



Ministero dell'Economia e delle Finanze

Background papers to  
Advanced Market Commitments for vaccines  
A new tool in the fight against disease and poverty

*Report to the G8 Finance Ministers*

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# Table of contents

## AKNOWLEDGEMENT

<b>1. THE RATIONALE FOR ADVANCED MARKET COMMITMENTS (AMCs)</b>	<b>1</b>
<b>2. KEY FEATURES OF THE AMC FRAMEWORK</b>	<b>10</b>
<b>3. THE APPROPRIATE SIZE OF AMCs</b>	<b>19</b>
<b>4. SCOPE AND FUNCTIONS OF THE INDEPENDENT ASSESSMENT COMMITTEE (IAC)</b>	<b>26</b>
<b>5. ENSURING EFFECTIVE EXECUTION AND PUBLIC HEALTH IMPACT</b>	<b>30</b>
<b>6. LEGAL ARRANGEMENTS</b>	<b>37</b>
<b>ACRONYMS</b>	<b>39</b>
<b>ANNEX – LEGAL TERM SHEET</b>	<b>40</b>

## AKNOWLEDGEMENT

The papers collected here provide the analysis underpinning Minister Giulio Tremonti's Report to the G8 Finance Ministers *Advanced Market Commitments to Vaccines. A new tool in the fight against disease and poverty*. They are the fruit of a collective work carried out by a team at the Italian Ministry of the Economy and Finance, Michael Kremer, Owen Barder, Cheri Grace and a team at World Bank led by Amie Batson and Susan McAdams with guidance from Geoffrey Lamb and Jean-Louis Sarbib, with the contributions of Samantha Naidoo, Alastair West, John Hurvitz, Roy Widdus and Applied Strategies Consulting.

## 1. THE RATIONALE FOR ADVANCED MARKETS COMMITMENTS (AMCs)

### Summary

This paper discusses the rationale for AMCs. The main points are:

- Immunization is a very cost-effective development policy; paying for vaccines is a very well-targeted and effective form of aid.
- R&D for medicines for rich countries is funded by a mixture of public funding and private investment. But for diseases concentrated in poor countries, there is insufficient private investment. This gap in the pipeline reduces the effectiveness of public and philanthropic funding of basic research.
- There are two important challenges. First, vaccines are not being developed for diseases which mainly affect poor countries. Second, vaccines for rich-country diseases are not being made available quickly and affordably in poor countries.
- Two market failures contribute to these problems. First, R&D is a *global public good*. This means that in the absence of a coordinated policy intervention there will either be inefficiently little innovation, or the resulting products will be inefficiently expensive. Second, policy-makers' incentives are *time inconsistent* – once a vaccine is developed, policy-makers' interest in creating incentives for R&D are overtaken by the need to ensure affordable and widespread access to the vaccine. Knowing that policy-makers' incentives will change in the future, firms have little incentive to invest today.
- AMCs correct both these market failures. They create a differential between the price needed to reward the company for its R&D and the lower price needed to ensure optimal access to the product, thus reconciling the conflict between these two objectives. They also limit policy-makers' future discretion, preventing them from later re-optimising and reducing the price after a vaccine has been developed.
- The goals of AMCs are to encourage private sector firms to accelerate the discovery of new vaccines; develop effective and safe vaccines; develop second and subsequent generation products that improve on the first; invest in large volume production with low unit costs; reliably provide vaccines at very low prices in the long term; and use their expertise, resources and managerial drive to complement public sector research. Other interventions – such as the establishment of a purchase fund without a legally binding commitment – achieve only some of these goals.
- AMCs are complementary to other interventions, such as supporting public-private partnerships and public research to develop new vaccines and increase their effectiveness. Because they increase the probability that the results of public research will be picked up and translated into products that are actually used, AMCs complement, and do not substitute for, other policies to support R&D on diseases concentrated in poor countries.
- The commitment should be set large enough to create incentives which will accelerate the development of new vaccines, while providing excellent value for money for donors. Analyses suggest AMCs would be cost-effective at a wide range of commitment sizes. Larger commitment sizes would stimulate more R&D and so be expected to produce a better vaccine, with more certainty, sooner - and so save more lives.
- AMCs create incentives analogous to the incentives for R&D of medicines for diseases of affluent countries. The prospect of a valuable market for vaccines for diseases concentrated in poor countries creates incentives for small firms to invest in new technologies, in the hope of selling or licensing their technology to larger companies that will produce the vaccine. The existing activities of the biotechnology and pharmaceutical industries in response to those incentives, together with empirical evidence of the effect of market size on investment in R&D, suggests that an AMC would be likely to increase R&D. Furthermore, donors have little to lose: if no vaccine is developed, the commitments are not disbursed.

### I. Vaccines are a very cost effective development intervention

Immunization has been one of the most important successes in public health during the last 40 years. The Expanded Programme on Immunization (EPI) was launched by the World Health Assembly in 1974, aimed at increasing coverage of vaccines against six diseases (tuberculosis, diphtheria, neonatal tetanus, whooping cough, poliomyelitis and measles).<sup>1</sup> As a result of these vaccinations, an estimated 3 million lives are saved each year, and an additional 750 000 children are saved from permanent disability.<sup>2</sup>

In 1993, the World Bank concluded that the six EPI vaccines together with hepatitis B vaccine, yellow fever and vitamin supplements (“EPI plus”) were among the most cost-effective health interventions for developing countries, ranging from US\$16-22 per life-year gained<sup>3</sup> in low income countries and US\$33-39 per life-year gained in middle income countries.<sup>4</sup>

**Table 1 Estimates of cost-effectiveness of vaccination**

Immunization	Cost per life-year saved (US\$)	Source <sup>5</sup>
Measles	<11.7 (2-15)	Foster <i>et al.</i> in Jamison <i>et al.</i> 1993
EPI cluster: polio, DPT, BCG, measles: Low-income	14-20	Jamison <i>et al.</i> 1993
EPI cluster: polio, DPT, BCG, measles: Middle-income	29-41	Jamison <i>et al.</i> 1993
Hepatitis B Low-income countries, prevalence < 2%	42-59	Miller, McCann 2000
Hepatitis B Low-income countries, prevalence > 8 %	8-11	Miller, McCann 2000
Hib (Africa)	21-22	Miller, McCann 2000
Hib (low-income Asia)	55	Miller, 1998

As a benchmark for judging the cost-effectiveness estimates set out in Table 1 above, development interventions are generally considered to be extremely cost effective if the cost per life-year saved is less than \$100.<sup>6</sup> More recently, a country’s annual GDP per capita has been used as a

<sup>1</sup> WHO Vaccines, Immunization and Biologicals Department *History of Vaccination*  
<http://www.who.int/vaccines-diseases/history/history.shtml>

<sup>2</sup> Kim-Farley R and the Expanded Programme on Immunization Team. “Global Immunization,” *Annual Review of Public Health* 1992, 13, pp. 223-237.

<sup>3</sup> Life years in this paper are measured as Disability Adjusted Life Years (DALYs) throughout.

<sup>4</sup> World Bank. *Investing in Health. The World Development Report 1993*. World Bank, Washington DC. The figures have been adjusted to 2005 prices using the change in the Consumer Price Index.

<sup>5</sup> Quoted in *Vaccines are cost-effective: a summary of recent research*. GAVI Research Briefing. Available at: [http://www.vaccinealliance.org/General\\_Information/Immunization\\_informa/Economic\\_Impact/vacc\\_cost.php](http://www.vaccinealliance.org/General_Information/Immunization_informa/Economic_Impact/vacc_cost.php)

- Miller M and McCann L. “Policy analysis of the use of hepatitis B, *Haemophilus influenzae* type B, *Streptococcus pneumoniae*-conjugate and rotavirus vaccines in national immunization schedules,” *Health Economics*, January 2000.- Jamison DT, Mosley WH, Measham AR, Bobadilla JL. *Disease Control Priorities in Developing countries*. Oxford University Press. 1993

- Miller M “An assessment of the value of *Haemophilus influenzae* type b conjugate vaccine in Asia,” *Pediatric Infectious Disease Journal* 1998 Sep;17(9 Suppl):S152-9

<sup>6</sup> World Bank. *Disease Control Priorities in Developing Countries*. New York, NY: Oxford Medical Publications, Oxford University Press for the World Bank. 1993.

benchmark for cost-effectiveness.<sup>7</sup> On either of these benchmarks, the cost-effectiveness estimates presented in Table 1 show that vaccination is extremely cost-effective.

For comparison, in the United States the cost-effectiveness threshold for medical interventions is estimated to be \$50,000 to \$100,000 per life-year saved.<sup>8</sup> In the United Kingdom, the decisions of the National Institute for Clinical Excellence are consistent with an implicit cost effectiveness threshold of about £30,000 (\$50,000) per life-year saved.<sup>9</sup>

As we shall see, vaccines bought under an AMC for a malaria vaccine are estimated to cost just \$15 per life-year saved – well within the range of highly cost-effective interventions.

