

Making Markets for Vaccines: Ideas to Action

April 7, 2005

Frequently asked questions

Structure and arrangements

What would the advance market commitment consist of?

The advance market commitment would consist of:

- An agreed technical specification—in terms of outputs—required of a new vaccine.
- A price guarantee, consisting of small payments from eligible countries and a co-payment by sponsors, would apply to a maximum number of treatments. (For example, the price might be guaranteed at \$15 per treatment, with the eligible low-income country paying \$1 and sponsors topping up the payment with an additional \$14 for the first 200 million treatments.)
- An overall market size of about \$3 billion—enough to make it worthwhile for firms to accelerate investment in research and development for new vaccines, but well below the social value of the vaccine.
- An independent adjudication committee to oversee the arrangements and commitments enforceable under the law.
- A corresponding commitment from the producer, in return for taking up the guaranteed price on the first treatments sold, to produce and sell further treatments in eligible countries at a fixed, low sustainable price.

Can administrations legally bind themselves and their successors?

Yes: governments make legally binding contracts all the time. Think, for instance, of long-term procurement contracts, or the sale of government bonds. The US Congress has waived sovereign immunity for contracts signed by the US Government. The advance market commitment uses the same contract laws.

What is the structure of the contracts?

There would be two contracts. We have included contract term sheets drawn up by corporate lawyers specializing in the pharmaceutical industry to illustrate how the contracts would work. The first contract, the Framework Agreement, would be available to any firm that wants to be able to enforce the sponsors' commitment. Under the Framework Agreement, a developer that produces a qualifying vaccine is contractually entitled to sign the second contract, the Guarantee Agreement. In the Guarantee Agreement the sponsors guarantee the co-payments which enable the developer to recover the guaranteed price on vaccines sold to eligible buyers, up to the agreed maximum number of treatments covered by the commitment; in return for which the developer guarantees to supply subsequent doses at an affordable, long-run price.

Why not just have an open offer to pay whomever develops the product? Why bother with a framework agreement?

The Framework Agreement ensures that the contract is binding on the sponsor. To make a binding agreement, both parties need to sign. The two-stage contract therefore ensures that there is an enforceable contract with the sponsors.

How would the funds actually flow?

Here is one example of how the flow of funds could work. The developing countries would buy vaccines through tenders, as normal – for example, through UNICEF or the PAHO Revolving Fund. The supplier would offer to provide vaccines at the low price (that is, the amount of the developing country co-payment set out in the agreement). If the supplier's offer is accepted, and the vaccines are purchased at this low price, the supplier can then present evidence of the sales to the sponsors, who will be legally obliged to make co-payments for the vaccines purchased. The sponsors would pay the supplier directly, in accordance with the co-payment guaranteed by the commitment.

Government budgets & procurement

Can governments budget for a long-term commitment?

Yes: the advance market commitment is like any contract to pay for goods and services as and when they are delivered. There is no budgetary obstacle to making such a commitment, given political will.

Will governments have to allocate money in today's budget when they make the commitment? Will the spending compete with programs today?

No. The spending will only be counted towards government outlays and the budget deficit when the vaccine is delivered. This means that Governments do not have to allocate money from the current year's budget to make the commitment – though they will need to allocate money when the vaccine is produced.

Can the U.S. Government do this?

Yes it can. There is no technical obstacle to making this commitment, provided the Administration and Congress have the political will to do so. Full details are in the report; and on our website at www.cgdev.org/vaccine.

If the U.S. Government makes a commitment, will that necessarily squeeze out spending elsewhere in the budget before the vaccine is developed?

No: this does not need to reduce other spending unless and until the vaccine is developed, if Congress chooses to allow the Administration to make the commitment in this way. The report explains how the Administration and Congress can implement this without reducing spending on other budget items until the vaccine is developed.

Is this consistent with government procurement regulations?

Yes. Successful vaccine developers will be able to submit low offers in public procurement tenders, knowing that the sponsors will be obliged to top up those payments under the terms of the advance market commitment. No changes to the procurement process are necessary.

