

Answering concerns about Making Markets for Vaccines.

Owen Barder, Michael Kremer, Ruth Levine¹
Authors of the Report of the CGD Working Group

Some concerns have been expressed about the report of the CGD Working Group, *Making Markets for Vaccines*, including by Andrew Farlow and others.² The thrust of these concerns is that the report does not cover important issues and that more evidence is needed; that there will be insufficient incentives for subsequent innovation and competition, and that developing country suppliers will be excluded. An alternative approach is proposed in which R&D is funded entirely through public-private partnerships and non-profit research consortia, without seeking to encourage commercial investment motivated by the prospect of a market.

Andrew Farlow and his co-authors have made a valuable contribution to the evolution of the Working Group's thinking and proposals, for which we are grateful.³ We hope that the report has been improved in substance and in clarity of explanation as a result of the interaction we have had with these authors.

It seems that some of the concerns are based on a misunderstanding of the Working Group's proposal, and some are based on a misunderstanding of the scope of the Working Group's remit. But some of the concerns reflect a more profound difference of opinion on whether there is a role for market incentives as part of a balanced package to develop new pharmaceutical products.

We understand that there are people who, for respectable motives, are opposed to intellectual property rights as a way to create incentives for innovation, and who do not want to encourage the pharmaceutical industry to develop new vaccines on a commercial basis. From that perspective, all funds should be channelled through public private partnerships and non-profit research institutions and consortia.⁴

Our view is different: experience so far has been that the pharmaceutical industry has made a major contribution to the development of new drugs and vaccines, that

commercial investment is an important complement to public investments in R&D, and that, without the competition, energy and expertise of the industry, progress towards vaccines for diseases such as malaria is likely to be slow, and the flow of resources inadequate.

We agree with many of goals identified by Farlow and others. However, we believe that these goals are more, not less, likely to be achieved through an approach which includes public and philanthropic funding, collaboration through partnerships, *and* commercially driven investment based on the prospect of a more valuable market, compared to an approach which relies on public and philanthropic funding alone.

More specifically, Farlow *et al* say that a mechanism should:

- **Avoid “command and control” in which funding decisions are made by a committee.** The danger of command and control by a decision-making committee seems to us to be greater under a model of R&D which is only publicly-funded. By contrast, an advance market incentive which rewards successful products would complement public- and philanthropic-funded efforts by allowing a more diverse range of firms to undertake R&D, without having first to persuade policy-makers of the merits of their proposed approach.
- **Create opportunities for developing country suppliers to compete in the development and production of vaccines.** These opportunities *are* created by the framework of the advance market commitment, which allows low-cost suppliers to compete equally. Such opportunities are likely to be harder to secure if all funding is channelled by an allocation mechanism that depends in part on existing relationships, is susceptible to political lobbying and subject to the influence of donor priorities.
- **Create incentives for second-generation products and competition in addition to new vaccines.** This is very important if we are to secure the availability of effective vaccines at affordable prices. The funding now available for public-private partnerships is not sufficient to create a pipeline of second-generation products. An advance market commitment, by contrast, can

be designed to create incentives for new products and competition.

- **End the delays which prevent vaccines from reaching developing countries once they have been developed.** Public and philanthropic funding of research does not directly ensure access to vaccines when they are developed; and the cost of buying vaccines from producers would be additional to the funding of research. An advance market commitment would ensure that the funds are available to buy the vaccines when they are developed, and would guarantee that after the pre-determined number of doses has been purchased the price would fall to a sustainable level in the long run.
- **Avoid asking policy-makers to predict the future or choose among scientific approaches.** Under a model of purely publicly-funded R&D, policy-makers are responsible for creating a mechanism to allocate all R&D funding, and so choose among the most promising scientific approaches. Under an advance market commitment, by contrast, policy makers are responsible for specifying the policy goals but do not control all the research mechanisms – because firms themselves can decide which R&D approaches are most promising to achieve the goal.