Vaccination is also highly cost-effective compared with other public health interventions in developing countries. For example, insecticide-treated bednets are estimated to cost \$19 - \$85 per life year saved;<sup>10</sup> and anti-retrovirals for HIV cost a great deal more than \$100 per life year saved.<sup>11</sup>

Furthermore, most studies of the benefits of vaccination have focused on narrow medical benefits and the averted health care costs, and have not taken account of the broader benefits from improving health that could lead to faster economic growth. Healthy children perform better at school; and healthy adults are more productive at work. Healthy families are more likely to save for the future, have fewer children and invest more in their life chances. Bloom, Canning and Weston (2005) estimate that, including these broader benefits, the rate of return on GAVI's vaccination program might be as high as 18 percent.<sup>12</sup>

## II. Paying for vaccines is an effective form of aid

We have seen that vaccination is a cost-effective public policy. Supporting vaccination in developing countries is a particularly effective form of aid for several reasons.

- **The benefits are disproportionately targeted to the poor.** By choosing to pursue AMCs for diseases that are concentrated in low-income countries, the benefits can be focused on the poor. The poor are particularly vulnerable to communicable diseases, because they are more likely to be susceptible to disease, and because they are less likely to be able to afford health care and treatment. By reducing the impact of communicable diseases, the benefits of vaccination disproportionately accrue to the poor.
- **Vaccines are easier to deliver than other treatments.** Notwithstanding the logistical challenge to reach some communities with vaccines, in general vaccination can be delivered in developing countries more effectively than other health care interventions. Three quarters of the world's children receive some form of childhood vaccination. Vaccines require little training or

<sup>7</sup> Global Alliance for Vaccines and Immunization (GAVI). "Health, Immunization, and Economic Growth, Research Briefing #2, Vaccines are Cost-effective: A Summary of Recent Research," 2004. <http://www.vaccinealliance.org>. Also World Health Organization. "Less-Used Vaccines against Major Diseases Are Cost-Effective, Researchers Conclude," *Bulletin of the World Health Organization* 2000, 78(2):274.

<sup>8</sup> Neumann PJ, Sandburg E, Chaim AB, Stone PW, Chapman RH. "Are Pharmaceuticals Cost-Effective? A Review of the Evidence," *Health Affairs* 2000, 19(2), 92-109.

<sup>9</sup> Towse A. *What is NICE's threshold? An external view.* Chapter 2 in Devlin N, Towse A (eds) *Cost effectiveness thresholds: economic and ethical issues.* London: Kings Fund / Office of Health Economics. 2002. Devlin N and Parkin D, *Does NICE have a cost effectiveness threshold and what other factors influence its decisions? A discrete choice analysis.* City University Economics Department Discussion Paper 03/01.

[http://www.city.ac.uk/economics/dps/discussion\\_papers/0301.pdf](http://www.city.ac.uk/economics/dps/discussion_papers/0301.pdf)

<sup>10</sup> Goodman C, Coleman P, Mills A. "Cost-effectiveness of changing the first line drug for the treatment of uncomplicated malaria in Sub-Saharan Africa," *Health Economics* 2001, 10(8): 731-749.

<sup>11</sup> Creese A, Floyd K, Alban A, Guinness L. "Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence," *Lancet* 2002, 359: 1635-42

<sup>12</sup> Bloom D, Canning D, Weston M. "The Value of Vaccination," *World Economics* 2005, Vol 6 No 3.

expensive equipment to implement, do not require diagnosis, can be taken in a few doses instead of in longer-term regimens, and rarely have major side effects. Hence, they can be prescribed and distributed by health-care workers with limited training. Through herd immunity, the benefits of vaccination can also spill over to other, non-vaccinated individuals in the community.

- **There is little adverse effect on the exchange rate.** Some economists are concerned at the possible macroeconomic impact of exchange rate appreciation resulting from increased aid flows in aid-dependent countries. Paying for vaccines to be imported into developing countries which would not otherwise receive them, by contrast, has no direct impact on the exchange rate of the recipient country.

- **Research and development of new vaccines is a global public good.** Even for those who are skeptical of the benefits of some international aid, there is a sound economic argument for the international community to cooperate to finance the provision of global public goods. International cooperation is needed to provide enough investment in these goods, because all countries have an incentive to free-ride on the R&D investments of others.

For these reasons, donor support for immunization programmes is a very effective form of international development assistance.

### III. Medicines are developed by a mix of public and commercial funding

It is difficult for vaccine researchers to appropriate privately the fruits of basic scientific research – such as identifying antigen targets and developing new techniques. The scientific knowledge is used by the scientific community as a whole, in different ways, to develop new drugs and vaccines.

Later in the process, the results of R&D become potentially much easier for researchers to appropriate. Investment is needed in clinical trials to test the safety and efficacy of a particular product, and a much higher fraction of the benefits from the trials accrue to the firm investing in that vaccine. Though the success rates are higher than for early stage research, trials are very expensive. Similarly, investments in regulatory approval, production and marketing all have limited positive spillover benefits to other research.

Given this mixture of public and private good characteristics, it is not a surprise that R&D funding is provided by both public and private sectors. Of total R&D in pharmaceuticals worldwide, about 44% is funded by governments, 48% by industry, and the remaining 8% by non-profits, foundations and others.<sup>13</sup> The 48% that is funded by private firms is recouped through sales of medicines, to individuals and their insurers and governments.

A recent example how this mixed economy works in practice is Gardasil – a new vaccine developed by Merck which prevents four strains of Human Papilloma Virus (HPV). Two of these strains kill at least 300,000 women a year. This new vaccine was originally invented by Ian Frazer, professor of medicine at the University of Queensland. CSL Limited, a biopharmaceutical company, licensed the technology to Merck to carry out the trials. If the vaccine is approved, CSL and Merck will market the vaccine and both will earn royalties. This new vaccine is therefore the result of a collaboration between academic research, biotech and a large pharmaceutical company.

Commercial investment to complement public sector funding is generally the largest source of funding for pharmaceuticals. But for diseases concentrated in developing countries, there is very little private investment. Not only is the level of R&D for diseases concentrated in poor countries disproportionately low relative to the burden of disease, but it is almost entirely funded by governments

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<sup>13</sup> Global Forum for Health Research, *Monitoring Financial Flows for Health Research*.

and foundations. The reasons for this gap in the pipeline of overall R&D funding are discussed in the sections that follow.

#### **IV. Two related problems of vaccines for developing countries**

There are two significant problems which merit policy intervention, both products of market failures as discussed below.

First, total investment in vaccines which mainly affect developing countries is too small. Developing countries have greatly benefited from the use of vaccines – such as for polio or measles – which were originally developed for affluent countries. With three quarters of the world's children receiving these vaccines, developing countries have been able to share the health benefits. Firms originally invested in these vaccines not for the developing world, but because the vaccines had valuable markets in affluent countries. But there is no corresponding economic incentive to invest in R&D on vaccines against diseases such as malaria, for which there is little market in affluent countries.

Second, there has been a long delay before vaccines that were developed for affluent countries became available at an affordable price in poor countries. More than a decade after the development of vaccines for Hepatitis B and *Haemophilus influenzae B*, and their routine usage throughout the US and Europe, these vaccines are still not widely available in the developing world. These two vaccine-preventable diseases currently cause around 1 million deaths a year between them in developing countries. In the coming years, as vaccines for pneumococcus, rotavirus and HPV become available in affluent countries, there is little prospect that they will be available quickly and affordably in the poorest countries. Without a change in arrangements, more than four million people a year will die of vaccine-preventable diseases largely because these vaccines are not available at affordable prices.

#### **V. Two market failures underpin these problems**

Technically speaking, it is not a market failure that some people are too poor to afford vaccines. While poverty is a moral challenge and policy priority, it is not a market failure in the economic sense that people are denied a good or service because they are too poor to afford it.

There are, however, two important market failures which create obstacles to the development and availability of vaccines for developing countries.

First, R&D of new medicines is a global public good. Scientific knowledge is a non-rival good, and the social marginal cost of its use is zero. If the price of scientific knowledge is set at the marginal cost, then there will be no returns, and no incentive to invest. The result will be under-investment in R&D. The establishment and enforcement of intellectual property rights is a common way to correct this and encourage investment in R&D. Intellectual property rights have the advantage of creating incentives to invest in R&D, but at the cost of restricting access to the products that depend on the knowledge that they protect. Intellectual property rights do not solve the public good market failure; rather, they simply create a framework in which society makes a trade-off between innovation and access. In the case of life-saving essential medicines, it is particularly difficult to choose between these very important goals – society wants both innovative new medicines, and broad access to existing ones. The more we use intellectual property rights to increase the incentives to innovate, the more the resulting higher prices restrict access to those innovations. If prices are held above marginal cost by intellectual property rights, and if, as a result of these higher prices, the poor are excluded from access to life-saving medicines, then this is a market failure in the technical economic sense.

