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Advanced Market Commitments

Current Realities and Alternate Approaches

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Executive Summary

The purpose of an advanced market commitment (AMC) was to motivate research and development (R&D) based pharmaceutical companies to conduct research into the so called 'neglected diseases' that primarily afflict low-income countries. In addition, AMCs were to speed-up access to new vaccines that are often delayed by 10-15 years because of their high prices when new on the market.

The essential AMC idea is for donors to match the revenues that companies earn from developing medicines for affluent markets so they have the same incentive to research a neglected disease. The price and volume of this large buyout are pre-set by a committee, and winning companies promise, to make their product available at a low initial price, while keeping their intellectual property (IP) rights intact. Thus, a new medicine might be discovered for a neglected disease, made immediately available to low-income countries, and supplied forever.

Despite endorsements ranging from the World Bank to The Vatican, there are reasons for concern about the way the AMC concept is designed. Too many uncertainties and contingencies in the AMC design may keep companies from initiating research to discover new vaccines. A major study of proliferating research projects on neglected diseases found radically different patterns of funding, motives, and organisation than envisioned by the AMC 'big-payoff' model. The authors of this study warned that an AMC could seriously damage these thriving arrangements, especially those involving multinationals.

Because the AMC provides no funding until a new vaccine is fully developed and considered necessary by low income countries, it discourages all but a few large companies to participate because the investment costs remain extremely high. Secondly, its competitive design could undermine cooperative efforts and grant-based "push" funding. Thirdly, by favouring large companies with deep pockets over biotech companies and teams of researchers at universities or non-profit institutes that require intermediate funding, AMC could actually decelerate R&D, although alternative approaches could address these design problems. Finally, even the sharply discounted post-buyout prices would still not be affordable, and past experience with AIDS drugs shows that manufacturing in developing countries can supply medicines at much lower prices.

Before the current AMC model was designed by Michael Kremer, he considered a variety of alternatives for how to structure advanced purchasing, including patent buyouts, required licensing cooperative payback with push funders, milestone payments, higher technical requirements for follow-on vaccines, and bonuses for vaccines that are easier to administer or store. Yet, by 2004, Kremer and the Gates Foundation put these flexibilities aside. Donors would not have to pay anything for years, probably not until after they left office, a donor's dream but a developer's nightmare. Property rights were no longer mentioned.

Despite these substantive issues with the AMC, the design problems became irrelevant when the AMC idea was transferred to purchasing extra doses of already-discovered pneumococcal vaccines that have been developed and fully paid for by multinational corporations for large affluent markets. This

represents simply an advanced *procurement* commitment and so cannot be considered a pilot of an AMC because it is not an AMC.

By 2004-5, many impracticalities and inconsistencies with the AMC design had been presented to the Working Group assembled to launch it. Suggestions that the AMC design include sharing IP technology, helping developers fund late-stage trials, addressing issues of delivery, or coordinating with push funding were rejected as part of the AMC design. The AMC was promoted energetically well before its launch in 2005. Members with reservations about the AMC design withdrew their support or voted against it. Their names are not listed as members of the Working Group in the launch document. The AMC concept was thus presented to the G8 finance ministers as unanimously endorsed.

Recently, the Global Alliance for Vaccines and Immunisation (GAVI) reports have focused on ways to sustain the AMC-style procurement by giving companies higher prices and longer delays before delivery. This, it is suggested, will significantly increase the proportion of funds that to go extra profits for the winning multinational corporations and reduce the number of children saved from pneumococcal diseases. By requiring dedicated manufacturing facilities, the new terms preclude alternative approaches that would develop less expensive vaccines designed for prevalent serotypes in different regions of the world and use low-cost manufacturing in developing countries. If the goal were to maximise the number of children saved in the shortest time, one would not consider an AMC approach to a supply contract but work with the pharmaceutical industry to arrange for low-cost production under limited licensing.

Better designed advanced purchase commitments could complement funded research to increase the discovery of diseases prevalent in developing countries. More flexible approaches are needed in their design that require sharing or licensing intellectual property and know-how, and that help developers of promising products to complete their trials. One needs to use different approaches for diseases with large affluent markets than for diseases with predominantly low-income markets. AMCs need to strengthen the public health systems on which sustained vaccination programs depend as well as pursue manufacturing at prices that countries can afford.

Acronyms

AMC	Advanced market commitment
APC	Advanced purchase commitment
CGD	Center for Global Development
CIPIH	Commission on Intellectual Property Rights, Innovation, and Public Health
DALY	Disability-adjusted life year
EEG	Economic Expert Group
FDA	Food and Drug Administration
G8	Group of 8: Canada, France, Germany, Italy, Japan, Russia, the United Kingdom (UK), and the United States
GAVI	Global Alliance for Vaccines and Immunization
GAVI-eligible countries	Countries with an average income of less than $1,000 per person per year
GSK	GlaxoSmithKline
HAI	Health Action International
HPV	Human Papilloma Virus
IAC	Independent Assessment Committee (for AMC)
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IP	Intellectual property, such as patents and copyright
IWG	Implementation Working Group
KEI	Knowledge Ecology International
MSF	Médecins sans Frontières
NIH	National Institutes of Health
PAHO	Pan American Health Organization
PCV	Pneumococcal conjugate vaccines
R&D	Research and development
TB	Tuberculosis
TRIPS	Trade-Related Aspects of Intellectual Property Rights (Agreement)
WHO	World Health Organization

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I. What is an advanced market commitment?

The concept of an advanced market commitment (AMC), though untried, has been hailed as a revolutionary solution to the intractable problem that little research is conducted into medicines for neglected or Type III diseases that "are overwhelmingly or exclusively incident in the developing countries…"[1:25] and that access to new medicines can be delayed 10-15 years before they are affordable in low-income countries because patents prevent price competition by granting market exclusivity to the originator. In a major report on AMCs, the World Bank and the Global Alliance for Vaccines and Immunisation (GAVI) provide a succinct definition of the original concept: "An AMC for vaccines is a financial commitment [by donors] to subsidize the future purchase of a vaccine not yet available, *if* an appropriate vaccine is developed and *if* it is demanded by developing countries."[2:1]

The rationale is to match the lifetime revenues that a company typically accrues from developing a new product for profitable markets so that they have an equal incentive to develop a product for diseases prevalent in low-income countries. The purchase price and production volume are set in advance so that their total equals the estimated revenues. For example, in the report that launched the AMC, US industry figures on sales and profits were used to estimate that $3 billion would be needed as a buyout to motivate companies to compete to discover and develop a vaccine for malaria and thus the terms of $15 a dose for 200 million doses were proposed.[3] [b] In return for this guaranteed buyout, the originator company would agree to make the vaccine available to low-income countries at a post-payoff price, set in advance close to the estimated cost of production. Recipient countries would contribute a small co-payment. They would also have to demonstrate that they were ready to administer the vaccines. These original terms were subsequently made more complex and changed; but this summary provides a picture of the original model.

An appointed Independent Assessment Committee (IAC) would set the technical criteria for potential vaccines to be accepted as well as the AMC payoff price and volume, the post-buyout price, and contractual terms between donors, countries, and suppliers. The criterion for eligible recipient countries is the same as that used by GAVI, a gross national income per capita of US$1,000. These countries are referred to as "GAVI-eligible countries."[c] Since the entire health budget of some eligible countries is $50 or less per capita, they would not be able to afford vaccines that cost more than $0.50 or possibly $1.00 a dose.

According to GAVI and the World Bank, "[f]irms are assured of a subsidized price if they develop a product demanded by countries and agree to abide by affordable prices after the AMC is depleted. Donors are assured that funds will only be used if a highly valuable product is developed….Finally,

[b] To make provision for a second or third vaccine, the terms became more complicated, as discussed shortly.
[c] Which countries qualify is an issue. Using the average of $1,000 per person a year as a cutoff overstates the income of most people because the small, wealthy elites pull up the average and thus mask great poverty. Using the median income would be more accurate and fair.

and most importantly, developing country governments have early access to priority life-saving vaccines with the assurance of sustainable and affordable supply in the future."