We therefore believe that an approach which combines publicly-funded R&D with commercial investment is more attractive when assessed against these criteria than one which is limited to publicly-funded research alone. Furthermore, we do not believe that a purely publicly-funded approach is a practical option. It would require a substantial, sustained and predictable increase in up-front public funding: yet Farlow *et al* say, “previous promises from policymakers on funding for many of the components of the current mechanism have been betrayed”. They say that “the public-private partnerships are estimated to need an *additional* \$1-2 billion over the next 2-3 years alone” (and of course any actual vaccine purchases would be in addition to this cost of vaccine development) – resources which do not seem to be likely to be available even on the most optimistic assumptions. The public-private partnerships themselves say that, even if this additional funding were available, it would not be enough to generate the amount of investment needed to produce an adequate pipeline of vaccine candidates to produce a reasonable chance of second generation products and a vibrant market.

It seems especially perverse to describe the advance market proposal as untested and lacking evidence of effectiveness. The development of drugs and vaccines for affluent countries has been achieved by a combination of publicly funded research and commercial investment based on anticipated markets for the final product, and this combination has produced a range of drugs and vaccines which have transformed the lives of people in rich countries over the last century. By contrast, there are very few examples of successful pharmaceutical development based solely on public funding, without any contribution from commercial investment by the private sector.

We understand the position of those who believe that a non-profit model is a more cost-effective approach for the development of all drugs and vaccines. But this argument would apply equally to diseases of the rich as for diseases of the poor. If one believes that new vaccines for malaria and tuberculosis can be developed more quickly, more cheaply and with more certainty on a non-profit basis -- avoiding altogether commercial investment funded by risk capital -- then presumably the same should be true of the development of new medicines for diabetes or hypertension. We do not understand the position of those who advocate one system for the development of new medicines for themselves and their children, and a quite different one for the children of the poor.

While we respect the integrity of those who disagree with us on issues of substance, we completely reject the criticisms made of the process by which the Working Group reached its conclusions. These concerns are ill-informed and have no basis in reality.

We very much welcome this debate about the appropriate mix of funding, incentives and institutions to accelerate the development of new vaccines, and to ensure access to vaccines when they are developed. In the spirit of encouraging further debate, and to avoid misunderstandings about what is proposed in *Marking Markets for Vaccines*, we attach a note setting out a response to specific points which have been raised.

Owen Barder, Michael Kremer & Ruth Levine
8 May 2005.

1. Missing details?

Why don't the specimen contracts include details of how the long-term price is set, or the details of liquidated damages for non-delivery?

This question is based on a misunderstanding of the scope and purpose of the Working Group. The Group's remit was to assess whether an advance commitment could be made in practice and whether it would be effective. It was not intended to draw up a detailed blueprint for a particular product, nor to negotiate details of contracts with potential sponsors or suppliers. The Group used the process of developing specimen contracts to discipline its thinking, and to illustrate how an advance market framework might work in practice. It was not necessary to specify what the contract would say about damages for non-performance, partly because these terms are a standard feature of many commercial contracts. The details of these clauses would, in practice, depend on the jurisdiction chosen for the contracts are signed, on the sponsors' priorities, and on other contract details.

Similarly, the report sets out options for setting the long term price (either setting a fixed price in advance, using a formula based on actual costs, or some hybrid approach) – the choice of how exactly to do this would depend on the views of the stakeholders and on the disease in question. The decision not to prejudge these in the specimen contract does not reflect a lack of importance of these issues, nor any insurmountable legal or analytical challenges, but rather reflects the Working Group's view that these details are tractable and did not need to be specified to form an understanding of the concept and principles of an advance market commitment.

Why doesn't the report discuss the full range of issues outside the advance market framework, such as industry concerns about legal liability, and the broader challenges of vaccine delivery in developing countries?