The second market failure – which is related to the first – is that governments face time-inconsistent incentives. Before a vaccine is developed and factories are built, governments may want to provide incentives for producers to invest in R&D and to establish large-scale production facilities. But once a medicine has been invented and is being produced, governments have an incentive to insist on buying it for the lowest possible price, so that access is as broad as possible. Governments are the main

purchasers of vaccines, and vaccines are bought by developing countries through a small number of international agencies. The buyers can use their dominant purchasing power to drive prices down, squeezing manufacturers' profits. Firms know that governments will want to do this once a product has been developed, so firms are less likely to invest in R&D and large-scale production, knowing that they are unlikely to be able to maintain a price high enough to recover the costs.

These two market failures – the public good characteristics of R&D and the time-inconsistency of government incentives – create a potent mixture which explains the problems faced in the introduction of vaccines in developing countries. If innovators are to be remunerated for their R&D investment through sales, then the price of vaccines has to rise to a level which is unaffordable for many of the poorest people, even though those people would benefit hugely from the vaccine and it would cost little to supply it to them. And firms know that governments will endeavour to increase access for the poorest countries, by pushing the price down again, making it unattractive to invest in vaccines for developing countries, or for building sufficient supply capacity to meet their needs.

In short, the problem is that one price has to do two jobs. It has to provide a return to companies who have invested in R&D; and it has to regulate access to the resulting vaccine. Because of the market failures described above, there is no one price that does these two jobs efficiently.

### **VI. An AMC helps solve these two market failures**

A commitment to pay for vaccines if and when they are developed rectifies these two market failures:

- It creates a wedge between the price that is paid by the purchaser (which should be low, reflecting the low marginal cost of producing vaccines) and the price received by the producer (which should be high, to remunerate the substantial private investment in R&D). This differential is the commitment made by the donors to top up purchases to a premium price. By separating the price that is paid to producers from the price paid by purchasers, the AMC creates incentives for R&D without restricting access to the vaccine once it is developed.
- It addresses the time consistency problem by pre-committing governments and purchasers not to negotiate down the price once a vaccine has been developed.

This correction of twin market failures is the economic logic of making an AMC.

It is not part of the rationale for an AMC that it would, by itself, solve every problem affecting vaccines in developing countries. But a purchase commitment *would* change the economics of the development and production of vaccines for developing countries to create incentives for pharmaceutical companies which are as similar as possible to the incentives which lead to R&D and investment in production of vaccines for affluent markets.

### **VII. Strengths and weaknesses of AMCs and other possible interventions**

The AMC proposal is for sponsors to make top-up payments for the purchase of vaccines by developing countries, for qualifying vaccines, up to a fixed number of sales. Developing countries would pay a low price, broadly equivalent to the variable cost of manufacture; and donors would top-up those payments to a premium price aimed at rewarding producers for their R&D and investment in capacity. Once the commitment is exhausted, manufacturers who have chosen to benefit from the premium price would be contractually obliged to either sell further treatments at a sustainable low price related to the cost of production or to license their technology to other manufacturers.

Other solutions have been proposed to accelerate R&D; and a purchase commitment could be designed in different ways. This section looks at the advantages of the AMC approach.

The aim is to design a policy which encourages vaccine producers to:

- Discover new vaccines quickly for diseases which kill and disable millions of people in poor countries.
- Develop effective and safe vaccines.
- Develop second and subsequent generation products that improve on the first.
- Invest in large volume production with low unit costs.
- Reliably provide affordable vaccines in the long term.

A number of possible approaches have been suggested to achieve these objectives:

- Public and philanthropic funding of R&D.
- The establishment of a purchase fund for new vaccines, but with no prior commitment on price or quantity.
- Offering a prize for a suitable product (e.g. \$3 billion for a malaria vaccine). This is equivalent to offering to buy out the patents on a new vaccine.
- An *Advanced purchase* commitment, in which sponsors commit to buy a fixed quantity at a pre-determined price.

**Public and philanthropic funding** make an essential contribution to R&D for diseases concentrated in poor countries, as they do for R&D on diseases which affect rich countries. Without this funding of basic scientific research, we would have few of the medicines we have today. But for diseases in rich countries, this funding is complemented by commercial R&D, which adds additional resources, synergies with other products, the disciplines and incentives of private sector management, flexibility and an ability to innovate. The private sector contribution to R&D complements the public and philanthropic funding; and it is that part of the R&D ecosystem that is missing for diseases concentrated in poor countries.

A **prize or guaranteed patent buy-out** for a new vaccine would help to close the gap, by creating a financial incentive for firms to invest in R&D to produce a new vaccine quickly. But a prize would not incentivize the development of subsequent, second- and third-generation products, and it would not create incentives for firms to invest in large scale production facilities.

Conversely, a **purchase fund** would ensure that there were funds available to increase access to a new vaccine if and when it was developed. But it would not solve the problem of time-inconsistency: that is, firms expect that such a fund will aim to buy vaccines in the future at the lowest possible price, to maximize the number of vaccines it can buy. Anticipating this incentive, firms have little reason to invest in R&D, or to build large-scale manufacturing facilities, given the poor prospects of sustaining a margin on sale price to remunerate these investments. Furthermore, a purchase fund would not ensure access to the vaccine in the long term at an affordable price, as is envisaged in the proposed AMC.

An **advance purchase guarantee** to purchase a particular quantity of vaccines in advance. This would create incentives that would accelerate R&D and increase access when a vaccine is developed. But it would not create incentives for second and subsequent vaccine developers; and it would require a very detailed specification of the product in advance, because the demand risk is transferred entirely to the purchaser. (An AMC, by contrast, would only oblige the donor to pay a top up on vaccines for which there is demand from developing countries, which ensures that there is a market test at the time the vaccine is produced.)

Finally, **AMCs** blend the advantages of creating an incentive for innovators – such as would be obtained through a prize or patent buy-out – and the incentive to accelerate production and access – such as might result from a commitment to purchase or an advanced purchase commitment. The mechanism is designed to create the right set of incentives by limiting the discretion of government purchasers to seek lower prices when a vaccine has been developed, while leaving with producers the incentive to produce the best possible products that developing countries will actually want to buy.

### VIII. AMCs are complementary to other sources of funding

For diseases common in affluent countries, public funding (*e.g.* through the National Institutes of Health in the United States) and philanthropic foundations support scientific research. This research provides the basis for subsequent commercially driven R&D to develop products, manage clinical trials, obtain regulatory approval and produce the vaccine. The various funding streams are complementary. In the case of diseases of rich countries, publicly funded research is made more valuable because there is a realistic prospect that the results will be picked up by commercial companies and translated into products.

In the case of diseases affecting mostly poor countries, however, part of the pipeline is missing: there is little or no incentive for commercial investment. This gap reduces the value of public investment – for example, there are many vaccine candidates against diseases concentrated in poor countries that have been developed in the laboratory which have not yet been tested for safety and efficacy, because insufficient funding is available to do so. Paying for research that has little prospect of getting used is not an attractive way of spending public funds. Creating incentives for commercial R&D will therefore increase the value of the publicly funded research by increasing the probability that candidate products will be developed and used. It will also add value to publicly funded research by increasing the number of scientific researchers working on these diseases and creating network effects from supplementing resources going into basic research and increasing their efficacy.

The creation of a paying market for vaccines for diseases concentrated in poor countries would encourage pharmaceutical companies to license in technologies from biotech firms, academics, public private partnerships and others. (We saw how this works for products which already have a valuable market in the case of Gardasil, described above.) The existence of a market would create incentives for smaller companies – in developing countries as well as industrialized countries - to develop new technologies which could contribute to a new vaccine, knowing that such products would have market value. For example, GSK bought Corixa in May 2005 in order to obtain its MPL adjuvant technology.<sup>14</sup> Developing country firms are also likely to benefit from contracts to manage or participate in large-scale clinical trials in developing countries.

Broadly speaking, any increase in the expected market size for new medicines will be likely to increase the amount of private sector R&D aimed at that market. The larger the expected market, the greater the increase in R&D associated with it. This common sense is backed up by empirical evidence. Acemoglu and Linn (2003) find that a 1 percent increase in the potential market size for a drug leads to an approximately 4 percent increase in the number of new drugs in that category.<sup>15</sup>

AMCs should therefore not be seen as an alternative way to fund R&D in new vaccines, but as a way to complement public and philanthropic funding by filling the gap in the pipeline which results from the lack of incentive for commercial investment.

### IX. Cost effectiveness of AMCs

Any increase in the expected size of the market for a new vaccine would be expected to have some positive impact on private sector R&D. An AMC should be large enough to create significant incentives for companies to increase their investment in R&D, to reflect the economic and social benefits of a vaccine. The upper bound on the size of an AMC is that it must not be so large that donors are committed to spending more on vaccines than they are worth.