Every year, several million people die and many more suffer from neglected tropical diseases and diseases such as HIV/AIDS, Tuberculosis (TB), rotavirus, pneumococcal infections, and HPV (Human Papilloma Virus). In the view of the World Bank and GAVI, but not the WHO Commission on Intellectual Property Rights, "…the most valuable tool will be the availability of effective and affordable vaccines. However, the global resources invested in finding vaccines against these diseases are inadequate. Developing country markets are perceived as both low value and risky and thus unpromising commercial markets for vaccines."[2:1] In addition, effective vaccines developed for diseases that affect affluent countries only become affordable to low-income countries 10-15 years later. "As a result of these delays, millions of children have died from disease against which they could have been vaccinated."[3:5] An AMC can eliminate this delay, first by providing strong incentives to develop new vaccines for Type III diseases and then, by making them available immediately and affordable thereafter. That is the AMC vision.

Endorsements have been continuously sought from a long list of world leaders and organisations, including the Bill and Melinda Gates Foundation and institutions it launched, like the GAVI Alliance and the International AIDS Vaccine Initiative. It has also gained the support of The Vatican, the World Bank, major pharmaceutical companies, and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).[4-6] The governments of Italy, the United Kingdom, Canada, Norway, and Russia, together with the Gates Foundation, have committed US $1.5 billion to the first AMC.

This patent-centric, vaccine-focused perspective contrasts with other views, including the WHO Commission on Intellectual Property Rights, which emphasises the importance of maximising use of unpatented, inexpensive, and effective techniques; the concern of finding affordable and sustainable strategies; the key role of wider contributors such as hunger and poverty; and the conclusion that innovation "…must be situated within a wider picture of efforts across sectors to improve health and development."[1:21]

This report contributes to the AMC debates by opening up new ways to design and organise advanced commitments that are vital to developers, manufacturers, and purchaser/nations who wish to lift the burden of disease from their economies and reduce the suffering as well as the costs of disease. The original AMC embodied one set of design features, and the current AMC for pneumococcal conjugate vaccines (PCV) embodies a variant of that design. Discussions now focus on the latest refinements of it, losing sight of more fundamental problems. Forgotten is the history of alternate designs and features, of flexibilities considered but then dropped before the "AMC" design was set in stone. Forgotten too are the serious limitations and drawbacks of the design finally chosen for the AMC, only one kind of advanced purchase commitment. Learning about these provides the basis for new, more flexible development of designs that avoid the limitations and drawbacks of the current design.

The features of AMC in its original form:

- A legally binding guarantee to subsidise a large number of doses at a pre-set price equal to revenues of an average Western drug for a company;
  - if an eligible vaccine is developed
  - if and when GAVI-eligible countries commit to purchasing the vaccine and paying the co-payment
- No buyout until all conditions are met
- A commitment to make the vaccine available to recipient countries thereafter at a post-payoff price
- An IAC that sets terms, determines eligibility, negotiates with companies, and contracts with companies.

II. Origins and underlying rationale

The concept of an AMC was developed almost entirely by Michael Kremer, the Bill and Melinda Gates Professor of Developing Societies and Economics at Harvard University. The rationale is most fully articulated in his book with Rachael Glennerster, *Strong Medicine*, and we can gain insights and policy ideas from understanding why Kremer thought advanced purchase commitments were necessary.[5]

Vaccines suffer from "severe market failures," Kremer and Glennerster wrote, even vaccines for the wealthy, and it is easy to understand why. Vaccinating a population saves millions of people from suffering, disability, and medical costs; but they are invisible so they cannot be captured in the price. Society benefits much more than investors. Further, others benefit from those immunised through herd immunity. The large up-front investments in research and development (R&D) cannot be recovered because of pressure to bring prices down to just above production costs. Competitors can also develop slight variations for much less and undermine the ability of the innovator to recoup years of investment. Thus, Kremer and Glennerster asserted that low-income countries "free-ride" on the costly research to develop vaccines for rich countries.

These characteristics lead some to conclude that vaccines are public goods that should be researched, developed, and produced at public expense without patents. In fact, all medicines were exempt from patent law in several European countries until the second half of the twentieth century.[7] The insistence by industry that patents need to be especially strong and protracted for medicines is historically new, as are the arguments that without patents there would be no innovation.[8,9] Many of the most important medicines were discovered and tested without patents,[10] but today even this observation is considered foolish, even pernicious. Why would anyone discover anything, or invest in developing a new product, without years of patent protection? Consistent with current orthodoxy, Kremer and Glennerster concluded just the opposite; that patents and other market protections need to be especially strong in order for super-public goods like vaccines to be privatised. As Kevin Outterson and others have pointed out, patents and other intellectual property protections such as data exclusivity are essentially the privatisation of public goods by governments.[11]

A basic premise of Kremer's development of an advanced purchase commitment is that publicly funded research like NIH (National Institutes of Health) and other national research programs have not worked. "The record of projects that have received intensive public investment is littered with failures."[5:51] Programs that push development (so called "push mechanisms" for research and development), like grants or funded research projects to university and government laboratories, have the wrong incentives, he claimed. They "pay for inputs rather than results." Researchers emphasise the promise of their ideas and request more funding, even though no benefit results. Administrators find it difficult to admit that a program is producing few results and so continue to fund it anyway. Governments fund research for political reasons. What we need, Kremer contends, are the right incentives - promising to buy only successful results like effective vaccines. Then, any team can pursue any research strategy they want, while the buyer only pays for a successful vaccine that works.
Kremer and Glennerster concluded that the solution to the lack of progress is the "pull" of a strong advanced purchase commitment that mirrors the "pull" of a market with ready buyers. "A sponsor could guarantee a price of, say, $15 each for the first 200 million people immunized with a malaria vaccine."[5:68] This would unleash the potential of the entire private sector to find a solution. However, Kremer and Glennerster admitted that "it is usually difficult to stimulate basic research through pull programs, since the output of basic research is often difficult to specify in advance," a fundamental point forgotten when the AMC was designed. A year later, Kremer drafted the AMC design centred on its unique ability to stimulate basic research, and when it was challenged, it was considered heresy.[12]

Origins and underlying rationale:

- Michael Kremer, the creator and promoter of advanced purchase commitments, outlined the perverse effects that have kept vaccines for neglected diseases from being developed
- He wanted to unleash the creative potential of industry researchers to discover new vaccines for low-income countries.
- The AMC idea is to match the revenues that companies would make from developing a product for affluent markets so they have an equally strong incentive to carry out research into a neglected disease.

1. Early flexibilities that disappeared

In his book, Kremer and Glennerster suggested flexibilities in the design of a purchase commitment that dropped from sight a year later when Kremer designed the AMC for the Gates Foundation Working Group. They included ways in which an advanced purchase could be designed to address barriers due to intellectual property rights and could complement grants to help innovators bear the costs and risks of putting a new product through clinical trials. They wrote that the purchase agreement could include buying out patent rights, and Kremer had previously written about patent buyouts, commenting that, "[t]he sponsor could then place the patent in the public domain and encourage competition in manufacturing the vaccine."[13] Kremer pointed out that a patent buyout would be insufficient because manufacturing know-how is also critical; so technology transfer should be part of the purchase agreement as well. Kremer also recommended "requiring the developer to grant the program sponsor a restricted license to manufacture the vaccine and sell it in the poorest

countries."[5:69,99] This is what Outterson and others recommend,[14,15] but patent buyout, patent pooling, licensing, or reach-back grants or milestone payments to developers with a promising vaccine were firmly ruled out by Kremer in the Working Group as we discussed his drafts in 2004.

In addition, Kremer suggested bonuses for vaccines that involve fewer doses or are easier to store in tropical regions. Another flexibility that avoids paying again for a successful vaccine that was developed with push funding from governments or foundations is to use purchase revenues "to repay part or all of the push funds" that a developer has received.[d] Otherwise, one good vaccine might have involved ten years of self-funding, debt, and sunk investment, while another might have enjoyed ten years of all expenses being covered. A related idea was that push funding from contracts or grants might stipulate that if a product is successful, the money should be repaid from sales, thus allowing the next innovative project to be funded. One might add that contracts or grants might stipulate the price reflect the lower development costs so as to increase access.

Finally, most of Kremer and Glennerster's chapter on the buyout idea is devoted to describing prizes, and it is worth realising that an advanced purchase is a kind of huge prize at the end of the race for an effective vaccine against a Type III disease. James Love and colleagues at Knowledge Ecology International (KEI) have been developing alternate ways of accelerating R&D over patent monopolies and buyouts.[16,17] Prizes could be used to address a number of related needs on the road to discovery and development. There are Best Progress prizes, Solve Small Problems prizes, Supporting Cast prizes, Most Improved prizes, Best Collaboration prizes, and Access to Knowledge prizes as well as Grand Great Discovery prizes. Unlike patents, prizes can open or close doors to access by requiring winners to share their discoveries. These ideas for how to design an advanced purchase commitment were also not considered in what is now known as an "AMC."