The report does highlight these issues, primarily to emphasise their importance in addition to the steps that should be taken to increase the resources and incentives for the development of vaccines. Important though these issues are, they were beyond the scope of an investigation into whether an advance market commitment could work in practice.

The Working Group did not suggest that entering into a purchase contract should be a substitute for the important work of building up the skills and capacity of developing country health systems. On the contrary, the report says, "*It is essential to boost and strengthen vaccination delivery systems in developing countries, to improve demand forecasts and to extend long term procurement for existing vaccines. These measures would save lives today – and complement an advance market commitment by making the market for vaccines larger and more certain.*"⁵

The framework proposed by the Working Group would not require significant changes to the process of vaccine procurement: vaccines would be purchased by existing purchasers, such as UNICEF, and the arrangements for liability under those arrangements would remain in place. If liability becomes a more important issue for the supply of vaccines to developing countries, those purchasing arrangements may need to be adapted in due course, but this evolution does not have a direct bearing on the advance market commitment.

The Working Group has been clear throughout that there is no single measure that would overcome all the challenges in the development and delivery of vaccines for developing countries. But that does not mean that any proposal which has the scope to make a significant contribution should be rejected on the grounds that it does not solve everything at once.

Does the report ignore the intellectual property and know-how barriers which have been a cause of delay in achieving flexible, cost-effective manufacturing and in getting vaccines to poor countries quickly?

Far from being ignored, this issue is discussed throughout the report, and lies at the heart of the advance market commitment proposal. An advance market commitment would overcome the tension between the market exclusivity provided by intellectual property and the need to ensure affordable access to new vaccines immediately and sustainably, because vaccine purchases would be subsidized by sponsors until the price was reduced to an affordable level as required by the contract. This would ensure that the market exclusivity did not become a barrier to access to low cost vaccines.

Others have suggested alternative ways to change systems of intellectual property to ensure affordable access for developing countries. Typically these approaches require either some weakening the IP system as it affects developing countries, or ensuring that the relevant R&D is done under funding arrangements that limit commercial exploitation of that intellectual property. The Working Group believes that the advance market proposal has the merit of accelerating access to new vaccines, while respecting the system of intellectual property rights which has led to the development of new pharmaceuticals in the past.

2. A committee not a market?

Is too much discretion is left in the hands of a committee? Does the committee have the power to distribute funds?

This suggestion appears to reflect a misunderstanding of the role of the proposed adjudication committee, the role of which is described in detail in the Working Group report. The discretion given to the adjudication committee would be strictly circumscribed by the legally binding framework, and its key decisions would be subject to legal challenge where necessary. The sponsors would set a target vaccine

specification, and the main role of the adjudication committee would be to decide whether that target had been met. (It would have some other roles, set out in the report.⁶)

There are many precedents in contract law for the creation of independent arbitration processes as a mechanism to enforce the contract. Far from increasing policy-makers' discretion, these arrangements are designed to reduce the risk of policy makers reneging on their commitments, and to increase the transparency and predictability of future policy actions.

The power to distribute funds would not lie in the hands of the adjudication committee. No funds would be distributed unless and until developing countries decide that they want to use the vaccine. As developing countries buy vaccines at low affordable prices, the funds would flow automatically to the suppliers, as sponsors would be obliged to top up those payments. So once a vaccine is approved, the adjudication committee would have no discretionary role in the distribution of funds. In particular, it would not be responsible for allocating funds for R&D, or for deciding which company received the return.

To describe this as a “command and control” mechanism is therefore either an inadvertent misunderstanding or a deliberate misrepresentation of the proposal.

“Top down, committee driven approaches are incapable of the subtle, complex and adaptive adjustments required for developing vaccines for HIV, malaria and tuberculosis.”