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<sup>14</sup> <http://www.bizjournals.com/pittsburgh/stories/2005/05/02/daily1.html>

<sup>15</sup> Acemoglu D, Linn L. "Market Size in Innovation: Theory and Evidence From the Pharmaceutical Industry," *Quarterly Journal of Economics* 2004, 119(3): 1049-1090.

One way to estimate the size of market needed to encourage R&D by private companies is to look at the mean market size for which drugs and vaccines have in fact been developed. This approach has the advantage that it is grounded in experience of the incentives that have been sufficient in the past to drive private sector innovation. Berndt *et al.*<sup>16</sup> conclude that the mean market size for new drugs developed during the 1990s was around \$3.1 billion in NPV terms (US\$, 2004 prices). That analysis shows that, with a donor commitment of \$2.3 billion for a malaria vaccine, enough to provide an overall market size around the average for new medicines, the donor commitment would cost \$15 per life-year saved – a very cost-effective result in comparison with other international development interventions.<sup>17</sup> Even at *twice* this price - \$30 per life year saved – this would be one of the most effective development interventions in the world.

Furthermore, it is not just the future purchase of vaccines that would be cost-effective. Making the commitment is itself cost-effective. Berndt *et al.* estimate that even in the extreme case in which an AMC accelerated vaccine development by only one year and adoption in poor countries by only two years, and compared to conservative assumptions about the price of vaccines in the absence of a commitment, the program would cost about \$80-\$90 per additional life-year saved — still very cost-effective relative to other health and development interventions.

Furthermore, purchases under an AMC are cost-effective within a wide-range of possible commitment sizes. A larger commitment would not be likely to result in windfall profits for industry; instead, it would be likely to increase R&D expenditure by the private sector, and so accelerate the development of new vaccines compared to a smaller commitment. For realistic estimates of the size of a commitment, this additional spending would be a cost effective way to save additional lives. For example, Berndt *et al.* estimate that paying \$25 per person for the first 250 million people immunized (rather than \$15 per person for the first 200 million people immunized) would cost less than \$100 per additional life-year saved if it advanced development and adoption by only three years relative to the benchmark commitment size, and the commitment would cost about \$26 per life-year saved overall.

This analysis shows that the range for a cost-effective AMC is large, and that within this range a commitment would be both effective at inducing private R&D and cost-effective for donors. These results also assuage the possible concern that because of uncertainties, it is difficult to be sure that an AMC is set at the best possible size. For reasonable ranges, the commitment remains outstanding value for money in terms of expected lives saved; and, furthermore, the *additional* lives saved as a result of a larger commitment alone would justify the additional expenditure.

A variety of simulations conducted by Berndt *et al.* extend, under reasonable assumptions the conclusions discussed above about malaria. The estimated cost-effectiveness of vaccines for HIV and tuberculosis are similar: \$17 per year of life saved in the case of HIV, \$30 per year of life saved in the case of tuberculosis; and because of the very large numbers of people who are affected by these diseases, the total social benefits of these vaccines would make these just as attractive as for malaria.

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<sup>16</sup> Berndt E, Glennerster R, Kremer M, Lee J, Levine R, Weisäcker G, Williams H “Advance purchase commitments for a malaria vaccine: Estimating costs and effectiveness,” National Bureau of Economic Research (NBER) working paper #11288, 2005.

<sup>17</sup> These calculations were done before the recent announcement by the Bill and Melinda Gates Foundation for the partnership between the Malaria Vaccines Initiative and GSK, which will enable further progress to be made on a leading vaccine candidate. This development should be taken into account in the design for an Advance Market Commitment for malaria.

## 2. KEY FEATURES OF THE AMC FRAMEWORK

### Summary

An AMC is a market-based mechanism designed to accelerate the development, production scale up and use of life-saving vaccines by establishing appropriate incentives for private industry investment. The uncertainty about the size and timing of vaccine markets in developing countries has resulted in investment decisions that cause substantial and costly delays in the development of and access to priority vaccines for developing countries.

There are several key features to make the AMC framework effective in attaining the desired policy objectives.

**Engaging the private sector** in the development and scale-up of target vaccines is critical because of industry's expertise in this area. While the key scientific breakthrough that leads to a successful vaccine may well come from a university laboratory or small biotechnology firm, the vaccine industry is best equipped to translate this research into a successful product. But firms will not invest in these vaccines if they cannot foresee a market allowing them to recoup their development, and production investment and costs.

Given the long lead times and large investments inherent in vaccine development, robust assurance of future markets is essential. To this end, AMCs must be underpinned by **legally-binding contracts**, that commit donors to support future purchase of priority vaccines if they are developed and meet certain standards and if they are demanded by developing country governments.

The AMC approach is sufficiently flexible to be useful for vaccines at different stages of the research and development process. Within a common AMC framework, **AMCs will need to be sized and tailored** to the specific risks and costs that firms face for a **given vaccine/disease**. A single "umbrella" AMC for all vaccines (as opposed to multiple tailored AMCs within a common framework) could have the perverse effect of driving away resources from the development of more scientifically-challenging vaccines (such as against HIV-AIDS) as they become less attractive to the industry in comparison with the more advanced, later-stage vaccines.

Within an AMC framework, a number of factors may be assessed to **select vaccines** targeted to specific diseases. These include the seriousness of the disease in the poorest developing countries (mortality); the potential value of a vaccine versus other interventions; and the potential value of an AMC to motivate appropriate industry actions given the scientific and market risks.

To ensure long-term sustainability of the impact of AMCs, a **two-stage pricing structure** is needed. In the first stage, a higher price is guaranteed to firms and will be in effect until the AMC is depleted. In return for the AMC's guaranteed financing and guaranteed price, industry would be legally bound to supply further doses at a lower price during the second stage, or license the technology to other manufacturers. The two-tiered pricing system ensures that the vaccine will continue to be supplied at affordable prices if sufficient demand exists, while ensuring that industry recoup investment costs.

**AMCs are a market-enhancing instrument.** Because the AMC guarantee is not a one-time prize for the first to market but a multi-year commitment that is open to all developers, it encourages competition and incentives for continued innovation in second and third generation products. Attracting multiple developers and manufacturers of a vaccine helps increase the long-term sustainability of vaccine supply: multiple suppliers may provide more installed capacity to meet demand and competition to assure more affordable prices in the long term.

An AMC is a tool to provide financing which better supports – but does not substitute for – long-term political commitment of developing country governments to immunization.

## I. Introduction

Vaccines are not only one of the most cost-effective health technologies but also one of the few that can fundamentally transform global health, preventing and in some cases eradicating diseases that are major killers<sup>18</sup>. Vaccines are particularly important for developing countries where large portions of the population do not have access to the necessary screening, diagnosis, treatment and follow-up required for their treatment and care. HIV/AIDS, unfortunately, is a prime example of a disease for which there is limited access to expensive treatment. Growing drug resistance for diseases such as pneumococcal pneumonia (1.6 million deaths), tuberculosis (1.6 million deaths) and malaria (1.1 million deaths) will make treatment even less accessible and, for some diseases, less effective.

While AMCs have the potential to dramatically accelerate the development of and access to life-saving vaccines, they are not a panacea. Complementary actions are critical to advance research, strengthen national delivery systems and build political commitment. This paper describes: i) how the AMC mechanism uses market forces to improve global health by providing incentives to influence the decisions of individual firms; and ii) how the AMC framework would be tailored to the particular scientific and economic risks and costs associated with a vaccine against specific priority diseases.

## II. Vaccine development and production – a risky and expensive process

Despite its enormous health value, global and national commitment to immunization has not been sufficient to attract critical private sector investment in the development and production of vaccines needed in the poorest countries. Though the private sector does strive to serve the poorest developing countries by offering tiered prices, it still does not adequately invest in the R&D and production capacity to serve developing countries' needs. This is for five basic (and closely linked) reasons: (1) competing uses for resources are more profitable; (2) demand (e.g. financing) for new products is perceived to be low and uncertain; (3) costs of development and production are relatively high; (4) market pressures are intense and rapidly changing; and (5) products for the industrialized world are increasingly diverging from those for poorer countries – thus requiring more dedicated investments. The result is that new vaccines developed for industrial markets are only available to the poorest countries 15-20 years after their initial introduction in wealthier countries. Vaccines for which the primary markets are in developing countries have low levels of investment and suffer from significant delays in their development and scale-up.