Early flexibilities that disappeared:

- Patent buyouts and transfer of production expertise
- Licensing
- Higher standards for follow on vaccines to qualify
- Bonuses for ease of storage, transport, or administration
- Repayment of funders who supported the development process
- Interim prizes to reward and give money to research teams who make progress

III. Developing the AMC for official launch

A working group was assembled by the Gates Foundation and the Center for Global Development (CGD) in 2003-4 to developed the AMC concept for presentation to the G8 finance ministers in April 2005.[3] Kremer was the co-chair and wrote the drafts. Up to the final editing by an outside political writer, Kremer always called it an advanced *purchase* commitment (APC), or agreement, because it is

[d] "Push" vs. "pull" is a common, simplified dichotomy used to distinguish between incentives to push along research like grants and incentives to pull along research that reward successful outcomes like prizes or purchase commitments. Patents and market exclusivity reward outcomes and are considered pull mechanisms.

not a "market" but a single large purchase. The revenue/profit-matching core idea had pertained to the lifetime average revenue of a single new product for a single *company*, not for the revenues generated by the entire disease market for all companies. Thus, until the final draft of the CGD report, it was called an APC, not an AMC, and one can find on Google extensive literature and references to APCs. In fact, even the 2006 report of Commission on Intellectual Property Rights, Innovation, and Public Health (CIPIH) still refers to the idea as an APC, which is a more accurate term.

1. Serious design problems

The Advanced Purchase Commitment quickly emerged as the way to "make markets" where none existed and took the form summarised at the beginning of this report. As a member of the Group and a professor of comparative health systems, I became increasingly concerned about the millions of children who would become seriously ill and die from not being immunised by already existing and cheap vaccines each year that the $3 billion was committed to a possible future buyout for a new vaccine for malaria.[18] The trade-off in lives not saved and disability-adjusted life years (DALYs) not reduced by giving priority to a future vaccine and paying much more for fewer doses needs to be weighed against future benefits. The CIPIH expresses the same emphasis, that enthusiasm for new technologies not be put ahead of applying means to reduce disease and death now. If the goal is to maximise the number of lives saved and diseases averted, should we not focus on designing advanced purchase commitments for buying and strengthening the delivery of these vaccines now? Working Group leaders said that APCs are to induce basic research to discover new vaccines, not buy existing ones, and delivery issues are beyond the purview of APCs. Ironically, the final CGD report began, "In the time it takes you to read this preface, 100 people will die of diseases that can already be prevented with vaccines…"[3], the very crisis the report and design do not address. A year later, the renamed AMC was switched from discovering a future vaccine for malaria to purchasing additional doses of already discovered and developed vaccines by pharmaceutical giants for the blockbuster $5-6 billion market for pneumococcal diseases.[19]

While the design was being refined in draft by the Group, several technical issues related to the design of the AMCs were highlighted by experts. Andrew Farlow, an economist at Oxford University, wrote an important early review[20] and an extensive analysis[6] of Kremer's proposals, neither of which has been cited or used in AMC documents. He was joined by others who identified serious problems and limitations in the AMC design that none of the subsequent, official assessments of the AMC even cite, much less address and attempt to solve.[12, 21-25] On the whole, they remain as relevant today as they did when the AMC was launched.

- How can the executive committee set the technical requirements correctly ten years before one knows what kind of vaccine will be discovered? If too stringent, they would disqualify vaccines that would help. Even if set just right, a given set of requirements may have the unwelcome effect of not rewarding efforts to develop still better vaccines.

- How can the executive committee or anyone accurately set the AMC buyout price more than ten years in advance of knowing the cost, science, and technology of a successful vaccine for malaria (or AIDS)? If too low, the AMC inducement will fail. If too high, large sums of public funds would be committed that could be better employed elsewhere, or used to buy more

doses to save more children. On the other side, company executives also cannot know whether the AMC price is attractive or not, and that means the basic purpose of the AMC cannot be achieved.

- Likewise, how can the post-buyout low price be set correctly more than ten years in advance of knowing the cost and type of vaccine that will have to be manufactured? If too low, companies could simply take the buyout and renege on their promise to supply the developing world with low-cost vaccines. If too high, the new vaccines will be unaffordable and/or depend on a constant stream of aid. On the company side, executives again cannot know what they are promising and therefore are unlikely to sign. The AMC has the markings of a neat idea—put up a lot of money and new vaccines for low-income countries will follow, but the reality is impractical.

- Liability issues associated with vaccines are complex and have not been sufficiently addressed in the purchase agreement by sequential indemnifications.

- The core idea of matching revenues a company would earn from doing R&D on a Type I disease of the affluent is undermined by making room for a second or third vaccine and making revenues dependent on how many governments sign up for one's vaccine. These two provisions make it likely that a company will get only a fraction of the buyout for spending 10-15 years trying to develop a vaccine that meets the technical specifications.

- A large AMC commitment could easily lead funders of grants to shift to other priorities, thus depriving a Type III disease of grant-funded research. Yet, such research is vital to discovering new medicines and is more efficient, because one pays several times more for R&D if paid through purchases later. The AMC report asserts this will not happen, but without evidence, it seems likely.[3] It does not address complementary strategies, like Kremer's own suggestion to compensate push funders. The suggestion to include milestone payments to help the most promising vaccine-candidates through clinical trials was flatly rejected as part of "push," not "pull." In these ways, an AMC could decelerate funded research despite doubts about its ability to motivate new basic research.

- The need for a whole-system approach to strengthening public health infrastructure to administer vaccines and monitor campaigns, and especially reach the poorest of the poor, is not addressed at all.[26] Little attention is paid to, and no provisions are made for, all the other barriers to getting children immunised and monitoring the campaign, like upgrading the cold chain, organising effective public health delivery systems to administer them, and developing a good surveillance system. The AMC's focus on spending large funds solely to purchase successful vaccines is incomplete and does not address the source of inequities in vaccine programs. A buyer/donor concerned about reducing disease would want to structure the terms and purchase so that the goal is reached – not to purchase box cars of vaccines but to immunise whole populations at risk.

2. Motivating basic research

The breakthrough idea of Kremer's advanced purchase commitment is to unleash the research ingenuity of corporate R&D teams to discover vaccines for Type III diseases that no university or government team has achieved. Advocates do not talk about how daunting scientific obstacles might explain the lack of success rather than the lack of imagination and strong economic incentive.[e] The AMC report cites economic research that the "deep pull" for basic research will work, but actually the studies are unpersuasive.[3,12] Economic analysis presented by Farlow that it will not work was disregarded.[6, 27]

One of the studies, by Finkelstein, concluded that "for every $1 permanent increase in expected annual market revenue from vaccines against a particular disease, the pharmaceutical industry will spend an additional 6 cents annually in present discounted value on R&D…"[28:543] An AMC, however, is only a one-time increase in revenues that only one or a few companies might win. She shows that companies respond by taking already-discovered products off the shelf and testing them, or "shallow pull," not start-from-scratch deep pull.

The other major study used to "prove" that an advanced purchase would motivate basic research came to the implausible conclusion that a 1% increase in market size leads to a 4-6% increase in new *medicines*, not to 4-6 times more research (also implausible) but to a 4-6 times more actual new medicines discovered.[29] Although stated as if fact, this conclusion is based on an artificial econometric model with the simplifying assumptions that all individuals will live indefinitely and that there is only one firm at any one time with the best technology. The model defines "new drugs" oddly as including all generics and also assumes that anticipated future market size (not actual size) prompts more innovation over long periods. The authors note that "pharmaceutical companies may respond more to profit incentives at the later stages of the research process than at the earlier stages." Given the design features that make it likely a company would win only a fraction, if any, of the money, it seems implausible that companies would start a 10-15 year research program to discover a vaccine for a neglected disease. Thus, Kremer's own evidence indicates that his advanced purchase design is unlikely to achieve its basic goal and would overpay for a company taking a discovered product off the shelf to put through trials.