Incentives for industry

What happens if more than one product meets the specification?

If it is genuinely a separate product, which materially improves on existing products – for example, by having a higher level of efficacy, or by requiring fewer booster shots and so being easier to deliver – it is also eligible for the price guarantee. It will then be for developing countries to decide which eligible product they want to buy.

How will vaccine developers be confident that they will not see their expected market return taken by generic copies?

Second and subsequent products entering the market guaranteed by the commitment must demonstrate that they are superior to existing vaccines, and not merely generic copies. This is similar to arrangements under the Orphan Drug Act. (It is also worth noting that it is harder to make generic copies of vaccines than for drugs, for various technical and regulatory reasons.)

Will firms want a guaranteed quantity, so that they won't need to compete with other suppliers?

In consultations on this proposal, firms recognised that sponsors should have the ability to switch demand to superior products. That is the risk firms take in affluent markets, too – so they are used to having to make the best product they can as a way to keep their market share. It makes sense for firms to keep some demand risk, so that there is an incentive for firms to make the best possible products.

How will firms be sure that the sponsors will not change their minds and renege on their commitment?

The commitment will be in the form of a legally binding guarantee, enforceable in the courts.

Who will decide if the vaccine meets the specification?

An independent adjudication committee, established at the outset of the Framework Agreement, will be responsible for determining whether a vaccine qualifies for the guarantee. The decision is taken out of the hands of the sponsors themselves, to ensure that the sponsors cannot renege on the commitment to pay once a vaccine is developed, or arbitrarily amend the specifications.

Is the advance market commitment designed for multinational pharmaceutical firms, rather than the emerging suppliers?

The commitment is neutral about which type or types of suppliers would benefit. While multinational firms have a longer track record of innovation and ability to deliver new products, emerging suppliers are increasingly demonstrating capacity to undertake research (particularly at the clinical phases) and have a significant advantage in scale manufacturing for some types of products. It is likely that, as a market is defined through an advance market commitment, partnerships between innovators and manufacturers of all types will be created; some of these may favor emerging suppliers. Unlike funding for which sponsors pick the recipients from the beginning, an advance market commitment creates a level playing field on which suppliers of all types can compete.

Is the commitment too long-term to create incentives for biotech companies -- who have shorter time horizons?

Some biotechs – or more specifically, the venture capitalists that invest in them – are interested in returns over a few years rather than a decade or more. But biotechs will be able to invest in medical innovations, confident that they will be able to sell or license their technologies to other firms – such as pharmaceutical companies that are willing to take the longer term risk of developing commercial products. Biotech companies will be able to earn returns from these inventions in the same way as they do from products they develop for affluent country markets. Biotech companies, and venture capitalists, have been particularly enthusiastic about this idea.

What is the benefit of a commitment for late stage products – surely the R&D has already been done?

In the past, it has taken 10-20 years for new vaccines to be available at prices affordable to low-income countries, as manufacturers gradually scaled up production, selling first to the more lucrative markets in affluent countries. With an advance market commitment, producers can scale up production quickly, and so generate returns to scale and reduce the cost of new vaccines, with confidence. This means that a commitment would ensure more rapid and affordable access to new vaccines. It would accelerate the introduction of long-run, sustainable prices for the vaccine when the commitment is exhausted. This would increase the confidence of developing countries that they can sustainably introduce new vaccines. A commitment for a late stage product would be smaller than the \$3bn suggested for an early stage product, and would be negotiated with specific suppliers.

Are early stage products too remote for incentives to be effective?

The prospect of a market is effective in stimulating R&D for products for affluent markets. The existence of long-term incentives is translated by the market into appropriate short-term incentives, such as an increased willingness of pharmaceutical companies to licence IP from biotech companies, enter joint ventures with them, or buy them. This in turn creates shorter-term incentives for biotech companies to invest, and for investors to invest in biotech companies.