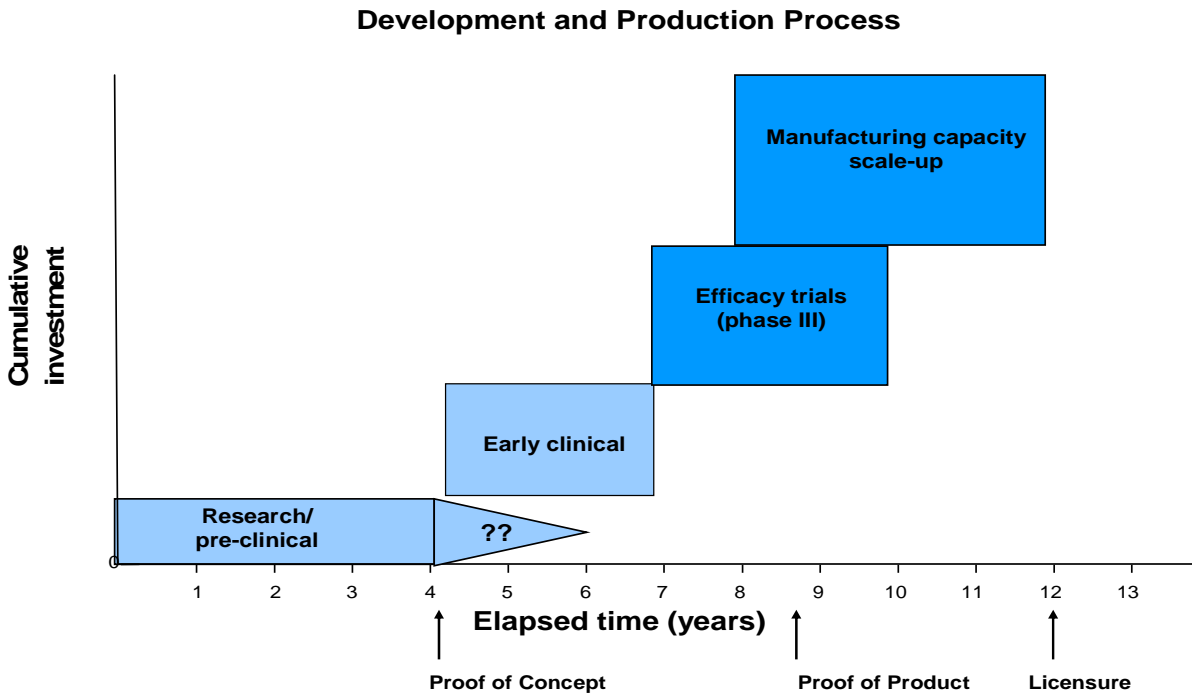
The development and commercialization of priority vaccines evidently depends not only on the scientific knowledge underpinning a candidate but also on the economic costs, risks and return for the given vaccine. Every step of the vaccine development process, from basic research, through proof of concept, proof of product, production scale-up and licensure is gated by investment decisions that are based on the likely returns of the future market.

Building on years of basic research that provide the scientific understanding needed to design a preventive vaccine, public and private entities explore different scientific approaches until one or more vaccine candidates show *proof of concept*. Proof of concept is an important landmark and is the point at which there is solid indication that a particular approach is safe and will likely protect people against the target disease. Continuing along a strictly regulated pathway, the vaccine candidate must then be further tested for safety, immunogenicity and

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<sup>18</sup> Current vaccines are estimated to annually prevent roughly 2 million deaths a year; and to have the potential to prevent an additional 3 million deaths. New vaccines would prevent many millions more deaths, and would save the costs of expensive treatments.

efficacy.<sup>19</sup> Each step brings the candidate closer to *proof of product*, when there is evidence of a viable, efficacious and manufacturable vaccine. A manufacturer will usually begin investing in production capacity for the vaccine before the data from the final studies is even available.



Source: Mercer Management Consulting analysis

As shown in Figure 1, with each decision gate, the level of required investment increases. Industry's scrutiny of the potential market for the vaccine candidate, and the likelihood that it will provide a return on investments, also increases. By the end of development and scale-up, a manufacturer will have spent hundreds of millions of dollars – all on the expectation that it has accurately assessed market opportunities and will be able to recoup its investment through its first sales.

Because of strict regulatory requirements and long lead times inherent in vaccine development, the decisions taken during the development and scale-up phases will have locked the firm (in the medium term) into producing a specific vaccine, in specific quantities, through a specific technological process. Changing any of these elements requires additional investments and new regulatory applications that typically cost in the tens to hundreds of millions of dollars and take many years. Far from being able to commoditize vaccines, each vaccine by each manufacturer is considered to be, and is licensed as, a unique product.

The capital and regulatory requirements of vaccine development and production also create barriers to entry into this industry that are reinforced by production economics characterized by sharp economies of scale, and experience-based knowledge barriers for the applied development and production scale-up of biologics. The result is not only limited market entry but a growing concentration in the industry with roughly 80% of the global vaccine market shared between just 5 suppliers. Emerging manufacturers are increasingly playing an important role in producing existing vaccines, often at lower cost, but tend not to be

<sup>19</sup> Efficacy is the clinical level of protection afforded by a vaccine against a given disease. Most efficacious vaccines induce over 80% protection in immunized children.

strong source of product innovation. Biotech firms are highly competitive and quick to enter the market for early stage research. However biotechs usually sell their scientific discoveries to larger pharmaceutical firms rather than competing to develop or produce the vaccine.

Given the long lead times and large investments inherent in vaccine development, robust assurance of future markets is essential. There is little incentive for the private sector to incur the risks and costs of a vaccine if the final market is considered unpredictable or small. And, unfortunately, the developing country vaccine market is just that – unpredictable and small. This is not surprising given that the poorest developing countries typically have government health expenditures of roughly \$14 per capita, of which 3-6% is for immunization. Donor support to national health programs is currently critical for vaccine purchase, but is typically uncertain, and aid commitments for vaccines are, in nearly all cases, short term.

Vaccine manufacturers have accepted the need to sell vaccines to developing countries at differential prices that are a fraction of prices charged in industrial markets. However, the volumes of vaccine required by developing country markets are orders of magnitude larger than volumes sold to industrial country markets. As a result developing country vaccine markets are characterized by large but unpredictable volumes sold at very low prices. Demand uncertainty means that economies of scale from large production runs may not be fully realized.

Unattractive vaccine markets in developing countries are resulting in decisions by firms that delay or completely halt vaccine development and production targeted at the neediest. Firms may choose not to invest in the early studies to develop and test vaccine candidates for proof of concept. Once proof of concept is established, each manufacturer may decide not to invest in any one of the activities needed to determine if the vaccines work in different parts of the world (e.g. Africa and Asia), if the formulation and presentation of the product are appropriate for developing countries, and whether production capacity is adequately sized to supply developing countries. All of these decisions will impact the long term efficiency and costs of production, critical factors in supporting a lowest tiered price for developing countries.

### **III. Market impact of AMCs and the need for reliability**

An AMC is a legally binding commitment by donors to support future purchase of priority vaccines at a guaranteed price. If an appropriate vaccine is not developed or if governments do not demand it, no vaccine is purchased and no public money is disbursed.

The AMC is designed to resolve one of the major developing country market risks – the unpredictability of adequate funding to purchase vaccines at prices that would allow industry to recoup its investments. The AMC could target the poorest developing countries (e.g. IDA-only), increasing their effective demand in the global market and helping to ensure that their basic health needs are met. By assuring that financing will be available years in advance of actual purchase, the AMC is flexible enough to influence decisions that ultimately determine whether a vaccine will ever become available (see the Chart at the end of the paper).

An AMC is a tool to provide financing which better supports political commitment of developing country governments to immunization but it is not a substitute for it. Strong health systems and appropriate national planning and budgeting are imperative if the AMC is to have an impact. Even if a vaccine is developed and produced, it will only reach the population if national commitment and health systems are in place. In the longer term, once an AMC is fully disbursed, developing country governments and donor partners must be willing to shoulder the (reduced) financial commitment to sustain vaccine use. In the absence of complementary national investments and commitments and continued donor investments in research and system support, AMCs will not succeed in achieving their goal of providing sustainable access to vaccines.

AMCs are a market-enhancing instrument. Because the AMC guarantee is not a one-time prize for the first to market but a multi-year commitment that is open to all developers, it encourages entry into the market, competition and continued innovation in second and third generation products. Attracting multiple developers and manufacturers of a vaccine is pivotal for the long-term sustainability of vaccine supply: multiple suppliers provide more installed capacity to meet demand and competition to assure lowest prices in the long term.

By providing a reliable market guarantee now, AMCs reduce the excessive uncertainty about markets in the poorest developing countries that arises, in part, from the fact that the financiers of the vaccines for the poorest are most often not national decision makers but rather international donors that commit themselves through legally binding contracts. By reducing the portion of the demand risk attributable to uncertainty about donor financing, the AMC encourages investments that must be made years in advance of actual use. This early financing guarantee also improves the predictability of funding to governments, helping them to make more rational and timely demand decisions. The reliability of these donor financing commitments is critical since the promised returns will not materialize for another 5-20 years in the future. If manufacturers doubt the reliability of pledged future payments, they will not engage in the AMC.

#### IV. Sizing and pricing an AMC

AMC funding that result in effective vaccines that are able to prevent millions of deaths in countries with high disease burden are likely to provide outstanding value for money for donors and may prove to be one of the most cost-effective forms of development assistance. Consistent with the existing principles of aid effectiveness, payments would be linked to results: if a commitment is put in place and no vaccine is developed, there will be no financial cost; if such a commitment succeeds, millions of lives can be saved at low cost.