The underlying assumption that an AMC would "liberate" researchers from bureaucratic control needs to be questioned. The same perversities that Kremer highlighted in "push" funding (such as grants and publicly funded laboratories) also happen in "pull" funded corporate R&D. For example, using the pharmaceutical industry's claim that only one in 5,000 compounds researched result in effective and safe medicines, private investment is also "littered with failures," as Kremer put it. When Carlo Monticelli, one of the champions of AMCs and a representative of Italy (the largest donor) said that directly funded research "boils down to a bureaucrat choosing a particular avenue of research as opposed to another," while the AMC model leaves companies free to choose any avenue they find promising, he cartoons both sides.[30] It is not a "bureaucrat" but a carefully selected review panel of leading researchers who know the field that choose which research projects to fund. And in

[e] Grant-based researchers in fact also have very strong economic incentives to win the next grant or close down. Grant research is a highly competitive market in which a small proportion of competitors win.

corporations large or small, the directors of research, or outside venture capitalists, choose which projects to fund and keep investing in despite failures and lack of breakthroughs because they "believe in" the project. It is equally hard for them to kill a pet project, and the longer money has been poured into it, the harder it gets. This is not just a public-sector problem; some "bureaucrat" always has to make such choices. In what ways, then, is corporate research more free or less bureaucratic?

A key issue in motivating basic research for Type III diseases concerns strategies that foster competition versus cooperation. The AMC design pits teams against one another and encourages keeping new techniques or discoveries as trade secrets, rather than using a collaborative approach. Ironically, the Gates Foundation has transformed research on neglected diseases by bringing together scientists from diverse places, forming supportive networks, and sharing information in order to maximise the benefits of cooperative research. The AMC, by contrast, motivates teams to compete against one another for a very large prize. Yet, cooperative research is most needed to overcome the scientific difficulties of developing a vaccine-cluster for malaria or HIV/AIDS. The President of the Center for Global Development calls for a "global commons" in which the best minds work together for "a global social contract," but the AMC is built on the opposite incentives.[3: vii]

How basic research to discover new medicines for Type III diseases actually works was investigated by a team headed by Mary Moran, who sent its unpublished findings to the Working Group.[23] Her comprehensive study found that neglected disease research was already growing rapidly and that the motivations and funding differed radically from Kremer's theory-based model. Public-private partnerships conducted three-quarters of the projects aimed at public health needs and were funded by a mixture of philanthropy, government funding, venture capital, neglected-disease institutes set up by industry, and companies from developing countries. About half the research projects were based on a non-commercial basis and half on a short-term, small-win commercial basis.[23] That is, venture capitalists put up small amounts and hoped to make a quick profit, not wait for years to see if a discovery could pass all trials and qualify for a billion-dollar payoff.

The big pharmaceutical companies contributed to half the projects for non-commercial reasons, such as fulfilling their social mission, improving their sullied public image, and keeping their best researchers happy by working on a humanitarian project of moral significance. Partnering was often based on a "no-profit, no-loss model." Budgets were small: 47 projects over four years, including 40 failures and 10 in clinical trials, cost only $112 million, an average of $2.38 million and for the seven that succeeded in discovering a promising medicine, only $16 million if one includes the costs of failed projects.[22] In short, the real world of neglected disease research is organisationally diverse, small-scale, and a far cry from the world of multinational giants on which the AMC is designed.

The investigators also developed several scales to gauge the efficacy, safety, suitability, affordability, innovativeness, and cost-efficiency of the new medicines. The new products developed by the big multinationals scored lower because they were less suitable for developing countries and more expensive. They naturally approached product development from an affluent-market perspective rather than from a developing world perspective. Novartis may overcome these problems by setting up two non-profit research institutes with "a nonprofit mission – to discover and develop vaccines for 'neglected' diseases of the developing world."[30]

Dr. Moran emphasised that large-scale buyouts like an AMC could undermine the financial and motivational ecology of partnerships, cooperation, small funding, and the pioneering spirit that supports neglected disease research. Furthermore, an AMC does not provide the assistance that researchers need for phase three trials, registration, and a working knowledge of how developing country markets work.[f] Despite the importance of this new major study, discussion of it was never put on the agenda of any meeting. The compelling rationale that Kremer had developed for the AMC design that ignored complicating realities or more effective options for saving lives drove the agenda, and still does.

Motivating basic research:

- Economic studies used to prove that an AMC will motivate basic research are unconvincing.
- The low chance of success and uncertainties about payoff do not make investment in a research program attractive.
- Actual research on neglected diseases involves partnerships, funding, and motives that an AMC is likely to destroy.

3. Designed for the multinationals

Farlow, myself and others were struck by the extent to which the AMC was designed for the four multinational giants still in vaccine development and manufacturing. As Farlow wrote, Kremer's advanced purchases "deliberately favour large pharmaceutical firms over small and new biotechs and not-for-profit, university-based, and developing-country-based research. Yet, they present no empirical evidence that such firms are the most efficient at vaccine research."[20]

First, Kremer's earlier idea of buying out the patents and licensing the manufacturing know-how as part of the $3 billion package played no part in the AMC design. One wonders why. The Gates Foundation has appeared protective of property rights, despite its dedication to reducing disease burden and improving access in countries that suffer from patent barriers to medicines. Microsoft played a key role in requiring that all developing countries have strong property rights protections if they wanted to trade.[8] AMCs tighten the grip of intellectual property rights, and patents provide strong incentives for a major company to crush or shut out a smaller competitor with a superior vaccine than its own.

Second, the virtue made out of not paying anything until a vaccine is approved and desired by recipient countries work against the small biotechs, where most discoveries are made, as well as university and government teams that need funding to work. Only the multinational giants have the reserves and revenue streams to subsidise R&D for 10-15 years on a project. Others might compete indirectly by partnering with a large firm if they make a promising discovery, but they would get no support for investigating research leads.

[f] An advance purchase commitment could provide any or all of these if one does not start with the current AMC design but rather with what innovators and developing countries need. This is the point of emphasising flexibilities in this report. Milestone payments, various kinds of prizes, or expert organisations to help with registration and marketing could be part a given design.

Third, the size of an advanced purchase should be based on a careful analysis of the economics of past vaccine introductions and sales that are analogous.[6] Instead, it is based on studies by industry-supported researchers of drug sales in affluent markets, resulting in a very high estimate of how large the AMC needs to be. Kremer's design of an advanced purchase also results in donors paying much more for development costs than the actual cost of research, because companies claim costs are much greater than external evidence indicates[31] and because built-in profits compound to double those costs.[32] The AMC design drew on the industry-supported studies that conclude it costs $800 billion on average to research and develop a new drug, now increased to $1.3 billion.[33] Independent evidence from audited tax returns, the NIH, the Food and Drug Administration (FDA), and other sources, however, indicate that the median net cost of R&D is about one tenth of this amount.[31, 34] The median net cost of R&D for vaccines may be different. Since vaccines are bought by governments as a societal good, one could hold that the true audited costs of development should be made public so that fair compensation for them could be determined.

Fourth, the legal advisers chosen to draft the legal terms of the purchase commitment came from Covington & Burling, one of the most powerful international firms in patent protection for the pharmaceutical industry[35] and the Group leaders chose to hold their press conference to launch the AMC at Covington & Burling's Washington offices. This sent a less than encouraging signal to biotech and innovative companies in developing countries outside of the circle of multinationals.

Finally, the goal of developing regional vaccine production capacity through technology sharing was put on the agenda early but quietly dropped. The AMC design precludes a global commons and discourages open research, though AMC rhetoric continues to emphasise openness. Instead, the economics, structure, legal terms, and handling of the AMC favour the few multinational corporations that do vaccine research. Yet, more than four-fifths of all money for basic research to discover new vaccines or medicines comes from public sources.[36] This fact implies a very different role and design of advanced purchases to complement basic research to discover new vaccines or medicines for Type III diseases.

In conclusion, the serious design problems and perverse effects described here cast doubt on the benefits of this AMC design but provide the basis for designing advanced purchases in ways that avoid them, complement push research grants, promote regional suppliers of affordable vaccines, and develop a whole-system public health approach to immunising as many people in GAVI-eligible countries as quickly as possible.

