, if there really is only ever one vaccine possible for a particular virus, then terms should be set such that *it* gets all of the potential funds so as to maximize the chances of discovering *it* and the speed of getting *it*. To offer less than the whole fund is suboptimal. If less than the whole fund is nevertheless offered and subsequent follow-on vaccines prove impossible, then the rules should specify how the 'left-over fund' is to be spent on the first-only-ever-discoverable vaccine at a later date (though also somehow designing *this* further mechanism so as to avoid paying for the non-best vaccine by mistake), even though this will also involve a yet higher dose of capital costs[110].

Is this just the beginning of the needed funding?

Or is it that the first APC is only the start? Given the problems of incentivizing follow-on products, maybe the implicit assumption is that there will be follow-on financial instruments?

> *"It is difficult to get the right quality, in particular to reward follow-on products that offer higher quality. Our view is that it should be possible to set an effective quality threshold, and that the terms of the APC must allow for superior quality follow-on products to be used… (However) there may not be enough money left in the initial APC to reward the R&D involved in developing some of the superior follow-on products. This is quite possible, as the commitment is only designed to generate at least one product that meets the quality threshold. Clearly a view would have to be taken by the donors as to whether they wished to finance follow-on products with additional money. This would be a separate investment decision from the original APC."* [111]

The problem is that if investor incentives are not to be harmed, this "additional money" for follow-on products should be credibly promised in advance if it is not part of the original APC–but that makes this 'additional money', by default, part of the original APC-type arrangement!

The danger is that the fund becomes unbounded at top, yet the eventual size is highly uncertain–killing dynamic incentives in a very wasteful fashion. The original (Appendix 3) model, by being entirely static and presuming one vaccine target, was able to ignore this.

This is not like other markets

This is all very different from standard developed economy drugs markets, where firms can 'take' market share from existing firms without the need to appeal to a committee to do so, and they have access to marketing budgets. Policymakers do not need to work out 'rules'–many years before the science or quality of products or epidemiology is known–that will generate optimal ways to split a fixed pot of subsidy over products, and firms do not have to rely on the discretion and extreme competence of a committee and of the poor countries themselves that are somehow free from even the possibility of ever being captured.

This also sets up a range of institutional issues. Usually 'quality' follow-on is performed through the patent system, with patent offices and/or courts deciding if a patent is valid or infringes. Marketing does the rest. The APC seems to be suggesting the creation of a supra-body to determine these issues. If so, what is the jurisdiction and how does this interact with those parts of the overall R&D system (PDPs, IAVI, etc.) working within the current patent and court system?

The dangers of promoting the lowest common denominator

One of the dangers is that the requirements would be set at the very lowest level that would be of any epidemiological value. In successive drafts of the CGD report, the requirements for a malaria vaccine gravitated ever-lower, standing in the final report's contract term sheets at a suggested 50% efficacy for 24 months from up to four doses, with room to lower the requirements even further. There was no clear rationale to support this. It may have been a response to a malaria candidate vaccine making the headlines in late 2004. Unfortunately, this candidate is based on a single component of one stage of the life-cycle of the parasite causing malaria, and may never have enough efficacy to be worth using widely. Even if it is successful in upcoming trials–by no means a foregone conclusion–there will be need to encourage the design of subsequent generations of better vaccines with much broader activity and higher efficacy. Blindly pitching minimum requirements ever lower simply works against this long-term goal.

The consequence of pitching lower is that there is no incentive for competing teams to develop vaccines that exceed the minimum requirements, because the first company to satisfy the requirements would have a huge incentive to try to harvest the full APC from the small portion of all potential sales that get the high subsidized price, even if its vaccine is later abandoned and follow-on vaccines are also stymied. No follow-on privately-financed innovator would invest the additional time and resources into a superior vaccine if the development of that vaccine would take several years longer than the minimum requirement vaccine and risk 'missing the subsidy'. Because the discretion to lower standards is especially risky to smaller and less powerful developers, and because the risk of political capture is high, most of the world's research teams and venture capitalists would be put off from investing private funds in the first place.

To make matters worse, the greatly reduced reward obtained from exploiting improvements in technology to generate higher quality products destroys incentives to make such breakthroughs in the first place; there is no relevant price signal.

Therefore, from many different angles, such approaches run the risk of actively discouraging the development of highly effective and safe vaccines.

The conflict with low prices and rapid access

Would we want to guide 'quality' this way anyway? Shortly we will see the key role of manufacturing scale in previous vaccine case-studies–for getting vaccine prices low–and capacity for rapid access. What we have just described conflicts with both of these objectives. If scale and capacity are key variables, it does not make much sense to be using the holding back of quantity of production and of sales in order to discipline 'quality'. Nor does it make sense to inflict uncertainty on those investors seeking to boost manufacturing capacity. The only reason we find ourselves considering doing this is because, by basing *everything* on the splitting of a fixed pot of funds at the end of the whole process, the only route we have left open to us for disciplining 'quality' are restrictions on the dispersal of that pot, especially the early dispersal.

If we knew for certain that we already had the best vaccine possible, then we could dispense with all these restrictions, scale up, and go for mass access from the start. It might be argued that the mechanism with the 'pot' of funds at the end could be adapted so that those running the program could guide firms en route, so as to weaken or dispense with these restrictions at the end. However, this contradicts the APC advocates' claim that those running the program are hopeless at such monitoring (given all the sunk investments, they would certainly face an even more difficult job than push funders in getting firms to be truthful) and, anyway, it takes us back to a model much like the alternatives that we were supposedly trying to avoid, with information held in the hands of those running the program, but with the added problem of a large prefixed pot at the end.

If the mechanism is made ever closer to the alternatives anyway in order to get around this problem, how does it not lose the supposed virtue that "firms choose" their research strategies and not the sponsors? And are we prepared to pay the heavy capital costs to get back to a system much like the one we were trying to get rid of anyway?

The paradox is that the mechanism that disciplines 'quality' en route is better able to achieve large capac-

ity and low prices than the mechanism that disciplines 'quality' via holding back in the end market. Indeed it is hard to see that, with the base level of treatments set at 200 million or so, any 'quality' control over the whole development process could be done in the end-market without conflicting with the need to get the manufacturing costs low. This aggravates the problem, discussed shortly, that firms will not believe that manufacturing costs will be pushed low enough ex post to make the whole investment exercise worthwhile ex ante.

Yet again we find that it is better to control 'quality' en route, and we are led away from commitment-based approaches for controlling 'quality'. And yet again we find that the pull working group should have called in one or two specialists, in this case industrial economists, to analyze some crucial underlying assumptions.

Countries not covered and those who use 'other approaches'

This 'quality' problem has many subtle implications for countries *not* covered by the APC– mostly because of the need to protect the 'initial market' for the products of the APC. If Russia, India, and China were, for example, not covered by an APC for an HIV vaccine, their markets must still be stopped from using any vaccine motivated by the mechanism (including those failing it though motivated by it) unless purchased from the 'winning' developer[112]. Vaccine developers would have to understand that if they did not make the standard required of the APC, they would be denied access to these *other* markets, otherwise their sales to these *other* markets would crowd out portions of the 'initial market' on which the vaccine that is being paid for under the APC is supposed to depend. An APC is a market 'enhancement' instrument after all, and the market being 'enhanced' needs to be protected. Just the knowledge that this protection might fail will make 'higher-quality' vaccine development more risky and hence more expensive[113].

No 'me-toos'

In addition, once a vaccine is developed under the APC, these non-APC countries would have to be barred from using 'me-too' vaccines based on it (even if the vaccines are not of the same clade but are somehow built off the first vaccine). Instead they would be have to be charged monopoly or tiered prices by those firms receiving payments under the APC, with vaccines manufactured under the terms of the APC by such manufacturers with 'me-toos' prevented. Given the segmentation of the market, this might even be at higher prices to them than would have been the case without the APC in place. Indeed, these non-APC countries would be tied to a much different and much longer mechanism, based on TRIPS-style IP or TRIPS-plus IP, than those eligible for vaccines under the APC. Clearly, this would get extremely complicated if the APC was itself allowing degrees of 'me-too' vaccines to eligible countries.

None of this is discussed in the 'Making Markets' or 'Strong Medicine' literature, but it is central to an HIV vaccine developed under the mechanism having 'additionality' of market. Incidentally, such problems (in particular *expectations* about such problems, given that it is investors who must worry about these things) are much less important for those vaccines[114] that already have much more exclusively 'poor' markets and are more late-stage and scientifically understood.

Russia, China, India will not go along with this surely?

It is not clear that Russia, China, and India would, or even could, bind themselves such that 'high-quality' vaccines do not suffer market erosion of 'initial' market. This is not referring so much to parallel trade in vaccines; being biological products and heat sensitive, vaccine procurement and distribution is strictly controlled, and essential vaccines are often distributed free or close to free. These factors greatly reduce the likelihood (compared to drugs) of vaccines entering into parallel trade or any forms of resale or piracy. Instead, the issue here is stopping others from using the *technology or science* of such vaccines in research or manufacturing processes. Incidentally, this creates a conflict with any 'vaccine enterprise' present if part of a collaborative mechanism is to encourage technology and information sharing[115].

At a very practical level, it is not clear that denying sales in non-eligible countries of non-APC vaccines or of 'failed' APC vaccines could be achieved, even more so if the competing vaccine achieved a similar or different result through the use of a different technique (plasma derived versus recombinant vaccines for example), or even if it was based on similar technologies but was hard to 'police' out, or if capacity for both

eligible and non-eligible markets were severely constrained. Additionally, the conditions in the TRIPS agreement that enable competition during the lifetime of a patent may also have some impact on the ability to protect the 'initial market'[116].

The effect on the dynamics of vaccine sales to non-eligible countries and R&D incentives is still largely unexplored, especially by those working on HIV vaccine APCs.

Similarly, if some sponsor countries or foundations had chosen not to join the APC and instead had chosen to adopt an alternative approach, then vaccine developers using those alternative approaches must somehow be denied access to payments under the APC to stop their use of the APC from damaging the investments of those relying on the APC exclusively. However, it is not clear that such developers could be denied access to the APC payments (especially, but not only, if they have a better vaccine) or barred from selling to countries supposedly covered by the mechanism (never mind those not covered).

Ex ante versus ex post information problems: An unhelpful caricature

'Push' approaches try to target 'quality' ex ante *during* the development process and naturally face a series of informational asymmetry problems between funders and researchers. APCs, on the other hand, (supposedly[117]) tend to let firms and those financing firms choose research leads, but with committees disciplining 'quality' ex post through sets of rules about distributions of APC funds across products, over time, over purchasers, over technology, etc.

So, while it is correct that pull mechanisms "require less knowledge on the part of policymakers about the likelihood of success *of particular approaches*" (italics added)[118], and that sponsors do not "need to identify promising avenues of scientific research,"[119] nevertheless sponsors do need a huge amount of qualitative and quantitative information–about the *overall set* of potential scientific, epidemiological, expected research and manufacturing costs, market possibilities, and chances of success–well in advance of product development in order to get the distribution rules right. It is claimed that those using APCs avoid the "need for them to take a position on the feasible approaches and the likelihood of success,"[120] but this is not true outside of individual approaches. Indeed, to be credible and to minimize the risks to firms, firms *themselves* need to trust that policymakers have this ex ante information. If the exact science is not understood at the start, rules will have to be 'made up' at the start and discretion used later to 're-optimize' the rules, and hence the allocations.

Firms know that it is easier to say that that there will be "payment-by-results"[121] than it is to ensure that this actually will be the case, given that firms need to work out the value of their investments many years in advance of payments, based on the rules about distribution of payments and expectations about this discretion. Yet, we are told, the size and terms of such contacts could be set "even when there is less clarity about scientific prospects."[122]

If practical applications of the mechanism are going to have to make heroic assumptions at the start about how to set payments to encourage higher-quality, or will have to adapt rules over time to target quality and be much more interventionary 'en route', it is not immediately clear that this is less demanding or problematic than what other approaches are trying to do. The mechanism ends up relying on a great deal of ex post discretion–the very thing it was meant to avoid. Worse, most of this discretion takes place *after* a lot of private costs have been sunk, and this raises a new set of 'dynamic inconsistency' problems–the very things the approach was supposed to avoid!

None of this is spelled out in 'Strong Medicine' or the No. 10 Policy unit material, where the problems of multiple developers and quality issues are largely swept aside as of minor importance. The issues are discussed somewhat in 'Making Markets'–where it is pointed out that it was "determined not to pursue a winner-take-all approach,"[123] and that "there is no winner-take-all"[124]–although the exact workings to get around the various problems are very confused and not practically resolved, never mind theoretically resolved.

Conclusion on 'quality' issues

Without very precise knowledge–at the time the APCs terms are initially set–of the underlying state of current and future technology and research and manufacturing costs, and without any external control over the quality of research, it is impossible to set terms in early-stage APCs that will allow *optimal* re-adjustment,

after vaccine development, of quantities, prices, and, indeed, of eligible firms. These adjustments, but most importantly *expectations* of these adjustments, are essential if such commitments are being used to encourage investors into R&D on vaccines of the highest possible quality, and to prevent pressures towards lower-quality vaccines[125].

It is not clear that ex post indirect control of quality via rules that are not likely to be credible or–now we discover–even desired, is to be preferred to ex ante, more publicly open, guidance of such quality issues, for example, via the more collaborative mechanism described in sections 4 and 5 below. The ability to manipulate outcomes for early-stage vaccine R&D through the end product market is based far more on optimism than on any concrete evidence that it can be done. It is a false dichotomy to suggest that some approaches suffer major informational problems while others do not.

Again, most of this discussion is largely now redundant. It is obvious that creating incentives for 'quality' is important, but it is increasingly evident that the current $3bn being proposed by the Center for Global Development for each of HIV, malaria, and tuberculosis are largely stand-alone pots of funds with none of these quality issues even thought about, never mind resolved. Again, the issue seems to be to more about getting a 'policy success' than to actually getting a successful policy.

Crowding Out' and the Difficulty of Achieving 'Additionality'

The effectiveness of early-stage APCs as described in 'Strong Medicine' and 'Making Markets', *compared to other mechanisms* and the incentive to develop higher-quality rather than lower-quality vaccines, depends on the creation of *additional* privately financed research and *additions* to currently existing vaccine markets. These are, after all, chiefly instruments of "market enhancement"[126]. It is claimed that APCs are especially cost-effective because "expenditures are highly targeted."[127] To the extent that this 'targeting' fails there is crowding out of a proportion of the commitments, and APCs are less cost-effective. In practical applications this targeting would fail in a very big way. To work out effectiveness, we would therefore like to know how much potential 'crowding out' will take place, and how it is suggested that it will be avoided. We would be interested in the following:

How are other forms of research support handled?

How are tax breaks, subsidies, and other push payments, and how are all other research activities covered by international initiatives such as IAVI, MVI, the European Community, WHO's Special Programme for Research and Training in Tropical Diseases (TDR), the U.S. Agency for International Development (USAID), the U.S. Department of Defense (malaria), other public-funding, and Foundations, all to be policed out of the payments received under APCs? After all "the proposal is that *private* investment would underpin R&D by *private* firms" (italics added)[128]. The mechanism should *only* reward the suppliers of this *new* private finance to avoid placing undue risk on private investors. If those using other forms of funding are not made *ineligible* for APC payments *in proportion* to their use of these other forms of funding, their activity will destroy the value of the APC for those who *are* relying on the APC to give a return to *their private* investments. Without a proper system in place to efficiently deal with this–especially in an area of complicated interplay between push and pull funded activity–those supplying this private finance will face large risks (in the expected value sense) and will refuse to invest in the first place without a large increase in APC to compensate (though this will also aggravate the problem further).

MVI case-study

As a very simple practical case, what if, encouraged by the presence of an APC for malaria, MVI bets all its available funding on one or two candidate vaccines in the hope that others will place *private* bets on other candidate vaccines? What if it is not clarified from the start that the MVI vaccines will never be allowed any of the APC? Otherwise, its chances of taking the APC fund will feed a lower expected payoff to other privately-funded investors (run the benchmark model to see) and MVI's behavior will crowd out some of these other privately funded investments (one-for one if it is equally efficient, more than one-for-one if it is more efficient).

But what if the MVI vaccine is the first and best vaccine? Surely it should be allowed to crowd out the privately generated vaccine?[129] Why should the APC then make an award to an inferior privately generated

vaccine that meets the requirements even though it is never used, just because it was incentivized under a 'separate system' to MVI? Observe that even a better MVI vaccine, developed under its own 'separate system', should not be allowed to replace the vaccine developed under the APC system, since breaking the 'separate system' rule will increase, ex ante, the risk to private vaccine developers and will deter them from the start. But this seems to suggest that only if the MVI vaccine is worse, does it not create a problem. But that is perverse.

What if MVI then wants to distribute its vaccine or vaccines at cost-price even in markets waiting for the APC-based vaccines? Should it be barred from this too? Since the commitment works on the basis of demand for the product, why should the MVI not be free to compete in those markets even if it means undermining demand for the APC-based vaccines? What if MVI allows its IP to be 'technologically transferred' to emerging developers for close to free, and, maybe even for free?

How *exactly*[130] is it proposed that PDP activities "complement" and not conflict with APC-based private activities? As always, this all shows up in investor expectations and investment incentives. The most likely result is that private investors will simply avoid facing potential unresolved dangers.

At first ignored: Now, accepted, but no explanation of how it is done

At first, this issue and everything based on it was stripped out in the key Appendix 3 model since no other research support devices were modeled as even being present. Only very recently has the issue been recognized, but still it is largely ignored in practical proposals. 'Strong Medicine'[131], for example, argues that "if push funding had been allocated before the announcement of the pull program, the winner might be required to use *some* of any pull revenue to repay *part or all* of the push funds it had received" (italics added). Regarding push funding received *after* the program was announced, it is "up to the push funder to decide" on any repayment and on the IP arrangements put in place in order to enforce repayment. This is not just simplistic; the economic logic is wrong[132]:

i) It is *not* up to the individual funders to decide. To keep their capital costs down and in order not be discouraged from their privately-funded research, those relying on APCs need to be *completely assured* that a *coordinated* response is being taken to deal with all activity that was *not* incentivized by the APC. Either other funders *should* be required to ask for push funding back from any purchase awarded, *in proportion to that funder's contribution* to any successful project, and they should collectively coordinate *their* behavior to support the efficiency of the APC, or–more likely–the APC to each 'winner' should be reduced to cover only the part of private activity actually incentivized by it. There is no excuse for allowing funders to act in an uncoordinated way by allowing the individual "push funder to decide"[133].

ii) If coordination of 'repayment' is not achieved, there will be temptations for individual countries and foundations to 'cheat' and unfairly advantage their own firms and researchers by allowing them to take APC payments that are out of proportion to the private costs they actually engaged in, thus disadvantaging, and disincentivizing, those being more honest. With the free-for-all emphasized in some of the commentary[134], it is clear that these countries would not deliberately weaken their own domestic producers by disciplining repayments of push funds (multiplied many fold) out of pull rewards. Who will police countries and foundations? Where will the information they use to police them come from? This would call for a global treaty and another committee/regulatory layer to police countries and firms.

In the best case, where there is wide participation of players and countries in response to the APCs (something very much doubted in this paper with respect to early-stage vaccines), this would not be an inconsiderable problem. In developing countries such as India, and China, and increasingly South Asia, Africa and Latin America, the governments have launched major programs of research and development for diseases of concern to their people, often in collaboration with the private sector both within their countries as well as with international companies outside of their borders. The paradox is that the more intense this activity is in response to those health conditions targeted by APCs, and the less coordinated is the removal of APCs payments not linked to fresh injections of private capital, then the more the value of an APC is crowded out as an additional funding instrument. In such circumstances it would make

more sense to use the funds that would otherwise have gone into the APCs by simply directing it at such emerging economy initiatives from the start, with more funder control over IP and with low prices in part-reward for financial assistance (ie. through PDP support).

iii) That firms would have to use "some of any pull revenue to repay *part or all* of the push funds it had received" (italics added) is wrong. Pull payment to any firm would need to be reduced by *many times* the 'push' payments *it* had *ever* received. As a simple example, if ten firms are working with equal strength on malaria vaccines (again we are presuming competition when this is not obviously going to be the case), and 70% of costs are capital costs[135], and we presume for now that there is one outright winner (we here presume no splitting of the $6.25bn), but the 'winning' firm benefited from 50% of subsidies, grant support, and all manner of non-private funding, then this firm would have to be denied just over $3bn of the fund[136], with the rest of the fund–for the sake of efficiency over time–left 'in the pot' for follow-on malaria vaccines. However, having only spent an expected $187.5m on out-of-pocket research costs (and an expected $437.5m on capital costs), the expected loss to the firm is nearly *seventeen times* what they would have spent on real out-of-pocket research. The marginal incentive to avoid that loss is *extremely* high.

iv) It could be that if PDPs are active in a particular field, those funding PDPs could specify a multiple of the PDP funding as potential future payment. An organization could fund, say, ten PDPs, one per vaccine lead and stipulate the one winning lead to, on average, repay *all* the PDP funding. However, this would require: All PDPs to use the same rules and all PDPs to behave in the same way with none of them 'cheating'; a much more complex accounting and repayment system; dangers of tensions between the foundation/public part of the PDP and the private part; to the extent the PDP was 'old' PDP funding (ie. funding that would have been used anyway) it would have to be understood that the APC payment would be returned to the APC funder, etc. And there would still be difficulties in correctly allocating payment.

v) Since repayments would need to take account of the *specific conditions of each firm*, it would require a great deal of monitoring of firms and high-quality historical evidence (adjustment would, for example, have to be made according to *when* the funding took place in order to appropriately account for capital costs[137]). None of the APC literature for early-stage vaccines deals with this. For a scientific area with a complicated interplay of push and pull funding and great opportunities for the pull-motivated to lose out to the push-motivated, this is simply not good enough.

vi) It is impossible to correctly 'price' these streams of 'other payments'. For example, what is the worth of the implicit subsidy on large pharmaceutical firms' capital costs of NIH research? And how is information on publicly-funded research and tax subsidies that is *only* connected to the research at hand to be correctly derived from aggregate firm-level data? Kremer himself argues that one of the big problems of tax subsidies targeted at certain strains of HIV is that large pharmaceutical firms can 'hide' the way they spend the subsidy on research for strains that already have rich-economy markets. We face the same problem here. It creates a headache to have to value all of these inputs, and is paradoxical given the argument that the approach is supposed to avoid all of this sort of monitoring activity. And it generates yet more layers of committees, discretion, and treaties, and/or 'repayment' side-contracts that may not unfold for ten or twenty years.

vii) In the last simple example, for every $1m dollar of subsidy and grant support that the firm could hide, they would benefit to the tune of nearly $17m. And who does this advantage? Large pharmaceutical firms have a heavy advantage in hiding such information, since smaller firms, biotechs, not-for-profit firms, etc. would have many fewer ways to hide research supports–if they could get them in the first place. Most biotechs simply work on one area, and their funding flows are much less opaque. This simply reinforces the argument that APCs are primarily an instrument of support for large pharmaceutical firms.

viii) In order to work out an optimal strategy, every firm needs to know how much *privately*-funded activity is taking place overall in response to the APC and how much is being covered by other research support devices. But the above logic suggests that

there would be great incentives to distort activity and hide information to avoid 'repayment' of subsidies and tax breaks. If this hiding were widespread, it would make it extremely difficult for individual firms to work out how much to optimally spend on R&D. This is because it would become extremely difficult to know exactly what genuinely new privately-funded research is actually going on in the aggregate in an attempt to win the commitment. This is made even worse if the push part of the mechanism has expanded too.

ix) Incidentally, standard procurement tendering for late-stage vaccines *is* capable of generating purchases that *only* pay for the additional private funds required to finish a process off or to cover manufacturing costs. The competitive tender in effect separates out the push from the pull funding. The problem is that the 'Framework Agreement', policed by the IAC, *is the tender*, and an extra, highly complicated side device has to be appended on to *it* to achieve a property otherwise inherent in more standard tenders. It is misleading to suggest that the properties of the two tenders are the same.

A simple example

As a simple example of the problems, if it is deemed that $10bn of incentives is needed to get a vaccine developed, and the current incentive is $5bn (push and market combined), if a $5bn APC were set up, this would seem to make up the $10bn required. If developed economy developers with access to tax breaks however do not have their tax breaks removed, they will spend up to $5bn, with a sizeable proportion in tax breaks (lets say 50%, or $2.5bn for now) and the whole exercise has generated only 2.5bn of genuinely new private funding. Those developers who did not have such push advantages are crowded out. It is much more complicated than this. See Farlow 2004 Sections 8.4-8.7 for more details of even greater complications.

'Others' should not be allowed to get payments

The above discussion too is a largely superfluous worry. The current Center for Global Development proposal, with its emphasis on getting a 'policy success' with politicians at any cost, has little interest in genuine *additionality*. Indeed this is the source of the myth (indeed encouraged by some of the supporters of early-stage APCs) that an APC would be 'open to all'[138] and that public–and foundation-funded projects could equally apply for payments under the scheme. However, to the extent that they had *not* used private finance, they should *not* be allowed to draw on the APC. If investors are putting private resources into projects that are dependent on an APC award in order to be viable, the last thing they want is large numbers of publicly-funded and foundation-funded developers also able to take the award, thus greatly reducing the expected value of the award to those using private finance exclusively[139]. In the expected sense, they simply cannot generate enough return for private investors. Allowing publicly-funded developers equal privileges on the APC will crowd out privately-financed activity, severely weakening the power of the commitment, and sending the cost to the public sector of eventual vaccine development much higher than originally claimed.

How is the 'currently existing' market dealt with?

How is the currently existing market for products factored out so that the market created is genuinely 'additional'? This difficulty is also recognized in 'Strong Medicine'[140], but it too is skated over. 'Making Markets' simply states that "The commitment *would extend* the overall size of the market in which firms operate"[141] (italics added) on the basic presumption that *existing* markets can be somehow fully excluded. This is a statement of pure hope; there is no mechanism proposed for how this might be made so in the case of HIV vaccines, for which the 'initial' existing market might be large and highly epidemiologically non-stationary. This is further complicated by the way the HIV virus is increasingly affecting countries with widely varying levels of income, and by the difficulty of excluding wealthier users within countries covered by the mechanism from accessing vaccines produced under the mechanism, but without payment.

On the other hand, it is fair to say that the more exclusive to the poor a product is, the more likely it will be possible to achieve this condition. We find yet again that APCs are highly variable instruments that belie the simplistic notion that all vaccine problems are the same.

In the case of HIV, developing countries would have to sign up at the start, as would even countries *not* covered by the mechanism such as, maybe, Rus-

sia, China, India, and Brazil. These non-eligible markets must *still* be protected for private sales of any vaccines generated by the mechanism. There would have to be the *credible expectation* that vaccine developers that did not make the standard required of the APC–even if they were motivated in their research by it–would be barred from selling to Russia, India, China, and Brazil, etc., even if there was still no alternative vaccine for anyone including these countries. Otherwise sales to *these* countries would crowd out the *initial* market for vaccines being paid for under the APC (with this being especially bad news for those trying to develop 'higher quality' vaccines).

How are incentives to improve technology not harmed?

How is the incentive to improve technology (in particular production technology) not harmed when the fixed technology assumption is dropped[142]? This is a form of crowding out, but one that is probably very hard to quantify.

How are priorities not distorted?

How would governments, firms, foundations and others be policed so as not to distort activity away from drugs and vaccines not covered by APCs towards those that *are?*[143] This crowding out shows up in research incentives of those *other* drugs, vaccines, and health products. For example, to the extent it has an impact, part of the rise in finance for HIV vaccines may be at the expense of finance flows into microbicides research[144]. The exact size of these effects we do not yet know. Indeed, one justification given for APC-type arrangements is to encourage the public and foundation sector to put more emphasis on research into neglected diseases. However, as a way of encouraging such involvement it is not the most efficient direct way of doing so. It sits uncomfortably with the notion that fresh private sector finance into neglected diseases should be protected from public sector and foundation encroachment on the APC. And, to the extent public activity does shift across, one of the added costs is the loss of activity in neglected diseases (and other areas) not covered by APCs.

How do the necessary tight patents not cause harm elsewhere?

Will the strong patents, secrecy, and increasing pressure to clamp down on compulsory licensing elsewhere in order to help an APC to function, help or harm research costs and access to drugs and vaccines *not* covered by such mechanisms?

How do Intellectual Property (IP) claims not eat up payment?

The development of vaccines involves a continual process of IP accumulation and assembly. Developers have to identify the need for patented purification techniques or for patented adjuvants or for patented antigen synthesis methods. Any developers that have signed an APC contract would be forced to 'share' the expected value of the APC payoff and thus would be constantly remortgaging a future income, thereby reducing the value of the payoff. There is no clear methodology in the CGD report for preventing this from reducing the 'additionality' of the APC, diminishing its power.

How is overlap and waste not encouraged?

How does the overlap of research and waste under this mechanism compare with that under other mechanisms? Below we show that overlap and waste persists under early-stage APCs and investigate whether some of this could be avoided under more collaborative approaches.

More dangerous forms of crowding out exist but are ignored. The exact details of these are in Farlow 2004 Chapter 7, but especially sections 7.11 and 7.16. The following two subsections provide a cryptic overview:

How is market segmentation, lower quality, and more extraction of consumer surplus avoided?

Because: i) There is loss of control over the ultimate intellectual property rights; ii) countries and firms are segmented into those covered and those not covered by APCs; iii) and co-payments are committed, a new incentive is created to segment the market, raise prices to extract more, deter others from research, and reduce the quality of vaccines. Again, just this possibility will raise the risks and hence the capital costs of 'higher-quality' developers. It is not so much that firms choose to behave these ways; most developers may be dissuaded from investing to try to avoid opening themselves to such situations.

This is aggravated somewhat by capacity issues. Initially–supposedly–manufacturers will have to pro-

vide much higher volumes than the eventual annual production size, to supply a large initial push of vaccinations. Given the 5-7 year lead times needed to put capacity in place, and the real possibility that only a low or medium level of capacity will be in place, who will get vaccines first? The poor or the rich? Those paying $15 a course via the APC or those prepared to pay, say, $50 outside the APC? There is likely no credible threat to make manufacturers serve the $15 segment first. The program organizers can build in a threat to override IP, but this is of little use if alternative idle capacity is not somehow available to make good on the threat, or if the vaccine just falls short of the initial terms.

A similar issue arises once the first 200 million or so high-value sales are gone, and the original IP owner chooses to devote their capacity to the higher value sections of the market. Why should they install more capacity to supply the low value sections? If they relinquish the IP rights for the poor section to the mechanism creator, what capacity does the mechanism creator have? What vaccine know-how?

How does it not become a financial option?

Early-stage APCs also create a financial 'option value' based on the fact that firms–since they own all the IP to the vaccine–can supply the end product if it is more profitable for them to do so, but that they are not *obliged* to do so. This option value may boost research even as it runs the risk that the results are not given to the eligible countries covered by the program, or are given to them but with delay–maybe by allowing the manufacturing price to remain high for a while to get around having to supply the eligible countries. For example, if the mechanism has specified a price of $15 for the first 200 million HIV treatments, if the treatment costs come in at $20, and there is a rich market prepared to pay $30 per treatment, the developer has a perfect right to sell to the richer market first, and an incentive to allow costs to drift above $15 per treatment to give them the right to do so. This is an especially knotty problem for HIV vaccine research because HIV cuts across a range of countries with widely varying income levels, it has different clades, and the existing non-stationary market size is growing and hard to control for in the terms of the commitment.

The details of all this are contained in Farlow 2004 Section 7.14. Key advocates of APCs were once in complete agreement with this problem, but it has now been politely dropped from discussion.

A summary on 'crowding out'

All of these problems have been ruled out in the core Appendix 3 model underlying all of the APC literature. APC payments only ever go to those who were incentivized by the APC, mainly because there is no other mechanism present in any of the modeling anyway. Failure on any of these fronts will weaken, by 'crowding out', the power of an early-stage APC for, say, HIV, and raise its global costs as an instrument for stimulating vaccine research. At a minimum, various treaties would be needed to ensure that all countries (both eligible and non-eligible) only purchased vaccines that satisfy the conditions of the contracts and the decisions made by the IAC (even if they disagree with those decisions). These treaties would also require countries to adopt the same post-development rules on purchases, police each others' research behavior, and rule out parallel trade for all time both between countries and within countries (both the eligible and the non-eligible).

Before giving the go ahead for a multi-billion dollar APC, policymakers should be given some evaluation of the size of these potential crowding out effects and the mechanisms for, and costs of, preventing them. We also have to remember that it is the *risk* of these outcomes that matters for private investors, not just whether these outcomes actually materialize, since this risk has to feed into capital costs. The effects will also vary depending on the vaccine being covered. There would be very much higher levels of crowding out for HIV than for, say, pneumococcus or the African trivalent meningitis vaccine discussed below, as well as for those parts of the vaccine development chain based on more standard forms of competitive tendering. Again, the key protagonists show hardly a hint of concern for these issues. Private financers would.

Capital Costs

There is both risk reduction and risk creation under APCs, and all risk has to be priced into the private capital costs of pharmaceutical firms and venture capitalists when investing their own resources. For currently extant vaccines or vaccines very close to development, purchase commitments achieve practically *all* risk reduction, given that most of the risk is market

risk, many other risk factors have fallen to zero, and the compounding of capital costs is relatively light. For current early-stage HIV vaccine research, there is next to no current value in market risk reduction (this is way too far off to have much of an impact now) and, indeed, market risk remains very high given the many forms of market-based crowding out and faults still in the mechanism described above. Meanwhile, all other risks (including that of the operation of the APC itself) are high. We therefore know that, to the extent it actually motivates *any* research, a sizeable chunk of an APC for an early-stage vaccine such as HIV will be taken up in the cost of finance. But exactly how much?

Emphasizing risk reduction: Downplaying risk creation

When it is stated that "by putting in place an advance purchase commitment, the overall risk, and hence the cost of capital that will need to be repaid, is lower"[145] or that a contract "does not call upon donors to spend more than they otherwise would; but it would increase the value of that spending"[146], the writers are emphasizing those parts of the R&D process where risk is reduced by purchase commitments, and completely ignoring those parts where risk is created. Indeed, they are essentially describing late-stage vaccines, even when applying the logic to early-stage vaccines.

This is careless given that the capital cost component is likely to vary significantly across vaccines and according to the relative position of a purchase commitment in a chain of incentives. It is also careless given that this is a key piece of empirical evidence for working out how to use other instruments alongside purchase commitments, for optimally placing (and sizing) purchase commitments in the chain, and for evaluating their cost-effectiveness compared to the alternatives. Thought of another way, the overall aim of using a combination of instruments is to minimize risk and maximize impact, and this *cannot* be worked out without first knowing how each instrument either creates or removes risk. It is difficult to comprehend the argument that this approach is part of a package of measures[147] to create a chain that is strong, when, in this crucial respect, it is not modeled as such.

As the mechanism deals with longer and more cumulative processes, and potentially more complicated vaccines such as HIV, the cost of capital locked up in research rises *exponentially* because:

a) The lengths of time involved lead to very heavy compounding. For early-stage vaccines "industry may still deem the commercial return to be too distant and uncertain to be worthwhile given the immediate, high-risk investments under consideration"[148];
b) The private sources of capital are expensive[149];
c) The scientific risks are very high, including (amongst many other things) the risks of ever getting a vaccine, and the risks of not internalizing the results of privately-funded research for oneself (especially if data has to be shared and the vaccine turns out not to be a pure preventative vaccine but instead a composite and therapeutic vaccine);
d) There are high perceived risks of the APC *itself*– that is of 'mechanism risk'–especially relating to the many institutional layers, the tradeoff between credibility and discretion (described in the next section), and the very real possibility that the mechanism will not work remotely as initially proposed. The latter seems to generate no concern from leading advocates, though it is a serious risk when rushing to use a completely untried mechanism;
e) The correlation of risks is likely to be high across APCs. It is standard investment logic (CAPM) to avoid investments that are highly correlated, and to price in the cost of unavoidable correlation. Since APCs rely on similar instruments and committees, and are untried, the faults on one APC will not be independent of the faults on other APCS, and using many APCs at once will impose higher required risk premia.
f) The 'Making Markets' report repeatedly asserts the centrality of long-term political commitment to make the program work, yet it is hard to imagine investors and senior executives in pharmaceutical firms making such political predictions and trusting multiple overlapping political administrations as far as the mid 2020s when launching major, extremely long-term, and expensive privately-funded R&D programs. This would add to the required risk premium, probably significantly.

Given this exponentiality, an instrument can be very powerful under a set of conditions but can rapidly lose that power as those conditions are not met.

For an HIV APC to actually work, *all* of this capital cost needs to be *fully* repaid by taxpayers and philanthropic foundations through the APC, and this also has to be worked out in advance if the overall payment is not to be set too low.

Incidentally, when the NIH does highly 'risky' research, the main, hidden, saving to industry is all the capital cost it saves by not feeding such research through firms, by passing it on to the public sector instead. This cost saving is never measured, though it really *ought* to be, to help in comparisons of mechanisms. Indeed, when one sees tables of spending on pharmaceutical research, the value of the contribution of the NIH and of others is always massively underreported compared to the contributions of private industry on account of this data limitation. That these capital costs get passed away from firms and on to the public sector is recognized[150], but the leap is not made to arguing that this risk should be properly valued and that its correct valuation would upset the relative evaluation of APCs against 'push' approaches (including, for example, the push parts of the Global HIV Vaccine Enterprise). Indeed, the appropriate distribution of the IP reward at the end of the whole process should be adjusted in the light of it.

The *core* justification for facing private investors and pharmaceutical firms with this risk is that APCs would so massively improve the choice of vaccine research leads and trial attrition rates for HIV, malaria, and tuberculosis over anything that the Global HIV Vaccine Enterprise or any other vaccine initiative and current PDPs, could possibly achieve, and that this more than outweighs all of these extra capital costs. We would therefore like to know how much of an APC gets eaten up in these finance costs, rather than in real out-of-pocket research costs, thus reducing its 'pull' power, and exactly how this might offset any improvement in the choice of research leads and trial attrition rates. Given the more recent acceptance that PDPs and sponsors would almost certainly do most of the choice over research leads and that PDPs could (and should) be greatly improved as selection mechanisms, it is even less clear that these extra capital costs would have much of a corresponding payoff.

One presumes these figures are being calculated and fed into the current calculations of HIV and malaria APCs, but these figures are not to be found *anywhere* in recent pronouncements. Without them one can only make guesses, something that will now be done for HIV. All figures below are nominal, ie. not adjusted for inflation, and the author would welcome the figures being challenged and recalculated in light of the actual evidence[151].

Some vague figures

One would imagine that the stock market and venture capitalists would take the view that current HIV vaccine research is a particularly speculative investment–especially in the first five to ten years or so (and maybe even much longer) after an HIV APC might be fixed. It seems reasonable therefore to presume that the required rate of return on financial capital would be higher than, say, the required rate of return calculated by TUFTS for drug development–a nominal rate of 14%-16%, with a mean of about 15%–by the very same large pharmaceutical firms now being targeted with HIV vaccine APCs.

Let us presume for the moment that there is no crowding out in the workings of an HIV APC (though this is highly unlikely to be the case). If the required nominal rate of return to financial capital invested in current HIV vaccine R&D was 25% (not outrageously high compared to speculative investments that venture capital firms normally make, but is it too high for this case? Or, indeed, too low?), and the average expected horizon until repayment was 10-15 years[152], it follows that each dollar of early pull-induced private R&D would require approximately $4-$9 of eventual payment at a ten year horizon, and $8-$28 at a 15 year horizon, with the bias almost certainly in the direction of the higher figures. That is, if the expected horizon was ten years, each $1bn of promised nominal APC would pay for, say, about £100m-$200m of early out-of-pocket HIV research costs, and if the expected horizon grew to 15 years, each $1bn of promised nominal payment would pay for, say, about $35-$100m of early out-of-pocket research costs[153]. One can see that getting a hold on the figure for capital costs is quite important. It is all the more shocking not to find any of the likely private capital costs discussed in the APC literature.

Adding in some 'crowding out'

If there was 'crowding out' too of, say, half (maybe push payments prove hard to remove from 'winners', and Russia, India, and China cannot be barred from

'spoiling' markets for products later), then this would lead to $1bn of promised HIV payment paying for about $50-$100m of genuinely *additional* early out-of-pocket private R&D in the first case and about $15m-$50m in the second case. In this instance, given that something as small as perhaps $15-$50m of crowding out is capable of seriously harming–by halving–the effectiveness of a $1bn payment, there are, clearly, easily imaginable scenarios where *most* of the effectiveness is 'crowded out'. So, a notion of likely levels of crowding out would be very useful too. Again, one presumes the figure must be out there entering into current calculations[154]. But none of the literature even discusses the evidence, and it is hard to believe that it is therefore forming part of the decision-making process.

As one can imagine, increasing the likely horizon to discovery, increasing the required rates of return to private financial capital, or increasing the levels of possible 'crowding out' creates increasingly dire-looking figures. Maybe this is why current levels of private funding are so low? Kremer claims it is 'no market'. Maybe, more likely, it is the very high risk and the high capital costs and crowding out?

In truth, capital costs would make up by far the largest portion of an early-stage APC for a vaccine such as HIV. It is likely that the capital cost component would remain huge for a very long stretch of the process of development, starting off at close to 100% today, declining to maybe still in the region of 50% at the late manufacturing stages within sight of vaccine development.

Would sponsors be happy with a mechanism that absorbed 80% or even more of the resources devoted to it just to make good on capital costs, thus reducing its pull power? Are the PDP alternatives so bad? Again, no evidence is provided in this literature to evaluate this.

It is important to get a handle on these figures, since if the ones above are even remotely correct, some of the current PDP-financed activity starts to look a much more cost-effective way to direct fresh government, G8, and foundation funding. Indeed, it is not clear why large pharmaceutical firms themselves would prefer to be stimulated in their HIV vaccine research in the current environment by an APC. They would be foolish to respond to the figures just described. Why would even a large pharmaceutical firm respond to a $6bn (never mind $3bn) HIV APC that creates no more than a few months' worth of what those working on the Global HIV Vaccine Enterprise says is needed?[155] Surely they would have to be crazy to believe that a vaccine would be achieved?

So, why the rush?

If this is the view taken, then it becomes even less pressing to set the terms of an HIV APC any time in the near future before good information is available on how to fix terms–perhaps revealed by experience on earlier purchase commitments. It would be doing hardly any cost-effective pulling in the near-term, yet it would impose higher costs by being prematurely and inefficiently set (there is an expensive option-price component to fixing the terms of an APC *now* before much of the information is available on how to efficiently and correctly set it[156]) and would be open to later adjustment that itself would be very damaging to its credibility and hence later effectiveness.

All of this may be slightly 'academic'. If, for example, a $10bn[157] HIV APC were permanently fixed yet could currently only generate at the very most a year or so of genuinely additional privately-funded out-of-pocket R&D, then the most likely reaction of private firms and venture capitalists would be to hold off on their R&D anyway, and, indeed, to simply not trust that the mechanism would ever work to repay them anything they spent now. Throw in the fact that it cannot be guaranteed that the vaccine will not cost $5-$10 or more to manufacture ($2.5bn for 250m courses of treatment), and it is very easy to generate scenarios where it simply is not worth investors bothering. The notion that if the APC were made even bigger, enough firms would react by investing, does not obviously follow. All this simply indicates how wasteful such instruments are for paying for HIV vaccine development.

Of course, funders, via the IFF perhaps, would still be stuck with the $10bn commitment, unless they can find some way to wriggle out of it that does not generate too much litigation. And alternative approaches would have to work out how to get around it.

A Trade-Off: Rules Versus Discretion

Even if we presume that any practical application of APCs to early-stage vaccines will follow the tenets of

the idealized benchmark case described above, with the 'quality' issues and crowding out issues also dealt with (though from recent policy announcements, this looks highly unlikely), there is no guarantee of the quantity of vaccine sold by any developer nor any guarantee that they will get all of their expected risk-adjusted development costs back even if their vaccine is developed and used. This is all from the perspective of the firm's decision problem *before* they invest anything. At *that* point the required return is calculated on the basis of expected trial attrition rates, all capital costs, and the expected portion of the market and pricing structure allowed to them by the IAC, so that even if a firm gets its development costs back in the ex post sense, this may be totally insufficient in the ex ante sense to justify the initial investment. When 'Making Markets' discusses two-stage pricing to ensure that the "producer received a fair return on their investment" but that "once this return had been achieved" prices could fall, it must be fully understood by all firms, buyers, political commentators, and the general public that 'fair return' is being thought of from an ex ante perspective. It will *never look 'fair' ex post*, and it must be credibly fixed in advance that it will *always* be calculated ex post from an ex ante perspective.

Dynamic inconsistency persists

The worry for firms is that there will be ex post bidding down of returns to make returns *look* more 'fair' ex post. Instead of getting the full $6.25bn reward for a couple of hundred million dollars' worth of out-of-pocket research costs (and the general public will know all about these costs given the information revelation described above), the firm will instead get, say, only $3bn, and will still 'look' greedy, even though this is actually not a 'fair' return for the efforts and risks borne by the firm. This is a worry under a procurement system, but applies equally under an APC if there is any ex post discretion.

Having a model that generates a fixed single value APC avoids such decision problems arising. Early proposals tended to concentrate on such outcomes (especially the No. 10 policy unit material). However, this is a far cry from what would be needed in reality for vaccines for HIV, malaria, and tuberculosis.

Once the drastic simplifications described above are removed and we get much nearer to a likely real world application, we face an elaborate trade-off between inflexible rules and discretion. The rules are based on expectations at the time the APC is set of the complexity of the science, expected publicly-funded research, expected technological improvement, expected 'qualities' of vaccines achievable, etc. Discretion would impinge on all of these features.

Fixed terms too difficult to know

'Making Markets' concedes that "it would be possible–though complicated–to agree to product requirements in advance," and that "a small number of public health experts were concerned that it would be difficult to establish in advance technical requirements that a vaccine would need to meet."[158] It is not clear whether this was a small *proportion* of public health experts, with a much larger proportion feeling otherwise, or whether it was most of the few public health experts who were asked[159]. In this author's sample of a 'small number of public health experts', *all* expressed extreme doubts about the ability to efficiently set technical requirements in advance for HIV, malaria, and tuberculosis. *Some* set of technical requirements can always be set for any mechanism, but 'efficiency' of those technical requirements (and the need not to intervene to change them later) requires some notion of the underlying feasibility of HIV and malaria science, the potential costs of manufacture and distribution, and a range of many other factors. And none of *these* public health experts felt *any* degree of confidence in knowing this.

The only way out, as 'Making Markets' concedes, is to have contracts "sufficiently fixed to ensure that the donors cannot renege on their commitment when a vaccine is developed, but still flexible enough to accommodate contingencies not foreseen when the rules were established"[160]. But this simply shifts the problem to a different level–that of having a good notion of unforeseen *potential contingencies* in order to set the flexible terms efficiently. On the one hand, Barder says that "It would be important that the experts from industry, the public private partnerships, the sponsors, and the public health industry, work together to finalize the technical specification… the technical specification would be set in advance and included in the contract." But then he claims that "the difficulty of setting a rigid technical specification in advance is met, at least in part, by the flexibility built into the Advanced Markets pro-

posal."[161] But this is, as it were, wanting to have one's cake and eat it.

A costly trade-off that cannot be avoided, and plenty of 'mechanism risk'

There is a trade-off. Non-flexible rules are needed for credibility but are inefficient and raise costs. But discretion and the other remedial features generate risks for developers and a higher capital cost component of a given APC, more complicated contract terms, much stronger informational demands, and the dangers of institutional failure or capture (or costly mechanisms to prevent it).

For example, if a piece of contractual language is missing such that there is a 75% chance of purchasing at the agreed $6.25bn and a 25% chance of reneging and paying only half (which may still 'look' like a very good deal for the firm from the public's perspective ex post), this yields an expected payment of $5.47bn[162]. If $6.25bn *was* the risk-adjusted figure required to generate optimal research intensity via this mechanism, and *if* we wish not for vaccine development to be slowed by this risk of underpayment, and *if* vaccine developers are risk-neutral, then the promised payment by the sponsor has to rise to $7.14bn[163]– that is a premium of $890m has to be added–to ensure the same intensity of research effort. If vaccine developers are risk-averse, the premium must be even higher[164].

The cost of this trade-off rises sharply the more complicated and risky the technology and the longer the process being held together. In addition, small acts of reneging on one APC have major damaging effects on other APCs via the way the latter's probability structure over reneging will shift. By ignoring these issues, the terms of idealized early-stage APCs would always be set correctly and would never be anything less than 100% efficient. This naturally maximizes their claimed 'strength' compared to alternative approaches.

Clearly this 'rules-versus-discretion' dilemma creates an awful lot of 'mechanism risk' for those relying on early-stage APCs. This is totally unmodeled in the literature promoting such contracts. Once we move away from the idealized setting, a picture develops of potentially huge levels of already (and sometimes long ago) sunk investment resting on the discretionary ex post decisions of a committee or committees[165]. The point of the original exercise was to get away from decision-makers having any power of discretion. At the same time, given the sunk costs build up under APCs, policymakers lose their ability to change the overall approach as they go along, since all ex post changes (after the costs are sunk) have to be somehow ruled out. A tension builds up between the need to modify the overall approach, but the inability to do so for reputation and credibility reasons.

Since we have no experience of operating such APCs, we have no evidence of how severe these problems with 'mechanism risk' might be, of how to cope with them, and whether the mechanism may even have to be radically overhauled (an act that in itself may generate litigation by any firm that operated, or claimed to have operated, under the original mechanism).

In summary, we find that we cannot set up product requirements. Yet discretion is very, very bad. Why do those advocating early-stage APCs for complicated vaccines not talk about this much more openly? Probably because, yet again, the objective is a 'policy success' and not successful policy. And, besides, these issues are really not such an issue when the idea is to target, with all of the funds anyway, the one large firm that first appears with anything meeting the most minimal of conditions.

Ratchet effect: Costs can rise but they cannot fall. Quality can fall but it cannot rise.

There is also a natural tendency to one-sidedness in this flexibility, putting excessive risk on any firm believing that the criteria would not be lowered. We are told that there should be "waivers from the stated eligibility guidelines"[166] and that there was "consensus that there should be a procedure to make the specifications *less onerous* in case a useful product were developed that did not completely meet specifications" (italics added)[167]. If this was not clear enough already, Barder explains:

> "*The Advanced Markets proposal that the Working Group has put forward does allow the independent arbitration committee to lower the bar. This would enable a vaccine which substantively meets the desired criteria, but fails on a technicality, to be rewarded. (By contrast, the arbitration committee would NOT be allowed to*

raise the standard after it had been set, to reduce the risk that sponsors seek to renege on their commitment.)"[168]

What does "fail on a technicality" mean? That the specifications were perfect to start with, and some minor detail was carelessly mis-specified? We see below, in the malaria vaccine case, the way the temptation to lower the bar easily creeps in once this reasoning process is tolerated. Lowering the bar–and risks about the ex post discretionary power to lower the bar–are risks for those who might invest in vaccines that are likely to follow the first vaccines. A lower bar on the first vaccines will lead to much, if not all, of the available funds going to the early vaccines, leaving none or little for these later vaccines. It also gives those working on early, less efficacious, vaccines less incentive to share knowledge with later developers. Or do later vaccine developers lobby for the bar not to be lowered? If so, how does the committee adjudicate the likely success of the later vaccine(s)? Does the committee not simply end up having to judge the quality of research leads, something we were explicitly reassured the committee could not and should not be doing?

Incidentally, if the interaction between technology and quality changed such that much greater quality could be expected for small changes in costs, why could '*more onerous*' specifications not be instigated? What if everyone can see that the 'more onerous' specifications are justified? What if forthcoming results from the malaria genome project indicate that low specifications set for GSK turn out to be too low? Would that classify as "failure on a technicality"?

Lessons from Bond Markets

APCs have been likened several times to Government bonds:

"*It is not unusual for Governments to enter into legally binding contracts: think, for example, of issuing Government bonds (which are contracts to repay money at a future date): these are legally binding, and credible with the private sector.*"[169]

"*One good example [of a long-term commitment] is the issues of Government bonds, which legally bind them (and their successors) to make payments in the future. Markets have no difficulty accepting these as binding contracts, even though future Governments could, in principle, renege on them.*"[170]

This is a highly misleading analogy, though the differences and similarities with bond markets also help us to understand just why APCs for HIV, malaria, and tuberculosis may face difficulties:

1) The value of bonds is fixed openly by millions of individuals on a *free market*. There are none of the central monitoring issues (supposedly) found in the case of APCs in trying to work out what the true value of the commitment is. Price bubbles aside, the price is an accurate reflection of the market value of the underlying payment stream. Bonds are much more easy to price in the first place.
2) Bonds are relatively simple contracts, dealing in a relatively simple underlying payment stream. The underlying payment in an APC (the value of, for example, HIV vaccine R&D to be repaid) is hugely more complicated to price in the first place.
3) It is quite useful to think of an APC as a bit like a bond. That is, it has a face value of, say, $6.25bn (or is it $3bn these days?) as set by the sponsor at the start, and a present discounted value now to the markets trading in such instruments (here, large pharmaceutical firms). One would imagine that the present discounted value of an APC for HIV would not be high. It might have a current face value of, say, $6.25bn, but (if there were a free market for such instruments to price it) would only trade for, say $200-$500 million[171]. Actually, it might be quite interesting to explore how such a market might work!
4) No one individual (or committee) has the power to manipulate the value of bonds in favor of or against the holders. Firms working under the incentive of an APC face a one-sided deal in favor of the issuer, unless somehow they can capture the issuer.
5) The government is able, on the open market, to issue fresh bonds to pay off old bonds, because the government has the power and sovereignty to tax. Indeed it is the only legal entity with such powers. So long as the economy is sustainable there is never any problem getting buyers for fresh bonds, though it comes at a price that varies according to the state of the economy. It is the ability to tax future generations (heavily if needs be, even if such taxation is 'damaging') that reinforces the credibility of bonds. Who do the IAC go to raise more revenue from to defend a collapsing APC (ie. to make it bigger to compensate investors for rising risks)?