Would a commitment be more effective for late-stage products than early-stage products?

Both would be effective. If you think it is going to be a good idea to make a commitment for a particular vaccine in the future, then it makes sense to make that commitment sooner and so also have a positive impact on firm's R&D decisions as soon as possible.

Setting the price

How was the proposed market commitment of \$3bn calibrated?

This is the estimated market revenue for the average product in a sample of recently developed commercial pharmaceuticals. In other words, this is the amount of sales revenues that has been large enough to spur R&D investments for existing products - so it is reasonable to conclude that it is large enough to stimulate R&D investment in diseases concentrated in developing countries. We recommend that further analysis be undertaken to confirm this analysis of average market sizes with alternative data sets on sales revenues.

\$3bn is far too big. R&D costs are much less than this. Will sponsors be overpaying for new vaccines?

This proposed market commitment is not based on an estimate of R&D costs, but on an estimate of the actual revenues obtained by new medicines. Clearly the expected value of these realized sales revenues were big to provide incentives to develop new medicines.

Estimates of R&D costs vary considerably: but in any case, sponsors should *not* aim to make a commitment which is exactly their estimate of the minimum cost to one company of developing a vaccine. The ideal commitment is one which is big enough to create incentives for several companies to invest in R&D, and so accelerate the development of a vaccine and increase the prospects for the development of second-generation products and competition in vaccine markets. A larger commitment will be likely to increase total R&D investment and so speed up more the development of a vaccine. Given the very significant number of additional people that would be saved by advancing the development and distribution of a vaccine by as little as one year, our estimates show that increasing the sponsors' market commitment would be very good value for money for sponsors, even with cautious assumptions about how much an addition to the commitment would advance the development of a vaccine.

\$3bn is far too little. Won't it cost much more than this to develop an HIV vaccine?

The proposed advance market commitment is designed to provide a return of the same size as the average sales revenues for new medicines. If scientific complexity means that R&D costs are much higher for an HIV vaccine than for other medicines, then \$3bn may be too low to stimulate sufficient investment. This is something sponsors should look carefully at when finalizing the commitment. Sponsors may wish to err on the side of a low commitment, as it remains open to them to augment the commitment later if it does not provoke the intended response. Such augmentation might take the form of additional investment in “push” funding, or enhancing the size of the advance market commitment. Note that, if the commitment is too small to stimulate industry investment, and therefore does not succeed, there is no cost to the sponsors.

Why pay \$15 a treatment when vaccines today cost less than \$1?

One way or another, society needs to pay for the R&D costs of developing new vaccines that will bring about the better health that the world enjoys today. Vaccines without large rich-country markets will be more expensive, at least in the short term, in developing countries, than existing vaccines which have been able to recover their development costs elsewhere. Hence the advance market commitment creates a two-stage pricing structure, in which a high price at the outset – which is subsidised by the sponsors - is followed by a guaranteed, affordable lower price in the long run. Over the long run, the total price paid for the vaccine may be less than for other vaccines, even if the price is higher at first.

Why not set a lower price, with a higher quantity, to give the same return but get more vaccines cheaply?

The guaranteed low, long-run price ensures that vaccines are available cheaply when the commitment is exhausted. So there is no cost-effectiveness benefit to extending the commitment to a larger number of vaccines but at a lower guaranteed price. The choice of combination of guaranteed price and maximum quantity should be determined by the amount of front-loading the sponsors want to create, not by the cost-effectiveness of the commitment, which is determined by the overall value of the commitment, not by the mix of price and quantity that is used to get there.

What impact would it have on firms' incentives to set a lower price, for a higher quantity?

The combination of price and quantity (e.g. \$15 for 200 millions immunized persons) that is chosen to deliver the intended market return (e.g. \$3bn) should be determined by considering the amount of front-loading that the sponsors wish to offer. A more front-loaded offer (e.g. \$20 per dose for 150 million immunized persons) would create greater incentives to produce a vaccine rapidly, but would lessen the incentives for development of subsequent improved vaccines. Conversely, a less front-loaded offer would make it easier for subsequent, superior products to earn a large return. The signals that the sponsors wish to send are reflected in the profile of the revenue stream that is created.