Unaddressed design flaws:

- The payout structure and design favour large multinationals and offer no incentives to most vaccine research teams.
- Yet, the buyout contingencies make payoff uncertain and unattractive for companies.
- The AMC commits large donations to possible future vaccines rather than maximising the diseases and deaths preventable now.
- Technical and economic terms cannot be set accurately years before one knows what kinds of vaccines are developed.
- AMCs pit competing teams against one another, while complex scientific challenges call for sharing and collaboration
- AMCs tighten the grip of IP protections, while access to vaccines calls for sharing.
- Staking a large sum for R&D could lead direct funders to change priorities. Paying for R&D later through higher price costs much more than paying for it directly.

IV. Misleading promotion of the AMC

Some members of the Gates Working Group expressed these concerns about the AMC draft report, and several minor modifications were made. Both Moran and Farlow gave the Group leaders their empirical evidence and economic analysis of how an AMC could cause serious short-term and long-term problems; but neither was discussed at Group meetings, probably because they would have required a fundamental redesign. It seems as though Kremer's model was decided on before the Working Group was assembled. It is the best strategy yet for the multinationals to address the pressure to make medicines available to the world's poor while entrenching their property rights, and it provides the means to make new money from selling products to hundreds of millions who have not been able to afford them.

Based on Kremer's and Farlow's documentation, the Gates Working Group appears to be part of a long, well-funded process of generating endorsements from major institutions and political leaders.[4, 5:115-6] A year before the AMC launch, Farlow reported on how extensive the campaign had been from 2000 to 2004:

> In spite of these hundreds of pages of material [on the Prime Minister's Number Ten Policy Unit website], there has been very little explanation as to the actual mechanism of the working of such APCs[g] in the real world and even less of a 'debate'. Due to the extremely stripped-down and idealised nature of the APC models used in calculations, the many unsupported assumptions regarding how they would work, and the extremely non-idealised modelling of contending approaches, it is not surprising that the figures so far produced favour the APC approach. …The figures produced in support of APCs for HIV, TB, and Malaria vaccines should be treated with a great deal of care – as will become clearer as the

[g] APCs = advance purchase commitments, what AMCs were called for years up to the official launch in spring 2005.

following sections unfold. The evidence presented for these diseases is almost entirely the work of one school of thought (in fact of mostly one person). An uncritically accepted interpretation of APCs – a heavily closed source approach – detracts attention even more from this broader debate.

If open collaborative research and treaty alternatives are so transparently bad, it is not clear anyway why so much effort should go into preventing analysis and free discussion of them. And if APCs are so transparently good, it is even less clear why so much of their actual workings should still be hidden from public gaze after so long.[6:8-9]

This process of promotion has a bearing on how one assesses the merits of an AMC and the Gates Working Group report. A political writer was brought in to manage its public relations campaign for the AMC report. He changed "purchase" to "market," edited passages that might raise questions, and managed the launch of the AMC. Farlow observed at the time that "the authors promote advance purchase commitments in much the same way that some pharmaceutical companies promote 'wonder drugs': emphasising the positive, burying the negatives, and suggesting that we now have all the answers that we need."[20] Emails to Working Group members at the time emphasised the importance of voting to endorse the report soon, in order to present it to the Finance Ministers of the G8 in April 2005. The goal was unanimous endorsement. Members of the Working Group who would not endorse the AMC had their names removed and are not listed as members in the final report.[3] Group members from UNICEF, Copenhagen; WHO, Geneva; and PAHO (Pan American Health Organization) withdrew from meetings and did not endorse the AMC report. They too are not listed in the report as having been members. Voting group members were either not informed or did not object, and the AMC concept was presented to the G8 finance ministers in 2005 as unanimously endorsed, because no negative votes or minority opinions were allowed. These tactics mirror those reported by Farlow during the previous four to five years and those analysed by Thomas Mathiesen in *Silently Silenced,* as invisible ways in which objections are made to disappear.[37]

After endorsing the AMC concept, the G8[h] finance ministers commissioned an assessment, written with help from the same group of AMC advocates. The resulting Tremonti report gave an unqualified endorsement, declaring that AMCs are "market-based", "cost-effective", and "encourage innovation" but with no evidence that they are any of these and with no consideration of public criticisms detailing how they are cost ineffective, not market-based, and could discourage innovation.[38] The same unqualified endorsement characterised the next two authoritative reports on AMCs by the World Bank and GAVI to the G8 and donors in 2006.[2,39] Many assertions in the report are unsupported, such as "[v]accine development public-private partnerships have confirmed that current market failures inhibiting rapid product development and access could be addressed through an AMC." This contradicts Moran's extensive evidence on how an AMC could undermine development partnerships.[23]

[h] Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States of America

Misleading promotion of the AMC:

- The names of major organisations and working group members who would not endorse the AMC model were quietly removed, and it was presented as unanimously endorsed.
- Reports assessing the AMC cite none of its critics or their concerns about impracticalities or potentially distorting effects.
- The GAVI-AMC claims to save many more children than realistic estimates warrant.

V. From vaccine development to overpriced procurement

The design problems of the AMC became irrelevant when the AMC idea was shifted from being used to spur research to discover an effective vaccine for malaria to purchasing extra doses of new blockbuster vaccines for pneumococcal diseases. This is simply an advanced *procurement* commitment for a large volume of supplemental doses for low-income countries of vaccines with heavy corporate R&D investment because so much money can be made from sales in affluent countries. While purchase commitments are vital for suppliers to plan and maximise efficiency, the goal shifts from "How can we accelerate and enlarge R&D for neglected diseases?" to "How can we accelerate access of new blockbuster vaccines to poor countries at the lowest cost and price possible?" Other new blockbuster vaccines for Type II diseases that can benefit poor countries much more than the rich countries if made available at low prices are those for preventing rotavirus and cervical cancer.

1. Overstated claims

The campaign for the AMC-type procurement of PCVs is misleading because it blurs the original AMC with this one. Speeches, slide sets, and statements by GAVI often begin by featuring the vision of incentivising research to discover new vaccines for neglected diseases and then shifting over to how many million lives the AMC for PCVs will save, without mentioning that this AMC has nothing to do with the R&D of these new vaccines, or that all R&D costs will be recovered from affluent sales, not from this AMC.[19] This borrowed glory is part of a wider blurring of Type II with Type III diseases, as when HIV/AIDS or rotavirus or pneumococcal diseases are mentioned with malaria. The first three have large affluent markets and thus significant commercial investment in R&D, as well as government and foundation support, even though 80-90 percent of the disease burden occurs in GAVI-eligible countries.[i] The role of advanced purchase commitments is therefore quite different for Type II than for Type III diseases like malaria.

Second, it is clear that an AMC is not an advanced *market* commitment but an advanced *purchase* commitment re-branded as a market commitment. It cannot be a pilot of an AMC because it is not an AMC. The word "pilot" attached to a $1.5 billion project seems to have been added to deflect criticism

[i] In the case of AIDS, drug companies make far more selling drugs to sick patients than they would preventing it with a vaccine, even if highly priced, a classic tension between market and public health incentives.

and attention from its rather large size. Third, more borrowed glory is built into the title of the AMC website title: "Advance Market Commitments. Accelerating **innovation**. Creating new **vaccines**. Saving **lives**."[40] In fact, no innovation has been accelerated, no vaccines have been created, and no lives have been saved, so far.

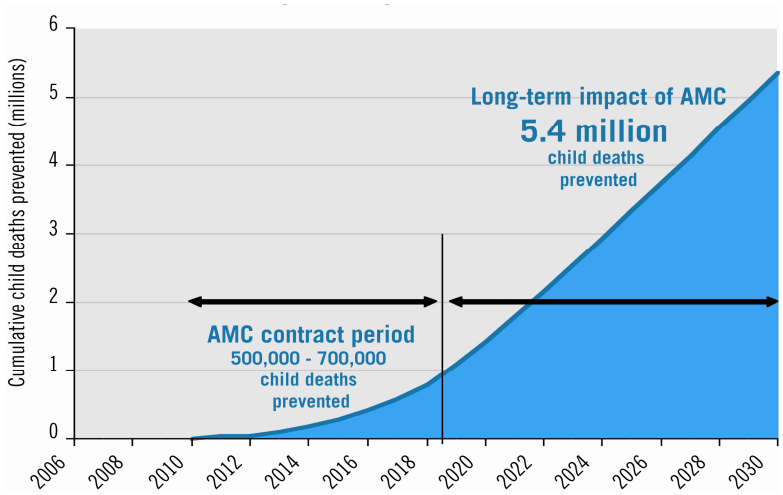
As Farlow pointed out in his Lancet review of Kremer's book,[20] the campaign has more the tone of multinationals marketing blockbuster drugs than the cautious, qualified tone of public health. One sees overstatement again in the claim on the website that "A successful malaria AMC would prevent roughly 2 million deaths by 2030." This is pure speculation about a vaccine that does not exist and faces serious scientific obstacles before being developed and approved. Nations and foundations that generously donate to global campaigns to lift the burden of disease and death deserve more realistic and responsible information.