6) The reason the US does not default on its previously issued bonds (with the US deficit so high at the moment, canceling the previously issued bonds would remove the deficit at a stroke) is because the future costs of issuing bonds–that is future borrowing costs–would spiral massively; current interest rates would shoot up and there would be appalling consequences for the economy. This huge adverse consequence disciplines the government to repay, and this reassures bond holders. No such disciplining device would exist for APCs as financial instruments. They would simply 'collapse', ie. fail to influence investment decisions.
7) Bond holders are still harmed by government acts. If governments behave in ways that send interest rates higher, the capital value of previously sold bonds falls. Similarly, the value of an APC depends on a whole range of government and funders' acts, including the push initiatives of government and expectations of expenditure on competing approaches, as well as expectations of how the faults discussed above will be dealt with.
8) Issuing fresh bonds does not affect, except trivially marginally, old bonds. If an individual non-coordinated APC is in place with one company, issuing a new one with anther company will weaken the value of the first one.
9) Bond markets are one of the most highly developed financial markets in the world with over two hundred years of history and many professional players knowledgeable in the workings of the market. APCs have never been tried before for anything. They have no history and no lessons have been learned.
10) Once bonds are issued, the government is tied into issuing fresh bonds regularly (IOUs to make up for the fact that previous IOUs have come up for repayment). Similarly, once APCs are in place, they increase the incentive to issue fresh ones.
11) Countries *do* regularly default on bonds, leaving huge losses to those who had originally believed in, and held, the bonds. Think: Russia, Latin America, Asia, etc. And that is just in recent years. Indeed, even as this paper was being written Argentina was in the throes of finalizing the largest debt restructuring in history for the largest sovereign default in modern history (of over $100bn), with an estimated loss to bondholders of about 70% of the original value of the bonds[172]. Perhaps the views expressed above about the wonders of bonds say more about the US-centric view of the world of some of those working on the APC proposal than it does about their understanding of bond markets? Perhaps the experiences of Argentina, other countries, and a range of practical experiences should make them more soberly reflect on the allegorical claim that large APCs are akin to large bond issues[173]?
12) The chances of default lead to a higher required return on bonds. Russian bonds in the mid 1990s were returning 60% per year because of the default risk. In the case of an APC, the risk that the APC would be allowed to collapse would translate into very high required capital costs, and very low R&D power. If, once in existence, there are any worries about the APC, capital costs would start to go up, and the APC would become increasingly less powerful. In such cases the incentive power of such an instrument would quickly grind to a halt. Developers would simply come not to believe in repayment of their R&D costs via the APC. Collapse becomes self-fulfilling.
13) Default is so damaging that, short of default, one is essentially stuck with having to repay the bonds even if the resources they generated when they were originally issued have been completely wasted. Similarly, the cost of default on APCs, including litigation costs (even if they were set up so badly that they were bound to fail from the start), means being stuck with them, short of default, even if they stop working.
14) At some point, markets realize that the only rational thing is to default, and then default becomes self-fulfilling. At least in bond markets, the government can keep trying to issue fresh bonds to put off the moment of default. This would bite sooner for APCs. However, there would probably be a terrible delay before recognizing it and 'bailing out'. Indeed, to avoid the embarrassment of having to 'bail out', the most likely trajectory is a period of non-reaction to the contract followed by the contract being left in place and all of the other incentive devices having to be ramped up. This is explained in detail in Farlow 2004 Section 8.7, Chapter 9, and 11.10. Viewing APCs as a financial contract clearly reveals their ability to suffer crises and collapse just like any other such financial contract.
15) Unlike bonds, the government or sponsor has no obligation to make good on investments sunk to-

wards APCs at the 'Framework Stage'. Firms are stuck with any losses if the APC is abandoned. Or rather, if the APC is terminated early, to the extent firms could prove that they were operating under an implicit contract, they could sue (and should for the sake of their shareholders), if they could prove that the Framework setters were at fault for the mechanism collapsing. It is, however, not clear to what extent worries about the very public PR consequences of suing would undermine the incentive to engage in the investment in the first place.

16) With defaulting bonds, the sellers (the government) gain something out of it in the shape of initial loans. With defaulting APCs, the sponsors gain the private expenditure on R&D up to the point they default, but they seem to have no obligation to make good on it. In both cases there are private sector losses.

17) You can engage in economic policy that risks bonds failing. But you cannot set up bonds *to fail*. You *can* set up early-stage APCs to fail (incorporated in frameworks such as the IFF that also take some of the brunt of failure).

18) Repeatedly, the APC literature alludes to cases where contracts are not honored: "The fact that these mechanisms have not been tested increases the risk, for example, that they will be subject to political 'changes of heart'. For manufacturers who must invest early and heavily, 'changes of heart' have serious financial implications."[174] Observe how, at very long horizons, small doubts are compounded very heavily into the value of the purchase commitment. Imagine what this would do to the value of a bond with an expected repayment in 15 years but with the niggling doubt that in any year between now and then there might be a decision to scrap the promise to repay the bond given the failure for it to work sufficiently well up to that point.

19) One would imagine that the fewer the existing bonds the less the penalty from reneging on those that exist, especially if it is clear that they are not working. Experimenting with HIV or malaria 'bonds' early could be a very risky way to explore the whole idea.

20) It ignores the huge range of problems listed above.

There are not many positive similarities with bonds. The analogy is more worrying than reassuring. Incidentally, if the APC is set low relative to the incentive needed, it may in effect collapse, have little or no incentive effect, rely on other approaches (such as PDPs and other funding) to drive everything, and then activate itself very late on to take all of the IP–and become a general nuisance at the end of the process. This seems to be the current proposal for the HIV APC.

Lessons from Standard Procurement Contracts

The contracts underlying 'Making Markets' are *not* standard procurement contracts, even though this is also sometimes suggested: "Governments also enter into long term private finance contracts, and procurement contracts, that the private sector is happy to accept."[175]

Features of typical procurement contracts

We observe that, ordinarily, when private firms contract–*after* a competitive tender has taken place–to supply services or goods to a government at a fixed price, the government will subsequently turn out to have paid 'too much' or 'too little' (though usually there are terms in contracts to allow for unforeseen circumstance) depending on how complicated the technology turned out to be, but that the firm would still be *contractually obliged* in both circumstances *to provide* the promised services or goods. Under the fixed price contract, the technological risks fall onto the company (and onto financial markets where the risks are, in theory, diversified away). The justification for doing this is the usual requirement to create incentives (especially if there is asymmetric information), mostly the incentive to produce the goods or services cheaply (with plenty of contract terms to make sure that the quality is not sacrificed). Even then, if the risks are great, it may turn out 'expensive' for the firms (in financial contracting costs) to operate under a fixed contract, but this will be passed on to the government in the contract price.

The government operating on a fixed price contract is, in a sense 'insured', and pays an 'insurance' premium as part of the price. The setting of the price and the premium require some knowledge of the distributions of possible outcomes (analogous here to the need of those setting up the APC to have some notion of what the technological possibilities are). If the risks are great, the premium might have to be large. However, if there is an efficient competitive tender, all of this can be left to 'the market'. The 'premium' is set by com-

petitive forces and there are incentives towards lower cost. None of this exists for early-stage APCs. We will shortly discover that the weakened ex post incentives to drive product prices lower is a particular ex ante worry for developers.

If the government is less risk averse than the private sector or (much the same thing) has much better access to credit markets, then even under a standard competitive tender it may make *more* sense for the government to bear the risks (or some of the risks) than for the private firms to bear all of the risks–in much the same analogy to the way that, under an APC, firms might rather prefer the less risk-averse government to bear the risks–but there is a tradeoff against the value of creating incentives.

Things are different for commitment-style 'contracts'
Under an APC, things are theoretically slightly different, but in a way that has very significant practical repercussions. The 'Framework Agreement' *is the tender*. Firms don't bid for it *before* sinking expensive investments; they sink their investments *in order* to bid for it. The two approaches are hugely different. All the risks and 'premiums' have to be 'paid', but since there are no 'contracts' with private firms until a vaccine is developed, firms always have the option to pull out (including if they find other markets, say HIV markets, more lucrative for the results of their investments) and they also always have to worry whether those operating the other side of the 'implicit' contract will renege. The scheme has to be adapted to avoid these eventualities–at a cost. And the costs are higher the more risky the technology and the more likely the mechanism itself will fail. Those 'players' able to take part are also different under the two approaches. Those who win the standard contract can use that fact to attract finance. Those seeking the APC must already have good access to finance and the ability to sink possibly mostly irretrievable costs.

The Adjudicating Committee

Because of all of the issues above, the independence, credibility, financial veracity, and legal aegis of the IAC are of paramount interest, both for policymakers and for developers who are naturally worried about risks, and who will need to price all risks into their investments. Others express this problem better:

> "*Although the credibility of market assurances theoretically can be increased through legally binding commitments, in reality it is difficult to imagine how they would be enforced against public institutions like WHO, UNICEF, or the World Bank.*" [176]

> "*More attention needs to be paid to issues concerning the legal aegis under which this program would be conducted. Vaccine regulation and IP are sovereign nation issues. (I use the term "sovereign" to include International Organizations such as WHO and the World Bank which must operate in accord with various treaties that have legal force. Foundations must operate according to the laws of the countries in which they are based.) A good beginning would be to specify the exact legal status of the IAC even though that specification may lead to complex political considerations*."[177]

> "*If the IAC is not an independent legal body, it would derive its legitimacy only through the legally established organizations that create it. Thus, one wonders how those organizations will deal with changing events, for example, without becoming directly involved in the operations of the IAC. The IAC could not, in my view, be intellectually and operationally independent. The founding organizations could and should be involved in its operations, which means, de facto, it is not independent. They are paying for it; their reputations are at stake; and they have vital policy and financial interests that they must be able to exercise.*"[178]

> "*As with all prize mechanisms, the potential for political rent-seeking is great, as the prize-awarding authority may be tempted to favour political or commercial allies. Senior individuals within the authority might even accept bribes. Furthermore, the donor's view of what constitutes a socially useful innovation will reflect their own priorities, and could result in areas being neglected or over-prioritised. Project choice, for example, might reflect the preferences of bureaucrats rather than those on the ground. Priority setting by outside agencies might result in R&D being directed only at one type of country, one region of the world, or one disease–with other equally needy causes missing out on the additional investment.*"[179]

The reason the legal aegis and credibility are issues is because of what the IAC is being expected to do at a very fundamental level. Essentially the committee is trying to take over the role of the IP system. Since, in the case of drugs and vaccines in poor countries, the IP system struggles to resist pressures to bid down the

prices of drugs and vaccines, the IAC is being asked to do what the IP system cannot itself do. The problem is not avoided, but shifted elsewhere–on to the IAC[180]. Instead of winners and complicated patterns of IP ownership being dictated by a patent system, they are dictated by a committee. Current worries about the patent system are transferred into worries about a committee (as well as the patent system, since results are still strongly dependent on that).

Not really 'market-based' instruments in the case of complicated vaccines

It is claimed that APCs are "market-based" instruments[181], indeed, that the mechanism is especially appropriate where there is wide "divergence of opinion on prospects for development."[182] This allows policymakers to avoid having to make difficult decisions about the underlying science. "Private firms, rather than funding agencies"[183] would make all the difficult decisions.

We have just seen that this is simply not the case. APCs for early-stage vaccines like HIV turn out to be surprisingly interventionist and much more radical than first presented. Instead of referring to anything unique, such commitments (if they are to work) end up involving variable quantities, prices, qualities, timing, and even the numbers of companies involved, with layers of institutions, committees and regulators with discretion, treaty-type arrangements (including across *potential* as well as actual sponsors and buyers), centralism of public research decisions, a very high degree of information processing and monitoring, and a very high willingness of firms to be 100% truthful, in a mechanism that is nevertheless still very heavily based on secrecy.

Worse, and paradoxically, policymakers have to have good scientific information even before the science exists that could have revealed it to them, and to have information about the 'quality' of potential vaccines to set up all the above features to reveal the quality of those vaccines! It seems, "divergence of opinion"[184] is not so divergent as to aggravate these decisions and the setting up of, and gyrations in, all these ex post rules.

By assuming a static state of science that is perfectly known by policymakers, 'Strong Medicine' ensures that all of these problems never arise in the first place. But by modeling on the basis that the quality and symmetry of information is unusually high–especially knowing in advance what *all* the probability distributions are–the mechanism cannot then claim that it solves the information difficulties that it has just ruled out. All of this rather numbs the criticism that other mechanisms require some of these features. And it is not clear what the point is in criticizing vaccine scientists, PDPs, and 'institutional failure', given the heavy use of administrators, executives, layers of institutions, *and* vaccine scientists in setting and constantly updating the terms of an HIV APC.

An Expensive APC to Compensate

The only way around these difficulties is to set the size of early-stage APCs for vaccines higher to achieve the same given impact on incentives. What if 70% or more of the payments for an APC for an early-stage HIV vaccine was absorbed purely in the costs of the financial capital wrapped up in that research, half of the rest was crowded out, and it proves impossible to set the size of the APC within a factor of two or three of the 'true' underlying terms? We do not know the magnitude of any of these imperfections; the literature does not enlighten us. We can say, however, that a mechanism that might use a dollar of funds to generate 'a few cents' worth of new research would hardly be described as 'strong'.

As a salutary indication of the low power of early-stage APCs, the only recent comparable example of such a mechanism is the $6bn budget for the US Project Bioshield. So far, no large pharmaceutical firm has shown any interest. For sure, this is partly because the legislation fails to commit to prices for particular products, so that producers are not guaranteed from the start larger markets. Once a product has been developed, the US Government would still have an incentive to bargain for a low price. But it is also partly because of the extreme uncertainty of such research, the huge expected capital costs, the difficulty of working on such projects in secrecy, and the fact that large pharmaceutical firms were not already active in the field. Failure to commit to prices, arguably, simply indicates the extreme difficulty of working out efficient terms of contracts for such very early-stage products. Meanwhile, the only firms to show any interest have been small companies. Given the dependence of these small companies on the large

pharmaceutical firms for markets for their outputs, even their response has been weaker than it might have been under other mechanisms.

Quality of Research Leads and Cost-Effectiveness: Who is Targeted?

Of the total $430-$470 million of HIV vaccine research per year, a very small fraction, only $50-$70 million, comes from private-sector activity[185]. Even this may overestimate the size of privately-funded HIV vaccine research since much of this private activity was publicly-subsidized[186].

Only $60-$70 million of combined public and private expenditure is spent per year exploring a malaria vaccine. Only $4 million between 1997 and 2002 went into exploring a vaccine against schistosomiasis. Underlying the mechanism in 'Making Markets' and 'Strong Medicine' lies the notion that there will be a massive shift in the relative pattern of R&D expenditure away from one based on PDPs and other approaches towards one based on large pharmaceutical firms with 'deep pockets' financially, the role of stock markets, and–to eventually pay for all this–there will be a massive increase in public funding to pay for APCs that is not being made available to other approaches to vaccine development. For example, there will be up to $6.25bn (plus co-payments), and maybe even a great deal more (once tax breaks and other subsidies are factored in) made available to large pharmaceutical firms for a malaria vaccine[187], dwarfing by well over a hundredfold what is currently spent in total globally per year on malaria vaccine research and many hundredfold current privately-financed activity.

The mechanism favors[188] 'deep pocket' pharmaceutical firms–even if they don't want it

Given this shift in emphasis, and given the high cost of venture capital and the extreme forms of capital market failures that many would-be vaccine developers face[189], real-world (as opposed to idealized) applications of early-stage APCs will tend to favor those with large free cash-flows and good access to equity finance–those with 'deep pockets' as the finance literature describes it (ie. large pharmaceutical firms in industrialized economies)[190]. Indeed this was the original intent of the lead authors: "A large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more."[191]

This would be even more the case if it were perceived that developed economy large pharmaceutical firms were more generously subsidized by push payments and, as we commented above, would not sufficiently have these removed from their pull rewards; after all, preventing this from taking place is a privately very valuable form of rent-seeking. It would also be amplified if developed country developers were able to use patents, know-how, and other strategic assets more effectively than developing country competitors, or if developed economy developers were perceived more able to influence discretionary decisions of the IAC and other committees after research costs had been sunk. We saw above, in a very simple calculation, that the ability to influence discretionary decisions is hugely valuable, since it can add literally hundreds of millions or even billions to the value of a research project and force similar-sized losses on competitors.

It has been claimed that the approach "is deliberately neutral, allowing any company, small or large, North or South, biotech or pharmaceutical, to benefit from the contract"[192]. But this is a bit like saying that the top suites at the Savoy Hotel in London are "available to anyone" regardless of their income–so long as they can afford to pay. Being technically available is not the same as being actually accessible. Incidentally, we will see later that–in contrast–well-designed late-stage purchase commitments *can* be made more accessible to all kinds of vaccine players.

This raises two questions. First, whether these large pharmaceutical firms are the most productive receptacles of the bulk of research for vaccines, in particular of vaccine trials–instead of, for example, university-based researchers, small and new biotechs, not-for-profit and developing country researchers. For maximal impact, these *other* groups of researchers, to the extent that they rely on other forms of finance rather than equity or venture capital, will be *ineligible* for any eventual APC. Indeed, it would be much easier, compared to large pharmaceutical players, to strip out from the payments of these smaller players their use of *other* non-private forms of research funding.

Second, whether using 100% equity finance is the best form of finance for research of a very 'collaborative' nature. Farlow 2004 Chapter 12 finds plenty of reasons to justify equity finance[193], but in the context of

developing complicated vaccines, we also find that there are some losses and tradeoffs to be priced in too. Do these tradeoffs become too costly in some circumstances, such as, for example, HIV vaccine research?

There is also a bias in the way decisions are handled on large programs that tends to favor large developed economy pharmaceutical firms. The current handling of the Global HIV Vaccine Enterprise is through the G7 finance ministers (because it involves up-front cash flows), part of whose remit is to act in the interests of G7 domestic industries, and not to be thinking in terms of supporting emerging economy and developing economy vaccine developers to displace G7 domestic industries. Meanwhile the vaccine APC notion is being fed through the G8, because of the notion that payment is a long way off. This decision-making process is not likely to yield the overall most efficient result.

Others may be at least as well or better placed for vaccine R&D

The justification for the emphasis on large pharmaceutical firms is the claim that the most efficient vaccine research takes place there. However, there is growing evidence that this is not the case. For example, the most recent *Financial Times Special Report into Biotechnology* points out that while the pharmaceutical industry has the commercial machine, "much of the industry is suffering from poor productivity in research and development."[194] It quotes the finding of Ernst & Young that half the drugs in clinical development belong to biotechnology companies ("a testament to the sector's creativity"), many of which are themselves a spin-off from publicly-funded and university-based research. However, most of these drugs are found in just a handful of biotech groups:

> "Hundreds of smaller biotech companies may have great proposals, but *hardly any have access to the hundreds of millions of dollars needed* to bring a new drug to market"(italics added)[195].

> As Erickson put it in a CIPIH Forum posting[196]: "*Without sustained watering, the best potted plants will abort before they have had a chance to reach maturity.*"

Referring to the many novel but 'one-off' drugs in development by biotechs:

> "*It is easy to predict that the vast majority of these will not make it to the end zone–for many reasons. Not to pick on any particular company, but the usual reasons for drug failure by biotechs include lack of appropriate financing, improper clinical development strategy, poor regulatory tactics, lack of effective marketing strategy to big pharma, or just plain bad luck. We don't usually hear or read about the numerous failures only the occasional successes that make good copy for the media and good advertising for stock brokers and analysts. Besides bad luck, none of these problems typically plague big pharma, which has all of these capabilities in spades and lots of cash and momentum to withstand multiple failures. Another big difference between Big Pharma and biotechs is that Big Pharma does not place the same emphasis for survival on innovation and execution as do biotechs, which are chock full of ideas and risk-takers, but too often run out of gas before they can get to their destination. What Big Pharma does best is manufacture and sell drugs. To wit with many notable exceptions, the vast majority of innovative drugs in Big Pharma pipelines were in-licensed from biotechs, academia, or competitors as opposed to having originated from their own research teams.*"

Berkley quotes another:

> *"The pharmaceutical industry has virtually turned its back on HIV vaccine research, leaving the biotechnology industry as the gatekeepers of hope for a preventative vaccine, yet the number of biotechnology companies in the field is small and getting smaller."*[197]

If small innovative biotechs are already struggling to raise finance under the current 'blockbuster' regime, it is not obvious that a similar regime would work for early-stage vaccines if such work highly depends on small and new biotechs, not-for-profit, developing country, and university-based research. Analysis would be needed on devices to support *these*, and, indeed, such analysis should be done *before* instigating any large early-stage APC, since, to the extent that the situation of these other researchers can be improved, the size and terms of the APC would turn out to be wrong. A key component of APCs is to hold back on finance in order to incentivize effort and quality–but this is self-defeating if it locks out those who already struggle most in their access to finance.

PDPs

Indeed, PDPs have better vaccine (and neglected drug) trial attrition rates than large pharmaceutical firms, since they are able to choose across a much wider field of IP, and not just what they happen to

hold in-house. For example, Pfizer, is working on just one 'new' malaria drug based on its own in-house drug zithromax combined with off-patent chloroquine. Medicines for Malaria Venture[198], on the other hand, is working on 21 new malaria drugs and approaches based on IP from half a dozen companies, small and large, as well as academics, public domain and developing country IP (eg. Chinese artemisinin discoveries). Being able to pick and choose across a field of IP is much more efficient than an approach based on narrowness and secrecy.

MMV

The Malaria Vaccine Initiative[199] has 20 vaccine candidates at various stages of pre–and clinical development (with 8 having entered phase-I and phase-II clinical trials), and all achieved on resources of just $43m since 1999[200]; that is less than 0.007% of the $6.25bn (plus co-payments, subsides, foundation funding, and tax breaks, etc.) mentioned above as possibly being made available under the 'Strong Medicine' approach for a malaria vaccine. Again, why direct a hundred-and-fifty fold increase in funds to a small number of very large firms instead of creatively using it to fund other developers? The constant argument that push funding "poses a challenge" to policymakers "because funds are limited" and "not enough to bring the candidates through the pipeline" is not an argument *per se* favoring huge levels of APC funding, though it is often made[201]. The real issue is the relative impact of the last dollar spent on any particular funding route, and this is an empirical issue. Once this is settled, politicians have to bite the financial bullet.

Large pharmaceutical firms would similarly not appear to be well positioned in other respects for APCs for many developing country early-stage vaccines or, indeed, drugs. On top of the very high capital costs, they now have a very low level of in-house expertise in working on these types of diseases, no built up libraries of compounds active against neglected diseases targets, and little expertise in working with developing country patient needs and developing country regulatory authorities, or even on developing country drug trials (eg. for tuberculosis). IAVI reports that compared to their marginal impact in 2000, developing countries are now "helping to lead the field". 'Making Markets' also recognizes that "Manufacturers in developing countries, which have lower cost structures, are building the capability to supply low-priced products in the long-term."[202] It would make more sense to explore first how to extend funding to these 'neglected developers' before launching a mechanism that concentrates its financial impact on large, and often less willing, pharmaceutical firms. If "all these are having a positive impact on the structure of the vaccine market"[203], why not take care not to upset these positive trends?

Why base costs on high-cost developers?

And why, into the bargain, base the terms of APCs on the costs of large pharmaceutical companies?[204] There is evidence that so long as the volume is high enough, much lower profit margins (that is not 'blockbuster' margins) are attractive to emerging suppliers when they compete for procurement contracts even if they would not appeal to OECD firms, as the MVP project has highlighted[205]:

> *"We had assumed that a profit margin of about $0.50 per dose for 25 million doses per year would be a sufficient return on investment, if the public sector were providing the investment. However, if the costs of development also included opportunity costs that might be estimated at $200–$500 million for a vaccine company with a promising research pipeline, then the return on investment from sales of the meningococcal vaccine would be perceived as insufficient."*
>
> *"Finally, MVP negotiated a contract with a large manufacturer in Asia (Serum Institute of India, Pune, India)… willing to sell 25 million doses per year of group A meningococcal lyophilized conjugate vaccine in ten dose vials for less than $0.50 per dose, which includes cost of depreciation of facilities and an acceptable profit margin."*
>
> *"In short, what was viewed by established vaccine companies in Europe or the USA as an opportunity cost, was seen by the developing country manufacturer as an opportunity—[among other things]… the prospect of sales to Africa of many doses of vaccine at a low but profitable price for an estimated 10 years or more."*

A proposal that puts most risk onto biotechs?

'Making Markets' states that biotechs engaging in research on early-stage vaccines expressed much less interest in APCs compared to large pharmaceutical companies with vaccines coming to market soon. Yet, confusingly, the accompanying "Frequently Asked Questions" document claims that biotechs had been

"particularly enthusiastic about this idea."[206] The CGD report goes on to assert, without any evidence, that the program would initially motivate biotech companies while larger pharmaceutical firms would get involved after "further advances in the science… perhaps led by biotech firms". Indeed, it is this prospect of the taking over of the process by large pharmaceutical firms that is supposed to motivate the biotechs in the first place.

This initial reliance on the role of biotechs–even if ultimately it is large pharmaceutical firms who take over–is based on the claim that the expected decisions of the committee at the end of the process, in conjunction with the rules set at the start, and the interest of the large pharmaceutical firms–most of whom have abandoned the vaccine market and are not likely to return for just one difficult early-stage vaccine–will work all the way back to very early rounds of biotech investment. But this is where the difference between a genuine market and a committee-driven program bites. 'Mechanism risk' is extremely high for early investors into such non-market based programs. The further away from the ultimate committee decision, the greater the chances that the program will not work as intended–or that it may even collapse. There is a large investment 'option price' to be priced in by venture capitalists when investing early, a price that is especially high if a program is highly uncertain.

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. Furthermore, given the huge degree of discretion at much later stages of the program, the risk of 'dynamic inconsistency'–when decision makers take advantage of firms' already sunk investments by driving an even better ex post deal–is especially high for early investors. For these reasons–"and also because of the greater difficulties in internalizing the value of early investments compared to later investments for such highly complex vaccines as HIV–early developers will have a very high required rate of return. At a fifteen to twenty-plus year horizon, with highly uncertain science, a $3bn APC for HIV (as proposed by CGD in its final report) starts to have extremely weak pulling power, if any at all.

The report presumes that biotechs would be prepared to take on board much more risk than any evidence suggests that they would be prepared to bear. Their rapid (and needed) reaction in order for the program to work is based more on hope than on any solid evidence. To reassure early investors that the program would not be wound up early, it might be thought that the program could be made 100% permanently fixed. However, it is not clear which would be worse–having a reversible program that is not motivating biotechs because of the possibility of reversal, or being stuck with a non-reversible program the terms of which are set badly such that biotechs are not motivated by it.

Milestones for biotechs

One might imagine that in normal 'market-based' situations, large pharmaceutical firms would set milestone payments into contracts (if there are any contracts in place[207]), and that only the 'size of the pot' would matter. However, if there are concerns about the riskiness of the surrogate-market mechanism, this clearly will not hold, and biotechs may wish to be protected against the risks of the *mechanism itself*. 'Making Markets' points out that biotech companies had, indeed, requested that the mechanism incorporate interim payments for achieving pre-determined milestones, "to create incentives for research and early-stage development activities and encourage venture capital investment in emerging companies committed to the Framework."[208]

The worry is that by putting all of the pot of funds at the end of the process, and *because of the risks of the mechanism itself*, financially-constrained biotechs may not be able to get hold of the resources to take part very early on, and that in a highly iterative research process with elements of public-good to some discoveries, biotechs may be unable to internalize the value of all that they do[209]. But milestone payments were deemed too difficult to incorporate in the initial 'Making Markets' proposal.

Very recently, however, the argument swung the other way: "These types of interim pull payments would be particularly attractive to smaller biotechnology firms and could be *easily worked into* the Advanced Markets agreements" (italics added)[210]. Many things can be 'easily worked into' contracts. That the result would be pretty, efficient, or practical is a different issue altogether. Certainly, it is clearly very different if the mechanism organizers *themselves* have to do some-

thing *within* contracts that, ordinarily, large pharmaceutical firms would do *given* the pre-set contracts. It has not been spelled out how this would be done. For example, are milestone payments drawn from the eventual pot of funds? This would be the logical approach. But how then is the drawdown judged (a huge amount of underlying science would need to be understood in setting terms at the start), and what happens to the incentives of others as the pot shrinks (especially if the draw-down is badly carried out and not transparently clear)? When setting the terms of such interim agreements, one must worry that distortion and discretion at intermediary stages will distort incentives:

> "*[It] seems not to take into account the extraordinarily complicated way in which vaccine R&D takes place. Milestones are built into donor contracts, venture capital investment agreements, and even internally within companies. If the Advanced Markets agreements were to incorporate additional milestones, the complexity of the overall agreement, in at least some cases, would be extraordinary and would require great expertise in vaccine R&D on the side of the Advanced Markets program. For example, who would adjudicate whether a milestone had been reached when there was disagreement?*"[211]

What if it was a tiny emerging economy biotech or a large developed economy pharmaceutical firm? What if there is rent-seeking over such decisions? What if this favors some (larger) players over others? Given the importance of expectations for investors, what if this was even just a 'worry'? What if an interim payment was made that turned out not to be justified? As with many other promised aspects of the application to HIV, malaria, and tuberculosis, no proof has been provided that this could at all be 'easy'. Unfortunately, it is just another example of the way that certain parts of the audience (here, biotechs) are expediently soothed by rhetorically 'right-sounding' language. This is not to suggest that interim agreements might not have value as a way of reassuring investors and keeping down the costs and the risks of the mechanism to them. Just that the ease of making such agreements work cannot be casually asserted but must be proven.

The final version of the CGD report swung back the other way, dropping the idea of interim milestone payments altogether, stating that in spite of the issues discussed above: "We intend that intermediate incentives of this kind will be created by the commercial activities of developers in the expectation of being remunerated through sales of vaccines under the guarantee agreement."[212]

Nevertheless, biotechs have a high risk of failure, and venture capital is only interested in high-risk, high-return activity with some notion of rapid gain and an exit strategy, so that investors can move on with their resources to the next opportunity[213]. Having achieved some useful interim step, venture capital would not want to have to be locked in for the 15-25 year lead times that might be typical of HIV vaccines.

It might be thought that success at early stages of vaccine development could be converted into contracts, but this raises a whole range of valuation issues and worries for the firm about internalizing the value of its research (say in a collaborative setting). And besides, we already just saw that such contracts are not working to create access to finance for the "hundreds of smaller biotech companies" with "great proposals". This provides no reassurance for complicated products, such as HIV vaccines, whose potentially very much longer timeframes and mechanisms are high risk.

As the proposals stand, APCs for early-stage vaccines are heavily dependent on those with free cash flow, a history, and a likely continued existence, even if they are not the most innovative recipients. They also put risk disproportionately onto the shoulders of biotechnology firms for early-stage vaccines.

The global state of vaccine manufacture

The approach also seriously misunderstands the global state and direction of vaccine manufacture and, indeed, vaccine R&D. In the past, seven or eight leading industrial country manufactures would be working on five to six vaccine-related R&D projects each at any one time. The industry is now consolidated into just four major multinational manufacturers[214]. "R&D budgets have shrunk, and competition for capacity has become fierce,"[215] with dramatically reduced numbers of vaccine R&D projects, especially for developing country markets. This is partly, but not exclusively, the result of reduced competition and 'replacement effects'.

All of these four firms have products against which any vaccines they might seek to develop would have

to compete (including, for example, replacing relatively much more lucrative HIV drugs markets with cheaper one-off HIV vaccines[216]). With so few large players, any new R&D projects they initiate are more likely to destroy the value of projects they already have drugs for, which raises risks and hence capital costs. This is not to cast aspersion on executives of such companies. Capital markets feed these higher capital costs onto firms if they work on such projects[217]. They are also much less likely to engage in multiple research leads as a result. The cost of an APC has to be higher to reflect all of this. Having more, and different, vaccine players is more valuable than having the same few players being enticed with ever-bigger payments.

Even as the number of developing country manufacturers with products on the WHO pre-approved list to supply UN vaccines has risen, the number of industrial market manufacturers supplying industrial countries has been falling precipitously, and so "while new players are emerging to fill these voids, they have not replaced the multinational manufacturers, in some cases contributing to vaccine shortages."[218] At the same time, "Smaller and emerging market manufacturers are less likely–*and financially less able*–to take on the risks of product development" (italics added)[219].

Why not target differently to increase the number of manufacturers?

Why, in such circumstances, adopt mechanisms that *deliberately* favor a very few large developed economy manufacturers? Why not, for example, formulate a mechanism that instead targets more funds at emerging market manufacturers and those willing to work with them, and that tries to increase the number of manufacturers? Arguments have been expressed against this, including problems caused by poor regulation and control that can lead to inconsistent vaccine quality and unreliable quantities, and problems with access to foreign exchange to purchase raw materials. However, the first problem is becoming ever less applicable given the rapid expansion of the pharmaceutical industry in both India and China (and is slightly self-reinforcing logic anyway). As to the second, if the problem is lack of access to foreign exchange, it makes no sense to deliberately further feed this problem, and it is hardly a reason for holding back global finance for vaccine research, given that the finance is to be spent anyway. The second point does suggest though that access to these global research funds will more likely need to be front-loaded through a Global Vaccine Enterprise than end-loaded through an APC that will require dollar-denominated, free cash-flows running into the billions in the meantime.

This does *not* mean that biotechs and others would not respond to early-stage APCs (though, for HIV, the figures suggested so far do not add up to suggest that they would respond). The argument being made here is that the *marginal impact* of a given dollar spent on an APC on the financial resources made available to biotechs, emerging economy pharmaceutical companies, developing country researchers, and other researchers is lower compared to the marginal impact on the financial resources made available to large industrial market pharmaceutical firms, and compared to other finance mechanisms that might have been used instead to help the former groups. The flipside to this is that the APC for such vaccines is a more expensive instrument. Large pharmaceutical firms regularly express a lukewarm attitude to APCs for early-stage vaccines like HIV and malaria even though the logic seems to be favoring them. This does rather suggest that they are poorly-targeted instruments.

The need to expand the number of vaccine producers

The vaccine industry is dominated by a handful of companies. The share of the four major developers listed above has risen from 50% in 1988 to about 80% today, and capacity has become constrained. There are only five ways for capacity to expand:

1) Increased construction of facilities by the four majors;
2) Partnerships between regional and major manufacturers;
3) The growth of biotechnology companies into major vaccine manufacturers;
4) The growth of regional small manufacturers in countries such as Brazil, Cuba, India, Korea, and Japan;
5) Development of new institutions to make vaccines (perhaps as part of the Global HIV Vaccine Enterprise).

APCs impact the relative likelihood of these outcomes, though not all purchase commitments would be equal in their impact. Given their emphasis on free cash-flows and access to developed economy equity markets, and given the way in which APCs are heav-

ily biased in favor of large players[220], the order of greatest impact for early-stage vaccines is approximately as listed above, with the first relatively most greatly favored, and the fifth the least impacted. Is this the most appropriate response to expanding capacity for complicated vaccines? Given the competition that there already is for the vaccine capacity of the 'big four', is it sensible to have developing economy vaccine requirements having to compete against 'rich economy' vaccine requirements for the capacity of the 'big four'? As purchase commitments become more late-stage, and other instruments are used to support research (including the use of the sort of purchase contracts described in later sections), it could be that the order of impact on capacity is even reversed[221].

At the very least there should be more open discussion of whether 2), 3), 4) or 5) above offer the greatest hope, or whether sticking with 1), and pitching APCs to a handful of large multinational companies, since they are currently most dominant, is the best approach.

Furthermore–and something woefully underexplored–it is clear that much recent legislation, including BioshieldII, will intensify competition for the resources and the skills-base of the biotechnology sector, government researchers, and for any increase in vaccine production capacity. To offset this, would it be more sensible to seek to adopt strategies that emphasize the reverse order of the list above, rather than starting at the top and working down?

Contracts that risk locking out certain players

It was originally claimed that an open contract could be set up with no need for the APC sponsors to put financial resources aside to make good on the APC. It became clear that this could not be done. On the one hand, early developers would have too little hold over the APC without a contract, and so this *would* necessitate resources being put into an escrow account to reassure them and, more importantly, their investors. On the other hand, the APC sponsors also needed some claim on the firms for the sake of monitoring and knowing if the program was actually even working. The contractual arrangements therefore now call for the sponsor(s) and for all actual and potential vaccine developers to sign-on to the 'framework' contract within 36 months of the initiation of the program, and for all developers to agree to be monitored by the committee running the program and to abide by its rules and its use of discretion when determining the distribution of the payments many years later at the end of the process.

To prevent firms from 'cheating' by doing unmonitored, even largely 'hidden' research–and thereby taking advantage of that fact that others are being monitored and are having to give sensitive information over to a committee–those conducting current vaccine trials and failing to sign-on, and those initiating future vaccine trials without prior permission from the committee, will be penalized by being barred access to the eligible markets controlled by the committee. Such 'cheating' also makes it hard for the sponsors to know what is going on, and for firms taking part in the program to know the expected value of what they are doing and hence 'how much' of it to do. Entry of later developers to the program–who unlike early entrants will not be allowed to have done any clinical trials–will be controlled through the committee[222].

However, the development, introduction, and manufacture of vaccines are extraordinarily complex processes that take place over many years and involve many organizations. In addition, the global state of the development and manufacture of vaccines is rapidly changing, with centers in developing and emerging countries such as India, China, and Cuba becoming increasingly important. At a very early stage in the development of a vaccine, it would not be possible to identify all those who may potentially take part in such a program in ten to twenty, or even more, years time. Nor is it clear why the incentives of later innovative research teams should be stymied by contractual arrangements that unnecessarily constrict competition by potentially forcing them to go through large multinational pharmaceutical companies[223].

The problems of competition through a committee and one point in time

Given that, unlike the current system for vaccine procurement, there would be very little competition in the end market, with competition essentially via IAC decisions relating to actions many years before, one naturally has to consider carefully whether the mechanism would achieve this 'virtual' competition, or whether large companies or developed economies could in any way stymie it (via suitable choice of patents or pressure for relaxation of strictures of the IAC on them,

including weak monitoring of activity[224], failure of the IAC to shift product demands to emerging–or developing-economy vaccines, etc.).

It risks capture

One of the dangers of 'policing' all competition and quality through just one point in the development process and just one committee is that it risks the capture of the process, and higher risks and capital costs of those least likely to do the capturing. Fear of this by smaller players makes it self-fulfilling. For example, if the IAC had any degree of discretion, is it conceivable that the IAC would do something very financially 'damaging' to a dominant developed economy pharmaceutical company in favor of a developing country manufacturer, like entirely replacing the former with the developing country manufacturer? One doubts it. And so would developing and emerging country manufacturers who would struggle to believe, from 15-20 years out, that the IAC committee would be truly independent[225]. Regarding this independence, we are (somewhat ironically) told that: "The Working Group believes this is possible, and has set out a detailed proposal in the report which has had positive responses from senior industry figures."[226] The irony may not elude developing and emerging country manufacturers, and they would stay away in the first place.

The signs are already not looking good

'Making Markets' points out that there was "Strong opinion in favour of having current or recent industry experience represented on the committee"[227] but that most (and recently all) of those consulted on the proposal were in rich developed economy markets. However, the more we study the likely reality of a real-world early-stage APC, the clearer it becomes that being able to influence the discretionary decisions of the controlling committee (or indeed any of the layers of committees involved) is potentially hugely valuable. Yet we are told that very little contact was made with developing country developers in trying to work out the terms of such a mechanism, with no input from, for example, Brazil, China, Cuba, and Korea (one of the major developers and suppliers of hepatitis B vaccine) and only one developer from India, the Serum Institute (that represents less than 1% of the global vaccine market). If this cannot even be achieved during discussion at this very early stage of setting up such a mechanism, what are developing country developers to believe about later stages?

For example, we are told that the committee would have the power to terminate the entire agreement if "certain interim milestones are not achieved in a timely fashion" and "if the Framework does not appear to be stimulating productive research and development activities"[228] or "not enough is being done," but it is not clear what legal redress, or compensation, emerging economy developers would have if they disagreed with this and were forced to lose all their sunk investments. Developing and emerging countries would worry that the mechanism would be unfair to them if not enough vaccine research was simulated amongst the large pharmaceutical firms–something hardly the fault of developing and emerging country vaccine firms.

APCs Lose Power when Vaccines Replace Profitable Treatments

APCs pitched to the current big developers have to work *against* another serious problem.[229] The possible development of cheap, one-off vaccines risks replacing profitable, long-term drug treatment programs. This generates less of an incentive to develop vaccines in the first place. Total (expected, discounted) *industry* profits will be lower if vaccines for HIV are developed[230]. This has nothing to do with the motives of the CEOs of large pharmaceutical companies. It is an effect that is being forced on them through the natural workings of equity-based finance–as well as being a function of the structure of the pharmaceutical industry and the nature of IP. The issue is certainly controversial, but this should not prevent us from tackling it. If it turns out that 'replacement effects' are part of the problem in raising private finance for the R&D of vaccines, such as for HIV, then better policy will result from considering rather than from ignoring such effects–as the following section will hope to show.

How the replacement effect comes about

If equity markets correctly price all future expected discounted profit flows, then those firms working on projects with the mere *possibility* of reduced overall profit flows caused by the replacement of profitable programs (profitable in the expected sense, which may be an important sense for a growing treatment market like HIV/AIDS), will experience a depressing influence on their equity valuations, and this will increase their capital costs generally–not just for this research project but for other activities too[231].

This leads to firms requiring an even higher rate of return on projects. The figures are not inconsequential. Even at the currently much lower prices than a few years ago (one can imagine how the equations must have looked then) the costs of the drugs alone for lifetime treatment of HIV/AIDS, generate a cost of nearly $1,200 per DALY saved in developing countries[232] compared to a few dollars per DALY saved for a vaccine. If there is already a 'lack of a market' for HIV vaccines, this simply reinforces this problem.

On the one hand, equity finance has much to recommend itself as a method for driving pharmaceutical R&D incentives in a world of asymmetric information (see Farlow 2004 Chapter 12). The ponderings of this section do not alter this. But we should recognize that there is a tradeoff between the incentive effect of equity finance and other, less positive side-effects, such as, in this case, the replacement effect. A different configuration of financial markets and other sources of R&D funding and a different industrial structure would feed a different set of constraints. For example, the fewer the number of firms that are already being relied upon for *both* treatments and vaccines, the larger the 'replacement effect' and the lower the incentives to invest in vaccine R&D. Conversely, the more competitive the pharmaceutical industry, then the stronger the incentive for firms to work on vaccine R&D, since success would replace the treatments of *other* companies.

But there may still be constraints on even this. In a competitive pharmaceutical industry (where the IP system would allow entrant firms to acquire technology that might undermine current firms), one might expect that those companies developing vaccines would still have an incentive to do so, since vaccines would replace the treatments of *other* companies. But a system heavily dependent on the *same* few companies for both treatments and vaccines generates a much larger replacement effect and less of an incentive to develop vaccines. This problem is reinforced if biotechs and not-for-profit firms cannot raise finance to take a vaccine 'all the way', since the only viable market for their output is created by firms that face a replacement effect, thus feeding the replacement effect onto the biotechs. One of the solutions would be a mechanism that allows for more players in the market, not bigger incentives for the same few players. The replacement effect is also stronger the more incumbents able are, through tight IPR, to restrict access to information that might undermine their competitive positions.

It follows that part of the reason for the collapse in global vaccine R&D is related to the structure of the industry. A research device such as an APC would have to devote a sizeable portion of its size to fighting against these structural issues (even as it risks making the problem worse) when really it would make more sense to tackle the structural issues head-on.

The problems of an aggregate condition

This is also complicated by the fact that the replacement effect is an *aggregate* condition. Clearly, if the expenditure on HIV/AIDS treatments in Sub-Saharan Africa is already pitifully low, then vaccine developers might not expect much of a replacement effect there. However, the HIV/AIDS treatment market also includes potentially very profitable segments, and the effect on *these* segments from vaccines developed for the *poor* segments (or from the discovery that a vaccine working on a clade in a low-value market is cross-reactive against clades in richer-value markets) works against private incentives to research towards vaccines for the poorer, low replacement effect, segments.

This is much the same logic as that found at work in anti-retroviral drugs markets, where firms have sometimes been very unwilling to price-discriminate (normally the profitable thing to do) by setting very low prices in very poor markets for fear that this will alert consumers in much richer markets to the potentially extremely low marginal costs of the drugs, risking agitation for prices to be set much lower there[233]. Given the one-off nature of vaccines and the very low prices that could ever be expected from them in very poor countries, the effect need only be tiny to undermine the incentives to research vaccines.

'Replacement effects' might even be at work for vaccines that do not obviously compete with treatment programs–such as vaccines for diseases that affect mostly the poor and for which there is low current treatment–if cheap only-once-ever-used drugs (costing cents or a few dollars at most) weaken pricing power in profitable treatment markets[234]. This weakening only has to be tiny for vaccines–maybe even only fractions of a percentage, given the size and duration of the treatment market compared to the vaccine market

(all compounded by the fact that the former market refers to multiple periods of future sales of treatments whereas the latter refers to one-off sales), and that the prices in the latter could never be very high at all. And the effect is strengthened further if there is any expectation that any resources being made available might otherwise go to treatments in the poor markets.

Similar logic affects how we view the consequences for the private finance costs of malaria vaccine R&D if we seek to encourage private finance into both malaria *drug* R&D as well as malaria vaccine R&D at the same time.

Reinforcing factors

There are three further financial mechanisms reinforcing this problem:

1) If the current system relies on 'small' firms (entrants, biotechs, not-for-profits, etc.) to work on vaccines to achieve this 'replacement', such entrants will need access to sources of finance[235]. If these firms are much more credit-constrained than large incumbents–Farlow 2004 Chapter 12 argues that they are–then their cost of researching vaccines is much higher and profitability much lower. Their ability to do the 'replacement' is much weakened as a result.

2) In addition, biotechs usually have to sell the promising discoveries they make to large pharmaceutical firms since they lack access themselves to the large amounts of capital needed to take projects through to an end product (and this may be especially so for something like an HIV/AIDS vaccine). Even if biotechs are marginal, competitive players and might not suffer from the replacement effect themselves, the need to turn to large pharmaceutical firms at late stages feeds the replacement effect onto them. Biotechs in turn find it more difficult to raise the finance to do early-stage vaccine work since financial investors know that they will face less of a market for the results of such projects because of the replacement effect of the buyers, and because of the risk that buyers will not be so interested in sinking heavy investments themselves to bring a project to completion.

3) Currently, not-for-profit firms and 'not-profitable' biotech firms can only take advantage of tax-breaks to the extent that they can be bought out by much larger pharmaceutical companies to 'cash in' on the value of the tax-break (the smaller firms amass all their unused tax-breaks as an asset reflected in their equity valuations until taken over). This is unfortunate given that more than 50% of current vaccine research takes place in biotechs. That their research needs to boost their share valuations in ways that appeal to large pharmaceutical firms, gives another route for the replacement effect to enter. A mechanism that is less reliant on this feature may enable a greater number of firms to exist in equilibrium and a lower impact of the replacement effect[236].

Incidentally, given the way the APC is designed to create 'additional' private finance and incentives 'additional' to tax-breaks, it would supposedly have to find some way to exclude the value of the tax-breaks of biotechs when it was being allocated (at least that is the assumption running through the cost-effectiveness calculations).

The APC, since it is differentially more targeted at large pharmaceutical firms over small biotechs and not-for-profits firms, makes this problem worse where it exists[237]. It is also an ironic strategy to pitch towards large pharmaceutical firms, if the reason for low vaccine research is, in some cases, in part generated by a replacement effect induced by just such an over-reliance on those large pharmaceutical firms.

'Replacement effect' crowding out effect reduces cost-effectiveness of advance purchase commitments

If there are replacement effects in the system, this may affect how we measure the cost-effectiveness of APCs. There is what might be called a replacement effect crowding out effect working against the APC. The APC has to be set sufficiently high so that the marginal positive return on vaccine research minus the marginal negative return caused by the replacement effect produces an overall return that equals that on all other research projects that the firm engages in. And this crowding out effect is worse if the APC concentrates incentives even more in a few large pharmaceuticals firms and leads to a tightening of IPR in ways that make research more difficult and expensive for small firms[238].

'Replacement effect' crowding in boosts the alternatives–especially the value of vaccine purchases

If there is a replacement effect, it is not clear why an APC would be preferred over alternative finance

mechanisms that more directly tackle the replacement effect–for example, mechanisms that feed finance more directly towards biotechs and not-for-profit firms (enabling them to take projects further without needing to rely on large pharmaceutical firms) and measures that generally create more of a competitive industry with ease of entry, greater numbers of firms, and an IPR system that works better to allow firms to freely acquire technology that might undermine those firms experiencing (and causing) a replacement effect. If there is a replacement effect at work, there is what might be termed a replacement effect 'crowding in' effect boosting the effectiveness of these alternatives[239].

It may be that this replacement effect 'crowding-in' effect can even be boosted further. The flip-side to the notion that overall (expected, discounted) industry profits are lower if vaccines are developed in areas with large 'replacement effects', is that large institutions who might otherwise spend heavily on treatment programs, like the World Bank and the WHO, would be better off. That this fact does not automatically lead vaccine developers (and their financiers) to reason that it is in their interests to develop vaccines *even if* they replace treatments is at least partly due to the previous under-purchase and under-use of vaccines by such institutions[240]. It is sometimes claimed that the simple purchase of currently available vaccines (and, indeed, acts that enable their usage) by these institutions has little effect on vaccine research incentives[241]. However, once the replacement effect is recognized, the 'demonstration effect' of the purchase of current vaccines is stronger.

Quite literally, the purchase of current vaccines in part unlocks the credit constraints (ie. makes finance cheaper) of biotechs, not-for-profits, and others by 'demonstrating' that the replacement effect is now weaker.

This also indicates the possibility of a 'demonstration effect' caused by investments into healthcare infrastructure too[242]. With a replacement effect present, a stimulus package including expenditure on previous vaccines and on health infrastructure might have the added externality benefit of 'crowding in' some privately-financed vaccine R&D[243]. This stimulus package would be strengthened further if finance mechanisms were set to give differentially greater impact to biotechs, not-for-profits, and all those working on 're-placement' projects, rather than to those suffering from and, indeed, creating the replacement effect in the first place.

Clearly, this would alter the APC cost-comparison figures too.

The 'Bunching' of HIV Drug and Vaccine Research

Resistance to HIV/AIDS *drugs* is an increasing concern. Correspondence on this issue in the CIPIH Open Discussion Forum points in the direction of lessons for vaccine research too, and also suggests we should re-evaluate APCs in the light of this phenomenon.

Harvey Bale[244] drew attention to a recent article by Gottlieb[245], which contains the following passages:

> *"It is now clear that the virus, which mutates rapidly to evade our best drugs, may be gaining an advantage over the research community that's trying to fight it… Nearly 18 years after the first HIV drug hit the market, all of the 20 distinct medicines we have address the same three targets on the same two HIV genes. In fact, 11 of the 20 drugs target proteins that are coded for the same exact gene in HIV, called pol, making it easy for the virus to alter a single gene in its genetic code and to evade most of our best medicines.*
>
> *The good news: There are nine HIV genes in all, and only one–pol–has been thoroughly picked over. Two of the other nine genes, gag and eng, have been worked on some, but the other seven remain un-drugged, giving researchers plenty of completely new turf on which to work. These include the regulatory genes named tat, rev, nef and vpr, which are all thought to regulate the speed by which HIV is able to replicate itself, and the "accessory" genes vif and vpu, which are less well understood, but believed to control its ability to infect people. Most of this novel development work is going on inside a few dozen small biotech companies with hardly household names.*
>
> *But the collective work of biotechs, however, is still no substitute for the deep resources of the big drugmakers."*

This repeats the logic that though small pharma/biotech research-driven organizations are often more productive at generating good drug/vaccine leads and clinical candidates, nevertheless, because they do not financially have 'deep

pockets', incentives should target those who *do* have 'deep pockets'.

At least as striking is the observation that previous research strategies have culminated in a situation where it is "easy for the virus to alter a single gene in its genetic code and to evade most of our best medicines." This–in the context of a virus long known to be especially prone to mutation–should make us sit up. It both suggests past R&D failures, and future R&D failures to be avoided.

Erickson corrected the Gottlieb reference to the pol gene:

> "*This is jargon, for which he (Gottlieb) may be unaware and innocent… The pol gene actually specifies three separate protein targets: protease, reverse transcriptase, and integrase.* ***The first two are the targets of all but one of the 20 FDA-approved HIV/AIDS drugs****. Merck had an integrase inhibitor in clinical trials but recently halted its development due to undisclosed animal toxicity. It claims it has a backup on its way into Phase I… A minority of potential drug targets have been successfully exploited by drug makers, but this is generally true of the entire pharma/biotech industry.* ***However, it is instructive to note the degree to which drug R&D groups all bunched together to go after the same few targets in HIV over the same time frame.***" (emphasis added) [246]

So nine genes in all for HIV/AIDS, and all but one of the 20 HIV/AIDS drugs rely on two of the three targets on just one gene. According to the models underlying APCs (the Appendix 3 model), this 'bunching' behavior does not happen. The probability structure is such that firms naturally 'spread out' and pick over different parts of the research space to maximize their individual chances of winning and the size of the expected win. In the process, this speeds up aggregate rates of drug and vaccine development and (not modeled in the APC literature) it would also increase the average quality of drugs and vaccines. So, in the Appendix 3 case, just make the pot bigger for the current 'big drugmakers.'

But the above passages suggest that the 'big drugmakers' 'bunch' in the same 'tried-and-trusted' areas. Is this a failure of public funders narrowing the field down too much? Or is it that such firms don't do what the models say they should do? If so, why so? Is it less risky for big players to 'bunch' than to 'spread'? Or is it a joint failure of public funders and private investors? And how does this help us to assess proposals for stimulating research into the 'non-tried-and-trusted' areas, especially if biotechs are not bunching even as the all the big players are? Why do biotechs not bunch so much but large pharmaceutical firms do? What does this say about who we should target with fresh resources, and how we should do it? Do not APCs just make this problem worse?