We agree. This is a succinct summary of one of the main reasons that the Working Group believes that R&D for new vaccines would benefit from the involvement of a diverse range of actors – small and large firms, in rich countries and in poor – each able to invest on its own account to develop new vaccines, with the incentive of an expected return if they succeed. Alternative models in which all funding for vaccine research is allocated by or on behalf of a committee of donors, by contrast, might suffer from exactly the problem described here: such an approach would be likely to involve a centralized, top-down committee allocating resources to the scientific avenues it considers the most promising.

3. Choosing the right value?

Has sufficient rationale for the market size been provided? Has the market size been determined by political expediency rather than a thorough analysis of the history of the introduction of various kinds of vaccine, and on the expected complexity of science?

An entire chapter of the Working Group report (Chapter 5) is devoted to a discussion of setting the market return at an appropriate level; and a technical working

paper on the topic is also available (<http://www.cgdev.org/vaccine>), has been presented at the American Economics Association, and will be submitted to a peer-reviewed journal.

The Working Group argues that there is no single “correct” value for the market size, but rather a range of values within which an advance market commitment would be likely to accelerate the development of new vaccines and still be outstanding value for money for the sponsors.

If an advance market commitment is implemented, the sponsors would need to decide what level of commitment they are willing to make, based on the extent to which they believe that a larger commitment will elicit more R&D activity and so result in a vaccine more quickly, the state of scientific progress, the likely technical difficulty of producing a vaccine, the size of other markets for the vaccine (*e.g.* for the military & travellers), and the size of the savings from reductions in other assistance (*e.g.* drugs). They may also wish to take into account the costs of R&D that they have already funded directly.

The illustrative figure of \$3 billion used in the report is based on a study of the revenues earned by new chemical entities developed for rich-country markets; and it is the mean of the data sample. It is wrong to say that this amount matches the value of blockbuster drugs, which (according to the data on which this estimate is based) earn much bigger revenues than the average. The estimate of cost-effectiveness shows that a commitment of this size would be outstanding value for money. The \$3 billion figure is intended to illustrate the concept, not fix a precise amount.

4. Competition, innovation and developing country suppliers

Is it impossible to predict the specification of a vaccine in advance? Have the requirements been set “at the very lowest level”?

It is indeed impossible to predict in advance what efficacy a new vaccine will have, or how it will work; but it is much less difficult to state what efficacy and duration a vaccine would need to have to make it a good buy for sponsors.

The technical specification would be drawn up by sponsors, consulting developing countries, industry and public health experts. The Working Group did not undertake this exercise except in the most modest form, and the example in the report is merely illustrative to show that it is possible, and to provide the basis for cost-effectiveness calculations.

Relatively low efficacy requirements were used in the estimates of cost-effectiveness to illustrate the point that, even at relatively low efficacy, a vaccine would be outstanding value for money. This was not intended to endorse a particular figure for the technical specification; and so concerns about whether the requirements have been set high enough are simply misplaced: the requirements haven’t been set at all. A spreadsheet tool has been developed to allow analysis of other possible specifications.

Does the commitment “close the door” on later innovators?

No: the commitment is specifically designed to encourage second generation products. The top-up payments offered by advance market commitment would be open to any firm or individual able to make a vaccine that meets the technical specification, and which improves on any existing vaccines that meet the specification. The commitment creates incentives for firms to produce vaccines quickly and at the highest possible level of efficacy, and also encourages subsequent innovations which can enter the market and earn a return on their investment, by allowing demand to switch to those products as soon as they are available.

Is there an incentive for vaccines that exceed the minimum requirements?

Yes, there is; and sponsors can decide how much weight to attach to this. The first developer has an incentive both to develop a vaccine quickly, and to develop one which meets the highest possible standard, so that they retain market share as subsequent vaccines are developed. Subsequent developers have an incentive to improve on the first vaccine, as a higher quality vaccine would be likely to retain a significant portion of the market for longer.

By selecting carefully the combination of price and quantity (which make up the market revenue guaranteed by the commitment), the sponsors can decide the extent to which they wish to focus the incentives on early discovery of a new vaccine, and the extent to which they want to use the commitment to reward the developers of subsequent improvements.