The specific GAVI-AMC campaign for procuring PCVs exaggerates the number of lives it will save. Figure 1 (below) is widely used in the GAVI-AMC campaign to claim that 500,000 to 700,000 child deaths will be prevented by 2019 when the AMC ends. One trial of an atypically healthy population is used to claim that deaths prevented would be 7 per 1,000 immunised or 1 per 143 infants vaccinated.[19,41,42] This trial, however, excluded subjects with chronic diseases, and only 1% were HIV infected. A recent, authoritative analysis based on many studies puts the figure at 1 per 259 infants vaccinated.[43]

The number of doses that can be purchased at $7.50 a dose with $1.5 billion, however, does not support such an inflated estimate. Since one would need to vaccinate 259 children with three doses to avert one death, 129 to181 million children would have to be vaccinated with 388 to 544 million doses to save 500,000 to 700,000 lives.[j] This is far more than the $1.5 billion AMC pricing model indicates can be purchased.[41, 44]

Figure 1

GAVI's Projection of Lives Saved from the Pneumococcal AMC



Source: GAVI web and slide presentations in 2006-2007

[j] Multiply lives saved by 259 times 3 doses.

The curve of deaths prevented rises steeply in the second part of *Figure 1* to 5.4 million by 2030. This ten-fold projection is based on *an accelerating use after 2019 after the AMC donations*, plus a large multiplier effect for herd immunity. This multiplier is based on a study of the wealthy US population in which 41% of the cases averted occurred in people over age 40 and 25% in people over 65[45], hardly the population in GAVI-eligible countries. Herd immunity in GAVI-eligible countries is likely to be much less. If one corrects for how few doses can actually be bought with the $1.5 billion, given the AMC pricing model, as well as for these two highly inflationary multipliers and the assumption that GAVI countries will continue to pay for the vaccines year after year, realistic estimates of children's lives saved would be a fraction of *Figure 1*.

2. Long project roll-out minimises benefits to the poor

This AMC-style procurement does not start until 2010 at the earliest and will stretch over the following 10 years. Each year after 2007 decreases the purchasing power of donations through the high returns built into the pricing model. The $1.5 billion dwindles to a net present value for the donors of $860 million and a risk-adjusted net present value for suppliers of only $238 million in the GAVI-AMC pricing model.[41:18] Recent revisions allow delivery to be delayed another four years to 2014.[44] This long roll-out means that at the present price of $22.50 per infant immunised and the need to immunise 259 infants per death averted, it would cost $5,827.50 per life saved. Thus, the GAVI-AMC can save only a fraction of the lives claimed in Figure 1. If the donations were spent over five years rather than the highly inefficient span of 10 years, and if the price were nearer the cost of goods, or $3-6 per infant, there would be more money to work with and far more children could be immunised.

The reasons given for the long rollout include building up solid demand (which the new report says is happening now),[46,47] accommodating a third emerging supplier (which according to GAVI's advisers report is unlikely),[41,46] and providing incentives for R&D (which are not part of the AMC implementation). Many companies are already trying to develop better vaccines for the $70 a dose market, not the one-time advanced procurement at one-tenth that price. For these reasons, the goal should be to maximise the number of children vaccinated and minimise donations lost to profit transfers by spending the money as soon as possible based on strong demand.[46] The Director of the Médecins sans Frontières (MSF) Campaign has noted that the co-payment from participating countries and GAVI "is roughly equivalent to GAVI's estimate for the cost of production. Given this, what will the $1.5 billion pay for?"[48]

3. Overstated costs for expanding supply capacity

The major explanation for GAVI's decision to pay several times the production cost is that the patent-holding supplier will have to make large investments over several years to build production capacity.[2,19,46] GAVI's own investment case, however, indicates that no capital investment may be necessary: "Supplying the high income markets requires only ~43M doses per year (this is the equivalent of the minimum capacity of any single manufacturing facility)."[19:74] The modest volume per year that can be bought with the money left over after the built-in profit transfers, long roll-out, and the high price could probably be met without expanding capacity at all.

Moreover, the business trade press reports that Wyeth, GlaxoSmithKline, and others are expanding their manufacturing capacity already, further evidence that capital costs for this procurement may be minimal. This is tacitly acknowledged in the GAVI's July 2008 discussions of manufacturing the doses out of "head room" (spare capacity).[44] Even if a new plant had to be built, like the state-of-the-art plant recently completed by the Serum Institute of India, it cost only $50 million and took one year to build plus another to fully qualify. Such facilities can produce 50-150 million doses a year for 10-20 years; so that even if additional capacity were needed, it would add only a small amount to production costs. If built in the West, the same plant would cost several times more and would be much more expensive to run. The large contracts would go to affluent countries when they could be used to stimulate hi-tech industry in developing countries. The GAVI-AMC report considers none of this evidence and instead emphasises "large" investments over several years without citing any facts or figures, and recommends raising the price further.[46] Based on this analysis, the reasons for paying several dollars more than estimated manufacturing costs or for postponing delivery are not persuasive.

4. Most donations go to extra profits

For these reasons, some investigators may conclude that most of the donations for the current AMC will end up as extra profits on the vaccines for pneumococcal diseases that GlaxoSmithKline (GSK), Wyeth, and others are developing for the large affluent market, where the price is expected to be $70 a dose.[k] A news team for Channel Four in the United Kingdom (UK) spent months interviewing experts and filming in Asia, Africa, and Europe. Their programme, broadcast on 15 November 2007, reported the high price being paid by the pneumococcal AMC consortium and the complexities that needed addressing beyond a focus on just a vaccine to prevent childhood pneumonia. This analysis echoed research concluding that $1 billion of the $1.5 billion in donations would go to extra profits, most likely to one company.[49] Manufacturing costs are estimated by GAVI to be $ 1 to 2 per dose.[19,41]

The Campaign for Access to Essential Medicines at MSF commissioned an independent economic analysis of the 2006 pneumo AMC pricing model, which concluded that $600 million of the donations would go to extra profits beyond the "regular" profits built into the pricing structure of AMC payments stretched out over 10 years.[48] Total profits probably come close to $1 billion, money that could be used to vaccinate millions more infants and children if the AMC paid a price close to the $1 to 2 cost of production. Tore Godal, the former executive director of GAVI, conceded that the AMC price of $5 a dose was too high. Tore Godal, the former executive director of GAVI, conceded that the AMC price of $5 a dose was too high.[50] Now it has been raised to $7 under pressure from multinationals.

Instead of appealing to companies to contribute to the global campaign at no cost to themselves by providing vaccines at cost, or allowing low-cost manufacturers in developing countries to provide them, the GAVI document on pricing continues to treat the procurement as if companies make no other profit on the vaccine.[46] This justifies building in substantial profit, thus greatly reducing the number of children that can be vaccinated with the $1.5 billion donations.

[k] The current, less effective 7-valent conjugate vaccine for pneumonia was priced at $66.44 per dose, or $275.76 per child immunised to the Centers for Disease Control in September 2008, and $335.52 to private practices.

From vaccine development to overpriced procurement:

- The current AMC is not used to accelerate research but to buy extra doses of vaccines that have been developed and fully paid by sales in affluent markets.
- The payoff price is about four times cost so that only a quarter of the children stated could be immunised. Most of the donations will go to extra profits.
- The high cost of enlarging supply capacity is cited as a reason for the higher price but those costs add only pennies per dose.
- Each year that money is not spent transfers profits to the company through the pricing model and further reduces the number of children immunised.