Several hypotheses suggest themselves for this 'bunching', or herding, behavior. It would be interesting to hear of others. No doubt there are plenty of possibilities, and several may be at work together. Importantly, different incentive mechanisms will impact on this differentially.

Financial herding

Models of financial market herding suggest that it is better to be wrong collectively than to be right individually. For example, when a stock market is in a bubble, those investors[247] who correctly assess this and try to break the bubble by 'selling the market short' will find–if other investors do not also do this, and therefore the bubble persists–that they have to make expensive margin calls. Given that they rely on other investors' money to try to arbitrage the bubble, they will 'look wrong' even if they are actually correct in their views, and will lose their sources of finance, business and market share. Even their jobs. In such situations it is easier to attract funds by going with the herd than by taking a contrary position. Similarly, for drugs and vaccines, the 'safer' strategy (for CEOs and stock market investors) may be to invest in something *similar* to other big players.

This may also suggest why smaller 'biotech' players feel less need to herd. They have no portfolio of other drugs that might be harmed by the fallout of 'looking wrong' compared to the herd, and it is more of a one-way bet for them; if they turn out right, they make a large gain (via stock options and other venture capital devices), but if they turn out wrong, the downside is capped. Similarly, holding a diversified portfolio of smaller players enables this sort of risk-taking to be diversified by VCs and others.

Large firms have less incentive to target multiple leads

Is there something about being large, other than herding, that causes lower risk-taking? Why do large pharmaceutical firms not *collectively* diversify their vaccine leads more? Are there economies of scale to a firm in following similar leads? Or is it because there is an inherent bias towards fewer leads per large firm anyway, thus generating a less diversified set of leads? In the Appendix 3 model, although there is constant reference to targeting a few very large firms, the model presumes perfect competition in the choice of research leads. Once this perfect competition is missing, there is less incentive for individual firms to target multiple leads since each lead partly risks crowding out, in the expected value sense, other leads that that firm is pursuing. Using instruments that tend to target a few large firms is less good than using instruments (and finance) that allows many more players to take part.

The downside consequences of integrating upstream R&D and downstream manufacture and marketing

Or does a business model based on the integration of upstream R&D with large downstream investment in manufacturing and marketing capability simply mean lower risk-taking? Does the need to find the revenues to support the complementary downstream operations lead to conservative research strategies and over-reliance on production and marketing to the detriment of R&D? The literature suggests it does:

> *"Integration may reduce the innovative potential of the firm, because the acquisition of the complementary assets inevitably increases the size of firms and induces important changes in the culture of the firms and in the speed and fluidity of information flows."*[248]

Levinthal and March[249] note the way that organizations divide their attention between the pursuit of new knowledge, *exploration*, and the use and development of what is already known, *exploitation*. In this context exploration is similar to R&D, while exploitation refers to downstream production and marketing. March[250] and Levinthal and March[251] show that while a blend of exploration and exploitation is desirable, the internal dynamics of large firms may lead to exploitation driving out exploration. Learning processes driven by experience–the typical case for manufacturing and marketing–tend to favor exploitation since exploitation generates clearer, earlier feedback.

> *"These dynamics are hard to resist in larger organizations. Large organizations are unable to provide the high-powered incentives for exploration… Large organizations can try to encourage exploration by forming and nurturing small sub-units that are isolated from the rest of the organization. 'Corporate ventures', however, have inherent limitations… they tend to yield modest returns at best. In sum, there are reasons to believe that as a research-intensive company converts itself into an integrated firm, with in-house manufacturing and marketing units, its research productivity is likely to decline."*[252]

This contrasts sharply with the incentives of bankruptcy and stock options that small exploratory start-ups face. Stiglitz and Weiss[253] show how limited liability means that smaller organizations with fewer fixed assets at stake will be more willing to undertake more risks.

This would suggest that sticking with the current industrial structure and concentrating on incentivizing large pharmaceutical firms is misplaced. Industry consolidation has made the vaccine industry a subset of the pharmaceutical industry and it must now compete in that marketplace, even as it is impacted by some of the dis-incentivizing effects of that restructuring. It might, for example, be better to use financial instruments more targeted at start-ups, adopt IP systems that allow them to undermine large incumbent players, and give them better access (maybe via processes of competitive bidding) to manufacturing facilities (for trial vaccines) that are independent of any large pharmaceutical firm. This would also enable emerging and developing country developers to have access to the same support.

Besides, if marketing is not part of the deal with HIV/malaria vaccines (it may still be, if the level of firm subsidy is linked to 'demand' for the product) we may gain none of the 'advantages' of using companies with a large element of marketing in their constitution, even as they (and we) suffer all of the drawbacks.

Patent stringing

If the reward to R&D is a patent of limited duration, then the build-up of resistance and eventual replacement of earlier drugs with later drugs is, perversely, more valuable than 'killing the golden goose' by building a more resistant drug from the start. As with

the case where vaccines replace more lucrative treatments, the interest here is not with the motives of pharmaceutical CEOs but with financial market pressures, however worthy CEOs personal motives might be, and, indeed, however worthy the motives of investors in financial markets might be.

So long as there will be more resources later to support higher drug prices for a new round of patents, financial markets may feed incentives to go for the efficacious short-run HIV drug than for the long-run once-for-ever drug that 15 or so years later falls out of the patent system and becomes widely, cheaply, generically available. If the needed drug is composite and requires firms to coordinate to create it, the incentives to do this are weak, and less-composite drugs come out of the research process. But these eventually hit resistance and need yet more, less-composite, drugs to replace them in due course.

This affects our interpretation of the APC when applied to drugs and vaccines. It might seem that the precommitment 'pot' could be irrevocably capped, such that when it runs out that 'would be it' for R&D, and that maybe this would prevent 'bunching' and the lower quality products it generates. However, no particularly convincing reason is given for why the knowledge of this would enforce development of the globally 'best' drugs or vaccines. This is perhaps also compounded by very high capital costs concatenating the horizons of players. If drugs or vaccines are developed under such an APC, is it really credible to suggest that once the funds are gone, no fresh funds will be made available to develop better products?

If markets come to understand that an expansion of the 'pot' will be allowed, how can a limit on the size of the 'pot' (and expected decisions through a committee late in the process) be used to discipline behavior towards 'high quality' products early on in the process? Conversely, if the mechanism has failed to achieve the desired quality, then the uncertainty that the 'pot' will be expanded becomes a risk for researchers (especially those without 'deep pockets'). This generates the worst of both worlds: a 'pot' that is not strictly fixed, but with the possibility of further funds being highly uncertain. This author has long argued that the fixity of the APC 'pot' is a mirage. The APC literature has never really explained how the 'pot' could be permanently fixed in such an environment, and yet the fixity of the size of the 'pot' is a hugely important part of the disciplinary workings of the mechanism.

The bunching of public funders

Are firms simply responding to public funders bunching *their* research? Indeed, there may be a common feature to any mechanism that tends to reward previous 'good result' in that it becomes slightly self-fulfilling at supplying rewards to only a limited part of the research space–that is the part that produced 'good' results in the past! If one thinks of this as a dynamic optimization problem[254], the dynamic path leading to the highest quality vaccine is not a priori clear from the start. If one simply always picks off the stretch that has proved most productive at any point in time, the overall path thereby taken may not be the most optimal if the true optimal path involved slow or expensive stretches. Incentives that always reward vis-à-vis progress on the most recent part of the path are rarely globally the most optimal. Do any of the current proposals for incentivizing R&D achieve better reward for risk-taking behavior, in the sense of a wider variety of research leads? Does this suggest more need for a strategic overview and 'control', even if this does not fit easily into the ideological framework of some, including those driving the APC?[255]

Patent fees

Since patents have more value the greater the number of potential users, does this tend to reinforce the problem, especially in the early days of a new research direction? If most other firms are working in one area–and, indeed with the growth of others 'piling in' to this area–does this mean that the potential fees from discoveries are higher? Is there a standard coordination breakdown? If others are not working in a neglected area of vaccine leads, are there lower incentives to do so too, in complete contradiction to the APC models?

Relative versus absolute performance

If there is no way of measuring actual quality relative to some benchmark of overall *optimal potential* quality (before much of the information is revealed, this is very difficult to know in advance for vaccines), and if financial disbursements are made relative to other developers rather than relative to some overall possible benchmark, one can see that a firm's position relative to others is what matters and that this might weaken the collective incentive to get nearer to the

benchmark. How do APC payments not become a victim to this?

Secrecy and lack of openness

Does lack of openness and secrecy cause 'bunching'? In a world of asymmetric information, one can imagine models where it is easier to signal 'quality' and attract funds if one is working on areas in the core of the area of current active research than from working completely 'out on one's own'. Does lack of transparency, paradoxically perhaps, make 'spreading out' more costly and difficult, maybe because it is very difficult to signal good performance? Would more transparency help? How does this conflict with the APC notion of tight IP and secrecy?

Similarly, does bunching lower the incentive to *share* information (since research is more substitutable when firms bunch)? Or is the causation the other way around? Would some regimen that rewarded firms for 'spreading out', paradoxically also feed higher incentives to share information? The notion being that the ability to profit from a discovery in a highly dispersed research exercise is more likely to need discoveries elsewhere–say to produce a composite vaccine (ie. discoveries are more likely to generate complementarities). Conversely, does the relative lack of reward from sharing, and indeed *lack of a structure for sharing*, encourage 'bunching'? By concentrating on guidance through an end committee, APCs (at least as currently constituted) have little interest in creating structures for sharing information. There is a fundamental conflict between, on the one hand, the transparency needed to help prevent bunching and, on the other hand, the heavy use of equity finance and the lack of sharing of information needed to make the APC work.

Low levels of current funding

Do low levels of available finance and short investment horizons encourage bunching, in the sense that research strategies *have* to become much more risk averse? With limited funds, is it better to stand the chance of a medium quality result than gamble on a better quality result that may also mean no result? Would higher levels of funding weaken this tradeoff? Would an investor with a longer horizon be more inclined to search new areas where the early positive externalities are low? Instead of one very long horizon, such as that found in an APC, would rewards linked to much shorter horizons be better?

Positive research externalities

Are the chances of discovery, given positive externalities to similar research, simply higher from all firms concentrating on one area of research over all other areas (certainly in the horizons of interest to firms)? By spreading limited resources over more areas, are some of these externalities lost? Is this another reason for expanding levels of funding?

In summary

Far too little attention is being paid to how the various R&D mechanisms–and APCs are no exception–create incentives to deal with long-term drug resistance and the creation of drug and vaccine quality over time. Past and ongoing experience should be more sobering. We find again that while equity finance has much to recommend itself as a method for driving pharmaceutical R&D incentives in a world of asymmetric information (Farlow 2004 Chapter 12), there are tradeoffs. Here, it is between the incentive effect of equity finance and–especially when it interacts with an industrial structure dominated by a few big players–the less positive side-effect of short-termism and herding.

Vaccines: More need for diversity

We see similar 'bunching' going on in HIV vaccine development. So far, industry has tended to concentrate on those vaccines based on subtypes of HIV-1 found in developed countries. The idea is to prove the efficacy of the first vaccine, with the notion that others will be developed afterwards feeding off that knowledge.

> *"However, because numerous scientific uncertainties remain about the ultimate approach to HIV vaccine development, the simultaneous design and testing of multiple empirical approaches will be a faster route to safe, effective, and inexpensive vaccines that are appropriate for widespread use."* [256]

One side-effect of this concentration on subtypes of HIV-1 is that it restricts the sites where vaccines can be tested in clinical trials.

Can a HIV Vaccine be Manufactured for Less Than $1 per Treatment?

We are told that "manufacturing costs will not be an issue with respect to a qualified product for so long as it is subject to the price guarantee."[257] This turns out to reflect a major flaw of the whole approach. In reality "it is difficult to predict which technologies

will succeed and thus to anticipate the cost of production."[258] We have no figures, but let us say that some of the figures discussed above are remotely correct and that, in the best-case scenario, a vaccine costing $25[259] allows about $1-$2 to cover manufacturing and distribution. This is far more generous than some have hypothesized[260]. Can an HIV vaccine be manufactured and distributed (and, in the case of therapeutic vaccines, monitored too for many years perhaps) for $1-$2 a treatment? Or, more precisely, can developers *expect* this? The cost of the recent meningitis conjugate C vaccine was $21 a dose, subsequently falling to $12-18 a dose. What hope is there that the first few tens of millions of a HIV vaccine (or malaria vaccine) could be manufactured for a tenth or a twentieth of that?

Some simple sums

Since we have no access to data, we can only entertain simple sums[261]. It might be thought that if a firm develops a vaccine that costs $10 per course to manufacture and distribute (ie. it may take multiple doses to achieve one course), it would still be a good deal for the firm to take the $25 per treatment deal. $6.25bn minus $2.5bn (250million at $10 a course) is, after all, still a healthy-sounding $3.75bn, and this is far more than, say, the firm's $200m or so private out-of-pocket research costs (and even better if half of that was subsidy), and more than what is needed to cover the firm's capital costs too[262].

But it should be obvious that this is the completely wrong decision problem to worry about. What matters is the way things look when investment is sunk, before *any* firms know who will be the 'winner'. At *that* point, the expectations of a $10 per treatment cost will take $2.5bn out of the $6.25 value of the available fund. Even if the $6.25bn was set correctly to start with, this leaves far too little to motivate firms to bother investing in the first place. If firms responded regardless, they would end up collectively *subsidizing* HIV production to the tune of $2bn. More likely they would not invest ex ante. This is why it was pointed out repeatedly above that expectations about a whole range of issues, *including possible manufacturing costs*, matter.

Maybe the IAC will subsidize at $8-$9 per treatment to get around this problem? But we are told that the whole point in announcing in advance what will be spent on vaccines once they are developed is that it "does not call upon donors to spend more than they otherwise would; but it would increase the value of that spending."[263] If large cash injections to get the vaccine manufactured are going to be needed, surely the lack of any ex ante credible commitment that *these* levels of funding will be forthcoming gets us back into the very problem we were trying to avoid in the first place (aggravated by the pot being lighter to the tune of $6.25bn)? Besides, bailing out in this way wrecks the incentives to drive towards lower production costs. We pointed out above that the underlying modeling (Appendix 3) totally ignores the need for this incentive anyway, so perhaps we should not be too surprised that it now causes a problem.

However, this is probably a pointless discussion. The firm winning the $6.25bn APC will have only spent in present discounted terms a couple of hundred million dollars on-out-of pocket costs (if there was genuine competition). Its requests for multiple billion dollar top ups, even as it enjoys its entirely fair 'winnings' of $6.25bn, would surely 'look greedy' and not be worth the PR damage. If firms understand ex ante that asking for 'top-ups' is not a viable proposition, they will not invest ex ante.

Other systems put much more emphasis on manufacturing and distribution

Under other, much more competitive, tender systems (discussed below) with more emphasis on manufacturing and distribution, there is more drive to lower manufacturing costs (there is some incentive here but it is much lower). Here, if a firm has invested and has a vaccine, then ex post it is rational to manufacture at $10 a course and take the $6.25bn. Contrary to the claim that "the contract is intended to give developers the incentive to create a low cost vaccine that meets the technical specification, if at all possible,"[264] there is reduced incentive to push towards lower manufacturing and distribution costs, particularly if it risks delaying the payback–with capital costs growing rapidly–or of ever being rewarded at all because of taking too long. Besides, since it is crucial to the APC having additionality that the one or two firms holding the key IP must keep a tight hold over it, the firm is only competing 'against itself' in this cost-cutting exercise.

Lack of confidence in a low vaccine price undermines R&D

The paradox is that the knowledge that this will be the case, and that there will be little competition between manufacturers to drive prices lower at the manufacturing stage, will reinforce the notion that vaccines will *not* cost $1-$2 to manufacture and distribute, which undermines by backwards induction the incentive to engage in research in the first place. Indeed, we will repeatedly see in real case-studies below that access to technology and know-how and competition between firms has often been very important in driving production costs lower and in enabling access to vaccines for poor countries. Work on some recent 'pull' mechanisms (for pneumococcus and rotavirus) is all about getting the costs of an expensive product down. It is puzzling that when looking at potentially very much more complicated vaccines with likely expensive production costs (at least for the first few hundred million batches, and if the IP stays in the original developers' hands) there is not much more concern about production costs.

In the context of the malaria contract, Hurvitz argues[265] that:

> "*If a developer produces a vaccine that is more expensive than $15 per course, they are unlikely to want to avail themselves of the Advanced Markets mechanism (as this guarantees the price at $15). They would be in the same position as they are now, of seeking to negotiate an agreement with recipient countries and donors. The Advanced Markets commitment makes them no worse off than they would be in the absence of the commitment.*"

Not only, according to the analysis above, should developers stop bothering *way before* it looks as if it will cost $15 per course, but this is a very puzzling statement in other ways. The bygones-are-bygones nature of R&D is such that even if the overall costs including R&D are greater than $15, firms will still avail themselves of the contract so long as *manufacturing costs* are below $15 and they have no more lucrative markets elsewhere, so the statement must be referring to manufacturing costs exceeding $15. But, if so, with contract terms set on the basis of, say, 10 or more firms competing, why would those setting contracts entertain the notion that manufacturing costs per course of treatment could ever be 30 to 50 times the winning firm's out-of-pocket R&D costs?

This hints at the possibilities of perverse incentives too. If a firm has an HIV vaccine that meets the program's requirements but for which there are more lucrative sales to be made elsewhere (at least in the early days and given low production capacity), there may be little incentive to drive the production costs below the program's price if it means the firm will look as if it is keeping an eligible vaccine out of the program.

Given the claim that a vaccine would be "available to all eligible countries at affordable prices"[266] both during *and after* the APC allocation is used up, and also in countries *outside* of the mechanism (Russia, India, China for HIV perhaps?) while the mechanism is operating, a great deal more attention needs to be paid to the incentives to achieve affordable manufacturing prices, especially for very complicated and possibly composite vaccines such as HIV.

Incidentally, this is all pretty obvious logic. Yet, in all the bru-ha-ha about getting an HIV APC in place, and the suppression of proper debate, important details about major problems like this that might undermine the whole initiative don't seem to be of any interest. Like a whole range of issues, it seems that the strategy is that it is best not to look too close. This author happens to think that having something that works is more important than having 'something'.

Problems with Long-Term Price and with Secure Long-Term Supply

The final CGD contracts call for determining, at the time of signing, the 'guaranteed' long-term near-marginal-cost-of-production 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, in return for having had the short-term advantage of initial sales at high, heavily subsidized, guaranteed prices. This is described in the CGD report as a "critical component of the advance market commitment."[267] If it were possible to make computation of such a price or to lay down a methodology for determining such a price, the report would have referred to a proven, transparent methodology. The CGD Working Group heard expert advice that production costs could range anywhere between $0.50 to $15.00 per course, depending on the manufacturing complexity of the vaccine discovered, and that no such guarantee could therefore be inserted into contracts–but this advice was ig-

nored. Instead, this "critical component" is missing from both the report and from the contract term sheets.

The CGD Working Group should have reviewed the extensive exploration of this issue undertaken by the NIH in the early 1990s, which concluded that it was extraordinarily difficult to compute or even lay out a methodology for computing the price of an unknown product, and that competition policy and commercial law may well preclude engaging in activity that could be seen as price fixing and/or a subsidy to a favored firm.

A mechanism that relies on this presumption holding in order for it to work and in order to secure long-term vaccine supply should be treated with a great deal of caution, indeed skepticism–even more so when one sees that the CGD contract term sheets have also left blank those sections specifying remedies in the event of a breach of this condition.

The risk is that the first developer absorbs all the sponsor's funding and the long-term low price is not achieved, or even that the long-term eligible market is abandoned in preference for serving a more valuable non-eligible market. Crucially, the design of the CGD model precludes competition among different suppliers to develop more efficient production methods and lower vaccine prices to poor nations–as happened in case of the hepatitis B–as a back-up for any failure to supply the vaccine. Thus the central goal of an APC to buy out an effective vaccine so that it becomes available thereafter at a low price cannot be achieved by the route suggested in the CGD report.

Furthermore, the contracts call for a supplier to turn over its IP for the eligible market (not the non-eligible markets) to the sponsor, if the supplier "prefers" to abandon the eligible market in the long-term. However, this does not take into account that the supplier may not have the right to sublicense all the IP it has obtained by license or that the production of a vaccine is as much, or more, a matter of know-how than of access to patented technologies. Similarly, it is not clear that the threat means a great deal given the lack of capacity and the 5-7 years it might take to build this up. Alternative capacity could hardly be built up in advance of confiscation of IP (and, supposedly, forced revelation of know-how)!

Short of taking over the physical production facility of the IP holder and, somehow, forcing know-how out of the IP holder, the IP holder might argue that the non-eligible markets are just as important as the eligible markets and that they are needed to recoup their R&D costs (in the ex ante sense). They would refuse to hand capacity and know-how over. One can see the IP holders' ex ante dilemma too: they may not particularly wish to face this strategic situation ex post, and this may color their ex ante decision to invest at all[268].

Such threats are, therefore, not credible ways to discipline suppliers. It risks severe supply shortages and damaging delays in access to vaccines. The very knowledge that such threats might actually be used would undermine incentives to invest in both vaccine R&D and vaccine delivery systems in the first place. The strategy also creates a huge range of conflicts and further supply problems given that the supplier nevertheless retains IP rights to non-eligible markets.

Consideration of "other penalties"[269] is suggested in the contract term sheets attached to the CGD report. However, other than unspecified "liquidated damages provisions"[270], the details are left blank. Such "damages provisions" themselves inflict disincentives on firms to carry out R&D–even more so if the provisions are as vague as they are here. This author was advised by legal experts that including threats at 20-year horizons would be unrealistic and is simply not normally done.

IP and know-how barriers have been principal causes of delays in achieving flexible, cost-effective manufacturing and in getting vaccines to poor countries quickly in the past. Yet this practical issue is not addressed in the report either. All the emphasis is put on getting the $3bn to the supplier of the first 200m eligible treatments. Long-term price, and indeed secure long-term supply of these vaccines, is thus left totally unresolved.

PDPs, IAVI, the Global HIV Vaccine Enterprise, and Advance Purchase Commitments: An Awkward Fit?

Since all *other* mechanisms for incentivizing the development of vaccines have been stripped out of the key APC models (Appendix 3), it is unclear how such commitments, and the new institutions built around them, will fit alongside other research support institu-

tions such as PDPs, IAVI, the Global HIV Vaccine Enterprise, and other publicly-funded and foundation-funded bodies.

A core part of an APC for HIV (at least, as modeled so far) is the way the HIV vaccine IP is structured. All IP ownership goes to the 'winning' vaccine developer[271] during the period of the first several hundred million high-price vaccine treatments, the follow-on period of lower-price vaccine treatments to eligible countries[272], and for *all* sales to *all* non-eligible markets (possibly including Russia, China, India, etc.) for the full duration of monopoly patent rights for the vaccine. PDPs on the other hand tend to work on the basis of more of the IP rights being in shared ownership with the public and foundation sectors, and more firms with access to the IP. IAVI uses 'social venture capital'; instead of asking for return in terms of profit or intellectual property, 'return' is measured in terms of access of the poor to the product.

This all shows up in prices. In seeking to create access, APCs generate a very high price on the first few hundred million treatments in the eligible market (paid for by the sponsors of the mechanism), high prices in non-eligible markets until expiration of the IP, and (supposedly) low prices in eligible markets after the first few hundred million doses are gone (or no vaccines if this portion of the market is relinquished). PDPs and IAVI seek to achieve access to poor consumers (including in markets that may not be covered by APCs) through lower vaccine prices from the start.

How do PDPs and IAVI sacrifice *their* objectives in order to make room for APCs? Or, don't they? If not, what does the (complicated) IP regime look like? How is it enforced? Is it predictable how IP owners will be treated and how much investors should therefore invest? What if markets that are not covered by the APC are nevertheless covered by PDPs (either current ones or future ones) or IAVI? How is the clash in such cases between the IP system underlying the APC (and high prices) and that underlying the PDPs and IAVI (and low prices) resolved? What if the APC concentrates IP in one set of hands, and the PDP/IAVI route dictates IP spread into more hands along with technology transfer to emerging vaccine developers? If MVI or IAVI creates a vaccine, what if it wishes for its IP to be freely transferred and used by emerging manufacturers? Again, where does legal jurisdiction lie in all of this?

What if PDPs are more efficient?

Matters get more complicated once one recognizes that PDPs or IAVI might turn out to be the more efficient approaches. Why should PDPs concede space to let the APC run its IP and pricing schemes in order to help it enforce itself, if the APC is proving to be the less efficient approach, and may even not be working? We remember that PDPs should be barred from taking APC payments since this would crowd out, that is 'spoil', the value of the APC for those private investors relying on the latter mechanism. It might be said that PDPs, if more efficient, *should* be allowed to crowd out less efficient approaches. However we must remember that the commitment is still locked in place, and PDPs are constrained in their access to funds compared to the level of funds needed. So, if it is understood that crowding out will be tolerated, the overall level of funds active in vaccine research will be too low, yet the commitment can still be activated to take the IP, and therefore be a threat to the PDP.

How do the chances of this 'crowding out' not self-inflict the collapse on the APC in the first place or leave it as an expensive liability that is doing very little positive even if it is doing plenty that is negative? For the sake of 'credibility' and to prevent this self-fulfilling collapse, would irrevocable rules be set in stone to protect the APC for its full duration (30 + years)? How will the dilemma–of tight precommitted rules restricting PDPs and others in order to enforce an APC outcome, but the reality of a bad outcome–be viewed in policy circles in later years? How bad does the bad outcome have to be before abandoning the tight rules and reneging (given the litigation costs of doing so) on the APC?

Can PDPs really be excluded anyway? Or is there some sort of mechanism for feeding recipients of APCs through PDPs first and thus controlling some of their IP rights? But how does that alter the distinctiveness of the APC mechanism, given the claim of leading advocates that such mechanisms are far superior to any alternatives? And what does it do to the clarity of the investment signals supposedly being generated by the APC?

Furthermore, if, in contrast to the original analysis of leading advocates, an APC is only *part* of an overall solution–say, in the case of a HIV vaccine, covering the last 10% or so of effort leading to a vaccine–why is the APC mechanism modeled as giving *all* of the IP rights as reward to the firm doing the last steps? In more realistic models, how are IP and the reward 'split' across all developers if the reward system is imposed on top of a complex playing field of PDP and other IP rights-holders? How does the APC begin to attempt any of the post-development adjustments and redistributions of the 'pot', as described above, that it would have to be capable of doing in order to enforce 'quality'? How would private investors know what was going on and how much to optimally invest in such a mixed system given such a messy pattern of IP? How would they be certain of 'fair treatment'? How is all this interaction monitored?

More reputation risk

If a HIV APC is reward for only that last few percent of the overall effort–with tens of billions of dollars of prior public and foundation funds sunk in vaccine R&D–why should the firm get all the vaccine IP rights to non-eligible markets such as India, Russia, and China anyway? What if those countries feel this is an outrage given the role of (and their part in, and funding for) the Global HIV Vaccine Enterprise? And how do those bearing all the risks at earlier stages of innovation get repaid?

If the 'winning' firm represents only one of 20 firms[273] working on late parts of the innovation process, will they wish to be seen to be getting 100% of the IP for 1% of the overall effort *even if* this is the correct risk-adjusted reward viewed from an ex ante perspective? Remember that before they invest, firms adjudicate that they have only, say, a one in twenty chance of getting the commitment. So, the expected value of the $6.25bn is actually very low, and it is *this low figure*, and *not* the $6.25bn itself, that has to be assessed against the PR consequences of winning. From an ex ante investment perspective, firms can easily be tipped into preferring a strategy, such as PDPs, that is much less risky for their long term reputation and their PR profile.

Problems in coexistence

If instead of accounting for the last 10% or so of the overall effort, what happens if the 10% represents *some* vaccines generated under an APC with others generated under a (mostly) PDP framework? Are the latter developers barred from markets meant for the former developers? How does this aggravate the incentives of both groups of developers? If HIV vaccines prove cross-reactive, will the relevant parts of the IP of vaccines covered by an APC still be freely available to those working on other vaccines and under other mechanisms, including PDPs? Or will those IP rights 'reach through' to other vaccines and to other mechanisms? What are the implications of this for incentives (and the institutions) to create those other vaccines? What complicated web of IP rights and institutional arrangements, lack of transparency and poor investment signals, comes out of the attempt to make the various mechanisms coexist? How do they coexist?

We observe that removing all other funding mechanisms and IP schemes from all the APC modeling (Appendix 3, in particular) strips out an awful lot of knotty and interesting problems in practical applications. We need to know answers to all these practical issues before imposing new institutions on top of those currently active in stimulating vaccine R&D.

The Role of Developing Country Recipients

The CGD Working Group did not seek out the perspectives of countries that are supposed to benefit and implement the program. Neither do the current contractual arrangements include them as signatories. These countries would make their 'commitments' to the program, via purchases, only after the committee clears a vaccine, and they would pay only about 10% of the initial procurement price. Such an arrangement provides them, in essence, with a veto over the success of the APC. Their small, marginal contributions would be essential to make the whole program, involving billions of dollars, work, and therefore they could use their position to achieve additional benefits.

In return, the supplier (or the supplier's country) would come to realize the value of rent-seeking behavior and of 'subsidies' to developing countries–in whatever forms those 'subsidies' might take–targeted at winning the $13.50 per-treatment subsidy on the first small tranche of treatments (if priced at $15 per treatment as most recently suggested). The system of long-term multi-institution and multi-country monitoring and policing of such behavior does not bear thinking about, even if investors would need to be

reassured in advance that such monitoring and policing would actually take place. Farlow 2004 Chapter 7 looks at the issues in much more detail.

Meanwhile, non-eligible countries, even if still very poor, pay much higher prices for much longer. Neither were the views of these countries especially sought.

The Problems of Vaccine Delivery

Huge practical difficulties beset the delivery of vaccines to millions of people in developing countries. Field reports to the Bill and Melinda Gates Foundation and others detail problems of organization, qualified personnel, political interests, cultural barriers, and knock-on costs. Tackling these practical difficulties is not taken up in the CGD report. Nor are the knowledge of such problems and the lessons from past delays used in the report to help design more realistic, practical APCs that would help recipient countries to actually deliver vaccines. Indeed, many of these grave practical difficulties are deliberately fed back on to vaccine developers through the payment mechanism proposed in the CGD report. The Working Group did not contain a single person with hands-on practical experience in delivering vaccines in developing countries.

Liability Risk

Any program involving billions of dollars, large organizations, global institutions, and medical technologies must apportion and deal clearly and effectively with issues of liability risk from the start. The final CGD report calls for the sponsor(s) to fully "indemnify the members of the Committee for claims and losses arising out of the performance of their duties"[274]–even though the sponsor(s) lose all control over their funding to a committee with wide discretion. The report also calls for the eventual designated supplier to "defend and indemnify"[275] the sponsor and members of the committee. The former is impossible to imagine; what firm would want the PR disaster of suing the World Bank, the Gates Foundation, or a PDP? The proposal with respect to the supplier is not an impossible requirement to fulfill, although it does mean that only the world's largest companies will be able to participate in the program.

Failure to contractually cover liability risk has doomed previous such proposals and indeed is an important component of private sector worries about investing in early-stage vaccines, such as those for HIV, malaria, and tuberculosis. The report even recognizes this in the case of Project Bioshield, a project that no longer treats liability risk in the fashion that the CGD report now proposes should be applied to developers of HIV, malaria, and tuberculosis vaccines.

Sponsors of any proposed APC also have a responsibility to undertake 'due diligence' to check if the proposed mechanisms are economically valid for the types of candidate vaccines they target and if they are in fact likely to have the claimed effects. If the APC collapses through no fault of those firms taking part in it but because of the negligence of those setting it up, the sponsors would have some obligation for the losses.

It is hard to imagine–supposedly in order to achieve program 'credibility'–that sponsors, especially foundations and their legal advisors, would permanently relinquish key decisions to a committee with wide discretion, fail to work out the exact legal status of these new institutions alongside already existing institutions, and yet leave the issue of liability risk entirely unresolved. The contract term sheets leave all these issues blank.

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 APC itself. It will be interesting to see how this develops.

The Terms are Set by "Rule of Thumb"

In truth, terms would be based on information provided by large pharmaceutical firms themselves or highly contentious data. Indeed, chapter nine of 'Strong Medicine' and the HIV and malaria figures being produced by the Center for Global Development do just this, based on data that has nothing to do with the vaccines at hand. Kremer himself admits elsewhere that the figures are based on "rule of thumb"[276], and Kremer and Glennerster observe that we should not "attach even a moderate degree of precision"[277] to their own figures (though they do not use the same language to discuss the relative cost-effectiveness material they once generated to compare mechanisms–that relies on the same figures–most of which has since been quietly buried[278]). The No. 10 Policy Unit mate-

rial states: "There is a lack of clear evidence of the size of market needed to incentivize R&D. Estimates range between an annual market size of $100 million and $500 million (real terms) per product."[279]

These hugely important caveats are omitted from the recent material and from all policy discussion. Nevertheless, these are the figures used to persuade policymakers to set up HIV and malaria APCs. Repeatedly above we saw the importance of getting the size and terms right for efficiency to be achieved. Yet, no matter how sophisticated the framework (though this one is *not* so in practice), if it has no reliable data on which to base itself, how can a claim to superior efficiency over other approaches be sustained?

This "rule of thumb" approach even applied to the recent GSK malaria announcement. Discussion involving a billion dollars added or taken away here and there generated a politically acceptable figure of $3bn (though, this has since been raised back up by $1bn, to $4bn, in recent announcements by UK Finance Minister, Gordon Brown). An outside observer might think that if there was any scientific basis to the calculations, a billion dollars here or there might matter, and that the ability to drop a billion dollars just to make the deal more politically palatable might suggest that there was no particular scientific basis to the deal in the first place.

Indeed, the eventual $3bn per disease in the CGD report was–in spite of finding its way into the mass media with the help of CGD Press Briefings, being the title of one the chapters of 'Making Markets', and being quoted authoritatively in the Commission for Africa Report–admitted by CGD as "purely illustrative":

> *"The illustrative figure of $3 billion… intended to illustrate the concept, not fix a precise amount."*
> Barder, O., Kremer, M., and Levine, R., 9 May 2005. Page 8 of "Answering Concerns about Making Markets for Vaccines"

This "rule of thumb" approach is becoming ever more bizarrely core to recent policy pronouncements. We know that the APC for an HIV vaccine should be linked to the underlying costs and difficulties of developing such a vaccine (after all, the winner of the contract gets to keep an awful lot of valuable IP, and they should be paying for it by paying the expected R&D costs of generating it), and yet the size of the HIV APC has been allowed to fall precipitously (to $3bn in recent pronouncements) since it was first announced, and now bears absolutely no correlation (it never did) with any obvious level of underlying R&D costs for developing a HIV vaccine.

Since most of the evidence presented in favor of APCs for early-stage vaccines, compared to alternatives, is based on the hopelessness of other mechanisms at discovering information, it is a paradox that so many parts of *this* mechanism then require so much front-loaded information and monitoring in order to set the mechanism even vaguely efficiently. Then we discover that even the information being used to set terms does not have "even a moderate degree of precision," and is "rule of thumb" itself anyway.

The Failures of Command and Control

Despite its rhetoric of "making markets", the suggested CGD program has all the hallmarks of failed command and control mechanisms. Rather than being 'market-driven', the program is 'committee-driven', and should not be graced with language that suggests otherwise. The CGD report discusses the great difficulty of monitoring the performance of the program–particularly with respect to early development–in the absence of periodic reporting by developers over very long stretches of time. However, this heavy dependence on monitoring, evaluating, and approving activities creates clear incentives to distort evidence and to corrupt the decision-making process, and it seems somewhat ironic given that one of the initial arguments made in support of APCs over alternatives was that APCs would avoid many of these interventions.

The report proposes reliance on a potentially very small committee making critical decisions at a few key points in time, with the opportunity for large mistakes. Indeed, it is suggested that important decisions about specifications and eligibility of vaccines be taken out of the hands of the sponsors themselves and put into the hands of as few as two or three individuals. An alternative approach that spreads power and decision-making through time and puts decisions into more hands in a more democratic process would allow for more checks and balances, and thus for greater chances for mistakes to be discovered and averaged out. Giving to a few members of an already small committee the power to make or break an expensive

research strategy is a big risk to many firms–especially if such firms are unable to influence the committee.

Such top-down, committee-driven approaches are incapable of the subtle, complex, adaptive adjustments required for developing vaccines for HIV, malaria, and tuberculosis. Past experience teaches us that such highly centralized, heavily discretionary systems do not incentivize private efforts, and would work against private competition to produce a diverse range of vaccines, which improve over time.

The report also concedes that "it would be extremely costly"[280] to create a committee that was fully capable of doing all that would be required of it, and hence allows the committee to rely on third parties, such as the WHO and its procedures. Yet it is not clear why the WHO or others, including PDPs, would perform such acts and yet relinquish all decision-making power, with all of its consequences for liability, to such a committee. And it is not clear why there is need for yet more layers of committees and decision-makers with potential conflicts of responsibility in a complicated web of IP, institutional, and legal tangles of unclear jurisdiction.

Let's Not "Just Try It"

Given these many layers of unexplored and unquantified inefficiency and the potential dangers, it is very irresponsible to argue that, since the social value of vaccines *themselves* is so very high, our attitude should be "Let's just try it!"[281] We should not just throw everything at a particular mechanism and "see what happens". Unfortunately, the excessive costs of developing a vaccine for one disease show up in the loss of new vaccines and drugs and treatment programs (and clean water and housing and education, etc.[282]) that then cannot be afforded[283]. In the context of an International Financing Facility (IFF), these excessive costs show up as large commitments for the IFF to deal with at later times, just as the IFF may be winding down and being repaid. Given that the IFF already has plenty of risks of its own to contend with, it is not clear that it should be burdened with a pile more. This "let's just try it" attitude would be especially dangerous if a particular APC for one of the vaccines being targeted turned out to be a great deal more expensive than initially thought (and indeed initially pitched), imposed extra research costs on other drug and vaccine projects, or was even damaging to that vaccine itself.

The funds going into the research and development of many early-stage vaccines may be desperately short of what is needed, but this is no excuse for desperate, and ignorant, calls to throw huge sums of money into a mechanism without first checking that it will work and not just generate waste and hidden dangers.

3. The Value of Late Stage Vaccine Commitments and of Current Purchases

By concentrating so heavily on early-stage vaccines and the notion that APCs are the main driving force for their development[284], the danger with 'Making Markets' and 'Strong Medicine' is that the proverbial baby gets thoroughly lost in the bathwater. This is unfortunate since many of the problems and extra costs listed above fall–in many cases quite dramatically–as the mechanism concentrates on access to already available vaccines and the development of late-stage vaccines–such as some of those currently being worked on by CGD, including pneumococcus and rotavirus[285]. There are various reasons why late-stage purchase commitments might be useful instruments, even if a mechanism might not be based on such instruments as the principle driving force for complicated early-stage vaccine R&D. And vaccine prices need not cover large proportions of the total development and finance costs of such vaccines. Even late-stage vaccines create extreme challenges for purchase commitments, and in some cases it may not be clear what the exact form should take. The following section hopes to offer some pointers.

Lessons from Past Slow Vaccine Introductions

Hepatitis B

The first hepatitis B vaccine[286] was developed in the 1970s at the New York Blood Center in New York City (based on research done at the US National Institutes of Health in the 1960s) under the direction of Dr. Alfred Prince and Dr. Barry Blumberg using plasma from infected individuals. Merck & Co. was the first to commercially produce the plasma-derived hepatitis B vaccine, followed by companies in France, several institutes in China (with technology through the WHO

and the Kitasato Institute in Japan), and two companies in Korea (Cheil Sugar Co. and Korea Green Cross Co.). The Cheil technology was obtained from Dr. Prince and the Green Cross Technology from an expatriate Korean living in Canada.

Reasons for limited use

However, there was only limited use of this vaccine–in Europe and the United States and also in Taiwan, China, and Korea–for several reasons.

First, and most importantly, policymakers were simply unaware of the true extent of disease caused by the hepatitis B virus. There were also problems in creating a case for vaccines in vaccine programs. For example, in several Asian countries, it had been shown that the leading cause of death among adult males was liver cancer caused by hepatitis B virus, but this was not widely known. As information became more widely available, support for hepatitis B programs grew:

> "*With hepatitis B, the long period between prevention of infection and the improved health outcome*[287] *still made cost-effectiveness studies of this intervention difficult to conduct and interpret. Furthermore, the notion of vaccinating an infant to prevent an adult disease proved difficult for some agencies, such as UNICEF, to accept*."[288]

Second, the price of the vaccine was high. Initially, it was $54 per three-dose course plus the cost of the visits to the physician.

Third, plasma-derived hepatitis B vaccine was derived from human blood, just at the time when concern about injecting anything derived from human blood was at its height because of the HIV crisis (it turned out that plasma-derived hepatitis B vaccine is an extremely safe product and that this risk was unfounded).

A new form of hepatitis B vaccine

In the mid-1980s a new form of hepatitis B vaccine was developed using recombinant DNA technologies[289] that was just as effective as the plasma-derived vaccine. Initially it was produced by three international companies: Merck, SmithKline, and Pasteur. Pasteur abandoned the marketplace because its production methodology used E. coli cells and proved inefficient. Merck and SmithKline used yeast cells and improved the efficiency of production. However the cost of their vaccine remained very high and was unaffordable to developing countries. The cost of the plasma-derived hepatitis B vaccine produced in China was low, but most developing countries were reluctant to import because there were no adequate national regulatory control systems in China to guarantee the safety and efficacy of the product.

The approach taken

In the late 1980s, James Maynard, Alfred Prince, and Richard Mahoney formed the International Task Force on Hepatitis B Immunization with funding from the Rockefeller Foundation and the James S. McDonnell Foundation. The first priority was to lower the cost of plasma-derived hepatitis B vaccine, mostly by bulk purchasing it for use in developing countries. In the first purchase this bought the cost down to less than $1 per dose, with two manufacturers offering at this price, the Korean companies Cheil and Green Cross. This was part of a global strategy by the Task Force[290] with five key elements:

i) Defining the burden of disease and computing cost-effectiveness;
ii) Conducting demonstration programs in developing countries to show that the product could be integrated into immunization programs and prove that 'demand could exist at the right price'. This created the incentive to create supply at that price;
iii) Building global and national consensus for use of the vaccine;
iv) Stimulating competition among manufacturers to reduce prices;
v) Stimulating the creation of international procurement funds for vaccine purchase.

Three Korean vaccine manufacturing companies–Cheil, Green Cross, and LG Chem–spotted the large international marketplace for hepatitis B vaccine and set about developing the new recombinant DNA hepatitis B vaccine. LG Chem and Korea Green Cross were successful in different ways. LG Chem decided to establish its own in-house R&D program to develop the vaccine from scratch. Green Cross obtained patented technology from a European biotech company, Rhein Biotech of Germany, who took a controlling interest in Green Cross.

In the late 1990s, the Bill and Melinda Gates Foundation made a contribution of $750 million to

establish the Global Fund for Children's Vaccines, with a substantial amount of these funds set aside for the purchase of hepatitis B vaccine. With this level of funding, the Fund was able to procure recombinant hepatitis B vaccine at less than 25 cents per dose, a price considered almost impossible even a few years earlier. It was known that plasma-derived hepatitis B vaccine could be produced at this price but it was not certain that the same applied to recombinant DNA vaccines.

From the mid-1980s to the mid-1990s, Merck and SmithKline were the world's largest producers and distributors of recombinant DNA hepatitis B vaccine. Mahoney argues[291] that though there was concern that Merck and SmithKline held important intellectual property rights that might have blocked other companies from marketing, and that Merck and SmithKline were not interested in supplying low-cost hepatitis B vaccine for use in developing countries, these concerns seem to have been justified. Both LG Chem and Korea Green Cross developed their vaccines without infringing the patent rights of Merck and SmithKline (though they could not market in the United States and Europe for fear of infringing patents). And, in the late 1980s, SmithKline had committed itself to sales of the recombinant hepatitis B vaccine for about $1 per dose given sufficient procurement quantities.

Key ingredients

The key ingredients to innovation of the cheaper product were:

i) The creation of a market by the funding from the Bill and Melinda Gates Foundation, enabling manufacturers large enough quantities to offer low enough prices;
ii) The upgrading of the Korean food and drug administration (KFDA) under the aegis of the Korean government and the World Health Organization;
iii) The design, execution, and evaluation of high quality clinical trials. The fact that the Korean manufacturers could provide these data greatly facilitated the acceptance of these vaccines in developing countries.

India and other developing countries, such as Brazil and Cuba, have emulated the success of Korean manufacturers in producing rDNA hepatitis B vaccine, even further helping to drive down prices. By 2000 more than 100 countries had introduced hepatitis B, mumps, and rubella vaccines into their routine infant immunization programs.

If a program such as that currently being proposed for HIV, malaria, and tuberculosis had been in place for the development of the hepatitis B vaccine, it would have led to the payment of $3bn (or $6.25bn) to one or two developed country producers who are not today major suppliers of hepatitis B vaccine for developing countries. Such a program would certainly not have been favorable for China, India, and Korea, who are today's suppliers.

The hepatitis B case was included in draft versions of the CGD report but was removed in the final report perhaps because, as a case-study, it shows that the original vaccine developers were not the ones who developed and maintained the lower price market, and because the competitive situation for hepatitis B today–a key component in achieving long-term sustainable low prices and secure supply–reflects poorly on the non-competitive model being put forward in current APC proposals.

Haemophilus influenzae type B (Hib)

There has been a highly-effective Hib vaccine since the late 1980s used widely in developed countries, but largely unused in the developing world, where half a million children die every year from lower respiratory tract infections caused by Hib. As with hepatitis B, cost is cited as a factor, even at just $2 per three-dose schedule. This is far below those charged in developed countries, but at prices higher than traditional products at $0.05-$0.15/dose.

Another factor holding back usage was the lack of conviction on the part of developing countries that there was a problem, since Hib-related pneumonia is observationally equivalent to other forms of pneumonia. The first efforts therefore were to demonstrate that there was in fact a problem. Use was also hampered by various other barriers, including "weak delivery systems, inadequate national disease burden data, and the unwillingness of governments and donors to increase investments in immunization."[292] More recently GAVI set itself the target of vaccinating 50% of high-burden, low-income countries by 2005.

Smallpox

We can go even further back in history to look at previous examples of slowness of vaccine introduction. After development of a cowpox-derived vaccine, smallpox transmission was greatly reduced in Europe after WWI and virtually eradicated in Europe and North America after WWII. However, it continued to ravage populations in the developing world because of the much greater difficulty (and costs) of keeping the vaccine viable in field settings, something only resolved with the development of a stable, freeze-dried vaccine. Then it took from 1950 until 1967 to eradicate smallpox in the western hemisphere (with the exception of Brazil). In 1958 the World Health Assembly resolved global eradication, but nothing happened until 1967 when the WHA infused huge resources into the initiative. Ten years later eradication was achieved and in May 1980 the world was declared smallpox free:

> "*The huge operational obstacles that were overcome to achieve the eradication goal cannot be overstated–mostly related to management, supervision, reaching displaced or mobile populations, cultural beliefs, vaccine shortages, and insufficient funds.*"[293]

In the 20th century alone, smallpox killed more than 300 million people, more than three times the number killed in all of that century's wars, and many times the 22 million who have died from AIDS so far. This is not a story about incentives to create vaccines in the first place, but much more about their production and use once they had been derived.

Recent Purchase Arrangements

There are not many cases of the use of purchase commitments (let alone APCs), and even those there are do not remotely match anything described in Part 2 above. Nor do any of the products begin to match HIV or malaria vaccines in the extreme challenges that they pose.

African trivalent meningitis vaccine

One recent 'successful' late-stage vaccine purchase commitment is the WHO/MSF/GSK Biologicals commitment, which helped to spur development of GSK's trivalent meningitis vaccine (African A, C, W135 strain). But this is also a perfect example of our lopsided attitude to vaccines (hence the quote marks)[294].

Until recently, African meningitis outuberculosis-reaks were mostly caused by the A strain. Untreated it kills about half who get it[295] and leaves others suffering long-term neurological damage such as deafness or mental retardation. But in 2002, the W135 strain of *Neisseria meningitidis* infected 13,000 people and killed over 1,500 in Burkina Faso. The WHO, the affected African countries, and non-governmental organizations such as MSF mounted an international response. Traditional vaccines used in Africa thus far had only included the A and C strains. At US$4.50 per dose depending on where it is sold, the existing quadrivalent vaccine (A, C, Y and W135) was deemed unaffordable for most African countries.

After months of WHO-led negotiations, GlaxoSmithKline Biologicals agreed to develop and license a new, trivalent (A C W135) vaccine for use in the 2003 epidemic season through the International Coordinating Group (ICG) on meningitis vaccine provision. Delivered in record time, the first round of production was largely funded by the Bill and Melinda Gates Foundation. Two million doses of the new vaccine were used in Burkina Faso for epidemic control in 2003.

By mid-2003 six million doses were agreed at one euro per dose, a price low enough for most African governments. MSF has committed to purchasing one million doses of the vaccine itself, and some funding is available from the ICG from previous years. However, donor countries have not responded to an emergency appeal launched by the World Health Organization (WHO). The UK government has donated £1million (approximately 1.7 million euros) and the Norwegian government has financed some 200,000 doses, but a funding gap of approximately 2 million euros remains for the target of 6 million doses estimated as needed for the short term. Despite promises by the European Union and agencies such as UNICEF, the epidemic response may still fall short of cash and there might be a shortage of vaccine if a large-scale epidemic occurs.

The enthusiastic response to multi-billion dollar, largely ineffectual APCs for dim-and-distant vaccines contrasts sharply with the hopelessness in providing even the few hundreds of thousands of euros needed for this already existent trivalent meningitis vaccine, at what the developers themselves describe as a 'symbolic' price[296].

Meningitis conjugate C

Another recent 'success' is the quasi APC for a meningitis conjugate C vaccine. 'Quasi' since there was no

signed contract, but instead an initial tender followed by verbal senior-level commitments. Along with trial support and expedited regulatory reviews, this led to several firms producing a vaccine that was subsequently purchased by the UK government. All those firms who took part in the bidding process got something out of the Meningitis conjugate C process. This is in complete contrast to the strict 'Making Markets' interpretation for HIV or malaria, which in effect has many firms (supposedly) sinking resources in the bid process (the Framework Agreement) but very few, if any, getting anything.

The sums involved are also much smaller than recent proposals: the initial 18 million doses (split three ways) of meningitis conjugate C vaccine were priced at $21 a dose, making a total of $378m. Capital costs were not the majority of the payments. The science was already there. All companies who accepted the initial tender produced a viable vaccine, suggesting no major gamble on the science. There were no problems (or, ex ante, likely problems) with later developers generating products so much better than the first products–such that the first products might have to be discontinued, as would happen with HIV/malaria vaccines–nor any problems with the need to create incentives to generate follow-on innovation. Subsequent tenders have still generated prices of $12-18 a dose, something probably unmanageable for an HIV vaccine.

Some Lessons: What Purchase Commitments Can and Cannot Do

We can learn lessons about purchase commitments and contracting generally from these cases.

None of these matches the mechanism proposed for HIV, malaria or tuberculosis

The most obvious first observation is that none of these cases even remotely matches the model for an APC for HIV and malaria as described in Parts 1 and 2 above. Many of the case-studies describe vaccines that already existed, and the problem for them was under-used and not the incentives to do the original development. In many cases, the real breakthrough was achieving lower production costs. One, amongst many, keys to achieving low production costs and wide use was the creation of large dedicated procurement funds.

In the case of Hib, it was not 'lack of a market' leading to too little early-stage vaccine development, but a mixture of high dose cost and lack of decent diagnosis, along with demand prediction problems and lack of access to an already existing vaccine. Indeed, the Hib vaccine was developed, according to Kremer and Glennerster, "without any expectation of realizing substantial profits in poor countries."[297] The crucial requirement was creating incentive to improve production costs of the vaccine once it existed, and there, for sure, large sources of procurement funds–along with competition between suppliers–were important. Early-stage APCs along the lines of 'Strong Medicine' have nothing to say about this. In fact they would have got in the way.

Then there is a range of vaccines in need of R&D funding, at one end of which we find cases, including several above, that are helped by a commitment, and at the other extreme end of which we find HIV, malaria, and tuberculosis.

Indeed, in the cases above–and in upcoming purchases under the International Finance Facility for Immunization (IFFIm)–we have tested none of the underlying principles of such an APC model and have learnt next to nothing about its practical operation even for much more basic vaccines. For example, what if the 'Framework-Agreement-as-tender' approach cannot be made to work and has to be abandoned? Would this not be better to discover before, rather than after, initiating an HIV APC? What if lack of competition (indeed the expectation of low competition) at later stages undermines creation of cheaply manufactured vaccines, and manufacturing costs are expected to eat up too much of any 'pot' of funds, and firms therefore lose the incentive to do R&D? What if capital costs are too high? Given the role of credibility, what if the mechanism cannot be constantly changed as faults become clearer because it destroys credibility and inflicts too much risk on developers? Or, will the mechanism have to stay the way it was set up (to avoid litigation) however inefficiently it may turn out to have been set up? Is the latter situation just as bad for credibility? With no data on performance, terms have to be set on the basis of a set of hoped-for relationships. Is this the right way to set such terms?

Current short-run contracts are inefficient: A stable market matters

It really is quite ridiculous that UNICEF and other organizations be constrained in their ability to sign

multi-year purchase agreements simply because their funding streams are usually only guaranteed annually. It makes sense to either amend the rules governing UNICEF so that it can enter into long-term contracts, or look for new financing mechanisms such as underwriting agreements or promissory notes to help overcome the constraint, or, indeed large injections of fresh cash such as those announced recently by the Bill and Melinda Gates Foundation and the UK government. It is clear that unnecessary delay in access to already existing vaccines due to supply or demand creation was, and is, unacceptable in these cases. But none of this is about APCs like those being proposed for HIV and malaria.

With lack of reliable and predictable demand, the potential revenue stream is unpredictable and it is difficult to correlate production plans with effective disease burden estimation. Long-run contracts ensure long-run sustainability both for countries and donors. Both supplier and demander can be made better off than with a system based on short-run contracts. With lower uncertainty on both sides, overall potential profits and revenue are greater, so the seller is potentially better off. But the buyer is better off too since the number of immunizations is greater at lower average cost.