The objective is to set a market size large enough to attract serious commercial investment from manufacturers, while ensuring that the price of the vaccine is less than the social value of preventing the disease and better value for money than alternative uses for the funds. If AMCs are to be successful, they must be sufficiently reliable and attractive to provide incentives for firms to invest, produce and sell the vaccine to the poorest countries in both the short and long term. AMCs will need to be sized and tailored to the specific risks and costs that manufacturers face for a given vaccine/disease.

A single “umbrella” AMC with generic terms covering a host of vaccines is too blunt a tool to achieve the desired market impact. Industry would simply focus on the lowest risk, lowest cost products for which the “umbrella” AMC pay a relatively high return, ignoring other riskier products. Indeed, developing specific terms for an AMC against each disease, within a common framework, significantly increases effectiveness and probability of success. The main rationale for disease-specific AMCs is that there are different risks and challenges associated with earlier- and later-stage products, with the former still facing significant scientific and technical challenges, but both facing demand uncertainties<sup>20</sup>. A single “umbrella” AMC for all vaccines might even have the perverse effect of driving away resources from the discovery of more scientifically-challenging vaccines (such as the one against HIV-AIDS) as they would become less attractive in economic terms to the industry in comparison with the more advanced, later-stage vaccines.

The same line of argument applies to any vaccine/disease. Each of the potential candidate vaccines face specific scientific challenges and market risks that must be considered

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<sup>20</sup> Early-stage vaccines must go through all the steps of development – with a product likely to be available in possibly 15-20 years. Later stage products, by contrast have relatively few steps left and so demand estimates are 4-10 years in the future.

explicitly in the design of an AMC in order to maximize its effectiveness. Defining specific terms for each AMC within a common framework, would provide incentives for multiple firms to pursue different approaches of vaccine development simultaneously. The more specific the terms defined for each AMC, the greater their potential to attract firms' investments.

Once the size of an AMC for a given vaccine has been determined given the risks and challenges and the desired outcomes (e.g. attracting multiple firms to assure competition), a separate decision is needed to set the most effective price level. Pricing decisions require very careful consideration. A relatively high guaranteed price for a vaccine meeting the AMC specifications would provide increased returns for the first to market, creating incentives to accelerate development, but would also result in faster depletion of the AMC. As a result, other manufacturers would have a shorter period in which to develop a competing product, enter the market and recoup a return. More moderate prices would allow the AMC to provide financing over a longer period. These terms would support competition, and encourage development of second and third generation products, but would provide less strong incentives to produce the first vaccine quickly. Vaccine manufacturers have consistently stated their preference for an AMC that encourages competition rather than a "winner (first to market) takes all" approach. Clearly, if the price is set too low, however, it will not have the desired incentive effect. While there is an option to increase the AMC price at a later stage of development if the science and technology indicate higher costs of production, some fear that once price expectations have been set, they may be difficult to change.

Setting the AMC size and price terms will be challenging especially for early stage products that do not yet have proof of concept and for which there is little information on the total investment and likely costs of production. Using industry's own methodologies for evaluating potential markets and their probability of providing a return can improve the understanding of how an AMC will be perceived and what investment decisions it might or not motivate. Importantly, industry re-evaluates the market and its potential return before making each new investment as more accurate data on the product and market become available. Similarly, the AMC must also be periodically re-evaluated to determine if initial estimates on what constitute an adequate size and price continue to hold true.

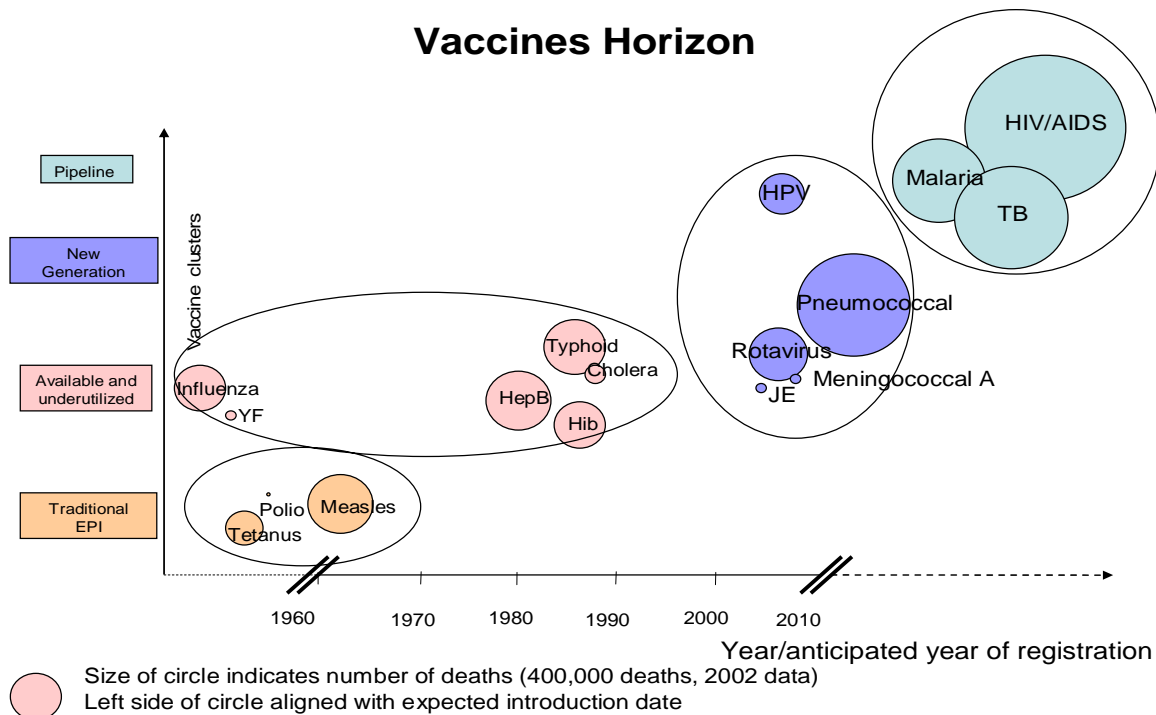
Although AMCs will address the part of demand risk that is attributable to financing uncertainty, actual demand levels and the timing of uptake by poor countries will still be somewhat uncertain. Complementary strategies to support national decision-making and reduce the remaining demand risk are essential. The implications of these different strategies must be carefully considered. For example, a purchase guarantee for a minimum quantity dramatically reduces industry's risk in very late stage investments (e.g. production capacity). However, it also reduces government's decision making and control of their own programs and reduces openness of the market to other firms. Identifying options to provide greater demand certainty while still maintaining an open and competitive market requires continued thought.

## **V. AMC disease candidates**

Although an AMC would likely accelerate access to almost every product, the selection of specific diseases and related vaccines that might be supported most effectively by an AMC will depend on critical factors such as (a) the seriousness of the disease in the poorest developing countries (mortality), (b) the potential effectiveness of a vaccine versus other existing interventions, and (c) the potential value of an AMC to motivate the appropriate industry actions given the scientific and market risks.

The following graphic illustrates the evolution of the vaccine pipeline and the licensing or anticipated licensing dates of a range of key vaccines into the industrialised market. The size of the circle relates to the number of estimated deaths from the disease. The  $x$  axis indicates the likely time until a vaccine is licensed for use. The vaccines have been divided into four groups,

the first two; Traditional EPI<sup>21</sup> and Available and Underutilized<sup>22</sup> are for vaccines that are already licensed, produced and sold and so are not of interest for an AMC. The New Generation group of vaccines is for vaccines where proof-of-product clearly exists. Some products have been recently licensed in a few countries but investments in late stage development and production capacity is still critical. The last group of vaccines, entitled Pipeline, includes vaccines which are still at early stage of development. In most cases proof of concept for these vaccines has not yet been established, and they are not expected to reach licensure until 2015 in the most optimistic scenarios.



Source: WHO and World Bank analysis

Products that may benefit from an AMC include vaccines against rotavirus (diarrheal disease), pneumococcal pneumonia (respiratory disease), HPV (cervical cancer), malaria, tuberculosis and HIV/AIDS. The following table highlights basic information on each disease and the status of vaccine development.

<sup>21</sup> Vaccines that are widely available through national immunization programs including measles, tetanus, polio, Diphtheria, pertussis, BCG. Most of these vaccines were developed 20-50 years ago.

<sup>22</sup> Vaccines that have been in use for 15-25 years but have only recently begun to be used in developing country programs including hepatitis B, typhoid, cholera, hib, yellow fever.