How can the vaccine price be sustainable in the long run?

The contract requires that the producer sells the vaccine at a sustainable low price once the guaranteed market is exhausted. This price should be set to be close to the marginal cost of production. This is economically efficient because the early price – subsidised by donors – will be high enough to provide incentives for R&D, while the long-term price – guaranteed by contract – will be low enough to ensure that there is access to the vaccine for those who need it.

How long run will price be set?

The purpose of the long run price is to insure that vaccines are sold at about marginal cost, once firms have recovered their risk-adjusted R&D costs. This marginal-cost pricing ensures the most efficient access to vaccines in the long run. Because we do not know what the marginal cost will be at the time the offer is made, the long-run price can be set either using an assumption for that cost (e.g. \$1.00) or a formula which gives suppliers an incentive to bring down the costs. One option is to allow the vaccine to be produced by generic suppliers in the long run, if the producer prefers.

What if the supplier refuses to supply vaccines at the long-run price?

The vaccine supplier will be contractually obliged to supply vaccines at the long-run price. If they do not do so, they may be liable for damages, and/or compulsory licensing of the technology to generic competitors.

Why not have a single price, lower in the short run but higher than the long-run price?

The price of a vaccine needs to do two things: it needs to provide a return to the manufacturer, and it needs to ensure that the vaccine is bought by consumers for whom it is worth the price. To pay the manufacturer for their R&D investment, the price has to be above the marginal cost of production. But prices above the marginal cost inefficiently exclude some consumers who could benefit from the vaccine but cannot afford that price. The advance market commitment solves this by allowing the purchaser to buy at a low price close to marginal cost, and using the guaranteed top-up from sponsors to recompense the vaccine developer for their investment. After the developer has been paid for their investment, it is efficient for the price to be set at marginal cost of production. The two stage price is therefore the most efficient way to ensure maximum access to the vaccine, while providing a return to the vaccine developer.

Why not just give a one-off prize to the winner?

There are several reasons why creating a market is better than giving a prize to the first vaccine producer. A winner-takes-all prize does not create incentives for the development of subsequent, improved products (which are usually very important, especially for vaccines). A winner-takes-all prize forces the sponsors to assess the value of the first vaccine when it is produced, rather than allowing demand from developing countries to signal which vaccines are most useful and effective.

Sponsors' interests

How will sponsors avoid being locked into spending \$3bn on a vaccine that is not needed?

The technical specification will define which vaccines are eligible for the commitment – and this will include standards for efficacy and safety. More importantly, the sponsors' commitment is to underwrite purchases of vaccines by developing countries: this protects sponsors by insuring that they only pay out for vaccines that developing countries actually want to buy.

How do sponsors know that the commitment will result in more R&D?

Both theory and evidence tell us that investment in R&D rises in line with the expected market size. We have seen similar incentives be effective in stimulating industry response, such as through the Orphan Drug Act and recent UK experience with vaccines for meningitis. Most importantly, we see similar incentives leading to the development of vaccines and drugs for affluent markets.

How will sponsors be able to monitor if it is working?

Sponsors will be able to see how many firms sign the Framework Agreement, and report progress to the Independent Adjudication Committee. It will quickly become clear to the scientific community whether commercial companies are investing more in these diseases if the degree of scientific progress is accelerating. (Of course, in the unlikely event that the commitment does not produce any results, there will be no cost to the sponsors.)

How will sponsors be sure that the vaccines they buy are good value for money?

Because vaccines are cheap and effective, the cost-effectiveness of buying vaccines is very high – much higher than most health-related investments in developing countries. Our calculations (see the spreadsheet tool available at www.cgdev.org/vaccine) show that the cost-effectiveness remains very high even if very pessimistic assumptions are made – for example, on the efficacy of the vaccine.