Observe how the benefit of this certainty is fungible, and equally beneficial *whatever* the source of funding for the original vaccine R&D and for purchases. There is none of the crowding out and lack of additionality described above.

Removal of market risk

Most of these practical cases indicate that vaccines can be in existence and yet there are a wealth of distribution and delivery problems that hold back their usage. Major access failures happened that were totally separate from the R&D problem. Clearly some kind of commitment to purchase (maybe via tender-based systems) is valuable in terms of ensuring access, even if not driving much earlier periods of R&D. The 'Strong Medicine' and 'Making Markets' proposal puts *all* of the emphasis on creating a large pot of funds to entice large pharmaceutical firms. There is no reference to this wealth of other practical problems that would need to be tackled once a vaccine existed, and, indeed during its development. There is no reference to a potentially much stronger commitment to 'Advance Distribution' contracts. Worse, the proposal even suggests that developers should be responsible for overcoming such practical problems. For example, in the case of HIV and malaria, the mechanism, in order to supposedly incentivize 'quality' (though we found that it struggled to do so), forces most of this risk of distribution and weak delivery systems back on to the developers.

Industry concern about the market risk of APCs

Indeed, industry representatives have expressed grave concerns over the operation of APCs of the sort described in part 2 above because, in its bias towards creating large pots of funds–probably because of the motives of most of those framing the thinking–to entice large pharmaceutical firms, they fail to tackle these problems:

> *"Weaknesses in the current system of procurement and delivery of vaccines for the developing world are a major deterrent to investment. Most firms supplying developing country markets through public procurement are frustrated with inefficiencies in the current system–the lack of long-term credible contracts, unreliable demand forecasts, under-use of existing vaccines–and this reality colors their view of future promises from the public sector. The public sector can improve its credibility by increasing use of existing products and by improving demand forecasts."*[298]

It seems highly ironic that late-stage vaccine purchase commitments are totally about removing such market risks, only for early-stage APCs to work them in as a key driving force.

Commitments are coordination devices

Countries can add to their immunization schemes since they know they will be affordable in the long run and they will not have to reverse programs later. Such commitments, especially 'advance distribution' commitments, are also *coordination devices* helping to overcome "the uncertainty about the willingness or ability of governments to buy and deliver medicines through less advanced health systems."[299]

The value of a vaccine's development is lower the less likely it is that there will be vaccination infrastructure to use it. At the same time, the investment in the vaccination infrastructure may be lower if those carrying out such investment (both privately–and publicly-funded) feel that investment in vaccine development and manufacture are low.

In the case of HIV, coordination of these two activities would also include better demand forecasting[300], accelerated approval, and studies of the impact of, for example, an AIDS vaccine in varied epidemiological and country settings.

Reduction of this uncertainty would help not just manufacturers but also low-income countries who would be more able to add vaccines to their immunization programs if they could be sure of reliable access.

The Importance of manufacturing scale and of low product prices, and the dangers of not supplying the eligible market first

The short-run nature of many of the current contracts for vaccine purchases for low–and middle-income countries creates unnecessary uncertainty that shows up in vaccine shortages, unused capacity, and higher than necessary prices. The lack of procurement funds to buy vaccines, the lack of infrastructure, and the lack of disease burden surveillance means that production capacity is not large enough and scale economies cannot operate. Manufacturers demand higher price from smaller production runs and have difficulty in scaling up later. Bulk purchasing is a traditional and highly effective way to overcome some of these issues.

In truth there are as many, if not more, issues *after* R&D of the initial vaccine product. Product price is still very important, even more so are *incentives* to improve the technology of production, to make the vaccine easier and cheaper to manufacture, and to cheapen the product price. The WHO/UNICEF/World Bank study "State of the World's Vaccines and Immunization"[301] worried that "new life-saving vaccines have become available–at prices that most low-income countries could not afford," not that such vaccines were not "becoming available." One reason that the hepatitis B vaccine was not perceived at the start as viable was the very high price. From 1981 to 1987 there were no viable courses of vaccine for under $50-$60. The current pneumococcal vaccines are still way too expensive for most developing country settings. There is little point in engaging in the sunk cost of setting up immunization programs at such high prices.

Part of the hepatitis B problem was the nature of IP ownership and control, and the location of manufacturing. Key to the hepatitis B success was the creation of low-cost production in emerging economies, using a finance tool suited to that environment, and access to underlying technology for those wishing to mount a bid. Clearly, "means will need to be found, within the patent system and outside it, to generate the competitive environment that will help offset the adverse price effect of patents on developing countries."[302] Tightening patents and concentrating manufacturing into the 'big' players creates way too little of this much-needed competition.

Price is still a big barrier

One of the more surprising CGD lines is that "price has continued to be a major barrier to the introduction of hepatitis B vaccine in the developing world (even as low of $0.30 per dose for the monovalent vaccine, it was 3-5 times more expensive than older vaccines)" (bracketed terms in the original, though the passage was removed from the final report). As of 2001, still more than 60% of the world's children were not getting the vaccine. Nevertheless, if even at prices as low as $0.30 this was deemed a "major barrier", especially to the very poor, it suggests that even practically given-away vaccines may not be taken up due to the large costs of usage that politicians and health systems may struggle to muster in very resource-poor settings.

If developers of HIV vaccines are supposed to be paid "according to demand", this would seem to indicate that even at very low prices, developers would, ex ante, expect still to face a great deal of market risk, and this would have to be reflected in the APC price. In the case of smallpox for example, a commitment of funds to roll out vaccine programs would obviously have been useful, but that the "huge operational obstacles" described above should have been placed on the heads of developers via the repayment structure is much less obvious (and that is why R&D was not done that way). The "according to demand" thinking in the CGD report illustrates the limited mind-set of the framers of such proposals; developing country markets are deemed much the same as rich economy markets–just without the money.

Competition to drive production costs lower

Incentives to improve technology are to be found *nowhere* in the APC literature (they are stripped out of the Appendix 3 model for example). The current 'Making Markets' and 'Strong Medicine' proposal for

early-stage vaccines does not even put any importance on the nature of competition at the manufacturing end of the process to drive prices down, and yet it presumes that HIV vaccines will cost (or, rather, be *expected* to cost) as little as $1-$2 per course of treatment to manufacture and distribute (and even monitor in the case of therapeutic vaccines).

In the practical cases above, many of the advantages were driven by competition at a very late stage of development and manufacture, the use of competitive tendering, and the ability to switch technology from high to low cost producers. In the case of hepatitis B, for example, bids that were perfectly profitable for the firms making them were as low as a dollar or less per dose. And we will shortly see that a large part of the proposed rotavirus solution will be about getting manufacturing costs down. Yet one of the prices of using APCs for *early-stage* vaccines is tight control over IP and know-how in a few hands and much less competition at late stages. This results in a paradox we described above, where this is ex post optimal given the mechanism, but not ex ante optimal, thus undermining the mechanism from the start. It is not clear that this is a price worth paying.

A dangerous incentive *not* to supply the eligible market first

If production costs cannot come in low enough, it might turn out to even make sense for firms to supply the non-eligible markets first before seeking the eligible market. This would be especially so for HIV vaccines. Indeed, this is part of the general problem we discussed earlier caused by the fact that an APC has an 'option value' such that the commitment might motivate research even if those relying on the purchase commitment for their vaccines either do not get vaccines, or are not the first to get vaccines, or get them with delay.[303]

The interaction of this problem with the problems of creating low enough production costs for developing economies needs to be explored further, especially for HIV[304], but also for malaria and tuberculosis. One possible scenario might be that there is an HIV vaccine, but it is much more profitable (given capacity constraints and production prices) to supply rich markets first at a price higher than the APC price. There is, however, no incentive to license and encourage competition to drive production costs lower for the poor markets earlier rather than later (the APC mechanism has no independent rights over the IP since the IP has been 'paid for' by private finance and the firm can choose not to use the APC mechanism).

If current production costs are greater than the APC price, why should firms be bound to the APC mechanism or denied it later? Could they be forced to push production costs down to get under the bar and *have to* supply the poor eligible markets? Or should they have their technology voluntarily licensed to dozens of firms to push the price down? Would not the APC, especially the IP aspects of it, not forbid this anyway? Or, having spent 'only' $200m or so on out of pocket research costs[305], could the firm hold up the culmination of a research process that has cost many times that? Would this (even just the expectation of it) not destroy this and other APCs? None of this is explored in 'Making Markets'. Farlow 2004 Chapter 10 explores some industrial organization aspects to the problem, and the concern that other developers may still be dissuaded from investing further in vaccines even as the first vaccine picks off the richer market first and the poorer market later.

It is all because the Framework Agreement *is the tender*

This is all because the HIV Framework Agreement "is the tender". Competition is not 'real' between firms like a normal tender. Instead, ex ante competition is controlled ex post through a committee, the IAC, based on whatever information it can garner from firms. Worse, it is controlled in the 'virtual reality' of the *expectations* 10-20 years out of this ex post control. We find the notion that this can be done is an unproven and dubious claim. Its main fault is that unlike a traditional tender, all the faults of the tender mechanism (and of the IAC) and the layers of 'mechanism risk' created, are passed through to vaccine developers, to funders, and thence to taxpayers and foundations. To the extent that these risks are high (they are not in the case of late-stage vaccines, but they *are* very high for early-stage vaccines) it becomes very risky for firms to use such a tender, and a very expensive way to discipline behavior. In particular, the levels of sunk cost being risked on the workings of a mechanism and a committee at a far-off future period are far greater for a currently set HIV APC than in any of the examples above.

One of the reasons that the recently announced Bill and Melinda Gates Foundation and UK government finance can potentially impact health through vaccines is because of pressures driving production costs down. It would be ironic to use these successes to argue for an approach that would have undermined this success had it been in place. And also ironic given that such 'purchases' had always been regarded as one of the least credible ways to generate fresh R&D by those most pushing HIV APCs!

Access to technology, patents, know-how, and TRIPS

Since low-cost technology and competition from multiple potential vaccine manufacturers were major factors in price and hence access, easy (even free) access to some of the underlying technology, know-how and patents, and imaginative and creative IP management were key to this. One of the costs of using an APC for early-stage vaccines is the loss of IP. This may turn out to be a high price to pay once the practicalities of production and access are fully considered.

In many of the cases above, issues surrounding patents were an important part of the delay; their relaxation or creative management were a part of the solution. Traditionally, we have had to wait for patents to expire before other vaccine manufacturers have been free to produce vaccines without payment of royalties. Over time this leads to competition. In the meantime, millions of children's lives have been lost in developing countries, where governments are unable to afford the new vaccines until the price is reduced, 10-20 years later. Incidentally, given the rate of discounting, these sales 10-20 years out have practically no incentive effect on vaccine development.

In the case-studies of practical 'purchase commitments'[306] described above, most of the IP issues were just 'end-point' issues anyway (that is the way they are modeled in Appendix 3 too), with relatively few problems modeled (or even considered likely) at intervening stages. Issues of highly-collaborative research and development did not arise. Being workable on such vaccine problems suggests nothing about the workability of APCs along the lines of 'Making Markets' for complicated vaccines, such as those for HIV, that require much more collaborative research. It would be ironic if patent failures in the past were rewarded with even higher patent failures in the future via aggravating these collaborative approaches.

Competitive tender-driven manufacturing contracts require fair access by competing manufacturers and potential competitors to the underlying technology, and, especially in the case of vaccines, to know-how. An APC, of the sort suggested in 'Making Markets' and 'Strong Medicine', would rely on heavily enforced patents and monopoly control over vaccine know-how. The Term Sheet for Guaranty Agreement (in Appendix C of 'Making Markets') specifies that: "The Designated Supplier shall own all right, title and interest in and to the Approved Vaccine,"[307] even, it would seem, if most of the cost of developing the vaccine had been borne publicly and via vaccine enterprises, and even by countries (including, perhaps, Russia, China, and Latin American countries) that then find themselves classed as non-eligible countries with respect to the vaccine now totally owned by the 'winning' developer.

The hepatitis B case shows the importance of competition. How easy, for example, will it be to mount sealed bid tenders of the sort undertaken by the Hepatitis B Task Force in any APC HIV vaccine market, if there are very few suppliers and monopoly rights over important parts of the technology and know-how? Post TRIPS, this is already a much-weakened mechanism as it is. Will it be made even more difficult?

Technology and 'know-how' transfer

It is not clear what these cases say about the likelihood that patent-holding OECD companies would, under large-value APCs, allow technological transfer to developing country emerging manufacturers so that they could grow and become competitors to OECD companies. This needs more exploration. One possibility might be voluntary licensing, but licensing is inherently less competitive than market competition. Licensing is a managed relationship between licensor and licensee. As Garrison points out, Cipla would not have been able to offer the sorts of massive price reductions we have seen for antiretroviral drugs had Cipla simply been a licensee of GSK. Likewise, Cheil or Korean Green Cross could not have offered similarly huge price reductions had they simply been licensees of Merck. This does not mean that all countries should have their own manufacturing capacity[308]. The key is to encourage international competition and not to lock in an industrial structure but to allow it to evolve.

Incidentally, it is not clear to what degree the 'Making Markets' approach might be possible anyway, since such intellectual property rights are granted by sovereign governments and can only be protected or voided in the courts of sovereign governments[309]. The IAC would need to come with an international treaty attached wherein the member countries agreed to pass over to the IAC their sovereignty with respect to patents. How likely is this?

Neither is it clear what would happen if the inventor (say funded by a foundation or governments) of one vaccine chose not to overly-tightly enforce patent protection in various countries of interest (maybe to speed up dissemination and production capacity along the lines of the hepatitis B case above). Incidentally, there are potentially profitable strategic reasons for doing this as well as philanthropic reasons, so we cannot even rule it out by some of the private players. It would totally mess up the workings for those relying on the APC, but should it be banned from the start? In order to make a high IP dependent mechanism work, should those who wish to share their discoveries for free or at very low costs be barred from doing so?

The dominant role of the IAC

Clearly, too, the IAC has such a dominant role–in place of traditional competition–that less 'powerful' developers must surely worry about capture of the IAC, especially as the days of hugely valuable decisions (15 to 20 years after investment was sunk) draw near. To the extent this worry is held *now*, the structure of the vaccine industry will fail to expand as hoped. In none of the practical cases above was control over the structure of the industry such an important issue. Though many of these issues are irrelevant to the main protagonists of HIV APCs, who visualize all of the R&D being done in the current few large firms anyway[310].

TRIPS

The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) will apply to all countries that are members of the World Trade Organization. In terms of vaccine development, a particularly pertinent feature is that developing countries will have to recognize product patents as well as process patents, making it much more difficult for developing countries to reverse engineer products that are first developed in wealthy countries and then to produce those products by different processes[311]. It is already the case that large developed economy pharmaceutical firms will be able to obtain product patents in a great many countries, thus reducing the number of countries in which emerging market developers are able to market a similar product. It is not immediately obvious that, instead of more innovative finance directed at emerging market vaccine developers, a large early-stage APC, together with the financial advantages of 'deep pocket' pharmaceutical companies, and the new uses of tighter IPR, will not instead disincentivize these emerging developers.

Support to biotechs and developing country developers

We saw in several places above (but also in Farlow 2004, especially Chapters 10, 11, and 12) that 'Making Market'-style early-stage APCs tend to reinforce the financial problems of firms who are already struggling in their access to finance and tend to benefit those with already strong access to financial flows, whether they respond to the APC or not.

> "*Daunting new hurdles are being erected. Will the increasing difficulties of vaccine development, the increasing costs of obtaining regulatory approval, and the new system of international IP represent insuperable barriers to biotechnology innovation for developing countries? Will these countries primarily be licensees of developed country pharmaceutical companies and serve the role solely of toll manufacturers for the license owners? Or will the new regulatory and IP systems spur government investment in R&D and the formation of international joint ventures that will lead to heightened levels of national biotechnology innovation in developing countries?*"[312]

One of the arguments of the current paper is that we should not approach the issue of creating finance for vaccine development without first considering the *types* of players who will relatively benefit the most from the mechanisms chosen and how these mechanisms might interact with other parts of the overall bundle of problems that are creating hurdles for developing and emerging economy vaccine developers.

PDPs, not-for-profit firms, government, institutional, and regulatory issues

The hepatitis B case involved multiple layers of institutional involvement, including the original initiative

of a non-profit organization, PATH, and its donors, to launch a global effort to accelerate the introduction of hepatitis B vaccine into developing countries. It also included the support of the Korean government for a first-class Food and Drug Administration, the interest and ability of international organizations, such as the WHO, to work with the Korean government to upgrade its FDA, and a combination of private and public sector effort. This case shows that emerging and developing countries can play a critical role in developing health products for the poor, but also reveals the importance of financial instruments that work in their favor rather than financial instruments that emphasize the big players.

Many agencies are involved in efforts to generate new vaccines, including the Global Alliance for Tuberculosis Drug Development (GAtuberculosis), the International AIDS Vaccine Initiative (IAVI), the International Vaccine Institute (IVI), and the Malaria Vaccine Initiative (MVI) of the Program for the Appropriate Technology in Health (PATH). These organizations are already facing a series of challenges, including R&D management, IPR management, regulatory considerations, access to manufacturing facilities, and many others (see Kettler et al. 2003[313]). It is not immediately clear that these sorts of organizations are particularly helped by an APC promised for 15-20 years time.

Regulation

The increasingly higher regulatory hurdles that are being developed by agencies such as the United States FDA are tending to lead to a worldwide increase in regulatory standards and greater burdens in terms of both the financial and human resources needed to create a sufficiently capable clinical research capacity. In combination with increased IP protection, this is central to understanding the future of vaccine research and development[314]. In this context, large scale early-stage APCs have very different consequences to the instruments described in later parts of this paper.

The importance of incentives to install capacity quickly and for use quickly

In the most successful breakthroughs in demand creation above, the time between capacity creation and capacity utilization was relatively short, and utilization was almost totally certain. In the timeframe of interest, the *net* present value of revenue streams was much greater than it would have been with a much longer timeframe–such as for HIV.

Neither was their much investment in capacity that stood a high chance of never being used because of a replacement vaccine coming along, for example to replace the meningitis conjugate C vaccine (all three 'winning' firms got something and went on to tender for more of the same vaccine). We discussed HIV cases earlier where capacity for complicated vaccines may need to be put in place even if not used because it is replaced.

In none of the practical cases above is there commitment to purchase if a better product comes along after the first vaccine is developed, but neither was this much of a risk to firms in these cases. The ability to target higher quality is much greater in all of the practical cases above than for complicated (and potentially 'only' therapeutic in some cases) vaccines such as HIV/malaria, and the costs and risks of doing so are much lower. One of the key differences is the use of the 'Framework Agreement' and ex ante perceived decisions of an IAC to drive quality. None of the practical cases faced this.

In all these practical cases, supply and demand were created near simultaneously. In contrast, in an APC for an HIV vaccine, most of the 'demand creation' happens, supposedly, long after much of the R&D costs have been sunk. This affects, to a much higher degree than in any of these practical cases, assessment of credibility, and hence ultimately the cost-effectiveness of the mechanism.

Product differentiation and vaccine market distortions

Many of these purchase commitment mechanisms are, in a sense, about creating product differentiation of drugs and vaccines, most of the science for which is already known. The WHO/MSF/GSK trivalent meningitis vaccine (African A, C, W135 strain) above is a case in point. The end product in this case was extremely cheap and therefore more accessible to these markets. Compared to an HIV vaccine, very little market uncertainty or developmental capital costs were absorbed in the product price. Similarly, the hepatitis B vaccine already existed, so contracts were not about high levels of sunk R&D costs that covered large levels of capital costs going back ten or twenty

years with huge risks from the science and with the cost of the mechanisms all needing to be incorporated into the price. The fact that all three developers in the meningitis conjugate C case managed to develop a product demonstrates that, relatively speaking, the science was far simpler than it would be in the case of HIV.

A number of features, especially in the US, have been pushing in the direction of higher vaccine production costs, and these too can also be partly offset, as part of a package of measures, by purchase commitments. First, more stringent regulation. Second, new techniques–including complex conjugate procedures, purification, and aseptic filling without preservatives–that require expensive equipment that adds greatly to the difficulty and cost of production, while also reducing the potential for economies of scale. Third, the banning of thimerosal in the United States. This is a mercury-based preservative that enabled multiple dose vials. Its removal forced US manufacturers to supply the US market with more expensive single-dose vials. Since developing countries feed off the same sources of vaccines, their costs have been rising heavily too[315]. Fourth, at the same time there is a growing divergence between the sorts of vaccine products demanded in the industrialized world and those demanded in the developing world. The emphasis in developing countries is on heat stability, safety and affordability, while in developed countries it is absolute risk-free vaccines at almost any cost. Developing countries can no longer rely on the residual supply from developed markets at tiered prices (though we have also seen the lack of tiered prices often in reality).

Of course, these are all arguments as much for creating better access to alternative forms of finance–including front-loaded finance–for other vaccine developers and manufacturers, as they are for large APCs in the hands of a few industrialized nation manufacturers. Some forms of purchase promise also sit perfectly happily in a framework that incorporates the new public sector institutions described by some as providing vaccine development and production skills in cases where the private sector will not or cannot provide the necessary skills (perhaps because of the high opportunity cost), even if such promises are not being set massively high in the hope of generating incentives way back in the R&D process.

Competitive tenders and accurate information discovery

Not only is continuous competition and reward more possible, but price is also relatively easy to set in most of these cases (compared to HIV, malaria, and tuberculosis), the more so the more late-stage the case. Everything in the hepatitis B case was done through competitive tender and–with plenty of competition (10 companies)–this was capable of revealing very accurately the underlying production costs without the need for heroic assumptions 10 or 20 years in advance. The 'Making Markets' alternative to these tenders as a way for extracting information is to monitor everything all firms do throughout history (keeping some sort of tally), with a side instrument to somehow extract APC payment in proportion to R&D expenditure that was not stimulated by the APC, and to set up an IAC to act ex post (but also whilst information is being acquired) on the basis of that information. This works *as if* it is a tender, but it is clearly radically different from an actual tender. It is also much more open to being corrupted by pressures that lower competition, and, as in the case of 'standard' tenders, thereby undermining its ability to function efficiently[316]. In a 'standard' tender it is much easier to spot and police corruption and strategic behavior that narrows the state of competition. And it is ironic, to say the least, that while tenders are usually used to extract information, in this case they end up *requiring* this information in order to work!

Relatively low capital costs

Capital costs are a *relatively* minor component of practically all of the above case-studies, and, in many, the overall impact on risk (incorporating the impact of 'mechanism risk') is to *reduce* it. In all cases, the proportion of the allocation going to the costs of finance is completely the opposite of that for an early-stage HIV APC. In the HIV case, all the early-stage risk being fed through the mechanism, along with all the new 'mechanism' risk being created, together swamp any later risks being reduced. Ironically, we even discovered that in its current set-up a great number of market risks are still very much fed into the HIV mechanism, completely contrary to many of the current APCs being discussed.

It is not obvious that making the size of the APC greater to try to overcome mechanism risk would work if one of the problems intensified by ever-higher

APCs is mechanism risk itself (eg. the 'pot' can be set higher to combat the risk of reneging by making payments high enough to compensate winners in the ex ante sense; but the problem of reneging probably just gets even worse with a bigger 'pot').

We seek a mechanism imposing as little of its own 'mechanism' risk on developers as possible, and with as much market risk removed as possible, and not the other way around.

> "*If the risks are linked to uncertainty about the science, as in the case of HIV-AIDS vaccine, then push mechanisms may prove more valuable than pull mechanism, which are too far in the future and too low probability. If the risks are linked to the market with little uncertainty about the science, as in the case of meningococcal A conjugate vaccine, then pull mechanisms become most important*."[317]

The current HIV and malaria APCs turn this all on its head.

Low crowding out

All of these 'purchase commitments' created a number of routes for efficiency gains that were equally transferable in their impact across public and private funders. There were none of the layers of crowding out discussed in Part 2, particularly those forms of crowding out that require large amounts of information gathering to correct. In particular, the tendering systems used are more capable of setting the fresh funding to match the fresh private finance needed. In contrast, the 'tender' underlying an HIV APC has to find some other way to do this (monitoring all firm expenditure for all history and then extracting in a side contract from payments a multiple of any funding not incentivized by the APC). Thus, the HIV APC is much more informationally demanding, and paradoxically, interventionist, than any other tender-based systems.

Purchase commitments can ease the last hurdle, but it is still risky

Late stages of vaccine development usually necessitate large investments in sunk production capacity based on a mix of hoped-for sales and of the need for quantities of vaccine for heavily scaled-up trials. Manufacturing issues are generally much more problematic for vaccines than for drugs. Being biological products, vaccines require complex, large, and early investment often many years before data showing the effectiveness of the product. Capacity decisions are often needed before a vaccine's potential market is even assured, or its efficacy and safety established to a level sufficient for licensure. Capacity is then often relatively fixed. It is difficult to quickly scale-up production of an existing vaccine–it can take anything from two to four years to scale up a filling line for example–and even more difficult to refocus a facility, since changes in the process have to be validated. Industry tends to build single-use production facilities, but these take more than 5-7 years to plan, build, validate and certify. Without knowing exactly what will prove effective in a vaccine it is impossible to know the best approach to ensure adequate levels of production.

There is also a risk that once vaccines are developed, buyers will use their buying power to bid prices lower than would be needed to repay manufacturing costs and the portion of late stage development costs that were paid for privately. Some guarantee on sales might help attract finance (both private and public) for such late-stage activities, though, again we must stress, it is not the only way to ensure finance. However, the return on investment need only cover the expected costs (including any private capital costs) of these stages of development.

There are also many problems specific to HIV and malaria that even casts some doubt on this 'late' stage of the process. These will become much clearer in the following two sections, but they largely pertain to the range of 'quality' issues discussed above, the need for composite vaccines, the much higher likelihood of only achieving a therapeutic vaccine, the much greater likelihood that products (and capacity to produce such products) *should* be totally replaced, and some likely special problems in arranging the distribution of purchase commitment funds and post-development problems linked to the vaccine being 'only' therapeutic. The ability for APCs, set very much in advance, to even be the last hurdle starts to look stretched. If all the risks have to be embedded in the terms of APCs many years in advance, firms might prefer alternative ways to insure themselves, for example through PDPs.

Besides, the problem of buying-power driving prices much lower (indeed even just the expectation of this) and thus undermining late-stage investment, is much greater when $25 is being charged for drugs and vaccines with a production cost of a dollar or so, than

if prices are already close to a dollar (we saw that there might still be worries of pressures for the IAC to drive prices down to 'look fairer' ex post, even if this was not ex ante efficient).

Goodhart's Law for vaccines based on 'quality' inefficiency?

However, in reality, the buying power inefficiency found in the current system will more likely metamorphose into 'quality' inefficiency in an early-stage APC. This is a sort of 'Goodhart's law' for vaccines[318]. The notion of that 'law' is that as one tries to control some economic variable based on some past observed statistical regularity (for example, a particular measure of the money supply based on its supposed link to inflation), policymakers will find that this statistical regularity will break down and the effect will show up somewhere else (for example, the targeted measure of the money supply may indeed be controlled but the link to the original problem, inflation, now lies somewhere else as agents work around the control).

In the case of vaccines, even if we get rid of the ex post inefficiency to bid prices lower (driven by the buyers in response to the producers), in exchange we get greater inefficiency, ceteris paribus, in the level of 'quality' (driven by the producers in response to the buyers, the IAC, and any country co-payment scheme in place[319]). This 'law' bites much less in late-stage or tender–driven processes than in mostly IAC-driven processes.

Late-stage APCs may not only speed access, but also lower the level of risk and capital costs. This is totally consistent with the notion that APCs would generate very high capital costs when used to stimulate early-stage vaccine R&D. Again, everything boils down to the relative positioning of the purchase commitment in the R&D process and the terms set. The terms of late-stage commitments are not being set to cover huge amounts of the overall previous development costs, just the bits that matter for late-stage risk.

The fact that one should have to go though all of these pretty obvious reasons for why some sort of commitment to purchase large quantities of vaccines is valuable even if it may not be particularly strong for overcoming the problems particular to early-stage vaccines such as HIV, shows just how confused and conflated the different vaccine problems have become. This section has shown that many of these features are very different from those underlying the currently proposed APCs for HIV, malaria, and tuberculosis vaccines.

Purchases are said to not matter, but they do

The paradox is that the mass purchase of currently-available vaccines (and, indeed, acts that enable their usage) by institutions such as the WHO and World Bank is argued to have little impact on vaccine research incentives by key advocates of APCs: "Increased coverage of existing vaccines, while desirable in its own right, will by itself be inadequate to convince potential vaccine developers that there will be a market for new vaccines when they are developed."[320] And yet in many of the case-studies above, large scale procurement-style contracts for already existing vaccines were able to stimulate a great deal of investment in both capacity and innovation targeted at getting the price of vaccines lower and access up. For example, the funding of the Rockefeller Foundation, the James S. McDonnell Foundation and the Bill and Melinda Gates Foundation were crucial in driving down the price of the hepatitis B vaccine. It was a huge part of the success of that program.

We also saw earlier the great importance of vaccine purchases in sending signals to biotechs and in overcoming the negative impact of the way vaccines tend to replace the lucrative treatment markets of large pharmaceutical firms.

Furthermore, the use of current vaccines not only increases credibility that any new vaccines will be used, but it also improves the vaccine delivery and managements systems that will eventually be needed for HIV, malaria, and tuberculosis.

Future Vaccines

The Center for Global Development originally set its sights on two vaccines, streptococcus pneumoniae (pneumococcus) and rotavirus. The emphasis was not at first on HIV or malaria vaccines, nor was there much notion that these were obvious targets for impending APCs, in spite of heavy lobbying by a tiny handful of voices. Of those involved in promoting pull approaches, it is probably fair to say that many have gone along rather than actively promoted the HIV and malaria application. Like a virus itself, the recent emphasis on early-stage vaccines has exploited the un-

derstandable interest shown in these late-stage vaccines and the weakened immune response of those riding that particular policy wave.

Pneumococcus

A leading cause of bacterial pneumonia deaths is a bacterium called streptococcus pneumoniae (pneumococcus[321]), that it is preventable by a vaccine similar to the Hib vaccine. Like the Hib conjugate vaccine, it has proven to be safe and very effective in randomized clinical trials. In studies in the US and Finland, it has been shown to reduce the incidence of severe pneumococcal infections such as meningitis, pneumonia, and septicemia, and to prevent ear infections. Since 2000, it has been in regular use in the US and other wealthy countries, but not in the developing world. The four recommended doses cost more than $200 on the private retail market. Yet again we find that "although the vaccine is highly efficacious, reluctance to use it arose because of the price."[322]

Widespread use of an efficacious pneumococcal vaccine could help to alleviate an estimated 1 million deaths a year, mostly in developing countries[323]. Development and availability is even more urgent given the increasing antimicrobial resistance of streptococcus pneumoniae.

Purchase commitments, if carefully designed, potentially fulfil most of the qualities claimed in this case:

i) First-generation products get tested in the populations that need it;
ii) Suppliers get fed sufficient incentives to supply sufficient quantities for the developing world;
iii) The contracts influence the presentation and characteristics of products so as to better fit the needs of developing countries;
iv) Contracts can be set to influence the long-term pricing of the product;
v) Sticking to the contracts will reduce wasteful investment in 'me too' products (which itself reduces risk to other products and hence costs of development).

These demand-side measures may help to overcome the problems that were caused by the slow use of hepatitis B and Hib vaccine. The may also impact positively on vaccine supply and even on some of the late-stage development needed to make the products more suitable for use. Competitive tender-type arrangements mean that crowding out can be largely avoided. Capital costs are also a potentially smaller part of the overall costs. Observe how, contrary to the HIV and malaria cases where it is simply presumed that treatment cost will be a dollar per head (without any thoughts for how this would actually be achieved), here the entire issue revolves around the currently high production cost and ways to get this down.

Rotavirus[324]

Worldwide, rotavirus infection is the leading cause of severe diarrhea and vomiting in infants and young children between 6 and 36 months old. If untreated, the virus can rapidly kill, since 10 to 20 episodes of diarrhea in a single day rapidly dehydrates the sickest children. Globally, rotavirus infections account for approximately 138 million cases per year of infantile gastroenteritis and are responsible for approximately 450,000 to 650,000 deaths of children–one child a minute. 85% of these are in low-income countries, accounting globally for about 5% of all deaths in children under 5 years old.

This disease affects both rich and poor countries. 95% of children worldwide will experience an episode of rotavirus disease by the time they reach 3-5 years of age, irrespective of race or economic status. Rotavirus infection is the most common cause of hospitalization worldwide for diarrhea and vomiting and is responsible for one third of cases of severe diarrhea globally every year.[3] The big difference is that in developed countries the rate of death is much lower and hospitalization and clinic visits take the brunt of 'costs'. Indeed it is one of the leading causes of hospitalization and clinic visits in such countries, with between 1 in 19 to 1 in 72 hospitalized in the first five years of life[325].

It might be argued that one of the reasons that the death rate is the level it is in developing countries is because of poor sanitation and hygiene and lack of oral rehydration, and that if these can be improved a vaccine becomes much less of a priority. However, it can also be argued that given that natural infection gives protection, a vaccine is much more clearly possible than for, say, HIV, and that, furthermore, in spite of pushes to encourage oral rehydration and improve sanitation and hygiene, rotavirus remains a major cause of childhood morbidity and mortality. In the US, for example, there has been minimal improvement in

the rate of rotavirus hospitalization in the past 15 years. It is estimated that 326,000 rotavirus deaths in developing countries could be prevented by a vaccine with features close to those in current development[326].

Many challenges

There are still many challenges. Two first-generation products are licensed or are close to being licensed for rotavirus (and a third product that was previously withdrawn that had been sold in the US market), at least one of which will be on the market in the next year or so. The GSK Biologicals vaccine–originally developed at the Children's Hospital of Cincinnati by Dr Richard Ward–has, for example, been in development since 1997, when it was in-licensed from AVANT Immunotherapeutics. More than 70,000 infants were enrolled in the global clinical development program, with studies conducted in Europe, the US, Latin America, Africa, and Asia. The Phase III clinical study has already seen over 60,000 infants aged 6 weeks to 6 months use the product, involving 11 Latin American[327] countries and Finland. The product is described as safe and well-tolerated, with efficacy of up to 73% protection against any rotavirus diarrhea and up to 90% against severe rotavirus diarrhea over the first rotavirus epidemic season. Clinical protection is maintained over two consecutive seasons, with, its makers claim, no increased risk of intussusception.

This does not begin to compare with HIV

This does not even begin to compare with the situation facing an HIV APC of the sort being proposed by CGD. It would be absurd to even suggest similarities. Rotavirus vaccine development is way down the path of development. In particular: "The comforting point is that the efficacy of repeated infection on the intestine with attenuated strains against wild viruses is beyond doubt, and *one can be optimistic about the eventual availability of a rotavirus vaccine*" (italics added)[328]. Very unlike HIV, we know that candidate vaccines based on attenuated live strains are possible (the source of most candidate vaccines), both human and animal rotavirus, and that various other more novel approaches are being pursued (including DNA vaccines, inactivated parentally administered vaccines, vaccine-like particles, etc.)[329]; indeed there already is one nonhuman strain vaccine[330]. Nevertheless, "although natural or vaccine-induced infection clearly protects against subsequent disease… the lack of clear immune correlates has made vaccine development problematic, because large trials are necessary to examine the efficacy of each candidate vaccine."[331]

The challenge is to make any rotavirus vaccine rapidly accessible and *affordable* in predictable quantities to developing countries. Rotavirus vaccines for developing country settings, and hence APCs for them, face a number of particular challenges, including: 1) The high cost of manufacture, 2) important issues regarding safety with respect of intussusception, and 3) big differences in rotavirus epidemiology between developed and developing countries. We will briefly look at these in turn:

Cost of manufacture

It might seem strange to recognize that the greatest problem with rotavirus vaccine is manufacturing costs, only then to *trust for no explicit evidence-based reason* on $1-$2 or so manufacturing costs for HIV vaccines. The HIV APC currently being pursued tackles none of the design issues that might help achieve these low production costs (competition amongst multiple manufacturers, access to technology and know-how, IP issues generally, competitive tenders, etc.).

Safety issues

Intussusception is a relatively common cause of bowel obstruction in children. Following licensure of the RRV-TV vaccine, 15 cases were reported in just under a year in the US. Various studies showed a slightly increased risk, though further studies are less suggestive. The vaccine was withdrawn, and the path of future vaccine candidates is unclear until further studies have been done into issues such as: i) whether other live oral rotavirus vaccines lead to intussusception (this will require good post-license surveillance of any new vaccine); ii) the pathogenesis of intussusception in general and RRV-TV–related intussusception in particular; iii) whether naturally acquired rotavirus or other enteric pathogens are associated with intussusception, so as to determine whether intussusception is likely specific to rhesus strain infections or a more general reaction to a broader set of gut infections; iv) given that the risk and benefits vary greatly across developed and developing countries, more on the exact risk-benefit in various settings.

Epidemiology

Big differences in seasonality, strain prevalence, age distribution, and outcomes will influence the op-

timal composition, schedule, dose and priority between developed and developing countries. For example, it may make more sense to include a neonatal dose in the vaccine schedules in developing countries because the age of first infection and severe disease is lower than in developed countries. It may also be necessary to use higher doses to overcome the inhibitory effects of competing gut flora, use of OPV, and high levels of maternal antibodies against rotavirus. Vaccines protecting against strains prevalent in the US are likely to perform poorly in developing countries. Clearly this indicates the need for more trials on more vaccine candidates in developing countries alongside the studies of the epidemiology of rotavirus disease.

Rotavirus vaccine trials have yielded poor and variable efficacy results in developing country settings[332] because of differences in host factors, virological characteristics, and disease epidemiology. Most trials used a single–or two-dose schedule, when in fact additional and/or larger doses may be needed (observe how this raises cost). There is even doubt that live oral rotavirus vaccines in vaccine programs will be effective in such settings. The science is not exactly easy, and there will be great challenge in creating vaccines that will be effective and safe in multiple settings. Even where purchase commitments can be set to motivate trials, it will be very difficult to set terms efficiently, suggesting the importance of other mechanisms for uncovering information. Nevertheless, the informational assumptions are a lot less heroic than for HIV or malaria, and there is potentially the benefit of using tenders to extract information. The description of vaccines as being a form of product differentiation may be apt in this case.

Some of the challenges facing rotavirus are potentially part of a purchase commitment solution; these include: programmatic issues regarding addition of a new vaccine to EPI programs, ability to produce enough to meet demand, and obtaining data to evaluate need and demand in countries interested in buying, and so forth. But it is clearly more of a challenge than simple APC notions might suggest, and such purchase commitments are much more likely to need, just like meningitis conjugate C vaccine, a myriad of non-APC devices too. Since repeatedly we find that many of the problems are about access to drugs and vaccines once developed and cheapness of manufacture, there are many potential lessons to be learnt from this case that might help in the design of much more challenging purchase commitments.

These are all very different from HIV, malaria, and tuberculosis

The vaccines being emphasized in 'Strong Medicine' in particular, are, however, many streets away from pneumococcus and rotavirus. It really is not very helpful to constantly conflate APCs for late-stage and currently existing vaccines with APCs for early-stage vaccines–so that one minute we are reviewing ways to solve a flu shot shortage (of a flu vaccine already in existence), and the next we are being told that developing an AIDS vaccine works on pretty similar principles[333].

The evidence of our hopelessness at procuring cheap vaccines that we currently have is good reason for guaranteeing procurement for vaccines, but not per se for justifying the use of a poorly-understood APC mechanism for the much more expensive and difficult task of developing complicated vaccines, such as those for HIV, malaria, and tuberculosis. This is a separate issue and needs to be independently proven. Planning ahead in this way would help to avoid access delays once an HIV vaccine is developed, though it may well also need public sector investment, and it is not the same as suggesting that an HIV vaccine could be largely (or even much) driven by such purchase commitments. And even if APCs were chosen to stimulate part of the development of HIV vaccines, they would still need many of the above problems sorted out in order to enable the level of the APC to be credibly set anyway.

Future vaccines will be expensive to develop

There is another way in which many of these cases may not be typical: their cost of development. The development of recombinant DNA hepatitis B vaccine was a "stroke of luck."[334] Nobody anticipated that genetically modified yeast cells would produce hepatitis B surface antigen that was identical in all important biomedical respects to that produced by the human body itself. Like many things in science, it was serendipitous. Since then no further recombinant DNA vaccines have been licensed, although a vaccine against human papilloma virus using this approach may soon be available. Hepatitis B vaccine may turn out not particularly typical of the vaccines to be developed in the

future. As Bloom points out, "The easy vaccines have been made."[335]

Is this good or bad news for APC advocates? This author suggests that it would be bad news. Given the dangers discussed above of setting the size of an APC too low, this would seem to suggest that policymakers should err on the side of making them too big. But if so, and given that they are already expensive devices, this serves only to make them even more expensive on average, and less efficient, ceteris paribus, than instruments that can adapt much more to future costs. Besides, policymakers, if anything, will be encouraged to go for the lowest-sized APCs that advocates think they can get away with[336]. The reality of this becomes ever more clear as time goes by.

Lessons for the International Financing Facility (IFF)

Britain, France, GAVI and the Gates Foundation have drawn up proposals to apply the principles of the International Finance Facility (IFF) to the area of immunization–an 'IFF for Immunization' (IFFIm). This would create a framework for donor funding of vaccines over the next 25 years that is pre-committed that would enable many of the above benefits to be picked off. Funding would be better planned, sequenced, prioritized, more predictable, and delivered sooner. With greater market certainty it would be easier to develop health-systems with capacity for vaccine delivery and to tackle important parts of the R&D problem.

There is no time here to discuss the IFF itself in detail, except to recognize that there is a vibrant debate about it. The IFF notion is that legally binding commitments today help to eliminate uncertainty about future behavior, and that this reduces risk and hence raises the productivity of current spending. The IFF is, in that sense, a risk-reduction tool. The one detail that is frequently observed as still in need of much clarification is what will happen when repayments fall due and future aid budgets are impacted. The mechanism rather relies on the current upfront funding bringing about the need for lower aid budgets much further off in the future. Otherwise, currently-reduced risk is simply offset by more risk much further out. At some point worries about *that* risk even start to affect current behavior. This paper leaves others to clarify this. However, a few points are worth making in the context of 'purchase commitments' for vaccines:

1) Stability of flows is good for vaccine researchers, manufacturers, and developers, whatever the method of funding of those flows and whoever the vaccine researchers and developers are. This is a separate issue from the IFF initiative and, indeed, from 'APCs' too. Even if the IFF fails to take off, a Vaccine Fund should still be a practically achievable reality. It will just require taxpayers to bite the bullet sooner. For example, UK Finance Minister Gordon Brown[337] says:

> *"Let me give an illustration of what–because of the IFF model–is already possible… The Global Alliance for Vaccines and Immunisation… is interested in applying the principles of the IFF to the immunisation sector–donors making long term commitments that can be securitised in order to frontload the funding available to tackle disease. If, by these means, GAVI could increase the funding for its immunisation programme by an additional $4 billion over ten years, then it would be possible that their work could save the lives of an additional 5 million people between now and 2015."*

But none of this *requires* the IFF model. In economic parlance, the IFFIm is a sufficient but not a necessary condition. The key issue is to have sufficient and stable flows. The novelty of the IFF is to delay payment (and the taxes to cover it)–and pay, via interest, for doing so. In this case the presumption is that the funding that would have gone on activities in ten years time can be brought forward to now. This creates a lasting effect if there is a backlog of immunization that needs clearing sooner and because immunization will prevent health costs and losses later, but there will still be need for yet more funding given that immunization (especially child immunization) is an ongoing and long-term phenomenon.

According to the statement above, increasing GAVI funding by about $400m a year could save five million lives by 2015. So, why not just commit more funding for GAVI? The IFF is neither the most obvious way to do it nor the cheapest. Purchasing vaccines via an IFF-type instrument should not be seen as a way to just, somehow, prove the 'virtues' of the IFF, although it may provide a low-risk way to test the instrument out.

2) Using fresh funds, IFF or otherwise, to launch vaccine purchases will yield a huge initial payoff. Clearly there is a spectrum of impact, with some currently existing vaccines so hopelessly under-used that

the impact will be great, and other vaccines much further out in the pipeline. There are so many 'low-hanging' fruit that the Vaccine Fund is likely to be very successful in the early days. Unfortunately, this says nothing about the application of the APC notion to complicated vaccine R&D;

3) Similarly, success on the Vaccine Fund, especially in the first few years, would say relatively little about the potential success of the IFF in general. Extrapolation from 'low-hanging' vaccine fruit to other developmental goals would not make for sound analysis;

4) The IFF is about bringing funding forward. The APC proposal for HIV is all about pushing funding back. If anything, IFF funding is more suitable for current purchases and front-loaded research, which is hardly the point of APCs for HIV. Furthermore, as currently proposed, any commitment issued by the IFFIm could only be outstanding for a period of 10-15 years–way too short to be of any use for early-stage vaccine APCs that would need 20-30 year horizons. Given the dangers to investors of 'sunset clauses', the funding route for early-stage vaccines would have to be much more open-ended.

5) Where IFFIm funds are used to speed up the introduction of two vaccines–for rotavirus and for pneumococcus[338]–that are in late-stage development, the funding will be used for a variety of both 'push' and 'pull' activities. It will therefore be difficult to determine the independent impact of any APCs present, though, again, it should allow lessons to be learned. However, because of this mix, it is less clear the extent to which any lessons learned would extend to early-stage vaccine APCs.

6) Nevertheless, given the need to create sufficient impact such that future aid flows can be reduced and the IFF paid back, it is still awkward to use IFF flows to pay for front-loaded HIV vaccine work, given that the outcome is highly uncertain, and may not impact development for a decade or even much more (or never). The improvements in health outcomes may therefore be too far off to help the IFF project to 'repay';

7) On the other hand, if APCs *are* used instead and turn out to be a great deal more expensive than proposed (with large chunks of capital costs, crowding out effects, problems of high manufacturing costs needing yet more injections of funds, large amounts of so far uncosted front-loaded funding, great problems dealing with quality issues, etc.), they potentially amplify the risks of the IFF, since the much higher level of repayment and associated costs will hit in future periods when the IFF is coming up for repayment. If, for example, a $6.25bn APC for HIV is only capable of generating (on the basis of the calculations of the Global HIV Vaccine Enterprise of the levels of funding needed) just a few months worth of fresh current vaccine research (and the impact shrivels to nothing based on the current $3bn figure), then even if the APC worked (it probably would not in these circumstances), it would leave a liability of $6.25bn behind to hit the IFF at a much later date in exchange for little current impact.

In addition, there may be yet greater needs for end-loaded funding to achieve maximum impact of a series of therapeutic vaccines, currently the most likely outcome of the HIV Vaccine Enterprise. Politicians seem to have lost sight of the fact that if 'only' a therapeutic HIV vaccine is derived, prevention and treatment budgets will remain very high way after any HIV vaccines are developed. Moreover, those vaccines may themselves require a stream of yet further-out vaccines. The APC literature has tended to treat the treatment budget as being replaced by the vaccine budget at horizons of ten to twenty years. The risks of the IFF and the risks of APCs need to be properly analyzed together. Neither is a panacea to the funding problems.

8) Since the IFF is paid from future aid flows, it is not an excuse just to throw large sums of money at problems, including vaccine R&D. Such behavior jeopardizes the whole IFF enterprise. With so many other developmental goals, and financial penalties if funds are wasted, there *is* a binding financial constraint, and the efficiency of the projects that the IFF will fund will matter greatly. If APCs for HIV end up being a great deal more expensive and less powerful than originally claimed, that is a risk for the *whole* IFF enterprise.

9) Global agriculture subsides are running at $1bn per day. Military spending in Iraq at $1bn-$2bn per week. IFFIm would be a ten-year $4bn program,

or roughly 4 days of the former subsidies and less than a month of the later military spending. What might it suggest about priorities that only immunizations get a borrowing instrument like an IFF (that has to be repaid too) rather than simply being paid for? Would it have been better to have gone for a no-strings stream of payment?

10) What if the IFF proves problematic to set up? Should the success or timing of an immunization program be linked to the timely and continued success of something entirely different, and much more risky?

Immunization is an emotive issue, the IFF a more controversial issue. Should controversy about the latter be allowed to be associated in any way with the former? How do those who wish to be critical about the former not end up harming, or sullying, the latter?[339] Or is the hope that–by virtue of its emotive content–the link to immunizations protects the IFF somewhat? Given the sensitivity of the issues, policymakers need to make very sure that, in all their public pronouncements, the IFF is there to support the immunizations and never the other way around.

4. Collaborative Global HIV Vaccine Enterprise

Introduction

The main problem with the emphasis of APCs on early-stage vaccines for HIV, malaria, and tuberculosis–and the greatest cause of their excess cost compared to alternatives–is that it misunderstands the nature of the vaccine research process. Let us examine this in the context of one of the major vaccines currently being heavily emphasized, HIV[340], a vaccine facing "daunting scientific hurdles."[341] While we may concentrate on HIV, it is worth pointing out that for parasitic diseases, like malaria for example, high-quality vaccines are also especially difficult to develop, in that case because of the difficulty of determining which portion of the multi-stage lifecycle to target. Currently three types of malaria vaccine are in development targeting different portions of the lifecycle: pre-erythrocytic, blood stage, and transmission stage. We will return to malaria in Part 6 below.

The Scientific Challenges of HIV

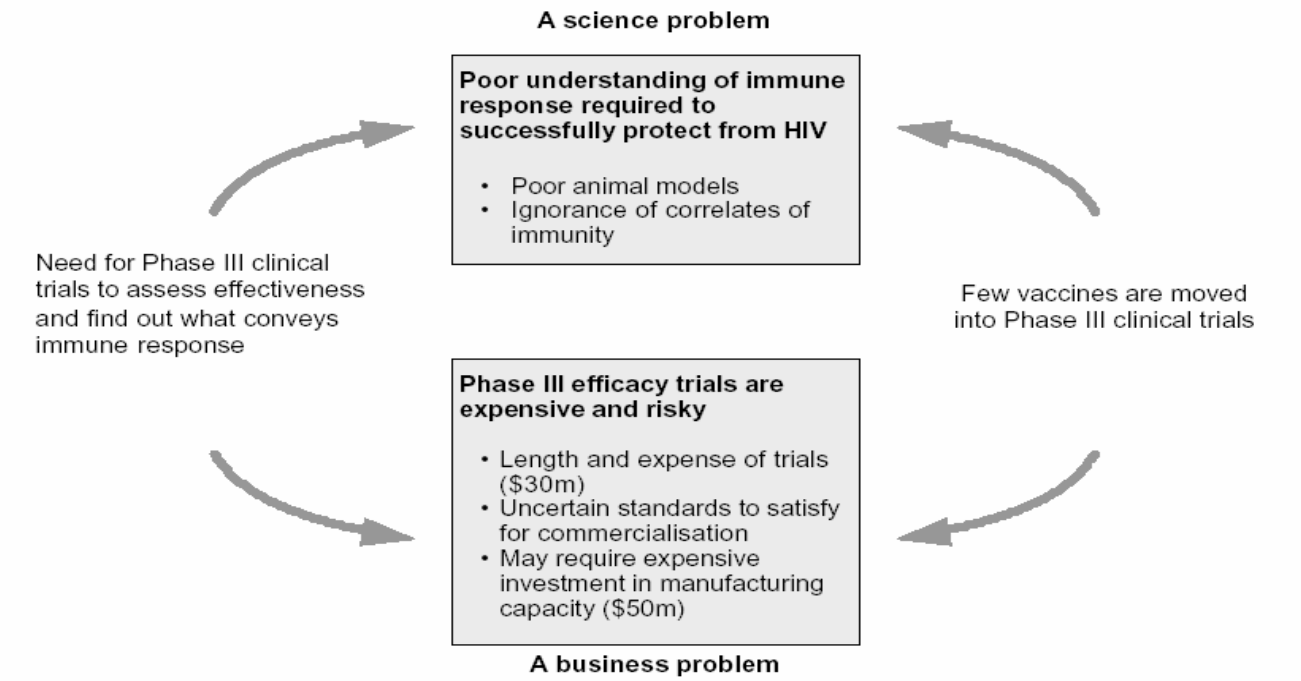
Klausner et al.[342] point out that many of the fundamental scientific challenges impeding HIV vaccine development remain unsolved very many years after the identification of HIV as the etiologic agent responsible for AIDS. These include:

i) The inability of current vaccine designs to elicit effective neutralizing antibodies against the circulating strains of HIV;
ii) The inability of current designs to prevent HIV from establishing persistent infection;
iii) The extensive global variability of HIV and the fact that in the process of replication in an infected individual it mutates rapidly, producing genetically distinct viruses such that a vaccine protecting against one particular type of the virus may be ineffective against another. There is "a population of viruses in a single individual that is so heterogeneous that an antibody that binds to one virus and blocks its ability to infect a cell may not be able to bind to another of these viruses."[343] Of particular current relevance, a high degree of HIV-1C diversity poses a significant challenge for the development of an efficacious HIV vaccine for southern Africa and the horn of Africa where the HIV-1C subtype is the main subtype causing HIV epidemics. The full-length genome sequence so far comprised finds 73 non-recombinant HIV-1C isolates;
iv) The lack of understanding regarding the mechanisms of protection in the most effective HIV vaccine animal model system–the live attenuated approach;
v) The lack of understanding about which HIV antigens induce protective immunity and which immune effector mechanisms are responsible for protection.

The problem is also circular (Figure 1).