Vaccine	Est. Annual Burden of Disease	At-risk populations	Vaccine Status
<b>Rotavirus</b>	440,000 to 500,000 deaths	Children under 5; between 6 months and 2 years most vulnerable	One vaccine licensed and under review in several middle-income countries. Clinical trials in developing country settings. Late phase clinical trials for one other candidate and submittal to FDA.
<b>Pneumococcal I</b>	1.6 million deaths, primarily due to pneumococcal meningitis or pneumococcal pneumonia	Up to 50% of cases in children under 5; highest at risk are elderly and children <2	7-valent vaccine available since 2000 and used in industrialised countries, but does not contain serotypes 1 and 5 which most impact developing world. 9-valent and 11-valent candidates in late stage clinical trials; Gambia trials demonstrate 77% efficacy in preventing infections caused by 9 serotypes and 16% reduction in overall child mortality.
<b>HPV</b>	250,000 - 270,000 deaths	Women, primarily in developing countries	Phase III trials have been successfully completed for one product and is in process for second product. Licensing expected in 2006-2008.
<b>Malaria</b>	1.1 to 2.7 million deaths	2 billion people in endemic regions; children under 5	Roughly 90 candidates in pre-clinical or Phase I or Phase II research. Recent Phase IIb trial in Mozambique among children 1-4 years old of one candidate demonstrated 30% efficacy against clinical disease and 60% efficacy against severe disease for six months (still under evaluation in study population).
<b>HIV/AIDS</b>	3 million deaths	High risk groups Continent of Africa	Phase III trial ongoing in Thailand. Roughly 30 candidates in Phase I or Phase II.
<b>Tuberculosis</b>	1.6 million deaths	HIV infected or others with compromised immunity	Six candidates in Phase I trials

Source: WHO data, GAVI Board document: The Evolving Vaccine Pipeline, revised July 2005

## VI. Two stage pricing as a way to ensure sustainability

To ensure long-term sustainable impact of AMCs, a two-stage pricing structure is needed. In the first stage, a higher price is established to allow industry to recoup its investments. This price is guaranteed to firms and will be in effect until the AMC is depleted. In return for the AMC's guaranteed financing and guaranteed price, industry would be legally bound to supply further treatments at a lower price during the second, post-AMC stage.

Two stage pricing is attractive for all the stakeholders. For public health community, it helps to ensure the sustainable and affordable supply of vaccines to developing countries, particularly after the AMC is depleted. For firms, it ensures a reasonable return on investment during the AMC, followed by an agreement that is economically viable. Two stage pricing will be most effective if structured to move toward a functioning, steady-state market. Achieving a balanced and viable post-AMC market can be further supported through the following actions:

- Governments and partners must establish the national political commitment and strengthen systems for planning, financing and health delivery to assure uninterrupted demand and increasing national access to the new technologies.
- Each AMC should be designed to attract and support multiple suppliers to develop products and supply the developing world. In a competitive market, no single manufacturer carries the entire burden of supplying the high volume of doses needed by the developing market nor is any single manufacturer in a position to set monopoly prices. The AMC could ensure more installed capacity so that wealthier markets can be supplied without taking volume needed for the poorest markets. As discussed already, the AMC terms would need to be designed to ensure a long enough duration (7-10 years) to attract second and third entrants into the market. AMCs might also encourage partnerships between firms who developed the vaccine and emerging suppliers that may be able to produce a vaccine more efficiently and be willing to provide a long term sustainable supply.

- The parameters defining the time during which or the volume of post-AMC doses that a firm is contractually obligated to make available at an agreed price must be defined in advance. This requires careful consideration but one simple option may be that for every dose purchased during the AMC, the firm must provide an established multiple of doses in the post-AMC phase.
- Post-AMC prices should be set consistent with the costs of production. It may be thus reasonable to define a process that sets the post-AMC price once information is available about costs of production,, rather than defining the price at the time of the launch of the AMC (for example, when they submit a product to the IAC for review against the Target Product Profile ). One option to consider is that this post-AMC price would also determine the country co-pay for this vaccine during the AMC. As the co-pay will be an important determinant of national demand for that particular vaccine, manufacturers will have an incentive to keep the price as low as possible. This strategy allows price to be a competitive factor that affects demand. This approach also has the advantage of providing countries with long-term perspective on the price for the vaccine, thus providing critical data for rationale introduction decisions. An alternative option could be to design a formula for the long-term price of the vaccine which guarantees the costs of production while creating an incentive to keep it as low as possible.

	Establishing proof of concept	Tailoring and testing a vaccine for use in developing countries	Assuring adequate production Capacity	Price and supply predictability
<b>AMC Goal</b>	Increased investment in candidates by academia, biotech and vaccine firms	Increased and targeted investment by multiple firms with track record for commercializing product (vaccine firms) to ensure product for developing countries	Incremental investment to build adequate production facilities to serve LDC demand in addition to other demand → competition with multiple firms	Assure longterm supply at predictable affordable price
<b>Issues</b>	<ul style="list-style-type: none"> <li>• Risk adjustment critical</li> <li>• Time till market payback is very long</li> <li>• Estimating required AMC size complex given limited product knowledge</li> <li>• Push investment critical</li> </ul>	<ul style="list-style-type: none"> <li>• Large and expensive Phase III trials are decision gate – (\$50-200 million)</li> <li>• Have product and technology so industry can estimate return on AMC.</li> </ul>	<ul style="list-style-type: none"> <li>• Each mfg must invest \$200-400 million in production capacity.</li> <li>• Each added mfg reduces market share and individual return</li> </ul>	<ul style="list-style-type: none"> <li>• Predictability essential for country introduction</li> <li>• Must be economically viable for firms</li> </ul>
<b>Products</b>	<p style="text-align: center;"> <b>Malaria (early stage)</b>  <b>Pneumococcal (late stage)</b>  <b>Rotavirus (very late stage)</b>  <b>TB (very early stage)</b>  <b>HIV/AIDS (very early stage)</b> </p>			

### 3. THE APPROPRIATE SIZE OF AMCs

#### Summary

An AMC and its total market size and price will be most effective if tailored to the scientific challenges and market conditions of vaccines against each disease. Understanding how firms will evaluate the AMC market provides useful insights into the AMC size and terms that will most effectively impact investment decisions. The World Bank, working with Applied Strategies<sup>23</sup>, has developed a model that builds on industry's methodology. This model is designed to be transparent, to allow comparison across different products, and to provide a tool that offers insights into the AMC terms that might best achieve the desired outcome.

For early stage vaccines with significant scientific uncertainty about both the disease and the mechanism that will afford protection (e.g. HIV/AIDS or TB), a reasonably sized AMC would be effective if combined with expanded push funding that targets the research and early stage development needed to solve key scientific problems. Funding for the push support may come from national scientific institutes, non-governmental agencies and foundations and would work in synergy with the AMC framework. Later stage vaccines with known technologies (e.g. pneumococcal or HPV vaccines) were often developed because of industrial country markets. These vaccines will require smaller AMC commitments to allow industry to recoup its incremental investment.

The table below presents the estimated ranges for the size of the AMC that, combined with a package of push support for early stage products, would provide adequate incentives for industry to invest in the accelerated development and production scale-up of critical vaccines.

	<b>Nominal AMC market*(\$ billion)</b>	<b>NPV \$ billion (2005)**</b>	<b>Estimated number of deaths</b>
Rotavirus vaccine	0.8-1.0	0.7-0.8	0.5 million
Pneumococcal	1.0-1.5	0.8-1.1	1.6 million
HPV	0.8-1.0	0.7-0.8	0.3 million
Malaria	4.5-5.0	2.4-2.6	1.1 to 2.7 million
HIV/AIDS	5.5-6.0	2.3-2.5	3 million
Tuberculosis	5.5-6.0	2.3-2.5	1.6 million

\* More precise estimates could be obtained with further analysis and validation of input

\*\*Based on 6% discount rate and assumes AMC disbursements beginning in 2 years for Rotavirus and HPV, 4 years for Pneumococcal, 11 years for malaria and 15 years for HIV/AIDS and TB.

These estimates have been cross-checked with other estimates available, including those obtained following different approaches, such as the estimate by the Centre for Global Development (CGD), which was based on the analysis of a sample of successful pharmaceutical innovations. It is reassuring to note that the results are all roughly comparable (when expressed in common units).

#### I. Introduction - Supplier perspective

The objective of the AMC is to motivate developers and suppliers of vaccines to make additional investments in developing and scaling-up vaccines to serve developing country needs. The required investments are at different stages along the vaccine development continuum, including product formulation tailored to developing country needs, studies to show the vaccine works in developing countries, and building capacity to serve developing country demand.

The primary concern of vaccine suppliers is to recoup their substantial investment in vaccine development within a reasonable timeframe. By focusing on high-income markets, where price and

<sup>23</sup> Applied Strategies is a life sciences consulting firm that works with firms and designs technologies to aid in setting strategy and valuing investment opportunities.

demand are relatively predictable, industry can assure adequate returns notwithstanding the scientific and market risks that exist even in these markets. Unfortunately, the vaccine market in the poorest countries has not, in general, proven to be valuable and predictable. As a result, expected returns on investment in vaccines for these markets are low and uncertain. Given the very small health budgets in most of the target countries (roughly \$14 per capita, of which 3-6% is for immunization), there is a heavy dependence on donor funding, most of which is short-term and unpredictable. Within these limited budgets, vaccines must compete against numerous other priorities creating even greater uncertainty about demand.