How do sponsors know that the vaccine would not have been developed anyway?

As is often the case with public policy, it is hard to know what would happen otherwise. However, we can see at present that the level of investment in these diseases is very low – a tiny proportion of global health R&D – and both theory and evidence tell us that increasing the size of the prospective market increases the amount of R&D. Moreover, even if the effect of the commitment were very modest – for example, if it only accelerates the development and use of a vaccine by just a few years – our calculations show the commitment is still very cost effective.

Will the commitment to a high price in the short run push up the price of other vaccines?

No. It is true that vaccines whose market is almost entirely in developing countries will cost more than vaccines with affluent markets that can bear the bulk of the costs of R&D. One advantage of the two-stage pricing structure is that it brings vaccine prices down more quickly and with more certainty than relying on negotiating the price down through normal procurement. Present vaccine procurement arrangements tend to drive up prices when resources for vaccines increase.

Might some sponsors be concerned about the making an open-ended commitment to buy vaccines?

The advance market commitment is a fixed commitment to a maximum number of payments, after which the prices are guaranteed to come down to a lower long-term level which would not be paid by the sponsors.

If more than once vaccine is developed, do sponsors have to buy 200 million of each one?

No: the commitment is to buy 200 million treatments – that is, enough to immunize 200 million people, or whatever number is included in the final contract – from all the suppliers. If there is more than one supplier, each will sell fewer than 200 million at the guaranteed price.

What happens if it doesn't work, and no product meets the specification?

If no eligible vaccine is produced, then the commitment does not cost the sponsors anything.

Developing a new vaccine is only part of the story – how can we be sure that the vaccine will be available to people who need it?

One of the attractions of an advance market commitment is that it both provides incentives for investments in R&D and large-scale production, and it also provides a source of funding to buy vaccines when they are developed. Vaccines already reach 75 percent of the world's children – so additional vaccines will be used if there is money to buy them, if firms have incentives for large scale production, and if the developing countries have confidence that the introduction of new vaccines is sustainable. An advance market commitment addresses each of these concerns.

Push and pull

If sponsors do this, can they stop funding R&D directly?

No: public and philanthropic investment in R&D is also essential and should be increased. Almost all new medicines are the result of a combination of public, philanthropic and private investment. Indeed, as commercial investment in R&D is increased, the value of those public and private investments will also be increased, thus strengthening the case for allocating more resources to them.

Wouldn't it be cheaper to fund R&D directly?

The funds available are not big enough; and sponsors would lose the benefits of private sector expertise, management and competition. Directly funded R&D might produce no results at all, or vaccines might only be developed very slowly. Directly funded R&D is less likely than private competition to produce a diverse range of vaccines, which improve over time. Furthermore, with advance purchase commitments sponsors can be sure that they will only have to pay if the R&D is successful.

If sponsors pay for R&D and also make an advance market commitment, are they going to end up paying twice for the same research?

The R&D which is paid for by push funding – which is mainly basic science and candidate identification – is predominantly different from the commercial investment that will be stimulated by the pull incentive – such as large scale clinical trials, regulatory approval and investment in production. Both need funding. There is a case for structuring the funding mechanisms appropriately to create the best incentives: for example, for the basic science to be funded predominantly by direct funding, and for the investment in developing commercial products to be funded by the prospect of commercial returns. This is similar to the U.S. government funding scientific research through the NIH while still buying drugs for citizens through public insurance programs such as Medicare and Medicaid.

Nonetheless, if sponsors wish to do so, they can amend the terms of the agreements under which they provide direct (“push”) funding – for example to ensure that they get money back if the directly-funded research leads to large revenues as a result of the advance market commitment.

How does this fit with the Global HIV Enterprise?

It would be desirable for the Global HIV Enterprise to be involved in the finalization of an advance market commitment for an HIV vaccine – for example, in determining the technical specification for vaccine eligibility. Conversely, the Global HIV Enterprise would benefit from the additional scientific and financial resources that increased private sector investment in R&D on an HIV would bring. This is an example of how “push” and “pull” commitments can complement each other and increase the value of both.