"Why is the process of developing an HV vaccine so drawn-out and complicated? The answer to this question lies primarily in the fact that natural immunity does not appear to have a strong impact on the final outcome of HIV infection. In fact, without chemotherapeutic intervention, HIV infection is responsible for an extremely high mortality rate. Because studies of natural selection have not guided scientists in understanding what constitutes protective immunity, it has not been possible to identify the critical viral sequences to include in an HIV vaccine."[344]

Figure 1: Problems and Solutions



"A lack of knowledge about protective immunity has hindered HIV vaccine development. This obstacle is to some extent offset by the knowledge researchers in the field have gained about HIV diversity, the structure of some key HIV proteins, the events surrounding HIV entry into its target cells, and host responses to HIV antigens. Even though many of these scientific gains have been, and will continue to be translated into HIV vaccine designs, it should be recognized that only through clinical trials will it be possible to evaluate the effectiveness of an intended immune response that is elicited by a candidate vaccine. ***HIV vaccine development needs to be an empirical process, involving repeated rounds of clinical testing of a large array of candidate HIV vaccines.*** *An efficacious HIV vaccine developed from such a process is our best hope of arresting the growing AIDS epidemic both in sub-Saharan Africa and in other regions of the world."*[345](emphasis added).

HIV vaccine research has the structure much more of cumulative and reflexive research, not the linear unidirectional research presumed in the key APC models (Kremer Appendix 3); trial-discovered knowledge links back to basic knowledge and helps to uncover other trial-discovered knowledge, and so on. Much of the information revealed has public good features to it, quite unlike the properties presumed in the basic APC models, which assume that the result of *all* research is a pure private good. The mechanism to solve this highly complex scientific challenge is, so we are told, "simple" and "easy to understand."[346] But how likely is it that simple economic models that do not match the highly complicated scientific reality will be able to guide scientific policy in a rational direction?

Combination and Therapeutic Vaccines

The scientific evidence also indicates that combination vaccine regimens will be needed to achieve a broad spectrum of immune response and the optimal balance of efficacy, safety, and cost for all regions of the world. On the one hand, with more and more recombinant strains of HIV around the world, and with more and more people traveling, there is a need for a globally applicable vaccine. On the other hand, it is possible that specific vaccines (made for locally circulating strains of HIV) based on the genetic makeup of specific ethnic groups or to cope with the needs of specific geographical regions will be required.

By dealing in only pure vaccines, such awkward issues as 'coordination' are not an issue in the APC

literature. And by thinking largely in terms of 'the' HIV vaccine, the size of the 'pot' of subsidy is conveniently fixed and can be used to discipline developers, in a situation where the bounds on the needed funds are highly unclear. When the 'pot' of subsidy is gone, will more funds be made available to cater for the ethnic groups left out (and on the basis of whose ownership of vaccine IP will such R&D take place)? Indeed, our lack of understanding of the significance of HIV genetic subtypes for vaccine design is a constraint on vaccine design but also on any APC set up to incentivize vaccine design and research. But these knotty scientific difficulties are mere inconveniences to the creation of neat, simple, economic models. Better to dispense with then than to spend much time dwelling on them.

Just for one example, HIV can be transmitted either by cells infected with the virus or by cell-free virus. The type of immune response is very different in both cases. Virus in a cell can be recognized and eliminated by cytotoxic or killer T lymphocytes, but free virus can only be controlled by antibodies. The vaccines eliciting such different immune responses are very distinct, one cellular and the other humoral, and some coordination is needed to make sure that both are optimally present:

> "*One of the main obstacles facing investigators in the field of HIV vaccine research has been the difficulty in constructing a single protein that is able to elicit an antibody response with activity against a diversity of HIV viruses… experimentation suggests that a combination of two complementary vaccine strategies will likely generate a more potent cytotoxic T-lymphocyte response than any single vaccine modality*."[347]

In consequence:

> "*The ultimate vaccine, therefore, will likely make use of a combination of strategies, an approach that radically departs from any vaccines that have previously been developed*."[348]

> *"From the perspective of both viral escape and HLA restrictions, the inclusion of multiple variants of key immunodominant CTL epitopes in an HIV vaccine could prove a more effective protection."*[349]

Needless to say, this is completely at odds with the modeling underlying 'Strong Medicine', the No. 10 Policy Unit material, and 'Making Markets', which all presume multiple competing *distinct* non-combination vaccines, and do not even pay lip-service to the notion that HIV vaccines will "radically depart from any vaccines that have previously been developed." The underlying model is based on 'vaccines as usual'. It does not help to rule out from the start one of the main drivers of the problem of developing HIV vaccines.

These combination vaccines would need to be developed and tested early with systematic evaluation of the strains and antigens used. This is complicated by the fact that gender, diversity in viral strains, duration, and magnitude of the ongoing epidemic are likely to influence vaccine efficacy, making the optimum vaccine regime something of a moving target. Only a system of collaborating vaccine developers (this does *not* mean that they do not compete)–based on an intellectual property regime that allows, and indeed encourages, sharing–would allow those working on cross-cutting technologies, such as novel adjuvant development or mucosal delivery, to work with the most promising antigens so that each component of a candidate vaccine would be optimized. This is currently lacking in HIV vaccine development. Early-stage APCs would not only fail to encourage it, but, as constituted in 'Strong Medicine' and 'Making Markets', would even make it much more difficult to achieve.

The problems of therapeutic vaccines

It may be that given the safety concerns about the use of 'killed' or attenuated virus methods (ie. worries that a defective vaccine could in fact infect recipients), it may not be possible to develop vaccines that prevent infection but instead 'only' therapeutic vaccines that slow the progress of AIDS. This is further complicated by the fact that for ethical reasons the efficacy of a vaccine alone, without prevention interventions, will be unmeasured in trials; in any clinical HIV trial, vaccine efficacy will be measured by comparing incidence among those who receive maximum prevention education alone with that among those who receive both maximum prevention education and the vaccine. Monitoring the efficacy of a vaccine used on its own will have to wait till after vaccine development and the vaccine is in regular usage.

An APC would have to take into account all of the possible variations in the epidemiology and treatment of HIV, as well as the question of whether the search is for a therapeutic vaccine or a prophylactic vaccine.

The delivery of a therapeutic vaccine would be fundamentally different than for a prophylactic vaccine. For example, a therapeutic vaccine would be delivered to a population of infected individuals among mainly adults, whereas a prophylactic vaccine might be administered to all individuals at an early stage of life. The two markets would be very different.

Quite how the structure of an APC of the sort currently being advocated could possibly reward such vaccine developments is not at all obvious. Imagine trying to do some of the 'quality' adjustments–or, more to the point, trying to credibly commit to doing such adjustments–with therapeutic vaccines. Payment (and, meanwhile, the racking up of very high capital costs) could hardly be delayed to see how much delay is being achieved in the progress of HIV and the onset of AIDS in populations using 'only' therapeutic vaccines. And, what if most of the APC subsidy is used up and it becomes clear that fresh vaccines are needed because the first are not achieving enough delay? And, unlike previous vaccines, what if other treatment and health provisions would impact on effectiveness and hence the reward to developers? Should they have this extra risk added to the risks they already face? We also, again, spot the moral hazard and extra costs caused by having the same firms dependent on income from drugs for treatment, also investing in developing therapeutic products that undermine the market for such treatments.

Overlap and the Need for Expanded Focus

Even given the paucity of prototype antigens in clinical trials, there is nevertheless significant overlap in the current portfolio of HIV candidates. IAVI comments that only recently have major stakeholders started to grasp the nettle that global efforts on HIV vaccine research and development "are fragmented, lack effective collaboration and are unnecessarily duplicative."[350] The current APC literature schools itself in this outdated thinking–embodied in its underlying probability distributions. It presumes that a very large APC is the best way to encourage diversity of approaches and incentive not to overlap. However, no empirical evidence is provided that this is what in fact would happen. Indeed, given the highly cumulative and interactive nature of much HIV vaccine research, the importance of information spillovers in real-world applications (both cross-sectionally and over time), and the importance of push efforts (pharmaceutical firms stay well clear of areas of pharmaceutical research with little or no push effort going on), it would in reality be difficult to prevent private finance from concentrating in those areas of vaccine research that are *already* well covered. We saw above that research 'bunching' is an ever-present problem that APCs tend also to encourage.

Several HIV vaccine concepts are yet to enter clinical trials, due largely to the focus of the global research community on the single scientific hypothesis of cell-mediated immunity. The 'neglected HIV vaccine' concepts include:

i) Whole-inactivated vaccines;
ii) Virus-like particles;
iii) Complex vaccines including host and viral antigens;
iv) Jennerian vaccines such as the potential for SIV-HIV chimeras to serve as immunogens;
v) Bacterial delivery systems targeting mucosal compartments;
vi) Vaccines specifically designed to target dendritic and other antigen-presenting cells;
vii) Safer next generation live-attenuated vaccines.

One hypothesis might be that APCs would broaden research to cover this wider set of possible leads. But this is an illusion. Rather than it being less risky to adopt a contrary approach to others, it is in reality *more risky*[351] and it would be extremely difficult, if not impossible, to use the ex post reward structure of an APC (in place of the guiding of activity ex ante) to compensate for all the risks incurred in exploring leads in highly unexplored research space.

While it may appear that setting an ever-more expensive APC may overcome waste, overlap, secrecy, and an overly narrow focus, it is not obvious that it would. At some point, perhaps, the early-stage APC would become *so* large that research *would* be stimulated, but it would then struggle to prevent firms from following anyway the comparatively less risky routes dictated by the current research emphasis. All the failures that prevented early-stage research on the current area of maximum interest would bite just as severely, if not more so. The result would be a slower speed of vaccine discovery and weaker vaccines than would have been the case under a more collaborative approach (if the APC did not collapse first given worries of vaccine players about its size). Again, this fail-

ing raises the costs of this approach compared to others.

This obsession with one or two large players[352] also contradicts the HIV science somewhat:

> *"Given the number of vaccine immunogens and expression/delivery approaches under development and the possibility of combined vaccines,* ***there could be a considerable number of potentially efficacious vaccine candidates available for testing in clinical trials****."*[353] (emphasis added)

The only realistic way to fill out the research space is through a greatly expanded Global HIV Vaccine Enterprise. Incidentally, this would reduce the value of any pre-agreed early-stage APC that had been based on the narrower set of research leads currently being followed; the logic in the model is that if a wider field of research activity is instigated, this will reduce the value of the APC to others. This is because it will reduce the chance of any private firm already working on a particular vaccine from being the one to get the APC. So, the expansion of research activity will simply increase the risk to those private players who have sunk resources already. This serves to show, yet again, the difficulty of optimally setting APCs in an area of highly variable science and where there is also a highly variable level of public–and foundation-financed activity.

An Alternative: A High-Quality Collaborative Mechanism

> "*I also see an enormous opportunity for pushing forward the initiative to create a worldwide infrastructure–or platform–for sharing and coordinating research in AIDS, and then for encouraging the development of viable drugs. But it is generally recognised that the sums of money required involve at least a doubling of research money for AIDS*." Gordon Brown, Council on Foreign Relations, New York, December 17, 2004.

> "*People working together in interpersonal relationships that are dedicated to a goal can produce incredible, incredible things. And that's what has happened here*." Alphonso Diaz, Associate Administrator for science at the US space agency NASA, on landing on Titan, January 15, 2005.

Klausner et al. suggest a radical alternative to that of 'Strong Medicine' and 'Making Markets' for HIV, the exact workings of which have yet to be fully articulated. The solution, and the best route for developing safe, effective, and high quality HIV vaccines in the shortest possible time, is, they argue, "a high-quality collaborative research system that goes well beyond the high-quality but separate research projects that we have today." This mechanism would be based on international coordination along the lines of the Human Genome Project, a mechanism whereby many of the funders agreed on a scientific road map, voluntarily divided the work, and agreed to an evolving set of production standards. The frequent sharing of progress and of problems allowed coordination, cooperation, avoidance of unnecessary duplication, and yet internal competition.

IAVI has, for example, urged for the creation of a mechanism that enables the results of small-scale clinical trials to be ranked in head-to-head comparisons, so that resources can be focused as quickly as possible on testing the best candidates in large-scale trials. However, so far the global consensus on laboratory techniques and benchmarks needed for this has proved illusory, but it is a very high priority. Such a collaborative framework does not easily sit in the simplistic distinction between push and pull as "Roughly… the difference between funding inputs and paying for outputs."[354]

Continuous, ongoing, competition, and not competition through one point and a committee

The collaborative mechanism puts a lot of emphasis on continuous competition–rather than, supposedly, competition policed through one point in the process and one committee–and on the rewarding of 'results'; it just does not do it with a large 'pot of subsidy' at the end of the vaccine development rainbow.

This is the antithesis of the modeling of 'Strong Medicine', with its emphasis on multiple (though probably few in reality[355]) independent research leads that provide no information spillovers whatsoever to each other, and that would involve heavy secrecy and strong patents in any real-world applications. It provides none of the circularity described above, all the risk is firmly placed on firms and financial markets, and reward is courtesy of the largely discretionary behavior of the IAC. Even if there were useful information across projects, the ever-growing level of sunk

capital costs in each individual project before any probability of commercial return[356] will mean that sharing of useful information is simply too costly, since it risks wiping out any pay-back of those costs (indeed, many times over[357]). Sharing may be globally efficient, but it is privately highly inefficient.

Indeed, one notable absence in the review of push and pull mechanisms in 'Strong Medicine' is any review of the pros and cons of open collaborative research methods for advancing knowledge, though Kremer and Glennerster are fairly downbeat about them[358]. This is even more surprising–ironic even–when one discovers the heavy, implicit, reliance of the underlying modeling of Kremer and Glennerster and 'Making Markets' on 'open-source' logic, especially the lack of patents everywhere except at the end of the process and the complete free flow of information, even though 'closed-source' logic is then put back in real-world applications.

IAVI states that the solution to the many challenges:

"will require multidisciplinary involvement… and creative mechanisms linking basic research scientists with vaccine designers, in fields as diverse as structural biology, robotic crystallization, glycobiology and large-scale non-human primate testing (and) flexibility to move resources among the elements as emerging priorities warrant; and creative intellectual property agreements to provide incentives for data sharing and cooperative research."[359] (emphasis added).

Early-stage APCs of the sort suggested in 'Strong Medicine' and 'Making Markets' have little to offer to this. In the case of HIV at least, the relevant yardstick for comparison with the cost-effectiveness of early-stage APCs would be the Global HIV Vaccine Enterprise that we are told will "serve as a forum for the best vaccine concepts and candidates to be prioritized, regardless of where they originate."[360]

Interestingly, the Bill and Melinda Gates Foundation is *also* spending resources looking into these more open collaborative frameworks, with the announcement last year of a Global Vaccine Enterprise[361]. The G8[362] and the Bush Administration[363] have also endorsed the approach, the latter describing it as "analogous to the successful alliance and strategic plan that characterized the approach to the human genome project". We explore the components of such an approach in Part 5.

5. Collaborative Global HIV Vaccine Enterprise: Four Interlocking Components

This section is here largely on the insistence of others, who rightly suggest that it is one thing to critique[364], quite another to create. This is the most tentative and exploratory section in this paper. Others will have better–and more–ways to put the pieces of the puzzle together.

"Development of effective HIV-1 vaccines requires global cooperative research in basic science, clinical applied sciences, and large-scale efficacy trials." Gilbert, P.B., and Eparza, J.[365]

"*The Enterprise proposes to coordinate efforts at a global level, facilitate use of common tools and technologies, and help ensure access to optimized resources. Furthermore, the Enterprise approach is a way of behaving as a global community of problem-solvers, more openly sharing information… Confronting major roadblocks and harnessing these new opportunities requires an effort of a magnitude, intensity, and design without precedent in biomedical research, with the Human Genome Project as a potentially useful model.*" The Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise.[366]

"*It is of course possible for people to believe sincerely that society's arrangements for funding medical R&D are all wrong, and that instead of competition between firms, we should have collaboration; instead of patents, we should have open access; instead of making consumers pay for R&D through the purchase price, governments should fund R&D directly; and that instead of lending from private capital markets, governments should exploit their lower cost of capital to fund investments.*" Berndt, E.R., writing on behalf of the Center for Global Development, 17 December 2004.

In their current cloak of strong patents, secrecy, and go-it-alone projects, 'Strong Medicine' and 'Making Markets' set up an unnecessarily confrontational stand-off with those who argue for more open

collaborative approaches, and even encourages some to suggest that the approaches should necessarily compete. Instead, the most powerful setting for a purchase commitment for a complicated vaccine like HIV is likely to be as a fairly late part of a much larger package of measures (or, in a collaborative setting, possibly relating to intermediate stage goals), and therefore comprising a relatively small proportion of the overall package's cost. Information revealed by earlier open, collaborative, mechanisms would be used to set the terms of the purchase commitments, the overall size of which would not be set in advance.

Purchase commitments would not be multi-billion dollar pre-determined pots of money to supposedly pay for large proportions of the *whole* R&D process (or even very much of it), giving all the IP to one or two large pharmaceutical firms at the end, but would be relatively much smaller, carefully-targeted pots, with the emphasis of public funding placed on the collaborative aspects of the process and much more public ownership of the eventual IP and know-how. The real issue is how the one mechanism feeds into the other and *not* how they might compete.

Since the underlying approach of 'Strong Medicine' rules out collaborative issues of any sort, it should not surprise us that we encounter some awkward problems making this collaborative framework work for something as complicated as an HIV vaccine. A combination of challenges leads us towards a solution with at least four *interlocking* components. Each is necessary. To have one without the others is, in most cases, worse than not having it at all. Readers' views on the following are especially welcome (this is, after all, a largely exploratory section):

Fresh Approaches to Vaccine IP

One of the reasons cooperation is currently lacking in HIV vaccine development is precisely because we do not have creative intellectual property agreements that enable open communication, and vaccine development paths that combine access to reagents, platforms, and technologies of potential commercial interest owned by different entities. This calls for some fresh approaches to IP, but this *must* be in *advance* of any permanently fixed contracts.

As a few simple examples, this might involve[367]:

i) Pooling of complimentary patents[368] common to all potential vaccine developers and the freedom for all potential developers to use them;
ii) More use of, and development of, open-source type licensing agreements;
iii) More use of liability rules, such that the use of small scale improvements could be made for vaccine purposes without needing agreement beforehand, and a mechanism (even just involving credits) to later repay if the IP proved useful;
iv) New ways in which the IP can be designed to more easily allow firms to acquire technology that might 'undermine' those firms experiencing, and creating, replacement effects (ie. the effect when pharmaceutical firms are less able to work on products, such as HIV vaccines, because they run the risk of replacing markets for other products, such as AIDS treatments[369], or when firms hold back from investigating multiple leads since each new lead imposes a negative externality on every current lead);
v) IP to foster competition, especially at the manufacturing stage;
vi) Less IP attached to the final vaccine and to the know-how of the final vaccine. We have found many reasons to doubt that the post development vaccine price could contain large portions of the cost of R&D without it continuing to cause a range of problems–from dynamic inconsistency to problems with eligible and non-eligible countries. Neither is it clear that developers themselves would want to bear the reputational risk of 'winning' the results of a highly collaborative global effort and face a legacy of pricing controversies in non-eligible countries, all of whom had paid heavily towards that global effort. It must surely be possible to design the IP and other features of the mechanism such that both developers and participants in the Global HIV Vaccine Enterprise are rewarded for their efforts. The paradox might be that long-term IP rights to HIV vaccines are quite the opposite of what developers operating under such a mechanism would want.

Incidentally, many of these approaches to IP are designed to reduce risk, and hence capital costs, in a collaborative setting. One of the few 'benefits' of the currently very low (compared to what is needed) levels of funding for HIV and malaria research is the op-

portunity to think through changes in vaccine IP regimes. It is easier to make changes now rather than later when any APC is in place and litigation and a raft of other issues would become much more intense. Pushing for large, early-stage APCs risks closing the door on this opportunity.

Novel Financial Tools: with the Type of IP, Finance, and Collaborative Process Inter-Related

In the HIV science described above, collaboration does not just end when vaccine research leads are released to pharmaceutical firm trials. Collaboration extends to the very end of the process, and, indeed, back to those working on earlier parts of the process elsewhere, with information provided late in the pursuit of one potential vaccine lead being fed to those working on earlier parts of the development of other potential vaccine leads elsewhere to help them adapt and improve. There is, however, a fundamental problem in using equity-based finance and allowing the build up of large sunk costs in order to fund such collaborative, highly cumulative, backwards-and-forwards iterative activity[370].

Part of the deal for those drawn into late-stage collaborative vaccine trials would involve sharing confidential information–well before a product is even near to being ready–for translational studies aimed at optimizing, combining, and comparing candidate vaccines with process development studies to concentrate on making sure that the leading candidates are developed. But this could mean that the successful vaccine will not be the one being worked on by a firm or will be a combination vaccine not including the firm's vaccine in its formulation, precisely because of some information the firm revealed during this collaborative process. Indeed, the incentive not to truthfully share both good and bad information in ways that risk undermining one's own research will rise as the sunk capital costs rise (ie. approaching ever-later stages of the process). Late stage trials are already very risky; they are even more so if individual firms are expected to 'give away' information in this way.

The sunk cost–information conflict

We face a conflict, with forces pulling in varying directions. For the sorts of activity connected to 'openness' and 'sharing', we would like finance to be such that risk is passed on to the sponsor and away from the company or whoever is carrying out the research. We may wish to 'insure' firms–in the shape of access to debt-like instruments and up-front sources of finance–when they engage in such acts. Indeed, we might like them *not* to use 100% equity finance–and hence to not fully be paid via an APC based totally on equity finance. However, insuring large pharmaceutical firms against risks will conflict with the fact that equity finance is central to the incentive structure of large pharmaceutical firms[371].

For those parts of activities that are of a less collaborative nature and where incentives to put in 'high effort' are important–for example achieving a certain 'quality' of trials and in reaching certain other benchmarks–we would like finance to be more equity-like, placing risk on the firm or whoever is carrying out the R&D. If, for example, collaboration becomes less important very close to the end of the development process, finance would, ceteris paribus, also become more equity-like, more like that being presumed from the start in 'Strong Medicine'. However, these tradeoffs are also affected by the level of built-up sunk costs and capital costs, suggesting there should be more 'insurance' even late in the process, when sharing and collaboration is important. It should be recognized that there is this fundamental, and difficult to calculate, tradeoff for HIV vaccine research right to the very end of vaccine development. One consequence is that both 'push' and 'pull' are likely going to be present to the very end of the process, and no pure pull mechanism of the sort presented so far (on the notion that pull 'takes over') is likely to be calculate-able in advance.

Much of the self-fulfilling 'quality' crowding out described above is driven by stock markets denying resources to those trying to work on higher-quality, or indeed 'different' research leads because, in a completely un-collaborative setting, it is too 'risky' to do so. In the collaborative framework, this guidance over quality ex ante means much more control over large pharmaceutical companies–especially at intermediate stages–than stock market finance would tolerate. Yet while this guidance imposes risks on individual developers, it reduces collective risk and improves the collective outcome[372], and it should be possible to coordinate in ways to share this gain. This is ultimately good for equity investors too.

More directly feeding finance to biotechs, not-for-profits, etc.
Another component of the finance mechanism involves more directly feeding finance to small biotechs, not-for-profits, and others so that they can take projects further. These already struggle to attract finance, and the APCs in 'Strong Medicine' are much less likely to improve this situation given their bias towards large pharmaceutical firms. In chapter 12 of Farlow 2004 the importance of venture capital and the way in which many firms and researchers are literally 'strapped for cash' is explained in much more detail. These firms are not helped at all by a mechanism that forces them to rely on a long track record of free cash-flow and 'deep pockets' finance.

It is not clear whether curious layers of venture capital could not somehow be created from some of the front-loaded funds, and a mechanism created for *all* potential developers to compete for these 'pots' of front-loaded funds on the basis of a track-record of vaccine performance and reputation for cooperation developed over time inside the vaccine enterprise framework. The record for this could be generated by the collaborative part of the process, and rewards could be linked to performance on pre-agreed criteria, including trials. This could involve a role for financial options, allowing these non-big pharmaceutical researchers and developers to trade part of the expected future rewards. As part of this, it is also not clear to what extent 'success' in a collaborative setting should *only* be judged on the basis of the end vaccine, since this is the very reason for the heavy dependence on free cash-flow and equity finance in the first place–and the build up of levels of sunk capital costs.

Curiously perhaps, in collaborative settings, these novel financial instruments are *needed* to support the market-creating purchase contracts at the end of the process. However, it can be seen that the exact proportion of equity finance could *not* be set in advance–which is another way of suggesting that the size of APCs could *not* be set in advance either. 'Strong Medicine' and 'Making Markets' implicitly presume that the proportion of equity finance could be set in advance, but this is not surprising given that the approach presumes away all collaborative features to the underlying science, replacing them with no build up in sunk costs, no information sharing, and all trial leads treated as totally independent drawings from a pool of potential leads. A finance mechanism build around a model that has been radically simplified to fit that mechanism is not that likely to suit real-world HIV, malaria, and tuberculosis vaccine R&D problems.

An Open Collaborative Information Processing Mechanism Linked to IP and the Financial Mechanism

The underlying principle is to create competition between a set of vaccine 'enterprises'–maybe one per region globally as suggested in the G8 and Whitehouse announcement in 2004–but legally *enforce* regular updating of information, and use IP and financial instruments to control the process and reward both effort and sharing. This is the part of the mechanism that draws heavily off the experience of the human genome project.

There is a big difference, however, between developing vaccines and releasing gene sequence data. In the case of vaccine development, there are potentially very large sunk costs both for trials and manufacturing but also in the shape of capital costs, before anything vaguely like a result can be posted. Meanwhile, information is being posted that can undermine the value of that investment. If anything, this makes matters even more challenging, and it also needs the other three components to work.

The 'open' collaborative part enables strategic decisions about where to expand research leads and also what quality of research leads to pass on to those working at later stages, and how much to 'insure' and how much to incentivize. This helps expand out the focus and reduce the overlap discussed above. Paradoxically, it is precisely the lack of collaborative thinking that is encouraged by 'Strong Medicine' that has held back the creation of a global consensus on laboratory techniques, benchmarks, and mechanisms. These would enable the results of small-scale clinical trials to be ranked in head-to-head comparisons, so that resources can be focused as quickly as possible on testing the best candidates in large-scale trials. We saw many times above that the notion of 'controlling' through expectations of a committee's behavior at a point late in the process simply does not work.

Expanded highly transparent clinical and preclinical trials

An important part of this iterative, adaptive, research process would be an expanded, integrated, interna-

tional preclinical and clinical trials system, with considerable transparency of information–of preclinical and trial results–among vaccine developers and regulatory bodies in a large number of regions or countries. Instead of emphasizing just those with free cash flow (regardless of their vaccine expertise) the collaborative enterprise would include full participation of all relevant parties, including those in developing countries.

Again, this is antithetical to the approach of 'Strong Medicine' and 'Making Markets', with their emphasis on decentralized, uncoordinated clinical trial and laboratory evaluation systems based on the notion that each (generally large pharmaceutical) firm already has internally *all* the information it needs. We nevertheless saw that in real-world applications of APCs there would already supposedly be much of this information being gathered about private firms and that there would also be a great deal of centralization of the public research process anyway, but none of it being shared or used in a collaborative way (in fact this would have to be ruled out from the start).

The need for trust in trials

There is also a range of issues relating to 'trust' in vaccines, and the general suspicion there may be concerning the motives of pharmaceutical companies and the use of inferior products on the poor. Any international trials program will be utterly dependent on the trust of developing countries. Given the ongoing controversies over clinical studies for nevirapine[373] and other controversies, the notion of secrecy of ongoing results (at the core of the model of 'competing HIV vaccines') would be simply unacceptable in the case of HIV vaccine trials and beyond.

Nobody has really explored the way the current system of vaccine research (especially for complicated, composite, therapeutic vaccines) undermines itself by it's own secrecy. There are obvious tensions between openness and proprietary information, yet at another level, the sharing of information, if strictly enforced, can mitigate some of these risks. Pharmaceutical firms, in particular, would gain nothing from taking a reputational and financial hit across their entire portfolio of products from keeping poor vaccines on the market.

Harmonized regulation

Key to many of the practical cases above were high standards of drug and vaccine regulation and quality control in emerging economies. There is a strong need to harmonize the regulatory procedures of all countries so that the same application can be submitted in most if not all countries, for example in Africa. The danger of complicated and different systems is that those applying for registration will choose to do so in other 'easier' markets first.

The special challenges of therapeutic vaccines

In the case of HIV, these are aggravated further by the realization that we may not (at least initially, but maybe ever) be looking for a preventative vaccine, but instead a therapeutic vaccine that 'only' delays the onset of AIDS. This may still be valuable. Since the rate of HIV progression is linked to the viral load in a person's blood and secretions, if vaccine-elicited immune protection can be achieved against disease progression, it may also slow the rate of HIV transmission in a population. However, it complicates the process of evaluating the success of a vaccine, since, unlike a 'standard' vaccine, detecting signs of prevention are replaced as markers of success by the much more long-term therapeutic effect (incidentally, how does an APC, or indeed prize, allocate itself over multiple developers in such an environment?). 'Ongoing results' on the health of those who have taken therapeutic vaccines should, and would, be very openly monitored for many years even after vaccines are released, something never experienced in quite the same fashion with previous vaccines.

This suggests that ways need to be found to encourage competition even as information on ongoing results is openly available, and that not *all* competition (and reward) should hang on the end vaccine itself as the APC and other models presume. For example, we discussed above the very real dangers (to developers) of therapeutic vaccines being replaced over time. Common knowledge that all are being transparent might, paradoxically, help some form of compensation linked to information revelation to help ease this particular problem.

Ethical issues

This is also complicated by a range of ethical issues surrounding vaccine trials–thus raising the issue of developing country willingness to take part in trials and to use vaccines–and by the need to mix vaccine with non-vaccine approaches and to continue major preventative and treatment initiatives long after, and

indeed in coordination with, vaccine development. This is summarized well by Choi and Letvin, and is worth repeating in full:

> *"Vaccines to prevent infections by other infectious agents have been evaluated in populations in the developed world and then used worldwide to eradicate a microbe. The testing of HIV vaccine candidates poses an unprecedented problem in this regard. The population at risk of HIV infection, and therefore the populations in which an HIV vaccine can be most readily assessed for efficacy, are in the developing world. If an HIV vaccine prevents overt disease but does not prevent infection from occurring, a highly sophisticated evaluation of vaccines will be required in any large-scale studies of vaccine efficacy. However, the infrastructure that will be needed to monitor such vaccine efficacy does not exist in these geographic regions. Therefore, the testing of HIV vaccine approaches in at-risk human populations presents a challenge to the medical and scientific community."*[374]

The analysis (contained in Appendix 3, and earlier sub-notes) underlying the modeling of APCs for HIV vaccines, presumes that there will be multiple independent competing vaccines, that information can be kept totally private (even though it is derived supposedly in secrecy and used by the IAC to make decisions), that collaboration (and the problems this creates for contracts and ownership) can be ignored, that efficacy results can be ascertained in real time (in order to arrange payments), and that risks caused by lack of monitoring and other infrastructure can also be ignored. Therapeutic vaccines as complicated as those for HIV do not fit this model at all well (indeed, the modeling makes no concession to the difficulties of HIV vaccines as compared to, say, flu vaccines). It is not at all obvious that an ever-bigger APC, with ever more gyrations to get around the paucity of information it would come to rely upon, with risk shifted heavily to private industry, would automatically crack such a complicated challenge. But this is the basic solution put forward in 'Strong Medicine' and underlying 'Making Markets'.

A more creative use of industry

The emphasis of 'Strong Medicine' is on the power of stock markets to discipline private firms. Yet Klausner et al. claim that the costs of developing new vaccine candidates, especially protein-based immunogens or noninfectious particles, and the scientific risk of failure are so high, that "reliance on industry to carry the major load for discovery and development for HIV vaccines is unrealistic". They call for "creative new public and public-private partnerships… with industry's development expertise a key element that must be marshaled effectively."[375] In particular, the lack of manufacturing capacity and of the uniformity in production facilities needed to produce vaccines to the standards needed for human clinical testing, has repeatedly delayed HIV vaccine clinical trials programs. This calls for the creation of dedicated manufacturing facilities and personnel devoted to the development, scale-up, formulation, stability, safety, toxicology, and production of experimental HIV vaccines. The skills for this are largely, but not exclusively, found in the private sector.

The importance of such manufacturing infrastructure is even more important given that the major focus of HIV vaccine development has shifted away from large pharmaceutical firms to small biotechnology companies, or nonprofit or academic organizations, which have little or no vaccine manufacturing capabilities and experience. APCs are not the most creative or efficient way to activate this, and we have seen that they tend to concentrate resources into a few reluctant hands rather than broaden the financial base. Why seek to concentrate the manufacturing infrastructure in the hands of those less likely to hold vaccine development projects in the first place, to the determinant of those who do?

The collaborative approach is very strongly in favor of a role for commercial players, but is much more creative about it than 'Strong Medicine' and 'Making Markets'. It is much more mindful of the need to handle the risks through contracts that allow an element of risk sharing, as well as the need to consider access to finance for the different players. Unlike the models of 'Strong Medicine', where all the risk is placed on the developer for all stages–here the risk is distributed in part (maybe even largely) away from firms.

More competition, but not all via a committee at the end

For all the talk of competition, systems based on early-stage APCs rely on a committee, the IAC, to enforce competition in the R&D process. This is very different from typical competitive tenders. The IAC seeks to achieve competition before it gets to act, but based on

the expected rules and/or discretion that it exercises in the end product 'market' (and only in the end product market) when it does act. That it would be a 'competitive system' for HIV is a dubious claim–no more than a caricature.

In contrast, there is plenty of room for competition in a collaborative mechanism as the human genome project proved, with opportunities for competition at multiple stages of the R&D process as well as, possibly even more so, in the end market where technology transfer is central to increasing competition and the driving down of manufacturing costs. In collaborative systems, competition is able to be in *real time*, at all stages including the competitive manufacturing tenders at the end. This, it is argued, is crucial for the success of cheap vaccines. It is false to dichotomize one mechanism as driven by competition–when it clearly is a very curious sort of competition and open to capture by special interests–while characterizing the other as weak and feeble because of 'lack of competition'.

Leading proponents of APCs for HIV constantly brush over the fact that the IAC, a committee, is *the* source of all competition, but then fail to give a convincing explanation as to how the IAC would perform such a function and/or not be captured. It is generally a bad principle–less robust to institutional, cultural, and practical failure–to concentrate the driving force for competition down to one point, institutionally and temporally, rather than trying to create competition at many layers and from many sources over time. This latter notion is much more capable of being a part of a Global HIV Vaccine Enterprise than of an APC.

Let's stop the caricature

The frequent distinction between push as referring to inputs and pull as referring to outputs is, in many ways, an unhelpful (though deliberate) caricature. The notion that collaborative mechanisms are not based on results or competition is stretching things: "It is of course possible for people to believe sincerely that society's arrangements for funding medical R&D are all wrong, and that *instead* of competition between firms, we should have collaboration… " (italics added)[376]. The point about a collaborative approach along the lines of the human genome is that there *is ongoing* competition between many more players, with evaluation and funding chances ongoing, rather than the much more limited competition between a few wealthy players driven by the potential vagaries of the decision of a committee at the very end of the whole process, based on a grand set of ex ante heroic assumptions.

How much private industry?

There is insufficient time here to discuss the degree to which the public or private sector might provide the skills needed to get products through the last sections of development; others are much better qualified to say. The general argument given in favor of the private sector taking over the last stages of vaccine development is that the private sector–essentially via the stock market–is more capable of incentivizing good over bad outcomes[377]. But there are other angles to this. One possibility is that equity finance is simply more appropriate for some activities over others, and equity finance is more amenable to private sector provision. Another possibility, however, is that it is much easier to 'rent seek' in later stages than it is in earlier stages. We also know that the early-stage activity is often very risky indeed, and that it is quite likely that private firms cannot internalize sufficient benefit to make this worthwhile.

One problem of feeding all late stage activity through private firms is that the development and regulatory approval of drugs and vaccines for the poor has to compete for the limited pool of skills with the development and regulatory clearance of drugs and vaccines for the rich:

> *"In effect the private sector, being the only source of the skills needed for the last section of the development pipeline, endows powerful (private sector) monopoly in its own right… The skills monopoly over the last section of the developmental pipeline therefore puts the private sector in a strong position to demand exclusive rights over any products that are developed. Is this an efficient way of stimulating the necessary R&D? It is an expensive matter to develop and license a vaccine product, but how expensive exactly? How can it be known whether the monopoly rights granted wildly over-reward the private sector for their contribution, or whether they simply make a viable return on the resources they have invested? Typically, it cannot be known as these costs are treated as confidential but it is now an open question… How much reward is provided for how much input?"* Christophopher Garrison[378].

Given the reluctance of the private sector to take forward candidate vaccines, an alternative sees the missing developmental pipeline skills bought in from organizations other than multinational pharmaceutical firms, or by the creation of a whole new entity such as a 'National Vaccine Authority'. Some have argued that the development of such an authority is long overdue[379]. From the perspective of the discussion here, the key issue is that there would be no point setting up an APC for HIV and then expending yet more resources on setting up such an authority, since it would either just crowd the APC out (by expanding, it harms the prospects of private industry 'winning' the APC, hence private incentives are harmed even for an APC of a given size) or (if the APC was failing) it would have to struggle to avoid the APC harming the ability of the vaccine authority to function. Clearly, deciding for or against a 'National Vaccine Authority' is not something that can be separated from the decision whether or not to go with an APC.

'Contingent Purchase Commitment' Contracts, With Much More Emphasis on Production and Distribution

The fourth component of the mechanism draws off recent 'pull'-work and seeks to incorporate this with the three components described above. But there would be a great deal more emphasis on the very real practical problems of ensuring vaccine delivery. It is crucial to realize that the contracts about to be described would be highly inefficient without the other three components. This is pertinent in light of the current GSK malaria case, which looks to be generating purchase commitments that break from the 'Strong Medicine' mold, but without any of the supporting components described above.

More like standard procurement contracts

Unlike the APCs in the 'Making Markets' and 'Strong Medicine' literature, the contracts set up to pay for 'results' would look much more like standard competitive procurement contracts, and may not (and probably would not) involve full equity-based finance. Since a lot of the overall R&D costs would not be covered by the contracts anyway, nowhere near as much would be extracted through vaccine prices to pay for R&D, and vaccine prices would be much nearer to average manufacturing costs to start with. It would be impossible to set the terms of these much smaller purchase commitments on the basis of the information available at the very start of the process as suggested in 'Strong Medicine' and 'Making Markets', but they could be set up in advance to be *contingent* on information as and when it is revealed. For lack of better terminology, we may call these *contingent purchase commitments*.

Variable equity finance and more control over IP

By being more contingent and variable until the terms are set, and yet much more like standard procurement contracts once the terms are set, these contracts enable the collaborative part of the process to vary the quality and number of vaccine leads being pursued by late-stage manufacturers. Yet it does so without harming those already working on late-stage leads and without increasing the risk of such developers further. This allows the proportion of activity covered by equity finance to vary.

Intuitively, it is impossible to know in advance what proportion is to be insured (collaboration) and what proportion is to be incentivized (by equity), and it all has to be adjusted to adapt to the credit conditions of those involved in the process. Risk, and hence payoff, are related to things researchers and developers have control over–such as *quality* of vaccine work and trials–and hence can be motivated on. In diametric opposition to the 'Strong Medicine' approach, quality would not be controlled entirely through payments at the end of the research process, but *during* the process, via the open collaborative part of the mechanism.

This would solve many of the problems listed above. There would be more guidance on the quality of vaccines, much less of a role for an IAC presetting conditions and the size of pots of funds years in advance based on heroic assumptions (even as it tries to avoid being captured by special interests), fewer APC institutions and pre-determined rules, more control over the eventual intellectual property, products priced pretty close to marginal production costs, and with faster release to mass competitive generic producers to drive manufacturing and delivery costs down.

The problem with large early-stage vaccine APCs is that because so much of the overall R&D is *still* being extracted in the final vaccine prices (we saw above how the logic requires that the payments rewarded to each 'winning' firm be *hugely* disproportionate to its

own costs) this starts to drive all kinds of distortions, not just on quality but also on information gathering, sharing, strategic use of patents, capture of the IAC, etc. Obviously, as the recovery of R&D expenditure shifts away from the end of the process to earlier stages in the process, this weakens some of the incentive effect of the pull (though we argued it was weak for HIV anyway, and there are plenty of ways that one can make up for this), but the amount brought forward is offset by gains. Again, this suggests a mechanism for locating the optimal point at which to switch from front-loading to end-loading, and certainly *not* that it should all be end-loaded.

The biggest gain is in quality

Probably the biggest gain is in the quality of vaccines. With less R&D extracted through end prices, this removes a great deal of the pressures described above and elsewhere[380] to dash for poor quality to get the 'big early prize' and–in a self-reinforcing fashion–it *helps* those guiding quality of vaccines in the collaborative part of the process.

Because they are less dependent on their exact terms being fixed at the start of the process, 'contingent purchase commitments' could be designed to adapt to intellectual property regimes that allow for much more sharing of information. The late-stage issues would be of a much lower order anyway, if there were less sunk expenditure to recover through vaccine prices.

Collaborative earlier mechanisms, by reducing the severity of many of these late-stage problems, might actually help the efficiency of 'contingent purchase commitments'. The exact workings of the Global HIV Vaccine Enterprise have yet to be finalized, but could easily incorporate some forms of late-stage, contingent, purchase commitments.

Flexible, but less of a problem with credibility than APCs

It might be argued that this lack of pre-determined size makes these contracts less 'credible' than those described in 'Strong Medicine' and 'Making Markets', but we already found that, in reality, this was a major problem with the APCs described in this literature. Any individual developer working under *that* mechanism faces layers of discretionary decision makers due to the heroic informational assumptions that would have to be made at the start. They would also be exposed to a great deal of uncertainty about what they would get from the mechanism (and this all shows up in the level of capital costs). In the 'Strong Medicine' mechanism, the fixity of the size of the APC at the start comes at a very heavy cost. We argue that this shortcoming is less of a problem anyway if the other components described above are also present.

Another way to think about this, is that if up to $10bn[381] is to be made available for tackling each of the more difficult vaccines, how exactly should that level of funding be split between the purchase commitments and other parts of the process? Since this cannot be known in advance, we either have to plump for a fixed split along the lines of 'Strong Medicine' and adjust afterwards through discretion, or face the reality of our ignorance and have a flexible split from the start, adapting other parts of the funding framework to this. 'Contingent purchase commitments' just bite this bullet from the start.

It is also central to the efficient working of the 'Strong Medicine' mechanism that the 'pot' of subsidy available for those who win APCs is large and *fixed* at the start (though in the details of the framework it is not fixed for any particular developer, and–indeed–the layers of uncertainty, discretion, and risk mean that the overall *expected* size is not effectively fixed anyway). Supposedly, the laws of motion push in the direction of the optimal number of firms working on research leads *given the size of the pot* of subsidy, with the optimum number of firms chosen via choice of the size of the pot (we saw that this would not be the case anyway if there were just a few large pharmaceutical firms, much hidden information, and a general inability to 'know' all HIV science for all time). It follows that it should not be possible under any circumstances for policymakers to alter the size of the pot after the mechanism has started to operate (in practice, this seems to have been interpreted as not lowering the size, though it actually also should mean not raising it at a rate higher than the rate of interest), and that firms form their optimal strategies on the basis of their expectations of the strategies of other firms, and never of the holder of the 'pot'. A couple of significant observations follow from this.

A mechanism more able to work out optimality

First, that in a world of a great deal of hidden activity and opaque use of other research support devices,

firms operating under the free-for-all 'Strong Medicine' and 'Making Markets' mechanism would struggle anyway to know how optimal their own intensity of activity truly was (it is anyway more likely that the mechanism would end up based on a few large pharmaceutical firms, which is decidedly non-optimal). Perfect competition and perfect information–and therefore no need to ever 'share' information–and perfect application of the mechanism always and everywhere, resolve this in 'Strong Medicine' and 'Making Markets', so that there is no risk to players *from the mechanism itself*. But it is hardly satisfactory to assume the problem entirely away by such extreme assumptions.

In reality, linking payments to the performance of the *whole APC mechanism* imposes a great deal of risk on developers, risk that does little to motivate them and is costly for them to handle (it shows up in the required size of the fund). Basing contracts on achieving a certain 'performance' may be more efficient than basing contracts, *per se*, on the end vaccine and the *relative behaviors of others*. Part of the purpose for making the 'contingent purchase commitments' more like standard procurement contracts is to remove this 'mechanism risk'.

Rather than an elaborate set of assumptions and the perfect application of an idealized–though essentially low-tech vaccine model–to high-tech vaccine problems, instead collaboration and sharing of information are used to achieve the right intensity of activity. But this does not sit well in the 'Making Markets' framework. Paradoxically, we saw that that framework did involve huge amounts of monitoring of 'intensity' and that it would struggle to do this against a background of complete non-collaboration. At least here the monitoring is working *with* the collaboration.

More flexibility to allow expansion and adjustment of collaboration

Second, once we shift attention to the collaborative mechanism, we realize that since we do not really know in advance how the collaborative part of the process will evolve, firms cannot therefore know in the aggregate how much of the overall 'pot' will be used in the non-collaborative part of the process and how much of it they collectively will be picking up in purchase commitments. Therefore, if they face 'Strong Medicine'-styled APCs, they cannot individually know how much R&D they should be doing to try and win an APC (though, at least, the sharing of information helps this problem).

In addition, once there is any control by those 'running' the collaborative mechanism over the research leads being followed, then the value of contracts for research leads is dependent on the other contracts so far given out or expected to be given out. When accepting a contract, a firm is aware that the contract-giver can 'harm' the value of the contract they have been given through giving out more contracts. But this creates a fundamental problem if there is a flexible need to increase or decrease the number of contracts or to re-target activity. One cannot re-target or ramp up activity without harming those already engaged in activity. The assumption of perfect competition amongst large numbers of vaccine players removes this risk in 'Strong Medicine', but this is totally at variance with the reality.

A practical example

As a very practical example, if an APC is set up on the basis of the current narrow focus of research leads for an HIV vaccine, how should it be set? How do private firms react if the collaborative mechanism expands (as it may well do if it ever has the appropriate level of resources) into the areas of neglected leads, including even funding some of the trials itself? This risks destroying the value of the currently-set APC based on the currently-active non-neglected leads. Firms could have one of two responses. Engage in research and sue whenever the value of that research is undermined. Or, expecting this anyway and not wanting the bad press, do not engage in research in the first place.

Or would the APC be set up on the basis of the expected future expansion of the focus of the Global HIV Vaccine Enterprise into these areas of neglected leads? If so, it ends up being set at a level that is totally wrong for the current limited focus.

The upshot to all this is that it proves impossible to set payoffs for the APC as part of the overall collaborative mechanism that would not in some sense have to be *absolute* through contracts that are much more like standard procurement contracts. Bluntly, it is impossible to handle, in the ex ante terms of an APC, the sort of scientific uncertainty generated by conditions such as HIV (or malaria or tuberculosis) or uncertainty

about where the collaborative mechanism will evolve over time to tackle it.

The cost of HIV vaccine distribution is likely to be high: The need for 'Advance Distribution commitments'

The total cost of all six EPI antigens is $1, but the delivery costs in Africa are $12[382]: "Thus financing vaccine distribution may be as important as, or more important than, financing vaccine purchases."[383] Yet 'Making Markets' spends no time worrying about the distribution issues. These are likely to bite much more for HIV vaccines, that will not, at first, be delivered to infants and children, the target of most current vaccination programs. It will not therefore be possible to use the existing vaccine distribution infrastructure. The initial targets will be high-risk groups–commercial sex workers, truck drivers, adolescents–for which there are currently few such distribution and monitoring mechanisms in place.

To this we might add that the greatest current need is in countries that have the lowest levels of infrastructure and the highest opportunity costs already (the opportunity cost is high where, for example, there are very few nurses per head and many other healthcare demands already). This lack of pre-existing infrastructure and the fact that many high-risk categories of potential recipients of a vaccine are much less likely to be amenable to tracking and multiple dose treatments, is yet another reason why multiple doses for an HIV vaccine may be less useful than a single dose vaccine, and is another reason why vaccine developers are put off from investing for such markets. Rather than putting all the emphasis on large payments to pay for a long process of R&D, precommitted payments should go into an 'Advance Distribution' mechanism, something that will benefit all investors into vaccine R&D–public and foundation as well as private.

As a reminder, these contracts become inefficient without the other three interlocking components.

The Real Challenge

There is a tendency in the current debate on this issue to visualize the solution as one pure system. In truth *all* mechanisms are highly imperfect. The best policy in such circumstances is to try to exploit various tools for different parts of the process up to the point at which each tool has a marginal impact on the problem equal to every other tool. The real challenge is to work out how each part of this larger mechanism creates and handles information and risk, and how different parts fit together to reduce overall risks and costs (including, and even especially, capital costs), to speed up discovery and generate high-quality vaccines. This would include working out the exact point at which a 'contingent purchase commitment' might optimally cut in.

We can only hope that these much more innovative possibilities are not simply drowned in a sea of large, yet ineffectual, early-stage APCs, or indeed a pond of inadequately-sized and ineffectual APCs that give just enough water for politicians to sale their boats, but such that the distraction stops them from taking action on the really important initiatives.

6. Malaria Vaccines in the Context of a Global Vaccine Enterprise

The Problems of Malaria Vaccines

We know that "*the parasites that cause malaria are much more complex than the viruses and bacteria that heretofore have been controlled by vaccination*[384]". This is picked up in the multistage lifecycle of the parasite, which generates a number of challenges for malaria vaccine research:

i) Frequently, the proteins expressed by each of these lifecycle stages are antigenically distinct. For example, if a vaccine manages to achieve high levels of antisporozoit antibodies (to defend against the sporozoits inoculated into humans by the Anopheles mosquito), these antibodies generally do not recognize the asexual erthrocytic stages that follow;
ii) For many of these genes-proteins, there is multiple allelic or antigenic variation. A single individual can be infected simultaneously with at least eight different strains all varying at critical T–and B-cell epitopes;
iii) This is further complicated by extensive within-strain antigenic variation.

In summary:

"Stage-specific expressions of proteins, the presence of multiple antigenically distinct strains in nature, and within-strain antigenic variation are critical to the parasite's survival, are unfavourable to the host, and greatly complicate the challenge for vaccine developers."[385]

This is all compounded too by the complexity of the human immune response. Unlike HIV, for which "*natural immunity does not appear to have a strong impact on the final outcome of HIV infection*"[386], this not the case for malaria. The human immune response in the case of malaria is a function of the human host genetics, transmission dynamics of the parasite, and even the age of the host. For example, in areas where transmission is most intense, infants are the most at risk of developing severe and fatal malaria. In areas of less intense transmission, it is older children who are most at risk. Similarly, the age of first exposure to parasites (or a vaccine when available) plays a heavy role in the subsequent immune response. Non-immune adults are more susceptible to developing severe disease after a first infection than non-immune children, yet adults acquire immunity faster than children:

"For a vaccine to be optimally effective, it must elicit the appropriate protective responses and sustain those immune responses over time, either due to vaccine administration or due to boosting by exposure to parasite… Much progress has been made, but no vaccine delivery system has been shown to be optimal or adequate."[387]

This suggests that the optimal vaccine will vary over time as the rate of transmission changes (eg. as malaria is eradicated from a given population and the levels of natural immunity vary across the age profile) and that different vaccines will be needed. If incentives are not to be distorted, this will require the complicated and precise disbursement of any 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.

The GSK Case

"*It could easily take a decade to develop malaria, tuberculosis, or HIV vaccines."*
Michael Kremer and Rachel Glennerster[388]

"The recent breakthrough which for the first time gives us a vaccination to prevent malaria that could be ready in three to four years time is a revolution in our time."
Gordon Brown, October 2004[389]

"Who has been briefing Mr Brown… ?"
Michel Pletschette, European Commission Directorate General for Research, 25 November *2004*[390]

There was a recent announcement that some sort of APC agreement was being struck to help GSK take forward a 'promising' malaria vaccine candidate[391]. In spite of repeated initial linkages to GSK, the recent UK Treasury line[392] is that this purchase agreement would be open to *all* malaria vaccine developers and not just GSK, and that the press had wrongly misinterpreted it as somehow attached to GSK. However, the exact nature of the commitment was expressed very unclearly–in what seemed to be an addition to a speech–at the time of the original GSK announcement, in a way that seemed to indicate that the commitment related to *these vaccines* in particular. The full text is:

"And let me just add. The recent breakthrough which for the first time gives us a vaccination to prevent malaria that could be ready in three to four years time is a revolution in our time. The challenge is in an area where there are insufficient purchasers with funds we need to ensure that ***the vaccine*** *does go into commercial production and is available at affordable prices. And therefore I can announce that the British Government working with other Governments is ready to enter into agreements to purchase* ***these vaccines in advance*** *to ensure a secure market and that* ***the vaccines*** *are available more cheaply–and thus avoid many of the 1 million deaths from malaria each year."* (emphasis added)
Speech by Gordon Brown at the BBC World Service Trust conference 24 November 2004[393]

As *any* malaria vaccine expert could have told Brown, the notion that we now have "*a vaccination to prevent malaria that could be ready in three to four years*" is completely and utterly wrong on all counts.

Similarly, Brown wrote in an op-ed in the British newspaper 'The Observer' in early June 2005:

"But the long-term search for an anti-malaria preventive vaccine has been boosted by recent medical trials in Mozambique arising from a partnership between GlaxoSmithKline and the Gates-led Malaria Vaccine Initiative… The challenge is that in an area where there are insufficient purchasers with money we need to ensure that ***the vaccine****, when developed, goes into com-*

mercial production and is available at affordable prices. That is why the British government is inviting other countries and companies to join us to explore a jointly agreed advance purchase scheme to underwrite the buying of millions of vaccines… "[394]

Given that GSK was putting all the investments in place to bring this research on, given that the research was being pursued through a PDP with opportunity to invest in that PDP, and given that any eventual vaccine that might have resulted from this activity was already lined up to become part of the standard package of child vaccinations, the "insufficient purchasers" phrase is also not a correct interpretation of the underlying vaccine development problem[395].

Indeed, the above quote seems to indicate that the purchases would lock in for "the vaccine" only "when developed", which is outside of the 'Making Markets' usage of APCs to cover the costs of R&D and "the vaccine" development in the first place, and it suggests that the heavy costs of vaccine development would be paid for from alternatives to those of an APC. If so, the figures of $3bn or $4bn, and the 'Making Markets' analysis are largely irrelevant to this case. At the moment, however, it is all rather unclear.