VI. Recent revisions

The Economic Expert Group (EEG) assembled by GAVI issued a report in April 2008 with important implications for the AMC-style procurement of extra doses of PCVs. New data showed strong demand for the new pneumococcal vaccines in developing countries, rising to 116 million doses a year by 2016 and 205 million by 2021. The strength of this updated demand forecast supports distributing the PCVs as rapidly as possible after their approval in 2010-11. Instead, the 10-year commitment "would start at the time the manufacturer is capable of fully supplying its committed level," and the EEG estimates it would take five years to do so. Thus, the first of the new vaccines would reach selected GAVI-eligible countries in about 2014-15.[44] Is this delay morally defensible when compared to the cost of disease and death they allow to happen? The human and economic trade-offs of these delays are not considered.

One reason given for a long roll-out has been to invoke the prospect that the AMC procurement would partly serve to incentivise the development for a third vaccine from an innovator in an emerging country. In fact, the EEG report, while using the language of markets and competition, acknowledges that the first qualifying company, widely believed to be GlaxoSmithKline, will be in a monopoly position and that only one other company, Wyeth, is likely to have a qualifying vaccine soon so that the donated $1.5 billion will be committed to GSK and Wyeth before a third PCV from an emerging-country innovator enters the market.

Both the EEG and Implementation Working Group (IWG) are primarily concerned that the patent-holding multinationals will not accept their terms. Given that this procurement of extra doses for GAVI countries is approached on a commercial basis rather than on a humanitarian appeal to the companies' social mission, they have reason to worry. They take on board the commercial rationale for terms that will increase profits, at the cost of saving fewer children. The first questionable rationale, assessed above, is that it will take a large capital investment over several years to build up manufacturing capacity. A second worrisome rationale is that this contract must be commercially viable on its own terms. Nowhere does either report mention that the companies are developing PCVs to profit from the $5-6 billion markets at $70+ a dose and that the two multinationals are likely to make $1 billion gross profit each from these vaccines. Omitting this is like negotiating with Microsoft

for extra copies of its Vista software program for Africans without taking into account how much profit it is making from selling Vista in Europe, Japan, and North America.

The EEG recommended, and the IWG confirmed in July that the price will be increased 40%, from $5 to $7 a dose, and the tail price cap will be increased by 75%, from $2 to $3.50 a dose for now and more later to adjust for inflation.[44] This builds profit into the tail price, contrary to the original vision of an AMC giving an innovator its windfall profit up front in the buyout so that, thereafter, a vaccine could be available to the world at an affordable price to developing countries.

None of the modelling or data or policy analysis for these decisions has been disclosed, and repeated efforts by MSF to make the AMC process more transparent have been thwarted.[9, 37] There are virtually no verifiable facts in the two long documents by the EEG and IWG. The increases are reported to result from pressure by the companies, and further pressure may lead to the buyout price being raised again. From the perspective of a marketing executive getting $70 a dose, $7 a dose seems unacceptable. For reasons detailed above, both decisions seem indefensible, especially when compared to the significantly fewer children immunised.

The AMC donations will pay half of the $7, and GAVI will pay the other $3.50 together with the low-income countries, as well as the $3.50 tail price after the AMC money runs out. The proportion paid by the GAVI-eligible countries will be determined by a sliding scale according to ability to pay. Both reports assume that GAVI-eligible countries will be able to make a "co-payment contribution that increases over time to the tail price." That seems unrealistic. Given that many GAVI-eligible countries cannot afford more than $1 a dose, how many will be able increase their co-payment to $3.50 by 2020? And how many have the political will to make these increases. They have many other serious demands on their small health budgets.

The EEG proposes a cap on the tail price in order to reduce the possibility of companies trying to maximise profit by setting a higher tail price for those GAVI countries with more income than for others. The question not addressed in these GAVI reports is why not buy the extra doses for GAVI countries at the tail price to begin with? Why structure this procurement so that most of the donations (mainly from taxpayers) go to extra profits? And how can the Board and the Chief Executive Officers of GSK and Wyeth defend their trying to make extra profits from the world's poor on hugely profitable vaccines?

The IWG and EEG are also concerned that the innovator companies might take the money and run, though they couch it in terms of not being sure the companies will provide a reliable supply. The Consequences of Breach section recommends provisions to avoid the long-time concern that companies have little motive to keep supplying the vaccines on time after they have received the AMC money. Several sections deal with possible problems such as, demand being lower than contracted supply, the tail price needing to be increased, mitigating circumstances, extraordinary events, and qualification being revoked. But these are discussed only in a general way. Two more specific provisions are the stipulation that a company will receive AMC funds in proportion to the percent of the 205 million doses a year it will commit to supply over the next 10 years, and the requirement that companies build dedicated manufacturing facilities. This requirement strongly favours global

corporations with deep pockets. It is also bound to lead to higher costs and make the vaccines less affordable for low-income countries, because larger companies build and manufacture in more expensive ways. The jaws of the unaffordability trap will clamp down sooner. An alternative is to make the supply commitment firm, with sanctions, but allow a company to seek low-cost, qualified suppliers.

The AMC Donors' Committee issued a 97-page draft Monitoring and Evaluability [sic] Study. It provides an official history of the AMC, with an oversimplified characterisation of vaccine research, development, and procurement. Like the other two reports by the EEG and IWG, no mention is made of the critical issues raised by independent analysts and addressed here. A discussion of intellectual property barriers is conspicuously absent, and there is no mention of nonrivalrous licensing, patent pooling, or similar provisions. The monitoring and evaluation section is almost 40 pages long and lays out numerous criteria in a generalised way. GAVI's Economic Expert Group is selected to "monitor and evaluate the AMC mechanism."[51:31]

Space precludes a detailed analysis but this decision removes independent assessment. Success is defined in several places in no-lose terms, such as comparing accelerated access to PCVs with having no $1.5 billion initiative at all, rather than comparing this AMC-style procurement contract with spending the money in better ways. Other passages could be characterised as "borrowed glory." For example, achieving the goal "to accelerate the development of pneumococcal vaccines that meet developing country needs" is happening because firms are working hard to develop global vaccines for the $5-6 billion affluent market for this Type II disease, which is prevalent in countries of all incomes. Likewise, percentage increases in plant investment since 2005, new investments in production capacity, percentage increases in doses of manufactured pneumococcal vaccines since 2005, and production agreements with emerging country suppliers are four evaluation criteria that enable the AMC to take credit for large increases that are taking place anyway because of the rapid growth of vaccine sales in large affluent markets. Evaluating the AMC in terms of reducing morbidity and mortality from pneumococcal diseases is mentioned but not developed as *the* primary measure. The baseline for measuring it should be the morbidity and mortality occurring each year after a PCV is made available. The moral and philosophical measure of success is how much this AMC-like procurement will reduce morbidity and mortality compared with the other ways in which the $1.5 billion could be spent.

To conclude, the tail price of $3.50 is the Achilles heel of the AMC design as it is not aimed at finding the partners and technology to make new medicines available for less than $1.00 a dose, as the meningitis vaccine project has done. Instead, it creates new markets among the world's poorest nations for patent-protected vaccines at discount prices that add another $1 billion in profit and keep GAVI countries dependent on charity. The 75% increase in the tail price, well above what most GAVI countries are able or willing to pay, tacitly commits GAVI and donors to subsidising 205 million PCVs a year forever, or else a vaccination program will suddenly stop for lack of affordable supplies and leave millions unvaccinated.

VII. Achieving the lowest cost possible

The costs of manufacturing are closely guarded, and pharmaceutical firms have long exaggerated costs to justify higher prices;[52, 53] so consulting with them leads to figures many times higher than one can glean from independent evidence.[31] GAVI has refused to disclose its confidential consultations, figures, or equations. It assures those who request them, like this author or MSF, that they are accurate, though the material above shows that GAVI has already exaggerated lives saved, vaccines created, capital costs, and what its AMC can do.[26,48]

Reports on production costs by Mercer and Oliver Wyman,[54,55] and interviews with experts indicate that the cost of producing these vaccines could vary from more than $3 a dose to about $1a dose. Cost depends on whether manufacturing is done by multinationals not specialised in minimising costs or in developing countries by companies known for creating cost-cutting efficiencies, and whether regional 4-6 valent vaccines are developed or global 10-13 valent vaccines. Low-cost technologies can cost one twelfth as much as high-cost technologies. While companies making vaccines for the $70/dose market do not have to work on developing low-cost technologies, companies selling to low-income countries do. Experts from Mercer estimate the volume cost of a 1-valent conjugate vaccine is only $0.26 and state that "[w]ith a highly efficient process the incremental costs of adding serotypes would be small."[56:6559] With large advanced contracts, assured pay, and stable demand (the key ingredients of a good advanced procurement), efficient, smart suppliers might produce a 10-13 valent vaccine for $1.25.[49] The GAVI-AMC estimate is $1-2 per dose.[41]

Negotiating 80-90% discounts on Western prices, as GAVI is doing, seems impressive, though GAVI itself recognises this still makes the pneumo vaccine much more costly than GAVI-eligible countries can afford.[19] Open supplier competition was the key to driving down the costs and prices on AIDS drugs far below the discounts that innovator multinationals offered under pressure.[57] Calling for 4-6 valent vaccines focused on predominant strains in each developing region would lower costs further. Yet the GAVI-AMC and World Bank reports use neither approach. They also need to consider how prices could be much lower for vaccines in low-income countries and still benefit the companies.[58] Instead, GAVI's economists frame the cost of building capacity as "the value of the return on the companies' next-best project,"[46:14] a losing proposition.