The illustrative figures in the report show that a vaccine that is 50-60% effective would save millions of lives and be very cost-effective. The Working Group also developed a spreadsheet tool that permits anyone who is interested to estimate the cost-effectiveness from the sponsors’ perspective under different assumptions for the technical specifications (<http://www.cgdev.org/vaccine>).

Would the program benefit big pharmaceutical companies rather than developing country manufacturers or biotech firms?

No: there is no reason to think that this incentive would benefit big pharmaceutical companies rather than developing country manufacturers or biotech firms. Unlike funding directed entirely by donors, the benefits of the advance market commitment are available to everyone equally. Access to resources would not depend on existing relationships with funders, and there would be less chance of the resources being allocated through patronage or by relatively conservative decision-makers. Any firm that can persuade an investor that they have a viable proposal can compete for the market. Indeed, firms with a low cost base stand to gain more than firms with a high cost base.

In the consultations, the proposal received positive reactions from biotech companies, and from executives at the Serum Institute of India. BIO Ventures for Global Health has welcomed the proposals.⁷ There is therefore no reason to think that only large pharmaceutical firms will be able to compete for this market.

By creating new markets for vaccines for use in developing countries, this proposal would be likely to benefit developing country developers, whose expertise in organising clinical trials in developing countries, for example, would become more valuable.

That said, the primary purpose of the advance market commitment is to achieve a public health objective, not to achieve an industrial policy to foster the development of particular manufacturing capabilities in developing countries. There would be considerable risks in aiming to achieve these two different aims with a single policy instrument; and there would be considerable risks of political capture of a policy which sought to achieve both at the same time.

5. Was the process flawed?

Does the work lack an evidence base?

It is true that an advance market commitment has not yet been tried in exactly the form that the Working Group proposes. Nonetheless, there is plenty of evidence set out in the report that leads the Working Group to believe that it would be effective:

- the markets for pharmaceuticals in affluent countries provide a compelling example of how the existence of larger and more certain markets provide incentives to develop new pharmaceuticals;
- the illustrative size of the commitment is based on the realized revenues which have in practice spurred innovation by the pharmaceutical industry;
- policy-based incentives have accelerated the development of new pharmaceuticals, including the Orphan Drug Act, the UK policy on Meningitis, and the effect of procurement guidelines from Vaccines for Children;;
- academic, peer-reviewed literature (*e.g.* Acemoglu and Linn, 2004) finds that R&D is positively related to expected market size; this was confirmed in a series of interviews with industry.

The empirical basis for choosing an approximate size of a commitment is set out in a separate, academic paper,⁸ though the Working Group report also encourages any sponsor which is considering taking the idea forward to validate the estimate of market size using alternative data.

Was advice from experts ignored (eg on the difficulty of setting a technical specification or a long term price)? Did the Working Group keep changing the proposal from one draft to another?

No advice was ignored. Not everyone who was consulted will agree with the Working Group's conclusions, but everyone's views were taken into account. So far from ignoring those who highlighted the difficulties of drawing up a technical specification or of setting a long term price, the report specifically mentions both concerns.⁹

It is perplexing to be criticised for ignoring expert advice on the one hand, and for changing the consultation proposal during the process on the other. The Working Group's thinking evolved during the process in the light of consultations, its own discussions and analysis, and the range of expert advice it received.

Were the views of developing countries sought?

Yes. Malaria program managers, Ministry of Health decision-makers, and Expanded Programme on Immunization managers in several sub-Saharan African countries were consulted during the process of setting the illustrative product specifications. These views were reflected in the proposals, and formed the basis of drawing up the illustrative framework of a contract for a malaria vaccine.

Since then, the Malaria Vaccine Initiative has commissioned a more comprehensive market analysis from consultants, looking at the demand for a malaria vaccine, which broadly confirm the analysis undertaken for the Working Group.