Given the scientific understanding above, and the clear dangers that in incentivizing one activity, it may be that all kinds of other activity are dis-incentivized, one of the main dangers to be avoided is to use APCs (and indeed funding into preferentially selected PDPs) that reduce the problem to one large pot of subsidy with all the required rules and structures required to drive good incentives simply missing.

From what can be made out from the information released so far into the public domain (that is, practically none), the apparent GSK 'deal' (if there is one in writing yet, which is not clear in itself[396]) is *not* along the lines of the recent 'Making Markets' proposal (that itself is a fairly vague proposal on many of the issues)[397]. *That* proposal in its purest application would be for, amongst many other things, a large fixed sum set at the start to cover *all* potential private vaccine developers, rules about efficacy limiting players' room for maneuver, plenty of monitoring to help set later rewards, modification to account for push payments not strictly motivated by the APC, and–so as to enforce credibility–no discretion by sponsors to engage in procurement behavior after product development that risks bidding the total value of the winning developer down to a level nearer to that firm's expected actual costs of development. All of this with–because of the scientific difficulty and ex ante problems in judging costs and epidemiology–lots of discretion. There would be a huge disconnect between what a developer would get from the APC and what they had actually spent on R&D, but they would still *not* get the whole pot of subsidy[398].

Instead, from what can be made out so far, the GSK APC seems to be much more like a standard procurement purchase commitment, as described above (though it is not at all clear what the nature of the contract is). If we know that there is a high likelihood of slipping into this kind of purchase commitment anyway, then some of the other parts of the collaborative mechanism described above start to sound slightly more sensible too perhaps? We noted above, however, that initiating only one of a package of measures that needed to be initiated together is not only less strong, but that it was even damaging, potentially harming the efforts of other developers to find a 'globally' superior set of malaria vaccines.

Incidentally, from the 'Making Markets' analysis, it is *required* that the exact nature of the contract be placed–and indeed be policed–in the public domain so that *other* developers will know exactly how to respond optimally. There could be no secrecy in the terms set for, or handling of, GSK.

The PDP Setting

"*Public-private partnership leads to scientific breakthrough in malaria vaccine development.*" Headline, GSK Biologicals website[399]

"*This project demonstrates the power of collaboration between the public and private sectors*" Jean Stéphenne, president and general manager of GSK Biologicals[400]

"*GSK Bio stressed how important public private partnerships were in the area of sustainable vaccine development and supply and how highly they valued their current working relationship with the European Commission.*" GSK Press Release[401]

"*GSK believes a public/private partnership approach to drug discovery and development in diseases of the developing world is vital. GSK currently works in partnership with the National Institutes of Health, Medicine Malaria Venture, Global Alliance on tuberculosis and many others. Companies provide to the partnership technology in which they have invested for decades and their discovery, development and distribution expertise. The public sector partners help fund the development costs while also ensuring that the medicines and vaccines get to the people who need them. This has the double benefit of encouraging R&D and accelerating the product's use in the developing world.*" GSK website[402]

The RTS,S/ASO2A candidate was conducted by the Centro de Investigação em Saude da Manhiça (CISM). GSK Biologicals and PATH's Malaria Vaccine Initiative (MVI) co-sponsored the trial, which was approved by Mozambique's Ministry of Health:

"*Development of an effective malaria vaccine can be accelerated through international partnerships between private and public sectors, including scientific institutions in endemic countries. In combination with existing and other promising new malaria-control measures, malaria vaccines could greatly contribute to reducing the intolerable global burden of this disease.*" Professor Pedro Alonso, University of Barcelona, who led the recent RTS,S/AS02A research[403].

Alonso, the principal investigator of the study, heads the Center for International Health of the Hospital Clinic at the University of Barcelona. Mozambique's Minister of Health, Dr. Francisco Songane, said his nation was proud of its part:

"*We did this not only for the people of Mozambique, but for the people all over Africa whose health and development suffer greatly from this terrible disease.*"[404]

To key advocates of APCs, however, PDPs for malaria are between only a quarter and a third of the effectiveness of an APC[405], and the latter is to be preferred anyway.

This all hints at one of the other big problems with this case when looked at in a much greater context. The RTS,S/ASO2A vaccine was and is being developed within a PDP framework, with strong support from the European Union and the European and Developing Countries Clinical Trials Partnership[406]. Strictly speaking, if GSK were drawing from a 'Making Markets' APC (with the drawing of subsidy related to the vaccine's 'quality'), the *proportion* of GSK's overall research carried out before the commitment was announced would have to be cut from any eventual APC payments (observe the disincentive to keep down the costs of later stages of development), as would any proportion of total funding accounted for by non-private funding in its development from now on (observe the incentives to distort this too), so that such APC payments would be reward for the *fresh* GSK equity finance brought into the project. Otherwise, the APC funding will simply crowd out funding that should have gone on alternative vaccine researchers elsewhere. And other researchers thinking of using private funding will realize that the value of the results of *their* private research spending (in the expected sense) is now lower. The overall malaria vaccine endeavor would be damaged at any given outlay of public funding.

It will be interesting to see how expected subsidy levels, tax allowances, and support from the European Union and others will be treated in the overall calculations of the size of the eventual purchase commitment payments, since it would require that the company be extremely transparent with the necessary information. Or will these issues just be ignored, thus weakening the instrument?

Without such adjustments, the rational (and, to live up to the APC modeling, also the economically correct) approach would be for the PDP funding to now be withdrawn from GSK, setting them free to get on with the RTS,S/ASO2A project fully equity financed, in pursuit of the APC payments. And the PDP sponsors should be free to find *competing* vaccines to support. It is not at all clear that when all risks are fully accounted for, and this reality is presented, that GSK would not prefer the PDP route were they to actually face the choice. Indeed, the Gates Foundation is currently negotiating a further major injection into this particular malaria PDP, suggesting that GSK is less convinced of the power and usefulness of the APC route for developing a malaria vaccine.

Barder[407] says that "the proposal is intended to complement… public private partnerships and other approaches,"[408]. Yet nowhere in the APC literature is the interaction of the APC mechanism and the PDP mechanism analyzed (by which one does not mean

statements about their intended interactions, but, instead, hard factual details of *how* they are to interact). For example, the typical PDP contract with private players involves risk-sharing in exchange for some control over the IP, lower vaccine prices and access in developing countries. How does this gel with a system based on the total ownership of the vaccine IP by the private 'winner' of the APC with high prices for the first several hundred million developing country users of the vaccine?

Or is the public/foundation allowed some IP ownership too? But how does that conflict with the need to attract more *additional* global private funding and the fact that giving IP to non-private players implies giving part of any APC away? For PDPs currently working on the basis of IP-sharing arrangements, what are the legal and technical problems of switching over? One implication of the No. 10 Policy Unit (Appendix 7) calculations is that the APC achieves additionality by being the only incentive device present. Are PDPs phased out? For a case with such a high PDP component and all of the associated problems this creates in the APC setting, one might hope that the claim about 'complementarity' might have actually meant something in practical reality. This rather contradicts the claim that this mechanism is not being promoted *regardless* of other approaches[409].

One can only presume that if the APC contract is set up badly enough, GSK could be incentivized to continue using large chunks of PDP funding, then (in the expected sense) to claim APC funding, even if this harms *other* vaccine players, the overall vaccine enterprise, and the expected quality of any vaccines generated (but the public will never notice, so the policymakers have less incentive to spell this out, never mind act upon it).

To complicate matters, Tarcisio Hardman Reis[410] argues that since such finance by a government to advantage its own domestic private companies is a form of subsidy, such contracts "might be considered as subversions for the purposes of the EU and possibly represents unfair competition for WTO." Furthermore, Reis argues that there is no international organization that is properly empowered to define the companies that are subject to such contracts, and that this is unable to exist under WHO or WTO Constitutions. The way this particular contract (or is there a contract yet?) seems to have been set up so far does seem to 'unfairly' advantage one domestic producer over many other European, global, and smaller companies. Just the risk of this being acted upon by competition authorities and others at some future point in time is a risk to the firm itself. Maybe this is why the firm is not so apparently keen on the idea in the cold light of day, and it gets no mention on the firm's website?

The Problems of Setting Minimal Conditions, Controlling Quality, and Crowding Out

Would this case have got a 'Making Markets' advance purchase commitment?

This case shows the difficulties of setting minimal contract conditions in advance. It is not clear how the GSK case would have faired had a pre-existent APC of the type discussed in 'Strong Medicine' been in place for the past five to ten years. Had the terms of *that* contract been categorically set to require a *minimum* of 80% of permanent protection against attacks in children bestowed by one malaria vaccine shot in a low resource setting (the 'results' so far are '30% protection for six months based on three shots in a highly-resourced setting')[411], and had other vaccine developers sunk resources working towards *that* goal, any GSK product would have had to be denied any promise of APC funding or, if the firm was offered a contract breaking the original contract, all other firms would have had to be compensated (perhaps after litigation).

It is highly unlikely that the British government would encourage the latter, since it would put developers off from trusting such contracts ever again, and these costs would weigh heavily against the possible gains from breaching the terms of the original contract. At the same time, firms other than GSK would worry ex ante about the PR disaster of having to litigate for a fair deal (in the ex ante sense) and would ex ante simply refuse to invest in the first place. Even the ex ante knowledge that GSK might be given APC funding 'against the rules' would damage the value of the investments of other developers.

It may be that the only reason this particular case might now be able to attract a large purchase commitment of a procurement variety (again, it is not clear what the exact state of play is on this) is precisely because there was no early-stage APC of the 'Strong Medicine' variety in place in the first place.

Difficult to use purchase commitment quality rules
The case also indicates the difficulties in using the rules of purchase commitments to control quality ex post. It would be very difficult to put off funding in preference for a supposed vaccine effective against 80% to 90% of attacks that is somehow 'out there' if policymakers feel that they have a 'bird-in-the-hand' 30%+ possible effectiveness, even if the rules dictated the 30% effective vaccine should be abandoned. The case also raises the issue of how to control vaccine characteristics over time through APCs[412].

On the first point, let us imagine for a moment that there is, somewhere in the pool of potential vaccine leads, 'a' malaria vaccine lead that will one day cut 90% (or, dare we hope, 100%) of malaria attacks in children in one shot, and that the level of APC to find and bring it to market is, say, $10bn. This includes an allowance for all the faults of APCs listed above. This is an expensive approach, though we do not know just how expensive (or, indeed, whether, given the use of APCs, the $10bn is still too low). Currently, on the basis of a narrow pool of research leads (based on globally really very small levels of malaria vaccine research) an early research lead might seem to 'promise' to 'cut 30% of attacks', with the low quality of *this* lead itself partly the result of the very poor levels of research in the past and also partly the result of the lack of past collaborative effort to generate high-quality vaccine leads. Let there be only $3bn made available for a purchase fund to cover the risk-adjusted development costs of *this* vaccine (should it, indeed, be successfully developed and should an APC be used to fund 'development'). This is the figure being offered according to the Center for Global Development, and much lower than many of the original figures that the Center for Global Development was presenting.

Let us presume that negotiation does not put in place the $10bn fund. Maybe for reasons of political expediency, quality (especially over time) is not deemed an important consideration, and a much lower target is set–something just enough to feed one big player perhaps and still hope to come out looking good. Two cases come to mind:

i) The first is where there is no absolute market promised for this vaccine, but a set of rules to allow this early vaccine to be easily replaced if a higher-quality vaccine is developed, with GSK barred from supplying any vaccine in this case or getting any of its R&D costs back. If there is a later big R&D push, with much higher levels of research funding and even a collaborative mechanism put in place to explore a wider range of new leads to try to find the 90% lead, this will destroy the value of the work being done by GSK on the 30% lead. They (and policymakers) will need to work out *in advance* what the chances are that the funders will encourage this greater body of research and the chances that it will destroy the value of what GSK is doing. GSK might indeed be interested in ways to insure against this.
ii) If, instead, an absolute level of market *is* guaranteed for this developer regardless of what is happening on other vaccines, and should the vaccine be developed, then the required fund to find and develop the 90% lead is now *higher*. Not only is it $10bn plus the expected $3bn of this vaccine (depending on whether it is likely to be claimed), but, since the company is being promised an absolute level of market, those working (or potentially working) on the wider range of leads will perceive the chance of a large initial market now reduced and the average expected cost of developing the 90% vaccine now even higher[413].

If a better vaccine is developed than this one, how will GSK be treated? Would 200-300 million of their vaccine treatments be purchased and never used? Would some countries have to take these vaccines, if capacity in the non-GSK vaccine is not built up fast enough? Does the first year or two of distribution of the GSK vaccine cost $3bn, but then the next developer or developers gets another $10bn? Or less? What if the follow-on vaccines are much better vaccines and need the $10bn to get developed? Ex ante what does GSK perceive to be its likely treatment? Will its $3bn promise be lobbied down by policymakers to be nearer its actual costs of development to look more 'reasonable' ex post even if this is totally inadequate in the ex ante sense with all risk factored in? Will GSK be disincentivized even as other developers are also disincentivized because they worry that the extra cash will not be made available and the 'easy' portions of the market will have gone?

The conclusion is that the terms of the $3bn deal, and the mechanism in which it is embedded, have to be set along with a commitment (backed up by re-

sources) to find 'the 90% (100%) vaccine'[414] spelled out to GSK from the start. Indeed this 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 efficacious lead is much more salient than the lost 90% lead that is never seen or felt (even as GSK has to face, and pay in its capital costs, the risk that the greater lead will be followed some time, and so even GSK holds back on its intensity of effort). We never know about what we do not get. Politicians (and policymakers) with limited horizons like to take credit for the self-fulfilling things they bring about by their own shortsightedness, especially if nobody notices. But this should not be encouraged by those who should know better.

Stymieing the criteria

The case also illustrates the very real dangers that changes in criteria will stymie those who are working on superior vaccines. Before the GSK case came along, most of the APC literature discussed efficacy rates of 90%, down to 80% as 'bad' cases[415], and emphasized the importance of minimizing the number of doses. The latter was because in very poor resource settings there is little point in having three or more booster shots given the high distribution costs of the last shots, there are low levels of health service personal and record keeping, and there is the likelihood that many would not come back for the required booster shots. Then, the CGD set the base case for a malaria vaccine at 60% effective protection for five years from a three-dose course[416]. This became: "It should prevent at least 50% clinical episodes of Plasmodium falciparum malaria in infants and young children for at least 5 years, with no qualitative or quantitative exacerbation of subsequent disease; requiring 1 to a maximum of 4 immunizations; presented in multi-dose vials,"[417] before, in the contract term sheets attached to the final version of the CGD report, becoming 50% efficacy for 24 months from up to four doses, with flexibility to lower even further.

It is pretty obvious why the criteria might be repeatedly lowered like this (along with the sums of money being proposed). But this does not look like a particularly good set of criteria in a poor-resource setting: If there are four immunizations in a treatment and if even 70% of those receiving treatment return for each boost (in some resource-poor settings this would be considered good), then only just over a third get the full treatment. If the vaccine is 'only' 50% efficacious, this will prevent only about a sixth of cases. The fixed costs of distribution are just as high as for a 100% effective vaccine, and the opportunity costs of distribution are higher the more immunizations that are required (this bites heavily in settings with already very low levels of health professionals). Likewise, the high opportunity cost of continuing drug treatments remain nearly as high as before. Is this a good deal for all the PDP funding absorbed and for the countries relying on this vaccine?

Incidentally, who pays for the distribution and health-system costs of the four-dose vaccine treatment and the continuing high levels of drug treatment costs? How do the costs of this approach compare to alternatives involving from the start better drugs and use of more preventative measures such as bednets? What happens in such situations to the cost-effectiveness arguments being made for such vaccines? And what happens after all the APC has gone on this vaccine?

An example of dynamic inconsistency

This is another form of dynamic inconsistency. It is probably fair to say that these vaccine criteria would not have been even considered, let alone vocalized, before the recent GSK case. This does not auger well. The ability to tone down criteria is a risk to other privately-funded developers, a risk to GSK (should other developers come along later), and a risk to eventual users.

Imagine the problems if another 'better' vaccine lead comes along. Is it set a target of 50% efficacy so as not to be treated 'worse' than GSK? Even if it is capable of 90%? If it is set at 90%, would the developer not object to the 'tougher conditions' when the earlier vaccine of GSK has been set only 50% or so (and may yet be allowed at something lower)? Why should the 40% or 50% lead get *anything*?

Incidentally, had a malaria APC been set 10 years ago, is some of the recent commentary from key players suggesting that the terms of *that* commitment would have turned out to be very wrong, and way too high? Have these ex post rationalizations for lower requirements demonstrated some of the difficulties of efficiently setting terms far in advance?

Bidding the price down?

When the original 'Making Markets' draft report came out, it happily talked about a range of costs for developing a malaria vaccine, repeatedly referring to a $6.25bn figure. A few months later the cost had dropped to $4bn, and then $3bn (in the space of the same meeting). By the time the report of the Commission for Africa came out in February 2005, the $3bn figure had taken on an air of authority and accepted wisdom:

> *"Advanced purchasing agreements guarantee the size of the market[418], providing an incentive to pharmaceutical companies to produce drugs[419]. For Malaria, the market size needed to deliver the malaria vaccine[420] is $3 billion (CGD, 2004)."*[421]

What happened to so drastically alter our understanding of the science of malaria vaccines in just three months? Given the dangers of pitching an APC too low–with unnecessarily delayed investment at first, followed by a perverse incentive to delay vaccine R&D *even further* when the APC size has to be raised–this is all rather astonishing. The Commission for Africa can only report what it is told. Such statements ultimately simply reflect the state of lobbying efforts, rather than any rigorous analysis of the issues.

What does all this say about the veracity of the original figures? Of the current figures? Of *any* figures? If a good-quality vaccine or flow of vaccines was calculated to need a $6.25bn fund just a few months ago, and policymakers (and lobbyists) are happy to sacrifice quality, just to sell an idea and get 'influence', what does this say to investors and developers thinking of investing in 'better' vaccines? If those promoting the approach do not trust the approach, why should developers? If the whole exercise is a game in political opportunism, why should investors treat it any other way?

Crowding out other private developers, and quality made worse

As a very practical example of crowding out and of the research distortions that may be caused (and pertinent given the recent GSK case), imagine offering an APC to a range of malaria vaccine developers, some at or near scratch in their R&D, and some who have vaccines much closer to market (helped there by a great deal of previous push funding perhaps, properly calculated to *include* funding of all failed leads and capital costs). If the size of the APC is set on the basis of all developers being at or near scratch, and if the near-to-market group do not have purchase payments removed commensurate with their position and previous help, then they will be massively over-advantaged (in the expected sense they are taking up too big a *proportion* of the 'pot' since they are more likely to 'win' it) and over-paid (they get paid too much for what they have done with their own private funds) compared to the near-scratch developers.

And it aggravates the 'quality' problem; probabilistically, quality is made worse. The near-scratch developers who have poor vaccines would not get purchase funding anyway, so if we knew about them now, on an equal playing-field as it were, their presence would make outcomes neither better nor worse than they currently would be. However, the near-scratch developers with 'good vaccines' would not make matters any worse, but would make matters a good deal better. There is option logic in pitching the mechanism towards current whatever-quality vaccines, which indicates that one probabilistically forecloses on the chances of better near-scratch vaccines.

On the other hand, what if, instead, the size of the APC is set lower and more commensurate with those closer to market? Well, obviously, that is bad for the near-scratch developers!

However one looks at it, near-scratch and near-market developers need the overall size and distribution of the APC to be modified commensurate with their current position (though think of the accounting and monitory issues involved in doing this). In real applications of 'Framework Agreement'-type tenders, the likelihood is that these ex post funding adjustments would not take place[422]. Other finance mechanisms are much more capable of being adaptable to the current condition of each potential user of them.

If anything, that we are considering £3bn to incentivize just one vaccine lead that has achieved, so far, 'only' 30% effectiveness against attacks in the first six months (and even this is hotly debated by some vaccine experts), does rather suggest the potential expensiveness of *not* using more collaborative approaches to achieve the 90%+ effective vaccines we ultimately seek. $3bn is *half a century's* worth of the entire public and private spending on malaria vaccine research at

current rates of expenditure, and over *three and a half century's worth of* what MMV has been spending, which for all its smallness, produced 21 drugs and is currently supporting 20 vaccine candidates at various stages of pre–and clinical development[423].

In this topsy-turvy world it is still possible to go from discussing umpteen-billion dollar proposals, most of which will go on capital costs anyway, to reading pleas such as this:

> "*An additional $20 million per year could lead to several new products moving to clinical trials. Similarly, an additional $20 million per year for the extramural program, which funds directed R&D as well as investigator-initiated grants, would greatly accelerate the development of new vaccine concepts.*"[424]

It rather begs the question of what sort of vaccine leads we would have to work on by now had even a fraction of what is now being proposed was poured into finding more and better vaccine leads in the first place. And it rather suggests perverse priorities. The GSK case, rather than pointing us in the direction of a 'Strong Medicine' mechanism, it turns out, challenges us to set our sights on much bolder approaches[425].

Interestingly, with the GSK case already seemingly fitting more into the 'standard procurement' contracts described above in the collaborative vaccine model, it does rather suggest exploring ways to use them in a collaborative setting, and to set terms accordingly. But this should be discussed and pushed for now, not in five or six or more years' time.

Various Malaria Vaccine Approaches and the Impact of the Malaria Genome

> "*Our understanding of the relationship between host genetics and the response to infection is very limited. The elucidation of the sequence of the human genome and the development of scientific tools to use these data should lead to a better understanding of the role of host factors in determining the severity of disease associated with infection.*"[426]

> "*In summary, whole-parasite-induced immunity could be directed at many of the 5000-6000 malaria parasite proteins. The malaria genome project and the single-nucleotide polymorphism (SNP) projects currently nearing completion may provide knowledge of all these potential targets and their variability at the epitope level, thereby laying the foundation for duplicating whole-organism immunity with subunit vaccines.*"[427]

There are three general approaches to malaria vaccine development. The most work and the most progress so far has been made in trying to get an immune response to a single or a few key antigens, with attention on getting antibody and CD4 T-cell responses, with interest too in CD8 T-cell responses. The second approach is to induce optimum immune response simultaneously against all of the 15-20 identified potential target proteins by immunizing with DNA vaccines or recombinant viruses and boosting with DNA vaccines, recombinant viruses, or bacteria, or recombinant proteins in adjuvant, with intent to elicit antibody and CD8 and CD4 T-cell response. The third approach is to try to duplicate the whole-organism immunity that is induced by immunization with radiation-attenuated sporozoites and natural exposure to malaria. However, achieving this depends on sequencing of the malaria genome and developing methods for exploiting this sequencing data. A great deal more needs to be done on this third approach.

That there are three competing approaches, with the third 'coming up on the outside' as it were, does raise interesting and complex issues that, again, point away from a 'Strong Medicine' approach and towards more standard procurement approaches.

Serious problems for private investors

How should a firm working on the first or second approaches respond if they are suddenly challenged to invest, in the expected value sense, billions of their own funds in developing a vaccine based on that approach? Given that only $60m a year of public and private research expenditure is going into malaria vaccine research overall, this is a huge increase in *expected* expenditure for one firm. Should the firm be mindful that if the third approach works better, the government might actually hope never to use any (or very little) of the vaccine based on the first approach? What if a firm invests heavily in response to the offer, only to see the government massively scaling up efforts on the third approach?

Conversely, what if the government 'blows everything' on the first approach by offering an open-ended lump sum even if it turns out *not* to have been the best approach? How does it avoid disincentivizing private

research on the third approach? How does the government work out *in advance* how to optimally redistribute the overall payment and how much should they pay up-front for vaccines based on the first or second approaches, so as to leave the 'optimal' portion over to be spent on vaccines based on the third approach?

Or is there a bottomless pit? Is the whole notion of a 'Making Markets' fixed size APC subsidy and the 'Making Markets' mechanism described above simply a mirage anyway? The attitude at the moment seems to be to concentrate on the immediately salient vaccine approach and to let other approaches worry about financing themselves later (or expect that the government, the IFF, or someone else will offer even more contracts later, or that these better vaccines can just be dispensed with anyway).

Of course, none of these problems really arise in the APC literature. We discussed above, and elsewhere[428], the way the key models (Appendix 3) assume a constant state of science. There are no technological shocks or technological improvements *ever* possible. There are no 'genomic revolutions' or the openings of new scientific paths to spoil the simple solutions of such models. Once this heavy simplification is dropped, things rapidly get very messy if APCs are the driving force. If things are about to get 'technologically unlocked' by breakthroughs in the malaria genome project, is it automatically obvious that we should be putting expensive APCs in place, pitched at the current players? And do firms really wish to be forced to risk only their own funds on *current* approaches?

Other Non-Vaccine Malaria Needs

> "*This tragedy need not happen. It is almost entirely preventable using technologies that are already available. Widespread use of insecticide treated mosquito nets and a new class of malaria drugs known as artemisinin combination therapy (ACT) can radically reduce disease and death… … We estimate that for £300 million we could have enough nets to cover virtually all pregnant women and children under five who need them in Africa. I can announce today that the UK is ready to meet more than its share of the total cost through a contribution of at least £45 million–to cut deaths from malaria in Africa. I will be pressing the G8 to make a commitment to meet the rest of this bill.*" Prime Minister Tony Blair, World Economic Forum, Davos, Switzerland, 2005.

The recent Millennium Project[429] identifies malaria control as a 'quick win', where rapid concerted action could have dramatic effects in improving people's lives, halve the numbers of malaria attacks in young African children and save more than one in five of all childhood deaths. The report calls for the mass distribution of mosquito nets treated with a long-lasting insecticide and effective anti-malaria medicines for all children in Africa by 2007.

The nets are one of the most effective ways of preventing malaria, and cost just $3-$4 each, and if used properly, last for at least five years. Studies find that such nets reduce malaria episodes by 50%[430].

New drugs are needed and are much more easily possible

Until about 20 years ago, the drug chloroquine was the standard malaria drug. It was cheap (about 10 cents per treatment) and worked well. However, chloroquine-resistant strains are now rife. But there are new effective drugs available. When the first signs of drug-resistant malaria appeared in Asia, Chinese scientists developed a family of drugs based on artemisinin compounds made from a common shrub, the sweet wormwood, that had been used for centuries in traditional Chinese medicine. These are now the standard malaria treatment in Asia, where they are described as the "best ever anti-malarial drugs"[431]. These are not 10 cents but about $1 per child treated. But that is still cheap. Africa does not get them, and millions suffer and die as a result, for the sake of $500m or so per year. That is about 3 to 4 days of current levels of military spending in Iraq.

To combat future drug resistance there is also the need to partner artemisinins with other anti-malarial drugs, creating what we already know to be well-tolerated artemisinin combination therapies (ACTs)[432]—the same approach that underlies the treatment of HIV and tuberculosis. In 2002, the World Health Organization urged governments to adopt such therapies rapidly. Scaling up the delivery of drug combination therapies–ACTs–will also be extremely cost-effective, even in the most resource-poor countries.

Kenneth Arrow argues that:

"The main condition underlying access to subsidised ACTs would be that they flow freely through public and private channels–just as chloroquine does now… Above all, in the case of anti-malarial drugs, centralised purchasing would provide the impetus for a swift change in the way the world treats malaria. Without a co-ordinated programme, the change is far more likely to be gradual and incomplete, the scenario most likely to jeopardise the effectiveness of artemisinins over the next few years… There can be no excuse for delay… All that remains is for the international donor and finance communities to embrace the logic, allocate funds and take action once and for all against malaria… What makes this situation more distressing is the existence of an effective alternative… With a modest global investment, these drugs could be mobilised today."[433]

Some hard-hitting truths

When the GSK announcement was first made, it triggered a flurry of commentary from vaccine experts. At the risk of taking their remarks out of context, the response to the Lancet study, in a letter to Chancellor Gordon Brown, by Professors Bob Snow and Nick White of Oxford University, stood out (these are extracts from that letter, the reader should really read the whole letter to see the more positive remarks too[434]):

"This was associated with vigorous and eye-catching publicity, notably the banner headline in The Times the preceding day claiming "New malaria vaccine will save millions of children".

But we have had false dawns with malaria vaccines before — and it would be prudent to be cautious. Under normal circumstances, this report would herald a concerted effort to confirm or refute the findings in different populations in different parts of Africa with studies large enough to measure the impact on mortality from malaria; one study is certainly not enough to be sure of anything. But instead, you announced a week ago that the British taxpayers would pre-buy 300 million doses of vaccine for sub-Saharan Africa, costing probably £3 billion (US$5.75 billion)[435]*.*

… We are seriously concerned, therefore, that while millions of people suffer every year, you are proposing to allocate precious funds to a future uncertainty. This good intention is misguided. We fear you have been advised poorly…

We have interventions now that are more effective and much less expensive than the weak vaccine reported in The Lancet… Less than US$20 would guarantee a poor African child access to life-saving interventions. The cost of a malaria vaccine will be in excess of US$60 per full immunization.

The sad truth is that, despite having now developed these effective tools (with substantial support from donors such as the UK government), the international community has failed in its promise to make them accessible to people most in need. Furthermore, partnerships such as the World Health Organization, Roll Back Malaria, and the Global Fund against HIV, tuberculosis, and malaria — also supported generously by the UK government — have missed opportunities to go to scale with comparatively cheap, life-saving interventions.

Weak strategic leadership, donor-driven agendas making poor people pay for bednets, inadequate planning for drug needs and policies, and lack of sufficient funds have all resulted in less than five per cent of children sleeping under an insecticide treated bednet, and a handful of African countries struggling to implement new effective drug policies.

Communities in Africa under the constant threat of malaria and maintained in a constant state of poverty cannot afford to spend US$20 per child to save them from malaria; rural households have to make difficult choices of putting food on the table or sending their children to school.

Why, then, has the UK government decided to invest in an intervention that is more expensive and less effective than bednets and effective drugs? One argument might be that the bill does not have to be paid today. And when it does, it will probably be paid to a British multinational pharmaceutical company.

We have truly effective measles and tetanus vaccines (they are much more effective than the current malaria vaccine), and we have had them for decades. But these vaccines still do not reach all those who need them. Together measles and tetanus kill over a million children each year (World Health Reports 2003, 2004). Similarly, although we have a pneumococcal vaccine, it does not reach anyone because it is so expensive that no developing country government can afford it.

The prospect of a new vaccine against a killing disease has a seductive 'high-tech', 'feel-good' allure that is appealing to donors who seek neat solutions in modern technology.

Yes, prevention is better than cure. But this works both ways. If we provide insecticide-treated bednets and make effective drugs available, this will also reduce the incidence of malaria, and we will achieve better effects than with a weakly effective vaccine — and importantly we will spend less money."

We need to raise sufficient funds from the rich world to support scale up and deployment of what we know works best, and we must do it now."

Tough words. But someone has to say them.

Jumping Linguistic Hoops

Challenged on the worries that the UK's response to the GSK case might distort incentives and disincentivize better vaccines by failing to even remotely live up to the idealized 'Making Markets' approach, Owen Barder said[436]: "I can't speak for the UK Government, but I can tell you how the proposal in the Center for Global Development Working Group tries to address these issues." This is a startling statement.

First, and around the same time as the proposal is going through with the UK government, the WHO CIPIH Discussion Forum is filled with calls by Barder and others not to falsely misinterpet the proposal, including, for example[437]:

"*James Love expressed scepticism about using a prize, or Advance Purchase Fund, as a way to create incentives for vaccine development, because of (a) the need to set the right incentives for the varied community of public and private researchers that collaborate on neglected diseases; (b) the difficulties of specifying the desired outcome; (c) uncertainty about the costs of development; (d) the need to reward both early movers and subsequent incremental improvements… **These are all valid criticisms of a winner-takes-all prize, or an Advance Purchase Fund**. However, the Working Group is not proposing a prize or an Advance Purchase Fund. In fact, **all these potential criticisms are explicitly taken into account in the design of the (rather different) Advanced Markets proposal** put forward by the Working Group… As expressed so far, they appear to be a critique of a different proposal from the one that is being put forward here… The particular proposal in the Working Group's report is somewhat different from other proposed advance purchase arrangements*." (emphasis added)

Of course, all of the above criticisms were, and remain valid.

Then, the CGD website boasts of the policy advice it has given to the UK Government and of the 'great success' of a malaria APC along the lines of the CGD proposal. Indeed, press releases claim that: "*Strong Medicine* argues that commitments to purchase vaccines, of the type proposed by Brown, can provide incentives for the private sector to develop these vaccines." [438]

Then, and *in spite of agreeing* with the list of 'valid criticisms' described above and arguing that the proposal is not for an 'Advance Purchase Fund', we discover that those involved in the CGD project have not got the foggiest idea whether the UK government is doing anything along the lines of the 'rather different' proposal and not just instigating a very large 'pot' of winner-takes-all funds or, even worse, specifically targeting GSK, and failing to put in place any of the parts of the 'rather different' proposal to avoid the potential dangers. It is not great encouragement to hear that the CGD "cannot speak for the UK government," who are supposedly acting on their advice, but they can tell you what the latest model says.

How did this all come about?

Maybe this situation came about because most of these 'design issues' were not in the 400+pages of material put on the No. 10 Policy Unit website, nor in 'Strong Medicine', nor, clearly, in any advice given to the British government. These design issues were raised in Farlow April 2004[439] *not* to indicate what needed to be "explicitly taken into account in the design" on paper (though the hope was that some fatal flaws could be avoided), but to indicate just how difficult it would be to instigate such design issues *in practical applications*. The truth, it seems, is that in response to 'valid criticisms', the paper model is simply changed a bit here and there to make it *sound* more palatable and to make the task of those who made the criticisms in the first place that bit harder, but, in all concrete respects, there is no genuine desire to achieve a better design in practice.

If the 'Making Markets' mechanism is as good as its keenest proponents suggest, why, when the first real chance arises to use it, is it not used? And if criticisms have genuinely been "explicitly taken into account in the design," it does not say a great deal about those advising the first users of the mechanism that the advisors are not bothered to make sure that *the first users* take the criticisms into account in *their* design. The very things that the advisors criticize others for criticizing, the advisors then go and do anyway. Grave worries about being misinterpreted. No worries about getting things right.

7. Conclusions and a G8 Strategy

Those working on pull mechanisms are to be praised for exploring fresh angles to this problem and for developing a key part of an overall treatment, and, best of all, for applying the proposal to some real-world, late-stage, underused vaccines that will shortly, it must be hoped, start to make an impact on unnecessary pain and suffering. However, success on currently existing late-stage vaccines would say little or nothing about the ability to solve the problems of developing high quality, but extraordinarily complex early-stage vaccines, such as those for HIV, malaria, and tuberculosis. And then, moreover, getting the vaccines manufactured at prices low enough to be of practical use. Claims of effectiveness on these latter problems have been very heavily exaggerated, and are entirely unproven. The whole Center for Global Development endeavor on late-stage and underused vaccines has been increasingly used to press a completely unproven experiment for early-stage vaccines just for the sake of getting a 'policy success', whatever the long-term consequences for vaccine discovery and development.

Ten Steps (and more) to Selling an Unproven Proposal to Politicians

It is never a good thing when lobbying takes over from rigorous and critical self-analysis. When it comes to an HIV vaccine, the real issues should be the level of resources needed for getting the job done, *and getting the job done*, and not defending one model over another and playing games to achieve a 'policy success'. This author welcomes critical feedback on every one of the ideas expressed in this paper, given that this is the only way for ideas to be improved.

'Strong Medicine' and 'Making Markets' (and similar literature) are an object lesson in how to sell a proposal without having to *prove* it works. Here are the main techniques:

1) Whatever method is chosen to stimulate vaccine R&D for vaccines such as HIV, malaria, and tuberculosis, the ultimate payment for that R&D will be from developed economy tax-payers and philanthropic foundations, and the emphasis should therefore be on *relative cost-effectiveness, and hence speed of discovery and quality of vaccine outcome*. To deflect attention from the need to prove cost-effectiveness, the first technique is to repeatedly suggest that low levels of current funding for R&D for vaccines *itself* inevitably leads to using an APC. So, for example: "In the absence of an incentive of this sort, there is unlikely to be sufficient research and development into vaccines and medicines."[440] Better still, not using this approach is "*waiting for a vaccine to be developed* without an advance contract" (italics added)[441], and *not* adopting *this* approach is equivalent to doing nothing, living with "the status quo", and condemning millions to death[442]. Promoters of no *other* mechanism for tackling vaccine R&D has ever made the case for the effectiveness of *their* approach, over all other approaches, on the basis of the truly appalling status quo and of doing nothing.

2) Again, to avoid having to back-up claims about the effectiveness of the mechanism itself, we are told about the effectiveness of vaccines *themselves*. Indeed, the two are constantly conflated[443]. It seems to work[444]. Worse still, the probable success of purchase commitments and procurement arrangements for a range of late-stage vaccines are constantly conflated with APCs for complicated early-stage vaccines for which the power of APCs is very low and unproven.

The extreme cost-effectiveness of vaccines is well known. Indeed, it might be entirely fair to say that "vaccination… has been and continues to be one of the most important public health interventions *in history*" (italics added)[445]. Most of the APC literature rightly points out the scope for dramatic improvements in health and life expectancy achieved in developing countries consequent on relatively cheap medical ad-

vances, yet the highly non-complete coverage of such treatments. The cost-effectiveness of vaccines stands out. But this is a general feature and applicable to *all* mechanisms for encouraging vaccine R&D. One of the dangers of such arguments is that even low quality vaccines can be ex post rationalized. We see some of this logic in the cost-effectiveness evidence that argues that even low quality vaccines are cost-effective given the very high cost-effectiveness threshold of vaccines (though this evidence usually ignores the level of push funding that went into R&D and the costs of delivery and distribution, which are all likely to be very high for an HIV APC and will way outstrip a $3bn APC).

No *other* mechanism for tackling vaccine R&D problems has ever made (or would be allowed to get away with making[446]) the case for its *own* effectiveness based on the effectiveness of vaccines *themselves* rather than any evidence of the cost-effectiveness of the mechanism itself.

Indeed *no* product or service is sold according to this logic. No transatlantic airline flight is priced to just pip the cost (including the value of time and hassle-avoided) of taking a transatlantic liner; no mobile phone call is charged according to the alternative of a foot messenger. If air-traffic controllers were to shut down or nurses were to go on strike for a week we would soon enough work out the 'economic surplus' of their services. But we do not use this principle in working out what to pay them (or anyone else).

No computer company has yet managed to get away with selling computers at ten times cost price because of the value of the Internet and the welfare losses of a society without computers–perhaps with advertising copy along the lines of: "Computer prices remain cost-effective under a wide range of assumptions about Internet connection, level and speed of Internet adoption, and the amount of money spent on computers in the population."[447] And they would not even try to argue that poor quality is fine since the cost-effectiveness threshold is so very high compared to a world without computers. Instead we expect high quality at the lowest possible prices.

Most other innovations in resource-poor settings could be talked about in similar 'cost-effectiveness' language. Following the recent Asian tsunami, the cost-effectiveness of bottles of clean water was extreme, but one suspects that the international aid agencies seeking to distribute them would have tried to do so in the cheapest and most efficient fashion, if only to maximize the range of other projects they could fund.

Some have even argued that "the constant assertion that vaccines are extremely cost-effective and that they could easily win in any competition with other interventions, has always been attractive as a rhetorical claim, but has never been matched by a real desire to put that assertion to the test"[448]. Certainly in very resource poor settings where there are many competing sources of morbidity and suffering, setting up vaccine programs may absorb large shares of medical and other human capital, and a case needs to be argued that they are more cost-effective than any other alternative.

3) Sadly, a large proportion of the early strategy to popularize APC for HIV, malaria, and tuberculosis amongst policymakers was to 'rubbish'[449] just about every other approach, while modeling *this* approach as having no problems and never failing. See the discussion in chapter 8 of Farlow 2004 of how this was achieved in the analysis presented to the UK government. Recent analysis similarly ignores nearly all of the practical difficulties of making such instruments work. A debate took place through the auspices of the CIPIH, but all this seems to have done is enable the idea to be spun better. None of the tricky questions were faced.

4) Policymakers are told that they do not need to pay till much later and that there are also "no opportunity costs to making the commitment. Because no cash expenditure from public funds is needed until and unless a vaccine is developed."[450] But the value of there being "no opportunity cost" only bites for two equally efficient approaches to solving vaccine problems. If using deferred payment requires the use of a greatly inferior and more expensive approach, the argument collapses. That policy advisors cannot see this simple truth is startling, and that they are prepared to apply the logic to complicated vaccines yet would never dream of applying it to other scientific endeavors (such as sending explorers to Mars) is an indictment. Besides, it is not even true; someone pays and bears the risks (eg. pension-fund holders through their holdings of pharmaceutical shares). Repeating

such mantras (and they are just mantras) eventually seems to work: "By committing to pay for results, these proposals ensure that if no vaccines are developed, no payments would be made."[451]

In truth, all that matters should be which approach is likely to achieve the most rapid development of a vaccine or vaccines at the lowest possible cost (or, and exactly the same logic, for a given cost the most rapid development and use of vaccines). Instead, as the policy pronouncements have proceeded, comparative 'cost-effectiveness' evidence has been ever more conspicuous by its growing absence. This is even more important in the context of paying for the mechanism via some facility such as the IFF, when part of the penalty of a failing and expensive R&D and procurement mechanism is the instability and cost it imposes on the IFF. As always, there is no such thing as a free lunch. Though it helps if it is someone else's lunch.

5) The opposite of the truth is said often enough in the hope that the truth becomes opposite. An early-stage APC is described as 'non-interventionist' even though it would be highly interventionist. Nobody 'directs investment'[452] when in fact a committee *would*, but in a manner that is very uncertain for many of those investing. It is 'making a market' when only sometimes this holds (when genuine competitive tenders are used) but at other times it is 'regulating' or ad-hoc decision-making via a committee or, worse, a politician. It is 'low on monitoring' when it is high on monitoring, and 'competitive' when the competitive element is the weakest link and one of the biggest worries is that there will be too little competition at both the R&D and manufacturing stages. It 'enhances other interventions' when it struggles to do so and is *not once* modeled as doing so, and not the slightest effort is made to tackle the difficult problems of doing so. It is "based on market principles" [453] when it is not, 'simple'[454] when it is anything but, 'practical'[455] when proper implementation would be a nightmare and potentially very litigious.

The biggest hidden truth of all is that the mechanism is principally a way to create a large pot of funds for just one or two dominant players, and *not* the many. This and a previous paper (Farlow 2004) argue that all the talk of competition is something of a smokescreen to dress this underlying reality for public consumption. It would be politically unacceptable for these large players, or probably more precisely those who think that they are helping them[456], to reveal this as their true intent, especially if they are not the most obvious recipients. The APC literature for early-stage vaccines and all its gyrations is simply the politically acceptable cloak in which to hide this underlying intent[457]. As one leading vaccine expert expressed it to the author, why not just say that this is the intention and we can then at least have an open debate about whether this is the right way to proceed, and whether we should just give GSK, or whoever, the money to get the task done? Instead we pretend it is a much more open mechanism. The recent ever-lower pitching of the level of APCs, even though this ultimately pitches the whole mechanism to only one or two large firms, simply makes this intent ever more clear.

6) It is argued that surely "the diseases of the poor deserve the same overall package of incentives for research as the diseases of the rich?"[458], even if the truth is that if HIV and AIDS were ravaging rich countries and escalating, it is completely out of the question that politicians would rely on (or get away with relying on) an untried, low-powered mechanism, with no rigorous analysis or critique of its foundations tolerated, no decent empirical evidence provided to support it before locking it in 'forever' (30 years is forever for our purposes), with payment pushed off many years into the future–instead of a fully-funded much more collaborative effort to find a high-quality solution. Our interest in APCs for driving R&D into vaccines for the poor only comes about because we do not feel that the poor deserve the same treatment as the rich.

7) Blame large pharmaceutical firms when they do not like the proposal. In many places in this paper it becomes apparent that large pharmaceutical firms (or smaller firms, when the details are properly spelled out to them), given the choice, would not necessarily prefer the 'Strong Medicine' and 'Making Market' approach over PDP and the more collaborative approach sketched above for diseases such as HIV, malaria, and tuberculosis. The APC route faces them with many risks–in particular a great deal of reputational risk once a vaccine is developed–that it is simply not worth it for the size of reward being offered. Perhaps this is why many large pharmaceutical firms are often so lukewarm. But their attitude is often dispelled with "they would be, wouldn't they?" logic–

the notion that pharmaceutical firms would always prefer not to be rewarded by results and would rather take subsidies instead. It is much more likely that, though they would be very willing to be part of an effort to hunt down an HIV vaccine or vaccines, they really *cannot* handle the risks of the 'Strong Medicine' route.

8) Proposals are discussed that are different from the one being promoted. So, for example, all of the language of late-stage purchase success is used even when discussing the merits of early-stage APCs.

9) When critiques are generated, the observations made are used to manipulate and improve the presentation of the proposal on paper, to make it more difficult to critique the proposal in the first place. It is made to sound as if the proposal has cracked the problem suggested in the critique, though only paying lip service to it. But then…

10) The proposal is not adopted anyway. Policymakers should not be alerted to just how problematic a proper application of the proposal would be by making them actually carry it out. That way, policymarkers are not diverted to competing proposals.

A plague of non-evidence for this…

The 'Strong' of 'Strong Medicine' refers to the alleged superior strength, dollar for dollar, of this approach compared to others. It was once claimed that, in the case of an HIV vaccine, a mechanism based on APCs would be four and a half times stronger than current publicly-funded applied research and joint ventures with private companies[459]. Such a staggering claimed difference in effectiveness cries out for justification. It is so central to the 'Making Markets' case for a large role for an APC for HIV, malaria, and tuberculosis, that we would hope to find plenty of evidence to support it. We do not get it. Instead, these once heavily-used cost-effectiveness figures are generated on the basis of largely non-comparable data and extremely dubious assumptions that include many layers of simple assertions about the extreme failure of all other approaches[460]. But this never applies to *this* approach, which is deemed to be perfectly applied every time. This in spite of the myriad of problems detailed above (that are simply ruled out) and the reality of unfolding applications.

Recently, these meaningless figures have not been presented as part of the argument, either in 'Strong Medicine' or in 'Making Markets'. It finally seems to have been recognized that this 'evidence' is not good enough and that its original production said more about its weight in lobbying than in any economic veracity. We found above that once we tried to explore the power of such instruments to motivate early-stage vaccine R&D, far from being "the incentive that has been so desperately lacking for biotechnology and pharmaceutical companies to focus attention on these (HIV/AIDS and malaria) vaccines"[461], this is far from the case.

But the memory of such 'evidence' lingers, spuriously hinting at some sort of empirical validity. The G8 Finance Ministers' 'Conclusions on Development' of June 10-11, 2005, even contained the following line: "We recognise also that advance purchase commitments (APCs) are potentially a powerful mechanism to incentivize research, development and the production of vaccines for HIV, malaria and other diseases"[462], even though *no* shred of reliable cost-effectiveness evidence has *ever* been provided for APCs for HIV, malaria, or other diseases–a fundamentally basic piece of evidence given their irreversibility. Increasing positive spin about the 'strength' of APCs has been in inverse proportion to the decline in the veracity of the originally purported evidence of their 'strength'. This is a truly appalling and irresponsible way to behave on the part of those advocating APCs for HIV, malaria, and other diseases.

A plague of problems with everything else it seems…

The *only* piece of evidence we are given for the "plague"[463] of failure of *other* approaches, including PDPs, and of *their* "politicization and corruption" is the retelling of the USAID Malaria Vaccine Program debacle of the early 1980s (wasting a couple of ten thousandths of one percent of the total NIH budget of the past 25 years). Fulsome details of this have appeared in just about every treatment of APCs[464]. This is sad. And ungenerous to the many who, often at great personal sacrifice, give their lives to research into these difficult areas[465].

It would be a bit like repeatedly tying the reputation of all those currently working in 'big pharma' to the behavior of the industry in the 1950s when it cor-

nered the tetracycline market, described by the Senate Subcommittee on Antitrust and Monopoly (1959-1962) as "profiteering and anticompetitive behavior with the help of the patent system… the public was ill-served by such practices." [466] Except that *that* behavior killed lives: "One can only speculate about how many peoples' lives might have been saved if prices had been allowed to fall earlier."[467]

After so many years, and given the gravity of proposing a highly *irreversible* mechanism to consume maybe several tens of billions of dollars of taxpayer and philanthropic foundation resources, we should expect a much more comprehensive and readily available body of *evidence* to support a core part of the argument. The fact that we do not get it betrays both a lack of such evidence and a lack of interest in such evidence.

The incentive to exaggerate, and a big worrying truth

One of the main criticisms of the current system made by Kremer and Glennerster is that if researchers do not have to prove the worth of what they are doing by results, they will "have incentives to exaggerate the prospects that their approach will succeed."[468] 'Strong Medicine' and 'Making Markets' are an excellent demonstration of this principle in action. Not only is the underlying empirical support distorted, but we will never truly know if early-stage APCs will work for HIV, malaria, and tuberculosis until *after* they have been tried. They are an experiment. It is no great reassurance to be told that if the experiment fails and we get no viable vaccines, it "would cost nothing"[469], or that:

> "*If thirty years pass and no substantial progress has been made on the product of interest, a vaccine commitment may not be the most useful approach, and the policy would be worth reevaluating.*" [470]

Not only is this an object lesson in understatement, it is also a staggering way to even consider evaluating a mechanism. It is hard to imagine that any *other* mechanism would absolve itself quite so crudely of the responsibility to prove its worth.

As the above line startlingly indicates, policymakers *really would have to wait at least 30 years* because of the legally binding nature of such contracts. The very knowledge that the sponsors might bail out if things do not seem to be going according to plan would itself make failure happen in a self-reinforcing manner (with litigation flooding in from any firm that had based its behavior on the contracts, or even just claimed to have done so). Therefore, the ability to bail out should be ruled out legally at the start, just as one might deliberately 'tie one's hands behind one's back' to defend an exchange rate mechanism even if it is becoming ever more absurd to do so. This is all aggravated if there are other purchase commitments in place that might be working and would be badly damaged by a breach in commitment elsewhere.

Incidentally, the 30-year quotation *really is* in *both* 'Making Markets' and 'Strong Medicine'. Does the fact that such startling lines can find themselves into both the Center for Global Development report and the supporting book, and that not one reviewer alerted the authors to remove it, rather indicate how few hands were at work in both? It is hard to believe that a truly collaborative effort would have left such a line in. Should we really be stuck with a failing APC for *thirty* years (perhaps because it was not rigorously stress-tested at the start)? Given Keynes's dictum that "in the long run we are all dead", 30 years is effectively 'forever'. Perhaps we should be told?

Given the enormous sums involved and the huge bias in the redirection of resources, such woefully created figures and dramatic–and damaging–assertions are simply not good enough.

That it would cost nothing is not even economically correct:

i) Taxpayers *will* pay via their holdings of pension funds and other savings in the pharmaceutical industry. There is no such thing as a 'free lunch'[471];
ii) It is not clear that if the mechanism fails, those who have sunk investments would not be due some recompense if failure was caused by failure of the mechanism itself, rather than their own behavior;
iii) If this *is* the approach adopted, *not* working is simply *not* an option.

Litigation?

The fact that failure of the framework (not of firms failing to perform under the framework) can trigger an "early out"[472], when billions of dollars of private resources may have already been sunk, is both a risk (of a self-fulfilling nature too) and also a source of potential litigation. Is 'failure' the fault of poor perform-

ance by firms, or because of the framework? If the latter, why should those who have invested in expectation of the framework functioning, as had been previously claimed, not have some sort of legal redress and compensation from those who operated or set up the mechanism? The mechanism designers had a duty of care after all. What if the mechanism was set up in ways that risked failure (for example, by deliberately failing to take on board publicly available critiques)? Such early opt-out decisions also require that monitoring has been performed correctly, which is another legal minefield when abandoning the approach. Bluntly, the more likely result is that those running the mechanism would stick it out with a poorly designed contract. None of this has been explored.

Simple ideas are politically easy and very persuasive

It is testament to the persuasiveness of drastically simplified proposals, the lack of the desire to think through tough issues, and the political appeal of programs the payment for which can be pushed way off into the future, that the mechanism described in 'Strong Medicine' and 'Making Markets' has "growing political support."[473] The danger is that the "political support" is built on the basis of relatively simple purchase commitments–with many of the end-stage benefits listed above–and not on the sort of mechanism described in 'Strong Medicine'. Unfortunately, "political support" can say very little about the quality of a proposal, and much more about the quality of lobbying. Contrary to repeated assertions by the authors of 'Strong Medicine', the workings of an APC for real-world early-stage vaccines are not 'simple', but the *apparent* simplicity of the mechanism has been a powerful recruiting device. Incidentally, Klausner et al.[474] *also* describe the–very different–global vaccine enterprise approach as having "substantial support from medical and political communities." Both approaches need to rely on critical, thoughtful analysis to win support.

Collaboration and dangers

Resolving how to deal with the presence of both more open collaborative mechanisms and APCs together is one of the next major steps[475]. At the very least, if one approach is to be favored over the other, the exact empirical basis for this should be presented, and the likely impact of each in real-world–rather than idealized settings–be ascertained. If, on the other hand, they *are* to work together, then the *exact way* in which they would work together should be resolved *before* enacting any irredeemably fixed, legally binding 'for ever' commitments[476]. In particular, the necessary reform of the IP regime underlying the collaborative part of the process would need to be resolved in a way that is also captured in the workings of the commitment[477].

Trying to collaborate around a badly-set purchase commitment

The worse-case scenario would be if many years, and much political capital as well as financial resources, were spent on setting up an early-stage APC, only then to find that it has limited impact on the speed of vaccine development, yet still has to remain legally in place, if for no other reason than *some* investment took place under it–or those who have invested would get *fully* compensated and the mechanism abandoned, which is even more wasteful.