Should sponsors invest in upgrading health systems and/or buying existing vaccines rather than make an advance market commitment?

Sponsors should do both. Buying existing vaccines and increasing vaccine coverage would save millions of lives right away, as well as increasing private sector confidence that they can invest in new vaccines. Because there is no impact on the budget of making an advance market commitment, unless and until the vaccine is available, sponsors should in the meantime continue with other investments to save lives and increase market certainty.

Will the advance market commitment detract political attention from other priorities, such as the IFF Immunization Initiative?

No. The advance market commitment would complement these other initiatives. The IFF Immunization Initiative can be used as a vehicle for an advance market commitment for the vaccines it would buy in the near-term– there is no trade-off between them.

Process questions

Was the Working Group supported by industry?

The costs of all the Working Group activities were financed by a grant to the Center for Global Development from the Bill & Melinda Gates Foundation. Input from industry executives and experts knowledgeable about the vaccine business was solicited throughout the process, but no industry representatives were members of the Working Group. In arriving at the proposal, the Working Group tried to balance the interests and needs of sponsors, suppliers and developing countries that would ultimately benefit from the development of new vaccines.

Why did the Working Group choose malaria? Are these firm recommendations for a commitment for a malaria vaccine?

To undertake its work, the Working Group decided at the outset that it would focus on two example products – one long-term (malaria vaccine) and one near-term (rotavirus vaccine). The examples were chosen simply as illustrations, to discipline the group's thinking and to provide a practical example. The choice of malaria as an example is not intended to signal a recommendation on the part of the Group, and the parameters developed (technical specifications, prices) were developed as an illustrative example to demonstrate proof-of-concept. If a group of sponsors is to develop a commitment for malaria or any other product, additional work on the details is required.

Why did the Center for Global Development do this work?

The Center for Global Development is an independent, non-profit, non-partisan policy research organization in Washington, DC, which examines the impact of rich-country policies on poor countries. CGD works on questions of development aid effectiveness, debt, trade and migration policy. In its global health work, CGD seeks to apply high-quality research to address important policy and finance questions that affect the impact of development assistance – in this case, the constraints to greater private investment in R&D for major diseases affecting developing countries. For more information about the Center's mission, work and funding, please see www.cgdev.org.

Do any sponsors support this idea?

Yes. Following the publication of the Consultation Draft of this report in October 2004, the UK Government said in November 2004 that, working with other Governments, it was ready to enter into legally binding advance purchase contracts in order to speed up the development of malaria vaccines, and to seek a similar agreement on HIV vaccines. The UK intends to take this forward during the course of its Presidency of the G7/8 and as a first step, at their meeting in London in February, G7 Finance Ministers agreed to explore the use of advance purchase commitments. The UK Government will also continue to consult stakeholders, including the pharmaceutical industry, on the parameters of these contracts. See blogs.cgdev.org/vaccine for the latest information about sponsor support for this approach.

Where can I go for more information about this?

If you want more information, please see:

- the CGD website at www.cgdev.org/vaccine, which contains the full report, a spreadsheet model to enable analysis of different assumptions, and other resources
- for the latest, up-to-date news, see our Vaccines for Development blog at blogs.cgdev.org/vaccine
- for a discussion of the underlying economic theory and evidence, see *Strong Medicine* by Michael Kremer and Rachel Glennerster (Princeton, 2004)
- for a discussion of the design issues, see *Vaccine Advance Purchase Agreements for Low Income Countries: Practical Issues* by Ernst Berndt and John Hurvitz, in *Health Affairs*, May 2005.
- for a detailed explanation of the cost effectiveness estimates, see *Advance Purchase Commitments for a Malaria Vaccine: Estimating Costs and Cost Effectiveness*, by Berndt, Glennerster, Kremer, Lee, Levine, Weizsacker & Williams (2005) – available on the CGD website at www.cgdev.org/vaccine