In the implementation of an advance market commitment, there is additional scope for input from developing country representatives and experts, and this would be an important part of the process.

Was anybody with any experience of delivering vaccines involved?

Yes. Two members of the Working Group had direct professional experience in the field of immunization program management and finance. Many of the advisors to the group had many years of experience in vaccine delivery. That said, developing recommendations for how to strengthen delivery systems in developing countries was not a central part of the mandate of the Working Group, and the composition of the group reflected the importance of understanding the dynamics of R&D and industrial behavior.

Did spin take over from rational and self-critical analysis?

Readers of the final report will judge for themselves whether this is spin, or a solid piece of analysis grounded in evidence and broad consultation. We make no apologies for presenting the conclusions in an accessible form and making the material available to a wide range of audiences who could use their material and technical

resources to hasten progress toward urgently needed products; but we have made no compromises on the integrity of the analysis to do so.

6. The political context

Does the report assert the centrality of long-term political commitment for an advance market commitment?

No. It is precisely because of the risk of volatile political commitment that a legally binding structure is proposed. Those who believe that R&D should be funded only through “pay as you go” grants, by contrast, are making a strong assumption about the likelihood of continuing political commitment over the years ahead, as there would be no legally binding framework to lock in such commitments.

Will attention be deflected from other priorities?

No: there is no reason for an advance market commitment to crowd out other policies and priorities. The report goes to great lengths to explain how and why other priorities – including funding the public private partnerships, publicly funded R&D, strengthening health systems and delivery, and funding of the purchase of existing vaccines, should be increased, and how these would complement, and be complemented by, and advance market commitment. The commitment has the advantage that it does not require funds to be set aside. Nobody who has actually read the report, or heard it presented, could be in any doubt that the Working Group sees an advance market commitment as a complement to these important activities.

What steps are being taken on the negotiation of contracts with existing developers of new vaccines for malaria, pneumococcus and rotavirus?

We do not have any role in the discussions between vaccine developers and sponsors, and can offer no insight or informed comment on this. We believe that the principles set out in the Working Group report can be applied in a variety of contexts, including those in which vaccines are partly or completely developed, and the report discusses how the proposal might be adapted for those circumstances.

Notes

¹ For biographies of the authors, see *Making Markets for Vaccines*, Center for Global Development, Washington DC, 2005; page 81. Available online at <http://www.cgdev.org/vaccine>.

² Farlow A., Light D., Mahoney R., and Widdus R. “Concerns Regarding the Center for Global Development Report ‘Making Markets for Vaccines’”, Submission to the CIPIH, 29 April 2005.

³ One of the authors (Light) was an original member of the Working Group and elected not to be a signatory to the report because the concerns he raised as the report was being finalized were not addressed to his satisfaction. The others (Farlow, Mahoney and Widdus) were not part of the Working Group but were part of a large number of individuals who have provided occasional commentary.

⁴ “Discovering vaccines for HIV, malaria, and tuberculosis are critical priorities, but they can and are best pursued through the excellent partnerships that the Bill and Melinda Gates Foundation and others have forged, and through directly funding both basic research and trials, and developing synergies among researchers working together”. Farlow et al, 2005. See also

<http://www.economics.ox.ac.uk/members/andrew.farlow/> for a range of papers setting out a similar view.

⁵ *Making Markets for Vaccines*, page x (‘Policy Highlights’)

⁶ *Making Markets for Vaccines*, pages 43

⁷ See *A Historic Call for Action*, BVGH 2005. <http://www.bvgh.org/APCpage.asp> accessed May 8 2005.

⁸ Berndt, E et al *AdvancePurchase Commitments for a Malaria Vaccine: Estimating Costs and Effectiveness.*, National Bureau for Economic Research (NBER) Working Paper #11288, 2005.

Available online at <http://www.cgdev.org/vaccine>

⁹ *Making Markets for Vaccines*, pages 44 and 47 respectively