In the simplistic models deposited at the No. 10 Policy Unit website, the science is modeled such that a larger APC does indeed encourage more firms to enter and invest. But the model does not even begin to describe the investment problems faced by typical pharmaceutical firms in 2005 given the current state of HIV vaccine research, some of which were highlighted above. At the current levels of science, firms are supposedly being asked to invest in vaccine research on something they cannot guarantee to internalize the benefits of for themselves, with an investment horizon that is effectively 15-20 years, with levels of uncertainty and capital costs for current research that are *astronomic*, with huge potential difficulties and costs even after a vaccine is developed on account of it being 'only' therapeutic rather than preventative, and probable vaccine production costs that risk eating up most of the fund anyway (with no mechanisms in place to prevent this).

It is perfectly possible to find, many years late, that we have to explore and then adopt a much more collaborative mechanism containing a pro-active forward-funded trial system, against the backdrop of a still existent APC that creates tendencies for behavior that undermines collaboration. If the APC were not abandoned by then, this collaborative mechanism would have to set up a side-mechanism to prevent those pushed through such a forward-funded system from having access to the end-funded APC program,

so as to avoid damaging the end-funded program and inciting litigation by those operating under it. At the same time, it would have to prevent those operating under the 'old' APC from wastefully exploiting the collaborative mechanism. Going for a large APC *now* presumes a strong degree of belief that forward funded trials are highly unlikely to be optimal.

Private pharmaceutical firms will be an important part of any mechanism to tackle these complicated vaccines. But a mechanism based on large APCs of the type described in 'Strong Medicine' and 'Making Markets' and a non-collaborative approach would *not* be a very cost-effective way for getting large numbers of them involved, and would lead to slower average speed of vaccine development and lower average quality of vaccines than a highly collaborative mechanism would achieve.

Why perpetuate, and fight, the current problem anyway?

'Strong Medicine' perpetuates the main problem in the current system: the cost of large amounts of the R&D has to be extracted through the price of the vaccines that have potentially low manufacturing cost. If one of the problems generating low vaccine R&D is price pressure on vaccines once developed, this approach fights these pressures in part only by creating a series of further difficulties related to the high end prices, including large tendencies to push towards lower quality and more expensive vaccines. The collaborative section above indicates that it *is* possible to create many of the incentive effects–and more–without trying to inefficiently replicate large 'additional' blockbuster (or even mega-blockbuster) markets from the start, and–with the help of 'contingent purchase commitments'–to handle late-stage issues, and still generate products at close to manufacturing cost, with strong competitive pressures to drive those manufacturing costs down.

After a seven year campaign to get this policy proposal to the top of the heap, it is disconcerting to find so little of the underlying mechanism laid bare for early–stage vaccines, and so little empirical evidence to support the assertion that the mechanism is 'strong' for such vaccines. Repeatedly we find that major problems have been ruled out at the start, only then for it to be claimed that the mechanism solves such problems.

The irony of copying public sector failures

Given their assertion that public sector failure is at the heart of the failure of many competing mechanisms, it would be ironic indeed if public sector failure might happen at the level of choosing the mechanism itself as a major part of the approach to developing early-stage vaccines. This choice will have been encouraged by those who paint an idealized picture of this approach, and who exploit the fact that while we have information on the failures of other mechanisms, we will not have information on the failure of *this* mechanism until it is too late (and even then we may not know how far we actually fell short). To avoid this danger, those supporting early-stage APCs should refuse to tolerate political support that comes without awkward questions or demands for solid empirical evidence.

'Strong Medicine' represents part of a growing movement–of many different persuasions–drawing attention to these issues. All sides in this debate exaggerate to get noticed; it is always nice to think that one's proposals are those chosen by policymakers. Disagreement is part of the discovery process. The author has come across many of those working on pull proposals who are much more sanguine than the chief authors of 'Making Markets' about early-stage APCs. However, the momentum in the proposal, the constant reference to its simplicity and, by implication, that somehow raising doubts about the workings indicates that one has missed the obvious, and the embarrassment in speaking against the herd (the "widespread enthusiasm"[478]) or even in admitting that one had previously accepted a proposal without asking too many questions, has made it ever more difficult to achieve a rational debate about the pros and cons of early-stage APCs.

When, at the end of Hans Christian Andersen's tale, a little child squeals that the Emperor has in fact got no clothes on, and the people start to repeat this, the Emperor realizes the situation, and yet carries on the procession to its bitter end, while his chamberlains continue to hold up the train of his cloak, knowing that it is not there. Let us hope that, after reflection, this does not happen in this case.

The Dangers of a Collapse in Funding for HIV Vaccine Research

Matters are worse. A series of recent articles have made it clear that there are strong pressures for the

trimming of current levels of funding for HIV vaccine research due to the size of government budget deficits[479]. This is revealed too in the 2005 Economic Report of the President[480] and in the proposed U.S. budget, which includes only a 0.5 percent increase in overall funding for the NIH, substantially less than the rate of inflation during the past few years and way below the rates of funding increase of the past decade. In a recent article, "US Belt Tightening Could Hit AIDS Efforts–Official"[481], discussing the way that the US administration has tightened the NIH budget in response to budget deficits, Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, NIAID, is quoted as saying:

> *"Our belt is being tightened for us... the previous largess that was associated with all research, particularly HIV, is now not going to be a reality for the future."*

Fauci argues that this tightening may well hit HIV vaccine research especially hard.

This situation is being repeated elsewhere with recent alarmist headlines about the deteriorating state of public finances in the UK as well as all over the OECD. As Harvey Bale put it in a posting to the CIPIH Forum:

> *"Unfortunately, as public budget deficits prevail across OECD countries, there seems little prospect of major new public initiatives on a scale to make a significant difference. So it is best to build on the partnership models that are succeeding (such as the Medicines for Malaria Venture and WHO/TDR), and explore new approaches (eg. advance purchase agreements) that will have a better chance of success within limited public resource constraints."* CIPIH Forum, 7 March 2005.

Several observations are in order:

The US carries more than its fair share. Others should pay more.

First, the US has been carrying a disproportionate share of the funding burden for HIV vaccine research. Worldwide funding for AIDS vaccine research has grown from just over $100 million in 1993 to $600 million in 2003, with $520 million being spent by the NIH, perhaps $60 million by the U.S. Department of Defense, and groups like IAVI making up almost all the rest. The rest of the world has not been pulling its weight in funding. If the world is to meet the level of sustained funding–£1.2bn per year[482]–that the Global HIV Vaccine Enterprise suggests is needed to achieve an HIV vaccine or set of vaccines, clearly this is not going to happen without a great deal more of a *global* effort on funding. Instead of giving in to the logic of budget deficits at this year's G8 Summit, the UK should be encouraging other countries to pay their fair share.

It is effectiveness and not the timing of payment that should ultimately matter.

Second, what should matter is *not* what *will have a better chance of success within limited public resource constraints*, if that means sub-optimally switching from front-loaded funding to end-loading funding just to fit within a resource constraint, but rather what *will have a better chance of success.* As Farlow 2004 Chapter 3 argues, ultimately what matters is relative effectiveness of approaches. The exact *timing* of funding flows should be a completely independent issue. If APCs are more effective, then so be it that research activity switches towards using them. But if APCs are less effective, the temptation to avoid early funding flows should not lead to APCs replacing other more effective approaches. If end-loading of funding is most efficient, then end-loading it should be–but it is a means and not an end in itself. Budgetary failings might make far-off payments more appealing for policymakers, but this should not be what dictates how research is financed.

Funding cut-backs are good news for APC advocates

Third, this is good news to leading advocates for an APC for HIV. They have long argued that APCs are a hugely superior mechanism to anything else, and should be the driving force for HIV vaccine R&D. The supporting cost-effectiveness data (though it is no longer used to support anything) argues this very strongly indeed by modeling every other approach as, comparatively speaking, hopeless[483]. Key advocates should be nothing if not happy that that analysis and previous lobbying for the cut in other approaches to make way for APCs is starting to have affect. Indeed, one of the reasons that the model underlying APCs (Appendix 3) has no role whatsoever for any other funding mechanism is because of the vision of APCs as *the* funding mechanism. One of the logical conclusions of the problems of achieving additionality for APCs is to not require them to be 'additional' to much of anything else anyway.

We should rigorously test APCs before risking funding cuts

Fourth, if the emphasis of funding mechanisms is to shift towards APCs, should not policymakers naturally first seek high-quality, independent analysis of the power of APCs for HIV? Surely we should know *for sure* that such instruments are going to work before cutting other forms of HIV vaccine research to make way for them? When, a year ago, this author discussed the use of APCs for HIV vaccine research with a range of those currently involved in promoting the idea, not one was convinced that they would be used for HIV (as opposed, for example, to pneumococcus and rotavirus). What happened in the intervening year to change the underlying logic? Observe how the figures for the levels of HIV research indicate that very little *privately-funded* HIV vaccine research is going on–a tiny fraction of what would be needed in response to an APC. Should not these extremely low levels of current privately-funded HIV research not alert us to the dangers of cutting what we have got for what is no more than speculative?

We did some simple math earlier to show that if an HIV vaccine might take 15 years to develop and need $1.2bn per year of out of pocket trial costs, replacing this flow with a pot of funds at the end of the process, would (if we presume no crowding out at all) require a pot of about $65bn to $165bn. The most likely private response to an HIV APC in the face of such figures is to hardly respond at all. Throw in the problems for setting terms, creating a fully credible adjudicating committee, and the huge reputational risks even large pharmaceutical firms would open themselves up to, and the chances of reaction are even lower. The most likely response overall, if the over-hyped power of HIV APCs is believed by policymakers, will be to reassure them that they can cut back funding, and a collapse in HIV research ensues.

One of the dangers of an ideologically driven approach is that everything is so self-evidently true that the need for proof can be dispensed with. If APCs for HIV will be very weak instruments for the next ten or so years, as this author argues, should we worry (or not) about the impending collapse of funding for HIV vaccine research consequent on such opportunistic behavior?

Why provide reassurance to those thinking of cutting HIV vaccine research?

Fifth, why is such a highly-respected research think-tank–normally working on resolving the problems of developing countries–providing the intellectual succor and reassurance to those thinking of cutting back HIV vaccine research in the face of tightening budgetary pressures, when the replacement mechanism is not even known to be capable of generating *any* of the lost vaccine R&D, especially over the next 5-10 years? Why adopt a PR-based approach rather than a fact-driven approach to doing it? Why encourage such cuts without any concern for the shaky empirical foundations once provided–but no longer trusted upon–as justification for the APC replacement? Why sacrifice intellectual rigor for manipulation of policymakers and blind opportunism regardless of the eventual consequences?

Should the excesses of the 1990s, and the consequent tightening of budgets, be visited on the poor of the 2000s?[484] Surely, the interests of the destitute should be protected most of all in times of budgetary tightening? Should we be quite so actively complicit?

Should we Experiment?

It might be thought that we should just let the experiment happen[485]. After all, within a few years or so we should have strong clues as to whether it will succeed or fail. Even just the *possibility* of profitable and efficient new arrangements should cause financial markets to react[486]. Indeed, given the tiny amounts of current private funding for HIV vaccine research and the supposed huge impact on levels of private funding to be expected in response to APCs, just a small absolute reaction should cause a large *percentage* reaction in private investment. No doubt, given the supposed overwhelming strength of such instruments, we should already be seeing such a reaction in the data (maybe advocates are already collecting the data to reveal this reaction to us?). A suitable policy announcement this year–something permanently fixed perhaps, the more permanently fixed the better for generating investment response–should strengthen this reaction dramatically and provide the data we need (though the 'Making Markets' paper does not discuss the information gathering mechanism currently being put in place to test this response in the next few years[487]). We would not need to wait 30 years (as the literature suggests) to test it. A few years

should do. Perhaps though, with the APC for HIV being so ineffectual (even more ineffectual according to current announcements), maybe those like the current author who think the approach utterly harebrain for early-stage vaccines such as HIV, should simply sit back and wait a few years for the evidence to come in?

The only problem with this, unfortunately, is that if the experiment fails and, meantime, other HIV vaccine research collapses (or simply fails to adequately expand) because policymakers have been fed the quick fix they need to avoid tough decisions, the experiment will put us back even further, with long-term consequences for the epidemic in Russia, India, and China that do not bear thinking about. Because it takes 2-6 years to do a Phase III trial, it is not as if doubling up funding at some future time will make up the lost ground; it will broaden the search, but will not be able to 'buy back' the time. And we are still stuck with the APC and all the concomitant institutional structure for 30+ years (a five year experiment could not have abandonment of the approach after less than 30 years written into it). For all this time we would have with us the danger that though it does nothing to stimulate HIV vaccine R&D, it deters smaller and less powerful developers by creating a convenient market stymieing device in the 'end-game' in the shape of IP ownership rights to the whole R&D endeavor for the one big firm that, after much research by others, has the most resources (and influence) to take the IP.

The sensible approach in the light of the inherently experimental, speculative, nature of knowing if such instruments will ever work, the dangers of losing time, the dangers of losing IP rights, and given that we have never *tried* such instruments on *anything*, even on the most trivial of cases, is to cross-examine–to 'stress test'–every aspect of the proposal, and to appeal to independent empirical evidence. But this is not currently on the agenda of the leading advocates. Maybe we really will have to experiment after all?

Some Thoughts on a G8 Strategy

It is pretty clear from all of the above that–in spite of claims to the contrary–a $3bn (or $6bn) HIV APC would do very little to stimulate an HIV vaccine (and the current $3bn pitch, even less). The sums are pretty simple. Because of all the many risks (especially of the science but also of the workings of the mechanism itself), finance costs would gobble up 80% at least of this. Crowding out, and many other failures, would take care of a good chunk of the rest. Result? Maybe six months worth of what the Global HIV Vaccine Enterprise is currently requesting. If the vaccines cannot be manufactured cheaply enough it will be even worse: 250 million HIV vaccines at a highly conservative $10 a shot costs $2.5bn. Where will that come from? HIV vaccine science might be close to 'rocket science' at the moment, but the economics of it is not.

It would be silly to fix terms now

Even if policymakers wanted to fix terms now, expecting little activity in the near-term (though this is hardly the language of the promoters of APCs at the moment) but intending that the APC be in place 'for later when it matters', it would be impossible to do so 'correctly' and cost-efficiently without resolving the relative role of other parts of the mechanism first. Even then, fixing now when there is no urgency to do so is not a remotely sensible proposal given that policymakers would lose the flexibility to learn from, evaluate, and scale up the much more collaborative approaches that are more likely going to be needed to generate HIV vaccines (and this in itself would help to more efficiently set a later-stage HIV purchase commitment as and when a vaccine is looking much more likely). Besides, we have no experience of using APCs. Surely, given the huge importance of credibility and of keeping the capital costs of developers down, the last thing investors want to see is a mechanism in place that then needs constant rounds of reformulation as it is realized just how unworkable it is? Hardly confidence inspiring. And wasteful if there was no real need for terms to have been set yet.

The big gambles

The discussion above suggests many big gambles would be taken in fixing an HIV APC. A few stand out:

1) The 'Framework Agreement-as-tender' that places a potentially huge amount of 'mechanism risk' on to developers, especially those we wish to encourage, and may simply prove non-credible and have to be abandoned mid-stream. The alternative is to be stuck with it even if it is not working and is extremely costly, so as not to 'undermine confidence' or trigger litigation. Credibility is a delicate subject. It is not always helped by something being fixed. If the thing that is fixed proves to be badly fixed and needs radical reform later, this harms credibility,

and it would have been better to have waited before making a fix;
2) The payment structure supposedly for incentivizing a range of quality and vaccine resistance issues but that puts heavy risks onto developers (especially the 'higher quality' developers) and would never work anyway. There is no evidence that there is the slightest intent to carry out such a payment structure in practice;
3) The lack of competition in tender structures at the end of the process that undermines the drive to cheaper production costs and ultimately weakens access;
4) The bias in the mechanism towards the current few large firms, even if they are not that keen to react to the mechanism, with the device simply giving a large, influential firm the ability to 'take all the IP' at the end of a mostly publicly–and foundation-financed endeavor, and the highly uncertain impact on the structure of the industry, with the very real danger that fewer and not more vaccine players are active;
5) The implications of the reputational risks to large players not fully understood;
6) A whole range of IP problems;
7) The dangers of aggravating a potentially better, more collaborative mechanism;
8) In the case of the UK, the huge political capital wrapped up in the IFF. A few early expensive white elephants would be the best way to sink the IFF[488].

Incidentally, purchases of currently existing vaccines and even late-stage purchase commitments may only hint at these problems and may even give quite the opposite signal.

We can learn a lot first

Given the leagues of extra complexity for HIV and malaria, it is brave to suggest that *nothing* can be learned from early applications. While 'Making Markets' argues that "the analysis in this report shows that such contracts can be developed *and implemented successfully*" (italics added)[489], a more balanced response of one vaccine expert to the 'Making Markets' report was:

> "*It has a continuous optimistic tone indicating that all problems can be solved while in fact many of the problems have never been solved before and may represent insuperable barriers.*"[490]

Maybe the Center for Global Development should adhere to its own previous wise counsel:

> "*These market-based mechanisms are not panaceas–like all experiments, they should be treated as pilots that are carefully evaluated at each stage.*"[491]

> "*A purchase commitment or price guarantees approach would need time and experimentation to evolve into an optimum design. The first step in developing these commitments as a tool for encouraging R&D would be to try in a few cases where current R&D incentives are inadequate and where the pull approach seems well suited to fill the gap.*"[492]

A permanent fix is a permanent fix

Contrary to the views some are starting to articulate, no permanently fixed APC could be fixed *now* with all the troubling details left to be dealt with later. First, the APC *is* a legally-binding contract, even before it gets any takers, because firms work towards it on the basis of publicly-declared terms. These terms *cannot*, and should not, be changed. If terms are set very sub-optimally from the start, not only will this jeopardize its own survival but it will also risk damaging other parts of a more general approach.

As an example from another area of economics, no country would ever consider entering a permanently fixed exchange rate mechanism without full consideration of the optimal parity. If the rate is set too low it runs the risk of excessive inflation. If it is set too high it runs the risk of deflationary pressures and unemployment. *Both threaten the credibility of the mechanism and its continued existence.* Once in the mechanism, any doubt about parity or even slight hint that the mechanism might be replaced even if it is not working, is itself damaging and will impose heavy costs, even if some major change in circumstances may have cast doubt on the original parity. Like badly-set exchange rate mechanisms, outside of the crisis situation when replacement of the mechanism is forced, policymakers are stuck with a badly-set APC.

The notion that the APC could be set very large to overcome these potential problems is damaging in its own right. If there is no rush to join, the more sensible measure will be to spend some time first learning about the behavior of the mechanism.

Private investors put off by an overemphasis on APCs and a lack of critical analysis

Besides, obsessing about an early HIV APC to the exclusion of obsessing about the other, perhaps more difficult and collaborative, parts of the R&D framework, will put private investors off *even more* since they will come to understand (and price in to their investment decisions) that the risks of ever getting an HIV vaccine are so high, and the expected time to delivery so very far off, that all the figures discussed above have to be multiplied so many fold that there is even less incentive to engage in early HIV vaccine research. Those lobbying hard for an early APC for HIV to the exclusion of lobbying for the more collaborative parts of the approach to developing a high-quality HIV vaccine, need to reassess whether it is the wisest use of their influence and not, in fact, counterproductive.

Private investors are also put off when they discover that investment proposals being put to them have not been fully thought through. How likely is it that private investors will believe that the APC mechanism will work for them, when they discover that the last thing those promoting it had shown any interest in doing was critically and rigorously cross-examining the validity of the mechanism rather than just lobbying for more supporters of it? Given the utter centrality of credibility for the 30+ years of the life of the mechanism, the rational approach, it would seem, is not to show the slightest interest in having yet another supporter, but loads of interest in finding out just why the critics are critics at all. It really is quite incomprehensible, and contradictory to the inherent logic of the mechanism, that transparent and critical analysis is not more openly encouraged. And it is not a good sign for investors either.

Private investors are also put off when the strategic and reputational risks to them are not fully spelled out. In many of the sections of this (and the earlier) paper we have come across potential strategic manipulations of the commitment mechanism, many with negative consequences for the mechanism even if positive benefits to those doing the manipulation. How should we interpret this? On one level it might suggest that the mechanism should be designed better to avoid these outcomes. On another level, and probably the more likely outcome, firms (especially large pharmaceutical firms) are likely to want to avoid mechanisms that put them in such unenviable strategic situations in the first place. Given a choice between a PDP with equal present discounted value compared with an APC, most large pharmaceutical firms would prefer the PDP, since it avoids placing all kinds of risk, but especially reputational risk, onto their shoulders. Yet again, we find that though the APC tends to pitch itself more towards the large pharmaceutical players, not even *they* are likely to want it over what is to them a less risky alternative.

A Set of G8 priorities and a Big Opportunity Being Wasted

The advice here (for what it is worth) is that those pushing heavily for an HIV APC should concentrate their efforts instead on the following order of priorities:

1) Fully funding the existing product procurement/donation mechanisms run by foundations, companies, non-governmental organizations, and international bodies:

> *"This would be a more tangible proof of sponsor commitment (as it is by The Gates Foundation) and could usefully 'lock–in' donors to the eventual, hopefully successful, outcomes… eg. for Malaria a major injection of cash over the next 5 plus years into MVI and into EMVI (and perhaps others)."* [493]

> *"The development of new medicines, however, must be viewed in the context of the wider health issues facing low income countries. A large proportion of the disease burden in such countries is unnecessary, since it could be reduced by the effective distribution of medicines that are currently available and inexpensive."*[494]

2) Asking sponsors (who would be those that eventually pay for the vaccines under any mechanism) to bite the bullet on the level of resources needed into some of the existing global/regional consortia/PDP's[495] and emerging Vaccine Enterprises, rather than issuing huge way-off, and largely meaningless, financial promises. Most of the current levels of funding for HIV research come form the US. There is no reason why the US should keep carrying the majority of the burden. The G8, especially the non-US members, should put in place the level of funding for this for the next ten to fifteen years (should it take that long), with suitable opportunities for review.

3) A combination of more targeted funding and, where applicable, purchase commitments for all the late-stage products in which they are likely to have at least some strength, including hepatitis B vaccine; haemophilus influenzae vaccine; rotavirus vaccine; HPV vaccine (when that product soon enters the market); a cholera vaccine emergency supply; and the conjugated typhoid vaccine emerging from research at NIH, IVI, Vietnam, and elsewhere; the meningitis C vaccine being developed by a consortium under WHO and PATH; and a pneumococcal vaccine against the important strains in developing countries. In these cases, the scientific risk is relatively low (not in all cases, but certainty much lower than for HIV, malaria, and tuberculosis), yet the market risk very high, the capital cost proportion of expenditure (relatively) low, and the advantages of purchase commitments in creating more certainty very high. The emphasis in many of these cases is about getting product price down, which requires much more use of creative IP and know-how and the opening up of the market to competition at late stages of development and procurement.

Later, the experience gained from this can be used to work out how purchase commitments might ever be made to work for greatly more complicated vaccines such as HIV (for example, the highly likely problems making the mechanism work for rotavirus will almost certainly require a major rethink on how to make the mechanism work for HIV). Even then, it is highly unlikely that purchase commitments for HIV or malaria should put much of their weight on the R&D of such vaccines. Instead, they should concentrate on the hugely important and difficult task of production and distribution.

4) Putting in place an 'Advanced Distribution Commitment' to fully fund the delivery mechanisms for HIV, malaria, and tuberculosis vaccines once developed. This would cut in *after* competitive tenders have driven the production costs of such vaccines as low as possible. This is quite the opposite of the current lobbying effort. It puts next to no emphasis on extracting R&D costs through the vaccine prices[496]. There is not even any talk within the 'Making Markets' proposal of ways to address the need for funds to distribute the vaccines (ie. an 'Advanced Distribution' scheme). Why not? Why the topsy-turvey priorities? This distribution commitment is not just a financial commitment. It includes 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. It also includes a commitment to tackle institutional failure and corruption that holds back provision of healthcare and access to medicines.

5) Meanwhile, totally downplay APCs for HIV, and instead push home to policymakers 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. The HIV vaccine enterprise should have complete control over whether or not it chooses to set competitive-tender style purchase commitments and should not have a large separate APC imposed upon it from outside in advance, given that this (especially the IP implications) risks aggravating its problems.

The hugely positive signal of success on the purchase commitments for the diseases listed above, the credible knowledge that they can be modified to make them effective and will be used again, coupled with the bullet-bitten approach of policymakers to doing something of real power to drive HIV vaccine research forward and the front-loaded funding needed to do so, will make eventual HIV purchase commitments–if ever they are used for HIV vaccines–more powerful, cheaper, and easier to set.

Do not waste this year's and next year's big opportunity

The G8 Summits of 2005 and 2006 could present a big opportunity to do something radical about achieving HIV, malaria, tuberculosis and other vaccines, and this should be played much more strategically than it is. One cannot rule out the possibility that many of the objectives that the UK is pushing for the G8 will fall well short. The IFF will stumble without US support and the dangers the other members perceive in going it alone. And the French have a very different proposal for increasing finance for development based on a 'Tobin Tax', so there is genuine tension over a key UK objective both within Europe and the US. On top of this, the environment package has been heavily watered down already. The debt right-off package is doing relatively better but is also struggling. The global HIV vaccine enterprise (and vaccine enterprises generally), coming up on the outside as it were, has much going for it.

First, the US has already expressed commitment to it with President Bush's announcement at the G8 Summit last year, and he and the US administration can be challenged to make good on their high-sounding promises. There is a tendency for the holders of G8 Summits to want to do something 'different' from previous holders, which they can label as their 'own' bold new initiative. This is not the time for such games.

Second, the next G8 holder, Russia, has *more than any other country to gain from a global HIV vaccine enterprise*[497] and could be a great deal more willing to take the baton than currently seems the case (and *can*, and should, be persuaded to do so). Russia's HIV/AIDS epidemic is already a nationwide phenomenon. Under worst-case scenarios, the rate of infection in less than ten years' time will be similar to sub-Saharan Africa today (11%). On conservative assumptions, by 2025, cumulative new infections are estimated between 4 and 19 million in Russia, 32 and 100 million in China, and 30 and 140 million in India with the cumulative death toll estimated between 3 and 12 million, 19 and 58 million, and 21 and 85 million respectively. Russia will suffer worst economically however. Even a mild epidemic, it is predicted, would cause the Russian economy to be completely stagnant to 2025[498].

In all three cases, in spite of the huge economic impact, the figures are swathed in secrecy, and political leadership is in denial. So, passing an emerging Global HIV Vaccine Enterprise onto the Russian G8 agenda would have a double impact by helping Russia and others to face up to their impending crises too[499]. From Russia's perspective, an HIV APC is the least desirable outcome, since by being a non-eligible market it would face much higher prices than for vaccines generated under a global HIV vaccine enterprise.

Third, a powerful case can be made for a Global HIV Vaccine Enterprise.

At a very crass level (but that is what strategy is all about sometimes) the UK could yet find itself looking for a 'success' from this year's G8 summit, and the Global HIV Vaccine Enterprise could be fitting enough to fit the bill. The UK could play a useful, and well-respected, pivotal role in getting it fully off the ground, taking it from the US and passing it forward to following holders of the G8 reigns including Russia. Given the increasing budgetary pressures both in the US, the UK, and elsewhere, now is a better time than later to do something to push the initiative forward. 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 (that would nevertheless be a source of instability to any emergent IFF), this strategic opportunity should not be squandered.

The truth is…

Large portions of this paper were written before discovering that the APC for HIV being proposed by the Center for Global Development had, yet again, been trimmed–to $3bn this time. Given that pitching ever lower is dangerous and also weakens the incentive, why keep pitching ever lower? We showed above that $3bn was an essentially random figure, unrelated (contrary to what it should be) to the underlying science and costs of developing a HIV, malaria, or tuberculosis vaccine[500]. At current rates of scientific risk, capital costs, horizons, and crowding out, a $3bn level of payment for an HIV vaccine could not, in the near future, possibly stimulate more than a few months of the current levels of effort that the Global HIV Vaccine Enterprise says is needed.

So, what *would* the $3bn do? With the payment coming at the end of a huge public and foundation funded effort, it is hard to imagine that most of the 'additionality' of the $3bn would not be crowded out, leaving the fund to essentially go to the one big private pharmaceutical firm that positioned itself best in the 'end-game'. And that is about it. The line that "a large incentive might bring in a single major pharmaceutical firm" [501] comes back to haunt us. Incidentally, it is not as if large pharmaceutical firms would ex ante want this, even though they may be pressured to behave this way ex post; it is just another example of the reputation risk they are expected to face by taking part in an APC.

The truth is that $3bn is not the figure generated by a serious discussion of the level of funding needed to create incentives to develop an HIV vaccine. It is the cost of political favor, of getting policymakers to say 'yes', and of allowing the chief APC advocates to declare their 'policy success'. The figure is pure opportunism, and is not based on any scientific or economic logic. It does not even suit large pharmaceutical firms

ultimately, given the huge reputational risks they would have to take on to try to win a 'highly lucrative' APC for HIV. For HIV and other early-stage vaccines they would be better served by decently funded PDPs. The only thing it could achieve for them is the stymieing of emerging market vaccine developers undermining their dominant positions. Ultimately the mechanism for early-stage vaccines does not really suit anyone except those lobbying for it.

Similarly, the Center for Global Development was set the task of critically and rigorously evaluating *if*, and *how*, APCs might ever work for a range of diseases, including HIV. The intent, it now appears, was to simply use it as a rubber stamp for a lobbying effort, the result of which had been set a long time ago. If this had not been the case–and in light of the permanence of the mechanism–then the most skeptical and troubling analysis would have been at the heart of everything, rather than analysis largely based on the faith of believers[502]. But, by this stage in the game, the notion is not to set in place a workable and fair 'mechanism' with an emphasis on very broadly-defined 'quality' (so all the stuff above about rules for distributing the APC to ensure quality and market enhancement and so forth, were just so much waste of breath) but simply to get a PR[503] and 'policy success', for which workable and fair mechanisms and troubling analysis are just a distraction.

For years politicians have managed to get away with putting extremely low emphasis on vaccine R&D and the distribution and healthcare systems for making full use of the results. Challenged at long last to put proper emphasis on vaccine development and use, and with all the impending dangers of collapsing research funding, especially for HIV, is our best response to feed them quite such an easy cop-out?

Acknowledgements

This paper is dedicated to the memory of Sanjaya Lall. This paper is based on "The Global HIV Vaccine Enterprise, Malaria Vaccines, and Purchase Commitments: What is the Fit?" submission to the 'Commission on Intellectual Property Rights, Innovation and Public Health', WHO, March 2005, www.who.int/intellectualproperty.

For more comprehensive explanations of some of the points in this paper, see the pharmaceutical, neglected diseases, and vaccine finance papers at www.economics.ox.ac.uk/members/andrew.farlow, especially www.economics.ox.ac.uk/members/andrew.farlow/VaccineRD.pdf and the PowerPoint Presentation http://www.economics.ox.ac.uk/members/andrew.farlow/Farlow%20Arizona%2016%20May%202005.ppt

Since this is part of an ongoing debate, these papers and presentations are more of an exploratory exercise than a statement of a definitive, fixed, set of conclusions. The author very much welcomes feedback.

The author has been influenced in his thinking by a wide variety of extraordinary and dedicated individuals across a range of public, private, philanthropic, and international institutions, academia, and the vaccine world. This paper has benefited from feedback, discussions, and interactions of all sorts. I am extremely grateful to these individuals in helping me to understand the issues, and to give me a flavor of the wide variety of views on how to go about solving the problem. None of them bears any responsibility for the content of this paper. I am especially grateful to (in alphabetical order) Charles Arntzen, Owen Barder, Amie Batson, Charles Clift, Nicoletta Dentico, Pierre Druilhe, John Erickson, Christopher Garrison, Gargee Ghosh, Spring Gombe, Cheri Grace, Adrian Hill, Ellen 't Hoen, Aidan Hollis, Tim Hubbard, Andrew Jack, Soren Jepsen, Warren Kaplan, Hannah Kettler, Anatole Krattiger, Paul Ladd, Richard Laing, Sanjaya Lall, Ruth Levine, Donald Light, Jamie Love, Richard Mahoney, Stephen Maurer, Barend Mons, Suerie Moon, Mary Moran, Kevin Outterson, Michel Pletschette, Fawzia Rasheed, Jerome Reichman, Anthony So, Hilary Sunman, Sandy Thomas, Adrian Towse, Saul Walker, and Roy Widdus. I would also like to express my thanks to the participants at conferences and seminars in New York (Columbia University), Penang, Malaysia (Drugs for Neglected Diseases Initiative and Universiti Sains Malaysia), London (Médecins Sans Frontières), Bellagio, Italy (Rockefeller Foundation, New York, and Consumer Project on Technology, Washington D.C.), and the Biodesign Institute of Arizona State University. Anatole Krattiger was a truly superb journal editor and this paper would not be what it is without his wise and perceptive comments and hard work.

Notes and References (all web pages have last been accessed on 29 June 2005)

1. 40,000+ per day divided by the time taken to read this paper.
2. 10%-15% of global pharmaceutical spending goes into R&D, and barely 10% of this goes into 90% of the global disease burden.
3. In the marginal cost sense. Once one gets above a certain production scale, most of the cost of an additional vaccine in the case of many already existing vaccines is the device for administering the vaccine and its wrapping. The actual vaccine itself may cost as little as a few cents; most of the value is in the 'information' contained within the vaccine, that is the result of the R&D process that led to the discovery of that information. The combined diphtheria, tetanus, and pertussis (DTP) vaccine costs about $0.09 a dose, and the measles vaccine costs about $0.14 a dose.

Nevertheless, some more recent vaccines and future vaccines, such as those for HIV, may not be as cheap to manufacture, at least in the first instance.

4. 'Advance Purchase Precommitment', APP, would be a more precise descriptor because in some cases policymakers really would be asked to commit themselves before they knew very much about what they were committing themselves to. The term 'Advance Purchase Precommitment' was used a great deal in the early days of development of the idea. However, due to its more common parlance, APC is used here. This paper also uses the term APC instead of the term 'AdvanceMarket' as used in the Center for Global Development (CGD) report, for several reasons. First, 'APC' captures the notion that it *is* a *commitment* to purchase. Second, because in a previous paper (Farlow, A.W.K., 2004, ibid.) APCs were described in ways that are essentially the notion captured in 'AdvanceMarkets' when they are properly articulated; once one recognizes that APCs are complicated devices supposedly attempting to create *additional* market–through a precise set of rules but also with layers of institutions and discretion–then there is no difficulty in using the terms interchangeably. Third, the sort of contracts negotiated will likely not be based on 'AdvanceMarket' logic anyway, but will be based on much narrower remits, such as just being an implicit subsidy to a domestic firm. Fourth, the language of 'AdvanceMarkets' would tend to suggest a fact rather than a hypothesis in need of evidence. It is not immediately apparent that much of an additional 'advance market' for an HIV vaccine would actually be created by an 'AdvanceMarket' instrument. That this can be achieved needs to be proven, not prejudged in our use of language.
5. Kremer, M. Appendix 3, www.pm.gov.uk/files/pdf/Appendix%203.pdf
6. 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.
7. CGD Press Release, 6 April 2005, page 1. This is an extraordinary way to judge APCs. *If* developing an HIV vaccine were to take $1.2billion per year for at least 15 years (as currently suggested by IAVI) and an APC only locked in to pay for very late activity and to allocate the IP rights, this would be like a plumber turning up to fix the plumbing on a $1million house and claiming that they had added $900,000 of the house's value by making it livable and that their work should be valued accordingly.
8. It might also be added that there is only one of me, whereas many of those making these points are part of huge teams working specifically on these issues (the Berndt et. al. paper above alone has seven co-authors), and have much higher levels of resources and much more time to do these things than just one author, who also happens to be working on many other areas of economics besides this. That I do not do a voluminous literature review on the problems of other approaches is, to say the least, a little unfair. Perhaps those making this criticism should stick to trying to make a better case for APCs for HIV, malaria, and tuberculosis, and see if they cannot beat the case being made here?
9. Center for Global Development, 'Making Markets for Vaccines: a practical plan', 2005, www.cgdev.org/publications/vaccine. Also see www.cgdev.org for some of the great variety of other, often excellent, development-related work carried out at the Center for Global Development.
10. 'Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases', Kremer, M., and Glennerster, R., Princeton University Press, November 2004.
11. www.number-10.gov.uk/su/health/default.htm
12. Farlow, A.W.K., 2004, ibid.
13. Given the discount factors involved, 15-30 years is effectively 'forever'. The dangers of signaling to investors that the program might be allowed to collapse, and hence sending capital costs dramatically higher, and bringing about collapse, also militates against opt-out and sunset clauses and against making the program reversible.
14. 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 2005 CGD report See Muraskin, W. "Vaccines for Developing Economies: Who will Pay?" Albert B. Sabin Vaccine Institute, New Canaan, CT, USA. 2001.
15. This means that many of the critics, including this one, fit into the group of pull advocates!
16. Given standard rates of time discounting, 30 years is effectively 'forever'.
17. 'Strong Medicine' p84 and 'Making Markets' March 2005 p46. This statement *really is* in both of these publications. Incidentally, we really would have to wait thirty years to abandon the approach if it was not working, as will be explained below.
18. It's job, after all, was to evaluate the feasibility of the proposal and *not* to advocate, or to rubber-stamp, policy made elsewhere.
19. The worst case is when policymakers promise the level of payments supposedly based on an application of the benchmark idealized model (ie. a large 'pot') but then do not actually enact any of the rest of the framework (though this paper argues that they would struggle to enact much of the theoretical framework).
20. Though, funders may also have an opt-out if the contracts fail to stimulate '*enough*' research.
21. See 'Making Markets' Chapter 5, titled "$3bn per disease," and the CGD Press Release: "Three Billion Dollars Per Disease… a market of about $3 billion is needed," and The Commission for Africa, February 2005: "For Malaria, the market size needed to deliver the malaria vaccine is $3 billion (CGD, 2004)."www.commissionforafrica.org/english/report/introduction.html page 409, Chapter 6 Footnote 92).
22. "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
23. Gordon Brown (The Observer Newspaper, June 5, 2005, page 30) quotes $4bn for malaria.
24. Indeed, the Gordon Brown op-ed mentioned a new tax credit to stimulate UK research into diseases prevalent in the developing world but does not clarify whether any of this tax subsidy would come off any APC payment or whether it would be an additional publicly-funded cost on top of the APC.
25. For some reason this description has been criticized (see Barder, O., Kremer, M., and Levine, R., ibid., p8). But if the APC model were chosen as the route to develop an HIV vaccine, we really would be scuppered if the model did *not* work in a 'blockbuster' fashion with multiple competing developers and very few 'winners', with winners therefore expecting 'blockbuster'-size payments. The 'blockbuster' nature of the model is a fact, and not a criticism. This fact does, however, lead to a number of consequences. In particular it is not clear how easily such frameworks work in an area of science that involves a great deal of need for coordination and 'sharing', such that investors may worry about sufficient return on their *own* investment. Neither is it clear that this feature does not create a range of dynamic consistency, credibility, and reputation risk issues for firms.
26. Appendix 3, Kremer, M., removes all of this by presuming only one mechanism and only one *type* of researcher is actually present.
27. Since this Appendix 3 factors other mechanisms out, by default this issue never arises.
28. This is highly simplified. There are chains of firms–biotechs and large pharmaceuticals–pursuing different product leads, with each 'chain' visualized here as a 'firm'.
29. For some inexplicable reason this has been described as some sort of 'criticism', it is a straightforward and well-understood fact.
30. We can only guess at these figures since none have been calculated. See the discussion below.

31. These are extremely rough figures to illustrate a point. The required rate of return, as well as capturing the required market rate of return, is also assumed to capture uncertainty about internalizing the value of research, of ever getting a vaccine, of the dangers of the misuse of discretion and of time-inconsistency in the mechanism, the risk of collapse of the mechanism, the reputation risk for the last big player in the chain, and the high required rates of early venture capital funding. Some have argued that these rates are even too low. We also presume no 'crowding out' at all and that the winner(s) get immediately paid everything at the end. These are low required rates by venture capital standards (normally 30%-40%), but they may be too high for other sorts of investors.
32. www.cid.harvard.edu/books/kremer04_strongmedicine.html
33. It would also need to be acceptable to non-eligible countries, as will become clearer below.
34. 'Making Markets' p 61 ($20-$25x250 million treatments). Recently this has been trimmed to $15 a treatment and 200 million treatments (ie. less than half the $6.25bn). Given the time it has taken to prepare this paper, it has become a sobering experience to have to keep going through it trimming the figures down every time a new policy pronouncement is made.
35. The individual chance may be low, but given how few other firms there are, if one firm wins, the greater the chance it will be oneself.
36. In practice, leading advocates have not hidden the fact that a few big companies are seen as driving everything, so most of this argument would not apply.
37. See Farlow, A.W.K., 2004 Section 7.16. The notion is that control over IP generated by the mechanism, and the market segmentation, strengthens the ability to price higher in the non-eligible, richer, markets.
38. 'Making Markets' March 2005 p6.
39. Other diseases affecting the developing world for which no vaccine is available include shigella, schistosomiasis, leishmaniasis, chagas disease, and dengue. There is a vaccine for tuberculosis, BCG (Bacilleus of Calmette-Guérin), but it provides only short-term imperfect protection against infection.
40. www.cgdev.org/publications/vaccine
41. Appendix 3, Kremer, M., p25.
42. The No. 10 Policy Unit Executive Summary, Kremer, M., page 1.
43. Berndt, E.R., WHO Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) Open Discussion Forum, www.who.int/intellectualproperty/forum/en/Discussion2_text.pdf, 17 December 2004. All Forum comments listed below are to be found on this website.
44. p17, p19 of reference 5.
45. See "Biotechnological Inventions", Chapter 13 in 'Patents for Chemicals, Pharmaceuticals and Biotechnology', Grubb, Oxford University Press, 1999. For examples of overly broad patents on gene sequences with consequences for research into global health problems, see also "Patents in Genomics and Basic Research: Issues for Global Health", J. Barton, 2001, CMH Working Paper No. WG2: 13. For a 'classic' paper on the situations where overly tight IP can harm research incentives, see "Can Patents Deter Innovation? The Anticommons in Biomedical Research", Heller and Eisenberg, Science, Vol. 280, 1 May 1998. The notion of the anticommons–the under-use of scarce resources–is the opposite of the 'tragedy of the commons', the over-use of scarce resources. Anticommons behavior happens when there are so many owners of IP relevant to a particular innovation that the power of some to block the others (even just the expectations of this) deters innovative activity and leads to fewer useful products for improving human health. This is said to bite especially in very technical fields such as biotechnology.
46. www.malariavaccine.org
47. Indeed, there is no notion of time.
48. www.who.int/intellectualproperty
49. Farlow, A.W.K., 2004, ibid. Section 10.2 explores some of the issues.
50. Observe how the desire to keep things like this secret will conflict with the requirement later that firms reveal all to the committee running the APC for it to set the terms of the mechanism correctly.
51. Farlow, A.W.K., 2004, ibid. Chapter 5.
52. Farlow, A.W.K., 2004, ibid. Section 6.3.4.
53. Ballo, W.R., in 'The Vaccine Book' Eds. Bloom, B., and Lambert, P-H., Academic Press, 2003, p85.
54. See Farlow, A.W.K., 2004, ibid. Chapter 6 for the problems that this can cause.
55. In Kremer, Appendix 3 there is the same per-period *continuation game*–a device that removes any connection across periods via, for example, sunk R&D costs.
56. 'Making Markets' March 2005, p52.
57. Strategic issues are considered at much greater length in Farlow, A.W.K., 2004, ibid., especially Chapters 10, 11, and 12. The general argument is that there are all kinds of ways that the APC mechanism can be undermined by lack of competition and strategic behavior (and worries about such behavior) that lead to lower levels of competition.
58. Kremer, M., No. 10 Policy Unit, Appendix 1 p9.
59. Farlow, A.W.K., 2004, ibid. Section 7.18 on the argument about 'quality space', and Chapter 7 on general problems with the quality issue. It turns out that there are lots of paradoxes in the quality of vaccines if 'quality' is driven through a committee at the end. See below and, for example, Farlow, 2004, Section 7.11.2, which discusses the paradox of needing poor quality vaccines to discipline behavior of firms.
60. Farlow, A.W.K., 2004, ibid. Chapters 10 and 11.
61. This naturally goes through if the APC part of R&D is fixed in spite of required flexibility. However, it also bites even if the APC is allowed to be variable but where the variability does not match that strictly needed for optimality (for example, if the science varied). This is discussed in Farlow, ibid, especially sections 8.3 to 8.7.
62. In fact there is an extra option-price component to be priced in to very early research.
63. Farlow, A.W.K., 2004, ibid. Chapter 7.
64. That these coordination issues and treaties do not seem to be part of the current thinking is confirmed by Berndt, E.R. ibid. who argues that it is "wrong to say that it would require centralized control of global public research–the proposal requires relatively little prescription on the part of governments." This is an argument relevant to late-stage and, indeed, most of all to currently existing vaccines, but is entirely inappropriate to early-stage vaccines such as those for HIV.
65. See Chapter 7 of Farlow, A.W.K., 2004, ibid.
66. See Farlow, A.W.K., 2004, ibid. Chapter 12 for more on the general problems faced by mangers and financers of vaccine and drug research.
67. See Farlow, 2004, ibid Chapter 12. If nothing else, that chapter demonstrates that capital market difficulties are fairly common to many of the suggested approaches to dealing with the vaccine R&D problem and need to be tackled too. These problems also bite more strongly, the more complicated and difficult the technology. The answer is not, automatically, to be found in an ever-larger purchase precommitment, or, indeed 'prize' in prize-based models. By drastic simplification some important financial market problems are left un-tackled in 'Strong Medicine', and, indeed, in the 'prize' literature generally. Policymakers need to face up to these problems and find new financial instruments to overcome these risks. More on this below in the section on the Global HIV Vaccine Enterprise.
68. Farlow, 2004, ibid. Sections 7.3, 7.6, and 7.7.
69. 'Strong Medicine' p95.
70. 'Making Markets' March 2005 p55.
71. With 'size' here presupposing some appropriate split of funds across developers and over time too.
72. This is all explained in Farlow, A.W.K., 2004, ibid. Chapter 11 on auction mechanisms for setting the APC terms, but also recognized in the early, Kremer, literature. It is not discussed in 'Making Markets'.

73. Maurer S. "The Right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research", Goldman School of Public Policy, University of California at Berkeley, March 2005. See p 75.
74. Referring to 'Making Markets' March 2005 p 52.
75. It is elementary economics. If the average cost of developing drugs is lower, and if investment in drug development is driven to the point where the marginal cost of generating a new drug is equal to the marginal private benefit of a new drug to its developer, in equilibrium more drugs are developed with each having a smaller market size. Large needed market sizes are driven by large underlying costs of development.
76. At least at first. It is all paid publicly later.
77. Apparently Bill Gates, on the day he received his honorary knighthood, said that he would eat his hat if an HIV vaccine were discovered in the next fifteen years.
78. www.cid.harvard.edu/books/kremer04_strongmedicine.html
79. Incidentally, instead of criticizing the no doubt very 'wrong' figures discussed here, perhaps CGD and others could come up with some calculation of the replacement figure for this stream of HIV vaccine R&D were it to be replaced with an APC– especially given all the current budgetary pressures to cut HIV vaccine R&D funding that the CGD is, perhaps unwittingly, helping to encourage?
80. Think of the underlying economic logic for a moment. Things that are trivial to discover get $3bn, just the same as those things that are extremely difficult to discover. The former are massively over-incentivized, which is wasteful. The latter are massively under-incentivized, which is also wasteful. Total waste in the system is maximized. The $3bn is given for something trivial, while the extremely difficult is now assured to be totally impossible.
81. Kremer, M., Appendix 7, No. 10 Policy Unit; Kremer, M., "New Vaccine Market II: Design Issues" in "Innovation Policy and the Economy", NBER Volume 1, pp73-118, and many other places.
82. Farlow, A.W.K., 2004, ibid. Chapter 11 shows how difficult it is to get an auction to work to reveal information about the correct size of an HIV vaccine APC.
83. 'Strong Medicine' p106.
84. Berndt, E.R., ibid.
85. Incidentally, it also sets up a conflict with the incentive to hide information (discussed in a moment) in order to try to avoid repaying large parts of APC-based on the proportion of research and development not funded by stock market finance.
86. 'Making Markets' March 2005 p44 (see also p38).
87. Economically, there is not a smooth relationship between the ever-rising price and the R&D activity that is taking place. As the level rises, or is expected to rise heavily, the level of early R&D activity falls. This is why it is always bad to set APCs too low at the start. The act of revising up (at a rate greater than the interest rate) causes investment to fall.
88. Dukes, G., CIPIH Forum, 25 November 2004.
89. Even if everything were known for certain, sunk costs, the time-cost of delay, and the limited size of the 'pot' of funds work together to create an incentive to accept outcomes lower than the target, disadvantaging those heading higher than the target (see Farlow, A.W.K., 2004, ibid. Chapter 10 and also Section 7.11.4).
90. "Incentivising research and development for the diseases of poverty," International Policy Network, 2005 p15.
91. See Farlow, A.W.K., 2004, ibid. Section 7.18 for 'quality space' proposals.
92. Kremer M. Appendix 7, www.pm.gov.uk/files/pdf/Appendix%207.pdf p10.
93. No. 10 Policy Unit, Kremer Appendix 2 p2.
94. Imagine also the dimensions and complications of this technology 'space', if research projects were also not independent– which is the case with HIV, malaria, and tuberculosis.
95. 'Making Markets' April 2005 p45.
96. Notice the way the trade-off between waiting or paying is tipped towards paying and not waiting because of the way capital costs are wracking up in the meantime.
97. 'Making Markets' March 2005 p52.
98. 'Making Markets' March 2005 p87.
99. Barder, O., posting on behalf of the Center for Global Development, to Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, 29 November 2004.
100. See, for example, "Under suspicion: the HIV drug that held out hope for millions: Fresh cause for concern over the side effects of nevirapine," Hodgkinson, N., in "The Business", 30/31 January 2005.
101. For example, if the true long-term effectiveness of a vaccine is only revealed over time, it is not clear that an apparently short-term, less effective, vaccine should be discouraged in favor of one that is seemingly 'more effective' in the short run.
102. Though this obviously creates problems for the first firm and may make it difficult to police firms not to strategically exploit this.
103. The Bolar exception allows activity relating to registration of generic products in the run-up to products going off-patent. This helps to speed up generic competition when a drug finally goes off-patent. But given that these are biological products and therefore needing their own individual set of test data, and given that know-how is so important, it follows that it is not clear how well this would work in practice either for vaccines going off-patent or for vaccines going 'off-APC'. Certainly it would work a lot less strongly than for drugs.
104. For more on this also see Farlow, A.W.K., 2004, ibid. Chapter 10.
105. Again, the logic in all of this analysis is based on *expectations*.
106. To include a penalty for delay.
107. 'Making Markets' March 2005, footnote 85, p115.
108. Yet again, we are talking in the expectational sense, with an eye to dynamic incentives.
109. 'Making Markets' April 2005 p105.
110. Where do fresh funds come from to compensate the firm for the loss of capital costs in the meantime? Strictly speaking this should be additional to the APC funds.
111. Towse, A., and Kettler, H., "A Review of IP and Non-IP Incentives for R&D for Diseases of Poverty. What Type of Innovation is Required and How Can We Incentivise the Private Sector to Deliver It?" April 2005, p87.
112. See Section 7 of Farlow, A.W.K., 2004, ibid. for more on this point.
113. Remember that supposedly there is no control over 'quality' by policymakers. The *whole point* of the exercise was that policymakers *do not know* such things, and that it is therefore better to have a mechanism paying 'by results' than having interventionist policymakers handling 'quality' en route to those 'results'.
114. And any other product, the R&D for which is being stimulated by an APC.
115. In non-collaborative settings, also observe the offsetting impact created by the lack of know-how.
116. Though, control of know-how limits the effectiveness of these provisions in the case of vaccines.
117. Since we just described the way that 'pull' can end up doing as much control en route as the push mechanisms they were supposed to be replacing.
118. 'Making Markets' March 2005 p27.
119. 'Making Markets' March 2005 p38.
120. 'Making Markets' April 2005 p26.
121. 'Making Markets' March 2005 p38.
122. 'Strong Medicine' p63.
123. 'Making Markets' March 2005 p115, footnote 85.
124. 'Making Markets' April 2005 p29.
125. See Farlow, A.W.K., 2004, ibid. Sections 7.9 and 7.10 for a range of other pressures pushing towards 'lower quality' outcomes, in that case driven by problems with developing country incentives.
126. 'Making Markets' March 2005 p94.
127. Kremer, M., No. 10. Policy Unit Executive Summary p1.
128. Barder, O., CIPIH Forum, 19 November 2004.