MSF's Tido von Schoen-Angerer rightly contrasts the GAVI-AMC approach with the Gates-funded Meningitis Vaccine Project, where Marc LaForce started with what African ministers said they could afford ($0.50) and created an alternative strategy to patent-based pricing that reduced the price of a conjugate vaccine from about $2.50 to $0.40 a dose.[59,60] This strategy represents a 6.5 fold increase in how many million children can be immunised with a given donation. If the capital costs of manufacturing per dose are small and if a country co-pays to cover the costs of producing the extra doses, the donors could negotiate to buy extra doses at their estimated cost of $2 a dose now so that 3-4 times more children can be saved before 2015. GAVI board members should reconsider their endorsement of the AMC strategy, especially when applied to buying additional supplies of profitable vaccines for rotavirus and HPV as well as pneumococcal diseases.

VIII. Conclusion: Towards better designs

Advanced commitments to purchase effective vaccines are vital for developers, suppliers, and public health programs. Each needs to know that a reliable and organised market is in place. Each needs to plan and set priorities. The great debt we owe to Michael Kremer is to shift the focus onto the demand side, which has long been considered hopeless because GAVI-eligible countries simply do not have the money for new vaccines, and propose that donors "make markets" by funding that demand.

The success of an advanced purchase commitment depends on how it complements other initiatives and tackles critical obstacles identified in this report and elsewhere. Ignoring these challenges and substituting bravado for sober deliberation, puts a promising idea in peril. This report identifies some alternate ways in which such commitments can help developers, address intellectual property (IP) obstacles, and seek innovative manufacturers at costs that low-income countries can afford. It contrasts these with the entrenched design of the current AMC that keeps new vaccines unaffordable. The current AMC design is just one combination of features, with several perverse side effects and technical problems. Advanced purchasing is probably best done on a smaller scale than Kremer's AMC design, in stages, like $30 a dose for the first 10 million, $15 for the next 20 million, $5 for the next 60 million, and $2 thereafter.

Kremer has made a contribution to the goal of accelerating R&D to discover new vaccines for neglected diseases by emphasising the creative firepower of private industry and the need to mobilise it. Yet, he understated the creative abilities of researchers in non-profit and public research organisations and the scientific obstacles to discovering effective vaccines. Better designs would complement push funding, encourage the synergies of cooperative research, and mobilise research teams in *all* sectors.

A matrix of prizes would help to accomplish the goals of advanced purchasing in ways that would motivate a wider range of research teams and biotech companies to work on a neglected disease problem, because they could be structured to provide much-needed funding at each stage.[17] These could complement forms of direct funding and be structured to support partnerships and collaborative projects.

Donor nations and foundations can play a vital role by offering the kinds of help that Mary Moran identified that developers need. These include helping to fund phase-3 trials, providing experience in doing trials in developing countries, offering regulatory know-how in applying for registration, and mobilising knowledge of markets in those countries. Enlightened purchasers will reward funders of research for their contributions, as Kremer once suggested.

In order to increase basic research to discover new vaccines and medicines for neglected diseases, the first task is to negotiate with nations and public research institutes to give them priority, because a re-analysis of the famous 10/90 report showed that 84 percent of all funds for basic research to discover new medicines comes from public sources.[36] The money is there, only neglected disease targets are not given priority. It is here that major donors like the G8 governments and the Gates Foundation can use

their political and moral weight to change the research priorities of national research institutes. They could also make a deal: double or triple the basic research funding for a neglected disease like malaria and we will put up the money to buy it. That kind of international cooperative enterprise would put up the money for R&D, include shared IP rights and result in much more affordable medicines.

A central problem of the AMC stems from leaving the protection of IP and proprietary know-how intact in the face of major international debate at the WHO on the need to revise IP rights to serve global public health needs. Why does the large buyout of an AMC, largely donated from taxpayers, not require that IP and know-how be shared and licensed? The globalisation of strong, long IP protection has made medicines for Type II diseases less affordable in GAVI countries and not helped to develop medicines for Type III diseases. It is worth remembering that medicines were exempted from patenting or limited to product patents for decades in many countries, because they were regarded as social or vital public goods. During that time, great discoveries were made, and the modern pharmaceutical industry flourished. The Western globalisation of IP protections for medicines should be reconsidered in light of this history.

The current design of the AMC strengthens the grip of patent protections by providing a substitute for countries invoking flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which is one reason why many organisations successfully lobbied to have the AMC dropped from the Global Strategy on Public Health, Innovation and Intellectual Property at the last World Health Assembly.[61] The Global Strategy promotes the transfer of technology to developing countries while the AMC blocks it. The Global Strategy aims to build the research, technical and production capacity of developing countries while the current AMC design keeps those capacities in the hands of the multinationals. Yet, other advanced purchase designs could advance these goals. Exercising TRIPS flexibilities and allowing compulsory licenses is critical, and donor nations and major foundations can play a vital role in persuading company executives and government leaders not to punish low-income countries for trying to manufacture affordable medicines.[57] The lower the price in low-income countries, the more children's lives are saved and the more sustainable the campaign.

1. Different strategies for different needs

Advanced purchase commitments need to be designed differently for different needs. *Figure 2* juxtaposes three purposes with Type II diseases shared by all nations and Type III diseases found predominantly in GAVI-eligible countries.

Figure 2

Six Different Advanced Purchase Strategies to develop and make vaccines more affordable for low-income countries

Functions:	Type II Diseases	Type III Diseases
To motivate discovery and procure for delivery	Motivation primarily from highly profitable markets. Much cheaper to fund promising projects directly than through high prices later. Advanced procurement contract a valuable additional motive. Require sharing of IP and know-how in return for large, long contract.	Lack of market incentives. Combine push funding with pull of long-term, advanced procurement. IP not relevant; find neutralizing solutions. Use a combination of prizes.
To adopt for regional use and procure for delivery	If additional regional trials needed, cheaper to fund directly or through milestone payments for successful trials. Best to develop low-cost versions with non-profit, low-cost partners, which protections for innovator companies.	If additional regional trials needed, cheaper to fund directly or through milestone payments for successful trials. Best to develop low-cost versions with non-profit, low-cost partners, which protections for innovator companies.
To procure existing vaccines for delivery	Negotiate very low price as part of social mission commitment. Reliable, long-term contract a valuable incentive for manufacturers and national public health programs.	Negotiate very low price as part of social mission commitment. Reliable, long-term contract a valuable incentive for manufacturers and national public health programs.

The first purpose is the original one and pertains to Type III diseases, only I have added "for delivery" to remind us that a good advanced purchase should address the whole-systems approach to strengthening public health systems that administer and monitor vaccines. The second purpose, to support additional trials in developing regions and perhaps alter a vaccine for them (like 4-6 valent PCVs that would cost much less to produce for each developing region than a 10-13 valent vaccine), and to procure them pertains to some vaccines for Type II diseases but not others. For Type III diseases, regional variations might be built into an advanced purchase design, or not, depending on the epidemiology of the disease and vaccine technology. The third purpose, to procure already developed vaccines, new or older, pertains to both types of diseases but with very different economics. For Type II diseases, companies will already be manufacturing them for highly profitable sales, so that the advanced purchase is a procurement of supplemental doses. For Type III diseases, the advanced purchase becomes the market itself. In both cases, an important goal is to focus on innovative manufacturing technologies with low-cost firms to get the price as close to what low-income countries can afford so that the vaccination program becomes self-sustainable.

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