129. All of this is done on the basis of there being just one vaccine, when in fact there would be a complex set of vaccines over time.
130. This is a polite way of expressing exasperation at the way the Centre for Global Development repeatedly asserts that something is so (in this case that APCs "complement" other activities) but *never* spells out how it could be the case *practically*.
131. 'Strong Medicine' p106.
132. All of the following is presaged on the notion that there are *many* competing developers. Most of this makes little sense if the number of developers has collapsed down to just the one. Maybe this is why those currently lobbying heavily for APCs–with their emphasis on feeding a large contract to one big player–seem to see very little in this problem.
133. This is also a route for countries to inefficiently favor their own developers, generating a negative-sum game overall.
134. Eg. Berndt, E.R., ibid. "The proposal requires relatively little prescription on the part of governments."
135. We are yet to be provided with any figures.
136. Presuming constant intensity of effort, and we presume that all firms started from scratch. Everything is in the expectational sense since we do not really know when success would occur. Another way to think about the logic is that it is a 'gamble' and half the fee to enter has been paid from public sources.
137. Imagine the argument over the capital costs!
138. Payment "rewards scientific advances *however they are achieved*," (italics added) Berndt, E.R., ibid.
139. Indeed, given their higher capital costs, they should expect to be disadvantaged unless somehow they can be protected from this.
140. 'Strong Medicine' p98.
141. 'Making Markets' April 2005 p37.
142. This links also to the problem of credibility. If, for example, technology is greatly improved via push parts of the process, the value of the pull part should be reduced, but if it is those who are working on pull-based approaches who improve technology, they should be rewarded and not be exploited in later parts of the price setting process. The Appendix 3 technology has ignored this, but it is a standard example of the trade-off between the need to insure and the need also to create incentives.
143. If large pharmaceutical firms do this sort of research partly for PR and 'responsible investment' reasons or as part of PDPs, the fungibility of their investments across projects could generate a larger distortion than might at first be expected. Public funders too might be tempted away from activities with no 'payoff' towards those that do now have a 'payoff'. It would be hard to control for this behavior.
144. The problem is compounded by the fact that the products compete somewhat.
145. Berndt, E.R., ibid.
146. 'Making Markets' March 2005 p38.
147. Berndt, E.R. ibid. made this claim although neither he nor the recent proposals made any concession to the position of other mechanisms, nor indeed to even their existence.
148. Batson, A., 'The Vaccine Book', ibid. p366.
149. For some reason this has been interpreted as a criticism when it merely refers to an empirical fact widely accepted within the industry. It is only reasonable to expect that any APC would have to reflect this fact.
150. See Kremer, M., Towse, A., and Williams, H. "Briefing Note on Advance Purchase Commitments," DFID Health Systems Resource Centre, May 2005.
151. Though a previous request for this posted to the Commission on Intellectual Property Rights, Innovation and Public Health Open Discussion Forum, received no reaction, except a repeat of the mantra that product market risk is lower with an APC (Berndt, E.R. ibid.), which we all know to be the case for a host of late-stage vaccines.
152. Kremer talks of most of the repayment for a malaria vaccine being 15 years or more away ('Strong Medicine' p74). Given the state of HIV vaccine science, this may even be overly-generous for HIV (cf. Bill Gates' "eat my hat" quote) though it also depends on what is being done on the push front and how much risk is being passed on to push funders.
153. All these figures presume immediate payment at the end of ten or fifteen year, when the mechanism instead is supposed to spread payment over several (if not many) years, even as capital costs are rising.
154. This is a rhetorical statement. There seems to be no interest taken whatsoever in these matters by those advocating the APC approach.
155. As I was preparing this for submission to the WHO Commission on Intellectual Property Rights, Innovation and Public Health, I discovered that this had become obsolete 'yet again'. Those controlling this particular research project at the Centre for Global Development said that the cost had suddenly halved to $3bn. It is getting rather tiresome watching supposedly important policy initiatives constantly being manipulated in order to get a 'policy success' rather than in the interests of getting a good vaccine. The drop by half says everything about the ultimate vacuity of the proposal. I've lost interest in trimming my figures yet again to a new lower pitch. The $6bn and $6.25bn figures stay; the 'new' $3bn pitch I leave to those making it, though I cannot help but refer to it from time to time.
156. See Farlow, 2004, ibid. Chapter 6.
157. Cut this figure by 70% to fit in with the current sales-pitch.
158. 'Making Markets' April 2005 p44. Incidentally, setting product requirements based on epidemiological factors is only part of the required solution.
159. One suspects the latter. The philology of the APC literature would make an interesting study in its own right.
160. 'Making Markets' April 2005 p42.
161. CIPIH Forum, 19 November 2004. Why are such statements tolerated without a single financial economist brought in to evaluate the actual risks and capital costs being described?
162. Farlow, A.W.K., 2004, ibid. Chapter 7 explains why situations like this are a very real possibility.
163. x such that 0.75*x + .0.25*0.5x = $6.25bn.
164. This calculation also presumes that the probabilities are not altered in the process of adjusting up to $7.14bn. This is unlikely to hold. The probability of reneging is likely to rise with the APC price, necessitating adjustment of the APC price *even further upwards* to compensate. Price would settle at the stationary point in this reasoning process. All of this would also have to be adjusted upwards in proportion to the degree of risk aversion, with some players much more disadvantaged than others.
165. Incidentally, in PDP models, at least more of the 'intervention' can take place before sunk costs are invested. This has a high risk-saving for firms. Again, why has the model not been run past some financially trained economists able to get *some* sort of handle on the risk costs and savings?
166. 'Making Markets' April 2005 p44.
167. 'Making Markets' April 2005 p44. What exactly does "not completely meet" mean anyway?
168. CIPIH Forum, 19 November 2004.
169. Barder, O., CIPIH Forum, 27 Nov 2004.
170. Barder, O., CIPIH Forum, 19 November 2004.
171. We do not know this. This is a purely speculative guess on a 10-15 year highly risky instrument.
172. And as this was being re-edited in the UK, before 'going to press', one of the UK's largest car manufacturers was defaulting, leaving at most one penny for every pound of debt owed to creditors.
173. Hint: What is it that the US has that Argentina, Russia, a host of other Asian and Latin American countries (and car manufacturers) and APCs may not have?
174. Batson, A., 'The Vaccine Book', ibid. p363.
175. Barder, O., CIPIH Forum 27 Nov 2004. Also 'Making Markets' March 2005 p8.
176. Batson, A., 'The Vaccine Book', ibid. p366.
177. Malone, R. CIPIH Forum, 21 December 2004.
178. Malone, R., CIPIH Forum 21 December 2004. It does not help to be told that contracts could only "legally be implemented by the

US and members of the EU," Barder, O., CIPIH Forum 19 November 2004.

179. International Policy Network, ibid. 2005 p15.
180. With the added difficulty that the IAC has to monitor and, supposedly, be completely transparent about information flows with both firms and the general public (at least the patent system allows firms more ability to hide information until they have their patents in place, and has a legal system to back them up). The APC also has to bear all the pressures for ex post adjustment and discretion that now show up in pressures on the patent system.
181. 'Strong Medicine' p64. Barder, O., "This particular proposal is in fact very market-oriented," CIPIH Forum 19 November 2004.
182. 'Strong Medicine' p27.
183. www.pupress.princeton.edu/titles/7830.html
184. 'Strong Medicine' p27.
185. 'Strong Medicine' p26.
186. Updated by IAVI, "Scientific Blueprint: Acceleration global efforts in AIDS vaccine research and development', 2004, to $650m and $100m respectively: www.iavi.org/viewfile.cfm?fid=409
187. 'Making Markets' p61. Adjust all figures 50% or so downwards in light of recent pronouncements.
188. There should be no need to put the word 'relatively' in front of this, since the word 'favors' includes this meaning.
189. This is all explained in far more detail in Farlow, A.W.K., 2004, ibid. Chapter 12, especially Section 12.2.
190. These are not the only features biasing the mechanism in favor of large pharmaceutical firms. See, for example, Farlow, A.W.K., 2004, ibid. Section 8.6.
191. Kremer, M., Appendix 1, p9.
192. Berndt, E.R. ibid. One supposes that this refers to the case of early-stage HIV vaccine research as much as any other vaccine, including late-stage vaccines, since no distinction is made in the comment.
193. For some reason, awkward questions like "What is the exact place of equity finance?" almost always get used to imply that one is questioning entirely the role of equity finance, and, by extension, private players. Private equity-financed players themselves are not helped by this dismissal of the issue.
194. Mills, L., "Great science not all that matters", Financial Times Special Report into Biotechnology, 10 November 2004, p5.
195. Mills, L., ibid.
196. CIPIH Forum, 2 March 2005. John Erickson is President and CEO Sequoia Pharmaceuticals, Inc. and Founder and Scientific Director Institute for Global Therapeutics and Drug Design, www.globaltherapeutics.org. We explore below, in the section on research 'bunching', more reasons for why such innovative activity is more likely to fall outside of the big pharmaceutical players.
197. Berkeley, S. "The Need for a Vaccine" p588 in Chapter 38 of "AIDS in Africa" Second Edition, Kluwer Academic/Plenum Publishers, 2002, quoting Glaser, V., "Number of biotechnology companies pursuing HIV vaccines begins to dwindle." Genetic Engineering News, 1997; 17:14,44.
198. www.mmv.org/pages/page_main.htm
199. Set up in 1999 at the Program for Appropriate Technology in Health with funding from the Bill and Melinda Gates Foundation.
200. See www.malariavaccine.org for details.
201. 'Making Markets' March 2005 p26 and p27.
202. 'Making Markets' March 2005 p7.
203. 'Making Markets' March 2005 p7.
204. All of the 'pull' papers are based on US industry figures.
205. See "Meningococcal conjugate vaccine for Africa: a model for development of new vaccines for the poorest countries", Jódar, LaForce, Ceccarini, Aguado, and Granoff, The Lancet, Vol. 361, 31 May, 2003.
206. The truth is that certain groups–such as– have been much more vocal than others. It would allay this author's concerns if supporters such as 'Bio Ventures for Global Health' would distinguish whether their support is based on early-stage vaccines such as HIV, malaria, or tuberculosis, or based on a range of late-stage and currently existing vaccines and products. If the former, then they should muster all those private venture capitalists they have lined up eager to start funding of HIV, malaria, and tuberculosis vaccine research and who must therefore be willing to make public irrevocable financial commitments to fund the necessary research *the moment* a $3bn HIV APC is in place, and get them to make such legally-binding pledges *now*. If these sorts of investors cannot be found, then 'Bio Ventures for Global Health' should reassess how vocal it wants to be in encouraging an APC for HIV. The problem with facing economic agents with choices based on *no* budget constraint (if more of an APC then *not* much less of another) is that they will support more of anything.
207. The issue is complicated for early-stage vaccines by the fact that many biotechs are investing in the hope, rather than the present reality, of large-firm pharmaceutical firm contracts, and therefore may not have access to milestone payments.
208. 'Making Markets' April 2005 p91.
209. There is a standard patent problem too. The value to the biotechs of their research depends on much later users of their ideas. With a patent of limited duration, any licensing fees generated by an interesting discovery may not materialize until late in the patent's lifetime.
210. Barder, O., CIPIH Forum, 27 November 2004.
211. Mahoney, R., CIPIH Forum, 21 December 2004.
212. 'Making Markets' April 2005 p91.
213. If nothing else, they cannot prove success to backers quickly enough to attract more capital funding.
214. Aventis, GSK, Wyeth, and Merck, with the rest made up of Chiron (7%), Serum Institute (about 1%), Bio Farma (<0.5%), and the remaining 10% made up of all the rest. This is based on 2000 market data, though this might also under-exaggerate the impact of domestic production in China, Brazil, and India on account of government suppression of prices in these countries (See Batson et al, 'The Vaccine Book', p 349 for details).
215. " Issues Paper: Accelerating new Vaccines", Glass, S.N., Batson, A., and Levine, R., 'Global Alliance for Vaccines and Immunization: Financing Task Force', 2001, p10.
216. If these are therapeutic and not preventative then there are all the problems and costs of having to monitor for twenty years or more (for a product that has supposedly cost only a dollar or so to manufacture, and is supposedly then pitched at a very low cost after the first few hundred million doses). The sums may simply not add up.
217. See Farlow, A.W.K., 2004, ibid. Section 12.4.
218. Glass et al. ibid. p5.
219. Glass et al. ibid. p9.
220. See Farlow, A.W.K., 2004, ibid., especially Chapters 10, 11, and 12, which all repeatedly suggest that there are inherent biases away from small, emerging economy, not-for profit, PDP and other players.
221. The author would welcome counter-arguments on all of these points (that go a bit further than just restating that the approach is "open to all"), since these are observations based on an understanding of the underlying logic of the approach, not based on any empirical evidence. It is, however, an interesting (and important) empirical issue. For example, since domestic producers in developing countries often do not get prices high enough to do much R&D or to create new production, could their access to finance be improved so that they could more easily compete for purchases? But observe that their distance from research institutions, such as the NIH, mitigates against them too; a more open collaborative mechanism may enable them to acquire more of the necessary knowledge.
222. It is not clear how firms will be treated if they seek to enter the program later *based on* the results of clinical trials performed elsewhere or performed within the program by other players. In normal market circumstances one would expect that such firms could exploit any opportunity open to them, and would therefore have the incentive to invest in such opportunities. It is not

so clear-cut under the contract-and-committee structure now being suggested.

223. Incidentally, emerging firms that later seek to break the APC by compulsory licenses or by creating 'me-too' products based on vaccines developed under the APC, may argue that the constricts of the system were 'unfair'.
224. Comments on behalf of the Center for Global Development suggest that this is already pretty well accepted (Berndt, E.R. ibid.).
225. Holding the launch party for the 'Making Markets' final report at the headquarters of one of the preeminent corporate law firms to 'big pharma', Covington and Burling, in Washington (and not at CGD itself or somewhere more neutral), with the support of Merck, probably did not do much to encourage developing and emerging country developers to believe that the mechanism would be neutral, or that the crucially-needed independence at a 20-year horizon was an automatic given. Barder, O., ibid. 19 November 2004.
227. 'Making Markets' April 2005 p43.
228. 'Making Markets' April 2005 p101.
229. This is largely taken from Farlow, A.W.K., 2004, Section 12.4.
230. Kremer, M., hints at something similar going on in the tuberculosis drugs market. Kremer No. 10 Policy Unit Appendix 1 p2.
231. Notice that it does not have to be 'actual' replacement; risk of replacement is sufficient.
232. Based on approximately $430 per year of drug costs (No. 10 Policy Unit Appendix 10). The author has no up-to-date (2005) figure for this based on $120-$140 per year drug costs, and would welcome a correct updated calculation (rather than improvising an approximate calculation).
233. Scherer, F.M., and Watal, J., "Post-TRIPS options for access to patented medicines in developing nations", Journal of International Economic Law, 5(4), 2002, contains a diagram showing the weak correlation found between price and country-level income for 15 antiretroviral drugs (They also point out that the empirical evidence is complicated by import duties, local tariffs, price controls, taxes and wholesale profits, etc.).
234. Kremer points out that one of the advantages of an APC is that it enables firms not to have to be transparent about what it actually costs to manufacture drugs, for fear of these effects. But, we also found that a key component of an APC is that firms have to reveal a great deal of information to those running the mechanism if an auction mechanism cannot be used to set the size of payment, and this clearly sets up an efficiency trade-off.
235. Observe that overall profits to all companies would be lower after replacement, illustrating again the low incentives to do such activities by any player other than a purely marginal player.
236. This observation affects other features of APCs, including the auction mechanism and other strategic behaviors that drive up the APC price.
237. All of this section is under *ceteris paribus* assumptions, since clearly the APC could be set so high that these problems become insignificant.
238. Observe that this refers to the crowding out effect, not the overall effect, of a dollar of government finance.
239. Looked at another way, it is *cheaper* to use other modes of support targeted at small biotechs/not-for-profit, etc, since they do not have to contain this extra cost.
240. This indicates that part of the problem may refer to the lack of healthcare infrastructure, and again emphasizes one of the arguments of a previous paper (Farlow, A.W.K., ibid. 2004) that the APC price would need to be set higher as much on account of the lack of infrastructure as on account of the 'lack of a market'. The hepatitis B vaccine and the Hib vaccine discussed above are cases in point. After 13 years of being largely unavailable, even though the hepatitis B vaccine is supposedly now generally available, 40% of children in Sub-Saharan Africa still do not receive it. After 11 years of being largely unavailable, Hib vaccine usage even when supposedly generally available is heavily skewed towards rich countries, with only tiny percentages of coverage in poor countries. Millions of children do not get a yellow fever vaccine costing cents to manufacture.
241. Kremer, M., Appendix 7, ibid. p46.
242. The unwinding of the 'replacement effect' boosts the marginal impact of investment in infrastructure.
243. It is not clear what the size of the effect might be, and the effect will be reduced somewhat by the fact that investment on vaccine R&D could well be a ten year plus program, followed by returns over a further ten years, with an average time to repayment of maybe fifteen years. And developers may still worry about the commitment of large institutions to such programs.
244. 1 March 2005. Harvey Bale, Director General, IFPMA, Geneva.
245. Gottlieb, S., "Let The Market Find A Cure For AIDS" Forbes Adviser Soapbax, 1 March 2005, www.forbes.com/2005/03/01/cz_sg_0301soapbox_inl.html
246. 2 March 2005, CIPIH Forum. Such debates and correspondences between such a wide variety of interested parties demonstrate just how extraordinarily valuable the CIPIH Forum has turned out to be.
247. Investors are financially constrained in that they use the money of others and cannot take on bets large enough relative to the market to cause correction on their own.
248. Arora, A., Fosfuri, A., and Gambardella, A., "Markets for Technology and Corporate Strategy", Chapter 4 (p94) of 'Economics, Law and Intellectual Property', Ed. Granstrand, O., Kluwer Academic Publishers, 2003.
249. Levinthal, D.A., and March, J.G. "The Myopia of Learning", Strategic Management Journal 1993, Vol. 14, pp95-112.
250. March J.G., "Exploration and Exploitation in Organizational Learning", Organization Science 1991, Vol. 2, pp 71-87.
251. Levinthal and March, ibid.
252. Arora, A. et al ibid p94.
253. Stiglitz, J.E., and Weiss, A., "Credit Rationaling in Markets with Imperfect Infromation", American Economic Review 1981, Vol 71(3) pp393-410.
254. See Farlow, A.W.K., 2004, ibid. Chapter 6.
255. Though we already saw just how heavily controlling an APC would turn out to be if fully enacted. The contrast seems to be between a system that has more 'control' at the end (APCs) and one with more 'control' en route (the Global HIV Vaccine Enterprise, perhaps).
256. Berkeley, S., ibid p593.
257. Hurvitz, J., CIPIH Forum, 16 December 2004.
258. 'Making Markets' April 2005 p51.
259. The interested reader will have to redo all of this in light of the $15 per treatment costs ($3bn for 200 million treatments) of the latest CGD briefing (or $4bn of the more recent Gordon Brown announcement). Clearly it makes the logic bite even more harshly.
260. Kremer and Sachs talk of "less than a dollar a dose" www.malaria.org/news125.html
261. The author would gladly be challenged, if only to get some possible data out into the open.
262. Clearly, it completely falls to bits if $3bn is fed into the calculations.
263. 'Making Markets' March 2005 p38.
264. Hurvitz, J., CIPIH Forum, 16 December 2004.
265. Hurvitz, J., CIPIH Forum, 16 December 2004.
266. 'Making Markets' April 2005 p38.
267. 'Making Markets' April 2005 p47.
268. A similar situation faces IAVI. If manufacturers contracted by IAVI do no provide the eventual successful vaccine in 'reasonable quantities at reasonable cost' (cost plus 'reasonable profit') to the public sectors in developing countries, then IAVI reserves the right to transfer production of its vaccine to another manufacturer. But at least IAVI potentially has more control over the IP.
269. 'Making Markets' April 2005 p109.
270. 'Making Markets' April 2005 p109.
271. Or, more precisely, is split in a complicated fashion across 'winning' developers as described in Section 2 above.

272. That is, if the vaccine developer does not simply relinquish these sales and concentrate on more profitable segments elsewhere, especially if the developer is capacity constrained.
273. It is repeatedly argued here that this is not likely to be the case, but this paragraph shows that *even if it is the case* the news is not good for individual firms.
274. 'Making Markets' April 2005 p92.
275. 'Making Markets' April 2005 p108
276. Kremer, M., "New Vaccine Markets II: Design Issues", NBER, Innovation Policy and the Economy, Vol.1. p76 and p94, and also Kremer, M. Appendix 7 ibid., p76 and p94.
277. Glennerster, R., and Kremer, M., Appendix 4, www.pm.gov.uk/files/pdf/Appendix%204.pdf "A Vaccine Purchase Commitment: Preliminary Cost-Effectiveness Estimates and Pricing", p17.
278. Generating, whilst en route, such lines as "Our quantitative analysis suggests that an APC is the most cost-effective means of encouraging the development of new health products," www.number-10.gov.uk/su/health/06/default.htm
279. www.number-10.gov.uk/su/health/06/default.htm.
280. 'Making Markets' April 2005 p95.
281. Pierre Chirac, Nature 2004; 431:629-630.
282. And the deadweight loss of all the needed tax revenues, and the loss of foundation-funded projects elsewhere.
283. Go to www.cambridge.org/uk/economics/globalcrises for some notion of the competition for resources.
284. Recently, there has been some backtracking on this. In early December 2004, reading all the promotional material for 'Strong Medicine' describing the "simple solution" within (www.pupress.princeton.edu/titles/7830.html), a solution "that has been so desperately lacking" (www.cid.harvard.edu/books/kremer04_strongmedicine.html) and listening to UK Treasury announcements, the distinct impression created was that APCs were at last '*the* answer' and 'just what was needed' to tackle the lack of an HIV vaccine. Recent announcements, thank goodness, have been more realistic and much more accepting of the overall collaborative approach required: "I also see an enormous opportunity for pushing forward the initiative to create a worldwide infrastructure–or platform–for sharing and coordinating research in AIDS, and then for encouraging the development of viable drugs. But it is generally recognized that the sums of money required involve at least a doubling of research money for AIDS", Gordan Brown, Council on Foreign Relations, New York, December 17, 2004.
285. These kill 1.1 million, and 0.8 million a year each.
286. This section draws heavily from "Public-Private Partnership in the Development of Hepatitis B Vaccine in Korea", Mahoney, R.T., in "Science, Technology and Society" Vol. 10 No. 1, April 2005. I also thank Professor Richard Mahoney for giving me an insider account of what happened in the hepatitis B case. See also 'Making Markets' penultimate draft version p105. This material was removed in the final version.
287. The real burden of hepatitis B is in chronic liver disease and liver cancer in later life.
288. Mulholland, E.K., and Bjorvatin, B., 'The Vaccine Book' ibid., p392.
289. A gene for the hepatitis B surface antigen is inserted into the chromosome of yeast cells, which then subsequently synthesize the surface antigen. The surface antigen was purified from the fermentation mixture, and it provided an excellent vaccine.
290. Mahoney, R., and Maynard, J., "The Introduction of New Vaccines into Developing Countries". *Vaccine* 17, No. 7-8, 646-52, 1999.
291. Mahoney ibid.
292. Batson, A. 'The Vaccine Book', ibid. p350.
293. Birmingham, M., and Stein, C., 'The Vaccine Book' Chapter 1.
294. See e.g. www.accessmed-msf.org/campaign/men01.shtm
295. When diagnosed early and treated with appropriate drugs (such as oily chlorampenicol or ceftriaxone) the fatality rate remains at 5-10%.
296. www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10379
297. 'Strong Medicine' p74.
298. Jones, T., CIPIH Forum, 29 November 2004.
299. 'Making Markets' March 2005 p20.
300. Better demand forecasting alone removes significant, and totally unnecessary, risk to all sides involved in both vaccine development and use, whatever the source of funding. See, for example, the Accelerated Development and Introduction Plans (ADIPs) for Pneumococcus and Rotavirus vaccines.
301. "State of the World's Vaccines and Immunization", a joint report by WHO (World Health Organization), UNICEF, (United Nations Children's Fund) and the World Bank, 2002.
302. The CIPR report p38, quoted in Garrison, C., "Background paper for WHO workshop Intellectual Property Rights and Vaccines in Developing countries," Geneva 19th-20th April 2004.
303. See Farlow, A.W.K., 2004, ibid. Section 7.16.1. This argument was accepted as valid and a serious problem in private conversations with some of those heavily involved in the pull research agenda, but nothing has been done since. The only interpretation I can put on this is that like so many other parts of the APCs for early-stage vaccines, it is deemed better to ignore knotty practical problems for fear of drawing too much attention to them and weakening the proposal in the eyes of politicians. But instigating mechanisms still replete with hidden dangers is hardly a sensible way to enact practical policy.
304. The option value is more valuable for HIV. Given the more widespread nature of malaria than was once believed (it is not just an African problem) this option logic would apply to malaria too, but may be less than for HIV. The problem is that we simply do not know, since analysis of this, just like every other problem, is completely suppressed.
305. To repeat, this is just a rough illustrative figure.
306. In quotes, since we have never had a pure APC yet.
307. 'Making Markets' April 2005 p108.
308. For some sense of the debate with g medicines, see "Is Local Production of Pharmaceuticals a Way to Improve Pharmaceutical Access in Developing and Transitional Countries? Setting a Research Agenda", Kaplan, W.A., Laing, R.O., Waning, B., Levison, L., and Foster, S., Boston University School of Health. This argues that for medicines there is no reason per se to produce medicines domestically since it makes it much more difficult to achieve economies of scale, though it also stresses potential data limitations underlying this finding and other positive side effects of domestic production. For vaccines, scale is probably more important, suggesting that international competition with rapid distribution of products is more viable than technology transfer to all affected countries.
309. See Mahoney, R., CIPIH Forum, 21 December 2004.
310. As Kremer puts it: "A large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more," (Appendix 1 p9).
311. Scherer, F.M. and J. Watal, 2002, ibid. pp. 913-39. A recent case going through is India.
312. Garrison, C., ibid.
313. Kettler H. K., White, S., and Jordon, S., "Valuing industry contributions to public-private partnerships for health product development," The Initiative on Public-Private Partnerships for Health, Global Forum for Health Research, www.iPDPh.org Geneva, www.globalforumhealth.org/filesupld/valuing.pdf 2003.
314. Mahoney, R., Pablos-Mendez, A., and Ramachandran, S., , "The introduction of new vaccines into developing countries III: the role of intellectual property," Vaccine, Vol. 22/5-6 2004pp. 786-92.
315. The economic logic goes as follows: Drugs are used on sick US children. Some side-effects are tolerated. Vaccines are used on healthy US children. Tiny probabilities of severe reactions lead to multi-billion dollar litigation. Developing country children are much more likely to die anyway without the vaccine. The tiny probability bad event is swamped by the lives saved (and they do not have access to lawyers). But the vaccine manufacturing capacity for the multi-dose vials is not in place.

316. Farlow, A.W.K., 2004, ibid. Chapters 10 and 11 describes in much more detail the strategic possibilities leading to insufficient competition in this mechanism compared to others.
317. Batson, A., 'The Vaccine Book', ibid. p361.
318. 'That any observed statistical regularity will tend to collapse once pressure is placed upon it for control purposes,' in "Monetary Theory and Practice," Goodhart, C.A.E., 1984, p96.
319. Problems with the latter group are covered in much more detail in Farlow, A.W.K., 2004 Chapter 7.
320. Kremer, M. 'Creating Markets for New Vaccines Part II: Design Issues' p46, and Kremer, M. Appendix 7, ibid. If actual purchases have such little impact, quite how an entirely inadequate $3bn HIV APC is supposed to do it is anyone's guess.
321. See www.pneumoadip.org
322. Plotkin, S. A., 'The Vaccine Book', ibid, p 186.
323. "The WHO position paper on Haemophilus influenzae type B conjugate vaccines", Weekly Epidemiol, Record Vol. 73(10) pp64-68, WHO, Global Programme for Vaccines and Immunization (GPV), 1998.
324. The case of rotavirus is described in 'Making Markets' p88, and rotavirus issues in general are covered in Bresee, J. S., Glass, R.I., Parashar, U., and Gentsch, J., 'The Vaccine Book', Chapter 6E.
325. De Wit, M.A.S., Koopmans, M.P.G., van der Blig, J.F., and van Duynhoven, Y.T.H.P. "Hospital admissions for rotavirus infection in the Netherlands", *Clin. Infect. Dis*. 32:698-704, 2000. Ryan, M.J., Ramsay, M., Brown, D., Gay, N.J., Farington, C.P., and Wall, P.G., "Hospital admissions attributable to rotavirus infection in England and Wales". J. Infect. Dis. Vol. 174 (Suppl. 1): S12-S18, 1996.
326. Bresse, J.S., et. al., 'The Vaccine Book', p230.
327. Incidentally, this may be why not one of the PAHO representatives who sat on the CGD Working Group at various times ever stayed around to sign off on the final document. Whilst Latin American countries were hugely important in clinical trials, they would not have come off well in the pricing under the eventual APC, and would probably be better advised to strike deals outside of any APC.
328. Plotkin, S.A., 'The Vaccine Book', p181.
329. Bresse, J.S., et. al. ibid.
330. Lanzhou Lamb Rotavirus licensed in China in 2000 for use in children, undergoing post-licence evaluations (see Bresse, J.S., Glass, R.I., Parashar, U, and Gentsch, J., ibid, p 233).
331. Bresse, J.S., et. al. ibid. p226.
332. Bresse, J.S., et. al. ibid. p239.
333. This analogy has been used to argue for early-stage HIV APC, but I will not draw attention to any specific author of the argument. Another analogy used is that of the $10 million "X Prize" for the first private flight into space (100km) and back twice within a defined period. The problem with this is that the top competing firms *between them* knowingly spent several times the prize fund to try to win it! So, either they were irrational, or they each had an over-exaggerated sense of their chances of winning (and were not disciplined by financial markets), or something else was at work. In truth, many of the (very rich) backers saw it as an inexpensive way to garner a great deal of kudos. The sums did not run into the multi-billions dollars as would be required to develop vaccines. The players could use their own private funds without any need to attract private finance. And the true 'prize' was a great deal more than the $10 million for the winning developers, who in the expected value sense would view the expected intangible asset of the prize (being first and getting a leading position in the emerging industry, etc.) at a great deal more than just the $10million. Add this to the value of kudos, and the size of the prize was a great deal lower than its true value. No similar arguments apply to any vaccine.
334. Mahone, R., 2005 ibid.
335. Bloom, B., quoted in "Vaccines for the Coming Epidemic", Howard Hughes Medical Institute News, www.hhmi.org/news/bloom.html, 2003.
336. I wrote this before I saw the precipitous drops in the size of APCs now being pitched by the Centre for Global Development compared to even just a few months ago.
337. www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_105_2004.cfm
338. However, at the time of going to press, it is not clear if the IFFIm will be too small to allow room to fund APCs for rotavirus and for pneumococcus.
339. See, for example, "Mr Bush opposes Gordon Brown's plan to help Africa using an international finance facility to fund vaccinations," news.bbc.co.uk/1/hi/uk_politics/4613987.stm
340. For illustrative purposes we use HIV and malaria as examples, but one of the dangers of doing this is to forget that other appalling diseases are equally desperately in need of vaccines. Tuberculosis has, unfortunately, tended to attract disproportionately lower attention.
341. Birmingham, M., and Stein, C., 'The Vaccine Book', p15.
342. "The Need for a Global HIV Vaccine Enterprise", Klausner, R.D., Fauci, A.S., Corey, L., Nabel, G.J., Gayle, H., Berkley, S., Haynes, B.F., Baltimore, D., Collins, C., Douglas, R.G., Esparza, J., Francis, D.P., Ganguly, N.K., Gerberding, J.L., Johnston, M.I., Kazatchkine, M.D., McMichael, A.J., Makgoba, M.W., Pantaleo, G., Piot, P., Shao, Y., Tramont, E., Varmus, H., Wasserheit, J.N., Science 300:2036, 2003, Vol. 300, 27 June 2003, www.aidscience.org/Science/Science–Klausner_et_al_300(5628)2036.htm
343. Choi, E.I, and Letvin, N, 'The Vaccine Book', ibid. p246.
344. Lee, T-H. and Novitsky "HIV Vaccines: Design and Development" Chapter 39 in "AIDS in Africa" Second Edition, Ed, Essex, M. et al. p596.
345. Lee, T-H., and Novisky, V., ibid p604.
346. Barder, O., CIPIH Forum, 19 November 2004
347. Choi, E.I., and Letvin, N. L., ibid. p252.
348. Choi, E.I., and Letvin, N. L., ibid. p252.
349. Lee, T-H., and Novisky, V., ibid p603.
350. IAVI ibid. p18. For example there are multiple poxvector candidates at various stages of development, but since they have not been compared with standardized assays it is not actually clear which is the most promising to develop. This needs coordination.
351. Though the probability functions underlying the vaccine R&D process in 'Strong Medicine' and the APC literature are modeled as being *less risky*, even though the evidence on HIV *drug* research shows that this is not the way firms treat it.
352. The notion that "a large incentive might bring in a single major pharmaceutical firm, a still larger incentive would bring in more." (Kremer Appendix 1 p9).
353. Gilbert. P.B., and Esparza. J., "HIV-1 Vaccine Testing, Trial Design, and Ethics" p615 in Chapter 40 of "AIDS in Africa" 2002, ibid.
354. 'Making Markets' March 2005 p25.
355. See Farlow, A.W.K., 2004, ibid. Chapters 10 and 11 (and also 12) for the strategic slimming down of competition that would more likely result from such a program.
356. This is ruled out in the 'Strong Medicine' and 'Making Markets' modeling by the assumption of constant per-period probability of discovery and the 'bygones are bygones' nature of sunk costs.
357. Ie. to make the gamble pay off in the ex ante expected sense.
358. 'Strong Medicine' p65-66.
359. IAVI ibid. p16-17.
360. IAVI ibid. p 5.
361. Klausner, R.D., et. al. ibid. Also see IAVI, 2004, ibid.
362. http://www.state.gov/e/eb/rls/fs/33571.htm
363. www.whitehouse.gov/news/releases/2004/06/20040610-29.html
364. Though this author feels that critiques alone are extremely valuable. No mechanism is going to be perfect, so knowing the exact degree of imperfection of each is extremely important. If mechanisms have fundamental flaws, much delay and waste can be avoided by discovering these sooner rather than later. And since one can only know after the fact whether a mecha-

nism will work and it is impossible to conduct 'trial runs', it is much better to spend relatively trivial amounts of time and money at this early stage. The notion of rushing in to do something is extraordinarily inept.

365. Gilbert, P.B., and Eparza, J., "HIV-1 Vaccine Testing, Trial Design, and Ethics", Chapter 40 in "AIDS in Africa", Second Edition, Kluwer Academic/Plenum Publishers, 2002, p612.
366. "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan," Plos Medicine, Volume 2 Issue 2, February 2005, medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020025
367. The reader is encouraged to add more to the list.
368. Not substitutable patents.
369. For more details, see Farlow, A.W.K., ibid. 2004 various places.
370. To avoid being misinterpreted (again), see Farlow, A.W.K., 2004, ibid. Chapter 12, for the reasons why large pharmaceutical firms are largely motivated via equity finance. The section here draws attention to the fact that there is a potential conflict between equity finance and collaboration (something that should be pretty obvious) that needs to be fully worked through for both equity finance and collaboration to work together.
371. Farlow, A.W.K., 2004, ibid. Chapter 12.
372. See the sections above that describe the way that more transparency of information can be used to guide firms to reduce the 'bunching' of research leads.
373. See, for example, Hodgkinson, N., ibid.
374. Choi, E.I., and Letvin, N. L., 'The Vaccine Book', p253.
375. For some reason such statements always seem to be interpreted by proponents of early-stage APCs as automatically meaning support for their approach. The statement is, of course, open-minded.
376. Berndt, E.R. ibid.
377. See Farlow, A.W.K., 2004, ibid. Chapter 12.
378. Garrison. C., ibid. p33-34.
379. Institutes of Medicine Council on Vaccine Development, 5 November 2001.
380. Farlow, A.W.K., 2004, ibid. Chapter 7.
381. This is just a guess; nobody knows the right figure.
382. Berkley, S., 2002. ibid. p590 and reference therein.
383. Berkley, S., 2002. ibid. p590.
384. Hoffman, S.L., and Richie, T.L., 'The Vaccine Book', p294.
385. Hoffman, S.L., and Richie, T.L., ibid. p295.
386. Lee, T-H. and Novitsky ibid. p596.
387. Hoffman, S.L., and Richie, T.L., ibid. p298.
388. 'Strong Medicine' p74.
389. www.hm-treasury.gov.uk/newsroom_and_speeches/press/2004/press_105_2004.cfm
390. Pletschette, M., CIPIH Open Discussion Forum, 25 November 2004.
391. news.bbc.co.uk/1/hi/health/3742876.stm and news.bbc.co.uk/1/hi/uk_politics/4038377.stm
392. Private communications with HM Treasury officials.
393. www.hm-treasury.gov.uk./newsroom_and_speeches/press/2004/press_94_04.cfm
394. The Observer 5 June 2005 politics.guardian.co.uk/development/comment/0,15709,1499651,00.html
395. That is if the "250 million vaccine courses at $15 per course, that would translate into a $4bn guarantee" later in the same op-ed has anything to do with this notion of "insufficient purchasers". It is all a little vague.
396. Nowhere on the GSK Biologicals or GSK websites is there the slightest hint of any APC, something one might think highly unusual if GSK Biologicals or GSK were to regard the announcement as a financial breakthrough worth signaling to their investors and useful for positive PR purposes. In addition, the most recent G7 Finance Ministers statement is slightly more toned down than previous announcements about such commitments, talking only of "exploring" the use of advance purchase commitments. Maybe policymakers have seen through some of the hyperbole and come to realize just how difficult it is to make such instruments work in practical reality? www.hm-treasury.gov.uk./otherhmtsites/g7/news/g7_statement_conclusions050205.cfm
397. It is not clear publicly exactly what it is yet, so this section will probably have to change over time. It would help if the details were placed in the public domain.
398. To restate the obvious–but to thus avoid caricature–this is the totally optimal result of such a mechanism and not in any way a 'critique'.
399. GSK Biologicals website: www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10392 15 October 2004.
400. GSK, ibid. London, Friday 15 October 2004.
401. "GSK in collaboration with European Union." www.gsk-bio.com/webapp/PressCorner/PressDetail.jsp?PressId=10379
402. science.gsk.com/about/disease.htm
403. Alonso, P.L., et. al., "Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial", The Lancet, Volume 364, Number 9443 16 October 2004 www.thelancet.com/journal/vol364/iss9443/full/llan.364.9443.primary_research.30985.1
404. www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=360 (and elsewhere).
405. And between a fifth and a quarter of the cost-effectiveness for HIV. See Kremer, M., No. 10 Policy Unit Summary p2 and tables on p4.
406. www.edctp.org
407. Barder, O. ibid.,19 November 2004.
408. Barder, O., ibid., 19 November 2004.
409. Berndt, E.R. ibid.
410. Tarcisio Hardman Reis, CIPIH Forum, 16 Nov 2004.
411. The vaccine, known as RTS,S/ASO2A, has shown potential against Plasmodium falciparum malaria, the most severe form of the disease. It acts at the 'pre-erythrocytic' stage, before the red blood cells are infected. A recombinant protein that fuses a part of the *P. falciparum* circumsporozoite (CS) protein with the hepatitis B surface antigen molecule, RTS,S, has been under development by GSK Biologicals for more than 15 years. In the phase-II double-blind, controlled trial, involving 2,022 children in southern Mozambique, half were given the vaccine and half a placebo. The study argues that malaria attacks were cut by 30%, new infections by 45%, and severe disease causing death by 58%. In contrast to the previous trials of this vaccine in adults, which suggested that vaccine efficacy was short-lived, protection in these children lasted at least six months. See Alonso, P.L., et. al., ibid, and "Vaccine efficacy: winning a battle (not war) against malaria," Van de Perre, P., Dedet, J-P., The Lancet, Volume 364, Number 9443, 16 October 2004 (The title of the latter article is rather telling).
412. For studies into the bacterial and viral resistance to existing malaria and tuberculosis medicines see: Zumla, A., Grange M., "Multidrug resistant tuberculosis–can the tide be turned?" Lancet Infectious Diseases, Vol 1, 2001; Ridley, R., "Medical need, scientific opportunity and the drive for antimalarial drugs". Nature, Vol 415, 7 February 2002.
413. Logically they should expect the first vaccine to be replaced and that they would get the *whole* market, but that would require paying for the first vaccine and never using it.
414. This is proxy language for a 'set of vaccines'.
415. See, for example, Kremer. M., Appendix 7, ibid. p10: "Unnecessarily stringent specification would discourage pharmaceutical firms from following promising leads. For example, it would be a mistake to require a vaccine to be 90% against all strains of the disease, since this would discourage developers from pursuing a candidate vaccine likely to yield 99 percent protection against most strains, but only 85 percent protection against others."

Appendix 4 p20 also discusses 80%. And see Kremer, M., 'Strong Medicine' p78.

416. "Advanced Markets for a Malaria Vaccine: Estimating Costs and Effectiveness," Berndt, E.R., Glennerster, R., Kremer, M.R., Lee, J., Levine, R., Weizsäcker, G., and Williams, H., 5 January 2005.
417. Barder, O., CIPIH Forum, 27 November 2004.
418. As we have shown, this is not the case and drastically simplifies a highly difficult set of issues. Such agreements supposedly guarantee an *additional* size of market–the whole point of such instruments. This statement is therefore a hypothesis and *not* a fact.
419. Of course they produce *some* effect. That they provide the required incentive to get early-stage vaccines developed is another issue altogether. Yet another hypothesis, and, again, not a fact.
420. Where did the notion come from that there was such a thing as "*the* malaria vaccine"? We saw above that even the most cursory view of the literature reveals the need for an evolving stream of vaccines.
421. www.commissionforafrica.org/english/report/introduction.html page 409, Chapter 6 Footnote 92.
422. As confirmed by Berndt, E.R., ibid.
423. www.malariavaccine.org
424. "Malaria Vaccine R&D: The Case for Greater Resources" at: www.malariavaccine.org/files/Two-page-funding.pdf
425. Incidentally, the author's understanding of what is going on at GSK and GSK Biologicals (from various internal and external sources) is that the more commercial wing at first regarded the contract as a 'success', but the wing dealing with MMV and actually having to *do* malaria vaccine research, regarded it as not so good, especially from a PR perspective, and a big negative factor in their multiple efforts to advance relationships with non-pharmaceutical researchers and others in malaria vaccine research. They would have preferred something else. Maybe that is why it gets no mention on the GSK and GSK Biologicals websites ,and why all the more recent emphasis on these sites has been on PDP funding?
426. Hoffman, S.L., and Richie, T.L., ibid. p298.
427. Hoffman, S.L., and Richie, T.L., ibid. p295.
428. Farlow, A.W.K., 2004 ibid. Chapters 5 and 6.
429. unmp.forumone.com.
430. allafrica.com/stories/200501260806.html.
431. Arrow, K., "No time to waste in the fight against malaria", Financial Times, January 6, 2005. Kenneth Arrow chaired the IOM committee on malaria that produced the report 'Saving Lives, Buying Time'. See also the findings of the International Artemisinin Study Group: "Artesunate combinations for treatment of malaria: meta-analysis", The Lancet, Vol. 363, 3 January 2004, pp. 9-17. Tuberculosis also can be treated with DOTS therapy, which cures up to 95% of cases, even in the poorest countries. And, of course, HIV can be treated, but often is not–but that is a whole other story.
432. And a need to discourage the distribution of any solo drug that might encourage resistance.
433. See Arrow. K. ibid.
434. Full copy at: www.scidev.net/gateways/index.cfm?fuseaction=printarticle&rgwid=2&item=Opinions&itemid=341&language=1. Bob Snow is Professor of tropical public health at the Kenyan Medical Research Institute in Nairobi and the University of Oxford. Nick White is Professor of tropical medicine at Mahidol University, Bangkok, Thailand, and the University of Oxford.
435. The latest policy briefings of the Centre for Global Development give a figure of $3bn, about half the figures quoted by Snow and White based on the previous policy briefings of the Centre for Global Development and the UK Chancellor. See also Commission for Africa 2005 (who *were* up-to-date with the latest sales-pitch it seems).
436. Barder, O., CIPIH Forum, 27 Nov 2004.
437. Barder, O., CIPIH Forum, 19 December 2004.
438. www.cid.harvard.edu/books/kremer04_strongmedicine.html
439. Farlow, A.W.K., 2004, ibid. Copies were given to key people on the Center for Global Development project.
440. 'Making Markets' March 2005 p39, and see also p35: "Direct funding of research and development in neglected diseases is beneficial, but is not on sufficient scale significantly to overcome the market reality." See also "Strong Medicine" Chapter 9, especially pages 93-95, and p87: "At present, funds are not sufficient to pursue enough of the possible avenues of research."
441. 'Making Markets' March 2005 p60.
442. 'Strong Medicine' p125-6.
443. See 'Making Markets' March 2005 pages 9, 10 (point 8), 16, 24, 36, 37 (especially), 51, 58, 59, 60, 61, p 87 ("a commitment of this size would create a market comparable to a developed country pharmaceutical, while providing a very cost-effective investment for donors"), and p94 ("A guaranteed market enhancement like advance contracting could unlock innovation today, speed the development of a vaccine tomorrow, and assure rapid access–and lives saved–for many years to come. It is one of the most cost effective development interventions available to us"). We showed above that an HIV APC would do practically nothing for innovation today (and maybe even nothing) and put *no* emphasis on access, and yet: "It is thus clear that purchases under a vaccine commitment would save more lives than almost any alternative use of funds," 'Strong Medicine' p93. "Once a vaccine meeting appropriate technical requirements is developed, purchasing it at the agreed price will be one of the most cost-effective health interventions conceivable." 'Strong Medicine' p94. The Princeton University Press promotional material for 'Strong Medicine' boldly states: "Ultimately, if no vaccines were developed, such a commitment would cost nothing. But if vaccines were developed, the program would save millions of lives and would be among the world's most cost-effective health interventions." www.pupress.princeton.edu/titles/7830.html (Who wrote t?is stuff). Incidentally with the HIV vaccine APC now down at just $3bn, and given the sums discussed above, it is clear that most of the effort to get an HIV vaccine will lie elsewhere, however much a 'winning' firm (or the proponents of HIV APCs) might wish to take all the credit along with all the IP rights.
444. "This would be among the most cost-effective public health interventions imaginable." A line from "UK Chancellor Gordon Brown Announces Vaccine Purchase Commitments for HIV/AIDS and Malaria" www.cid.harvard.edu/books/kremer04_strongmedicine.html
445. Birmingham, M., and Stein, C., 'The Vaccine Book', p3.
446. Indeed, Kremer and Glennerster, and others, make strenuous attempts on this score when it comes to *other* mechanisms. See Farlow, A.W.K., Chapter 8 on how they do it.
447. Based on Kremer 'Strong Medicine' p93.
448. Muraskin, W., "The Global Alliance for Vaccines and Immunization (GAVI): Is it a New Model for Effective Public Private Cooperation in International Public Health?" Queen's College, City University of New York, JLI Working Paper 1-2, March 2004.
449. It was not easy to leave this word in. Sadly it is a word (and there were worse) the author has repeatedly heard from those working on alternative incentive approaches and from vaccine scientists.
450. 'Making Markets' March 2005 p38 ('Making Markets' March 2005 p67, has the same statement but adds "and used"). 'Making Markets' March 2005 p33 states it "does not require outlays of public spending until the vaccine is available for use."
451. "UK Chancellor Gordon Brown Announces Vaccine Purchase Commitments for HIV/AIDS and Malaria" ibid.
452. Barder, O., CIPIH Forum, 19 November 2004.
453. Barder, O., CIPIH Forum,19 November 2004.
454. Barder, O., CIPIH Forum, 19 November 2004: "A proposal which is simple, easy to understand, and practical to implement." If you have read this far, statements like this should finally be the real give away of the shallowness of the anaylsis.
455. Barder, O., ibid. 19 November 2004.

456. Since it is not at all clear that a 'large pharma' executive when presented with the actual workings of the mechanism for an early-stage vaccine such as HIV would prefer the mechanism to other approaches. The profit incentive is also a self-preservation incentive!
457. The fact that these gyrations came way after the original intent was made clear in early versions, does rather suggest that the interest was never the gyrations themselves.
458. Berndt, E.R., ibid.
459. See www.number-10.gov.uk/su/health/default.htm Summary p4. This is, of course, a small sub-class of all publicly-funded research. Also, Glennerster, R. and Kremer, M., Appendix 4, ibid.
460. See Farlow, A.W.K., 2004, ibid, Chapter 8. None of these assumptions were ever backed up by empirical evidence. This did not deter a barrage of highly visible tables, diagrams, statements, graphs, etc. based on them. Try, for example, www.dfid.gov.uk/research/newresearchbgprivate.pdf p9 Table 4, and footnote 30, p13.
461. From "UK Chancellor Gordon Brown Announces Vaccine Purchase Commitments for HIV/AIDS and Malaria" ibid.
462. www.g8.utoronto.ca/finance/fm050611_dev.htm
463. Kremer, M., "Pharmaceuticals and the Developing World," Journal of Economic Perspectives 16(4), Fall 2002 p82.
464. The No. 10 Policy Unit website, NBER "Innovation Policy and the Economy", a range of Kremer papers such as "A Better Way to Spur Medical Research and Development: The purchase precommitment as a supplement to patents and government-funded research", Regulation, Volume 23, No.2. 2000, and more recently 'Strong Medicine'. When this author was asked to review 'Strong Medicine' for the Lancet, the first person he spoke to who had seen it quipped that the USAID case was yet again getting an airing ('A Cautionary Tale: The USAID Malaria Vaccine Program", 'Strong Medicine' pp 47-49). It should go without saying that criticisms of the repeated use of such cases to cast aspersions on others (in place of a greater body of evidence) does not condone the cases themselves. Intent, and words, can easily be inserted that were not originally there.
465. Referring to the criticism of the way those working on vaccine research are repeatedly tarred with the same brush as those who have behaved corruptly: "He is also wrong to say that it [where *it* refers to the proposal of an APC, and *not* the criticsm] is uncharitable to the many people who devote their lives to scientific research–on the contrary, it takes the position that these efforts should be rewarded by society as much as the efforts of those who research into other diseases." Berndt, E.R., ibid.
466. Dutfield, G. 'Intellectual Property Rights and the Life Science Industries', Ashgate, 2003 p120.
467. Dutfield, G. ibid. p120.
468. 'Strong Medicine', p49.
469. 'Strong Medicine' dust jacket and p63, and 'Making Markets' March 2005 p7, and numerous other places.
470. 'Strong Medicine' p84 and 'Making Markets' March 2005 p46.
471. 'There's No Such Thing As a Free Lunch', Friedman, *M.*, 1975.
472. 'Making Markets' March 2005 p 90.
473. 'Strong Medicine', p ix.
474. Klausner et. al. ibid. p2.
475. Maybe the reason they have so far not been analyzed together is partly to avoid having to analyze comparative capital costs and relative effectiveness generally?
476. This completely contradicts the assertion that APCs somehow magically (however badly they are set) "enhance the complementary interventions," 'Making Markets', March 2005 p38.
477. For example, if the IP regime were to be framed in a way that makes certain kinds of technology more open and shared, this would need to be reflected in the contractual terms. The terms of the latter should not clash with the former or work in a way that leads to greater costs overall (for example, terms may need to be lowered to the extent that those operating under them benefit from the openness).
478. 'Making Markets' p118.
479. Of particular note see: www.redherring.com/Article.aspx?a=11318&hed=AIDS+and+money&hed=AIDS+and+money§or=Capital&subsector=PrivateMarkets and www.aidsmatters.org (in particular the announcements of 23 and 25 February 2005) www.aidsmatters.org/uploads/Ch7.pdf
480. www.gpoaccess.gov/eop/index.html
481. http://www.medicinenet.com/script/main/art.asp?articlekey=43642
482. Admittedly, it is not clear what the basis of this figure is.
483. See Farlow, A.W.2004, Chapter 8 for the ways this was done.
484. Leaving others to argue the merits and demerits of the Iraq case, one might also observe that since front-loading the war in Iraq has added several hundreds of billions of dollars to deficits, why should this be allowed to oust the funding for HIV, malaria, and tuberculosis vaccine research?
485. And people like the current author should shut up (something he would quite happily do).
486. It is early days, but there must be evidence by now of private firms increasing their finance into malaria vaccine research for the open-to-all malaria APCs now heavily run in the media. Even by midsummer 2005 the Centre for Global Development should be able to add a table to their reports showing the rises in private malaria vaccine funding across a range of firms.
487. It is being put in place, is not it?
488. Though it looks increasingly unlikely that much, if any, vaccine development will be funded by an IFF.
489. 'Making Markets' p93.
490. Mahoney, R.T. CIPIH Forum, 21 December 2004.
491. "Give the poor a choice", Easterly, W. and Whittle, D., Financial Times, August 26, 2002.
492. Kremer, M. 'Strong Medicine' p114.
493. Jones, T., CIPIH Forum 29 November 2004.
494. International Policy Network, ibid. 2005 p17.
495. Just for current activities, PDPs are estimated to need an *additional* $1–2 billion over the next two to three years. Sander, A. and Widdus, R., "The emerging landscape of public-private partnerships for product development", IPPH, 2004.
496. Refer to the discussion of the collaborative mechanism above for why this can be made not to harm those performing the R&D.
497. See section "A Long-Term Threat" in Farlow, A.W.K., "Emerging Market Risks: An assessment of the balances of emerging market risk and the sources of crises." November 2003.
498. The principle reasons are: i) the demographic structure such that the loss of economically active cohorts is relatively more damaging in Russia than the other countries; ii) the rapidly revolving prison population and the brutalizing military service, both of which act as a giant petri-dish for all kinds of disease; iii) the very high rates of, and widespread nature of, needle usage (there are a quarter of a million needle injectors in Moscow alone); iv) the dislocation caused by the rapid move to 'capitalism' and the rise of commercial (and largely unprotected) sex; v) the fact that HIV is already much more widespread at such a relatively early stage in the its epidemiology.
499. The author's contacts in Russia suggest that there is a chance of making HIV a top priority on the Russia G8 agenda. Increasing those chances should be a high priority.
500. See section 2 above for the details.
501. Kremer, M., No. 10 Policy Unit, Appendix 1 p9.
502. The believers did not include many industrial economists, financial economists, or those involved in the practical aspects of vaccine manufacture and distribution–the most obvious sorts of people required to check the idea–but towards the end the believers did seem to include a lot of lawyers, who are good at contracts once an idea has already been decided upon.
503. This author experienced this PR-based approach to policy-making first hand. Having discussed in person a large file (Farlow, A.W.K., 2004) willingly contributed to the Centre for Global Development's effort, he was at first told that the APC idea would not be applied to HIV. Then he discovers that the approach borrows from *that* critique, including the importance (and difficulty) of the "Making Markets" angle, and is applied to HIV and other early-stage vaccines. Then, he is told that that

file had only been cursorily looked at and dismissed (remember, this is an irreversible policy with plenty of risks and dangers to it, so dismissing even what those receiving it described as something containing plenty of valid points, is foolish). Then, ideas from that file are quoted back at him in correspondence in the Lancet (ideas that were no longer in the public domain–the file had since changed, and there were no public copies available, so this correspondence was based on an original copy), and the first line of the final CGD report uses the first line of *this* paper and of the Lancet book review of 'Strong Medicine', to hook the reader in. So, in summary, an approach that is willing to take parts of a critique that could be used to make the PR more polished, but having no interest at all in the underlying critique.

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