Private firms seek ways to increase their return, including by developing new products and entering new markets. To make optimal investment decisions, the best practice in the industry is to use valuation methodologies that compare return across alternative investments and with the cost of capital. The valuation methodology:

- Identifies and addresses the timing and risks of each development investment based on the scientific knowledge and likelihood of success;
- Assesses the cost of product development, manufacturing and commercialization;
- Analyzes numerous product profiles and commercial market scenarios at every stage of development;
- Compares each investment decision to other opportunities and the cost of capital.
- Translates estimates of investment, cost and return into expected cash flows over time (in net present value terms) and (given the inherent uncertainty of whether a candidate will succeed at each stage of development) adjusts this cash flow for risk, (meaning the probabilities of success and failure). However, the financial return on certain life saving products may be bolstered by intangible value associated with being socially responsible.

## II. Market-based model

Commissioned by the World Bank, Applied Strategies has developed a model that replicates the industry's valuation methodology. This model is designed to be transparent, to allow comparison across different products, and to provide a tool that offers insight into how an AMC might be valued by industry. Like all models, this one only offers insight into whether the AMC provides adequate economic incentives to motivate desired investments. It does not reflect other intangible motivations such as a firm's desire to be a good corporate citizen or to be affiliated with the researchers who crack the science for a killer disease.

The model highlights three areas of data that are critical to firms' likely response to an AMC: demand forecasts, status of development and probabilities of success/failure, and estimated cost of goods. These are discussed, in turn, below. Concerns have been raised that poor information, compared to what is available to manufacturers themselves, will undermine public sector attempts to value an AMC using this type of methodology. While there is uncertainty and asymmetric information, experience has shown that reasonably robust estimates of the critical inputs are available through data collection and analysis.

- *Demand forecasting* – Reliable estimates of country demand that accurately predict uptake of a new vaccine form the basis to estimate market size. Forecasts vary from disease to disease and are based on the timing of uptake (year of introduction) and volume (based on the target population and the expected coverage levels). If the forecasts are inaccurate – for example, assuming a more rapid uptake by countries than actually materializes – a vaccine firm will not receive revenues, and will be left with inventory that typically expires in 24 months. To date, forecasts of new vaccine uptake in developing countries have been quite inaccurate. This contributes to industry's unwillingness to invest in these unpredictable markets. Forecasting is difficult especially as optimistic thinking about what "should" occur has, at times, had greater influence on forecasts than country input or historical fact. Country demand will depend on:

- Financing – donor financing in the short term (which would be ensured by an AMC), coupled with country perceptions of the long-term price and whether it will be sustainable given national and external resources;
- Available evidence – countries base their decisions about future vaccines on data about the national disease burden and the expected impact of the vaccine. Global, regional and national efforts to provide this data to decision makers in a timely fashion are critical;
- Delivery systems able to introduce a new vaccine and reach the target population;
- Trade-offs in introducing a particular vaccine vs. other health technologies or vaccines.
- *Status of development* – The level of scientific knowledge, the stage of development of a vaccine candidate, and predictions of whether it is likely to move successfully through each stage of the development process affects the amount and timing of investment and future revenues. It is financially risky to undertake early work to develop a vaccine against complex, poorly understood diseases, such as HIV/AIDS and tuberculosis. Each firm's prediction about whether cash outlays will result in a viable product at some point in the future heavily impact the risk-adjusted NPV calculation that forms the basis of their decision to invest in candidate vaccines.
- *Cost of goods (COGs)* – The COGs cannot be known until late in the development process (once there is proof of product). If the COGs is high, it is an important factor in evaluating financial returns. If COGs estimates are not available because of the early stage of research, companies re-evaluate their investment decisions as more information becomes available. Ultimately, the COGs will determine whether the firm will lose or gain at the AMC guaranteed price and in the post-AMC supply and price agreement. The higher the COGs, the less attractive given AMC terms become, up to the point where the AMC would need to be re-evaluated and possibly increased.

In addition to these three critical factors, modelling the needed size of an AMC can be made more precise by incorporating information on a country's likely product preference, on likely product characteristics, the percent of investment that is dedicated to the AMC market vs. other profitable markets, specific investment costs by firm (rather than industry averages), capacity investments, and the timing and amount of capacity available for AMC countries.

With this information, the model allows the user to explore how industry might value different AMC market sizes and price terms. Sensitivity analyses on the AMC terms including the total size, price per dose/intervention, co-pay, and post-AMC price provide the basis for estimating the market size that would attract additional investment in the development of target vaccines.

### III. AMC size for target diseases

The Applied Strategies model has been used to develop comparable estimates of an AMC commitment that might allow industry to make a return and provide incentives for their investment in the development and production scale-up of the target vaccines. More detailed data have been used to model pneumococcal, rotavirus and malaria vaccines and preliminary work has been done for an HIV/AIDS vaccine. However, further work on all products would allow both verification of the data and fuller vetting of the model.

**Rotavirus:** Trials of the vaccine have led to estimates that 3 deaths would be prevented for 1000 immunizations. Two manufacturers have licensed a rotavirus vaccine. Their investment in initial production capacity were limited largely because of demand uncertainty in the developing country market. If an AMC were established now for rotavirus, it would be too late to influence the development pathway, but would influence decisions to invest in studies to provide evidence of the efficacy of the vaccine in different parts of the world and to expand capacity to meet larger developing country demand. An AMC would also accelerate access to the vaccine by providing funds to purchase the existing products, which in turn would provide a signal to industry that the developing country market for vaccines can provide a profitable return.

- It is estimated that an AMC of roughly \$0.8-1.0 billion in nominal terms (all market sizes quoted below are in nominal terms, unless otherwise noted) would provide adequate returns for manufacturers to increase capacity to serve the developing country market.

**Pneumococcus:** Trials of the existing pneumococcal vaccine have shown 7 deaths prevented for every 1000 children immunized. It is estimated that a pneumococcal vaccine that is introduced as early as possible could prevent 3.6 million child deaths by 2025.

Two manufacturers have second-generation pneumococcal vaccines with established proof of product. These two products are expected to be licensed in industrial countries in the period from 2008 to 2010. Two additional manufacturers have dormant pneumococcal vaccines projects in their pipelines that might be reactivated in the presence of sufficient market incentives. Finally, several manufacturers are at very early stages of a third-generation pneumococcal technology. All of the products are expected to be highly effective and able to prevent the vast majority of pneumococcal infections in developing countries. An AMC for a pneumococcal vaccine would create incentives to invest in additional studies to provide evidence of the efficacy of the vaccine in different parts of the world (e.g. South Asia) and would also encourage incremental investment in production capacity to ensure supply to serve both industrial and developing country demand.

The model provides information that has implications for the size and price of the AMC.

- The AMC market size should compensate for investment dedicated to the developing world but need not provide a return on investment in assets to serve the industrial country market: Pneumococcal vaccines have been developed to serve the global market. Research and development investments have already been made and will be recouped by sales to industrial country markets. The AMC needs only to provide a return on, first, a small amount of incremental investment in studies to provide evidence of the efficacy of the vaccine in different parts of the world (such as South Asia) and, second, significant investment in incremental production capacity to serve the developing world demand.
- The AMC must be large enough to support multiple suppliers to develop and produce the vaccine in order to increase competition and increase the likelihood of long-term sustainable supply at more affordable prices. Given that a proven technology exists for pneumococcal vaccines and that two manufacturers are already in late-stage development, it is likely that two and possibly three firms would enter into AMC arrangements.
- It is estimated that an AMC of roughly \$1-\$1.5 billion would be sufficient to support a market for up to three manufacturers.

**HPV:** Informal estimates suggest that an HPV vaccine may prevent roughly 65% of the relevant disease in developing countries. Two firms have late stage vaccine candidates against HPV. Both of these products will likely be licensed within the next two to three years. There is a substantial developed world market for this products. However, the need for them is arguably greater in the developing world, where it is estimated that 80% of cervical cancer cases occur. The vaccine would be administered through a 3 dose schedule and would most likely be given to females around the adolescent period. An AMC for HPV vaccine would create incentives to invest in the studies and the incremental production capacity needed to serve the developing world. The current vaccines are likely to be targeted to women. Most national immunization programs reach women, immunizing them against tetanus toxoid and therefore providing a platform for deployment of an HPV vaccine. However, coverage levels vary widely and are usually significantly lower than those achieved for children.

- It is preliminarily estimated that an AMC of roughly \$0.8-1.0 billion would allow industry to recoup its incremental investment.

**Malaria:** It is difficult to estimate the cost-effectiveness of a malaria vaccine since its efficacy, duration of immunity, uptake and price are still unknown, but it is possible to derive

estimates based in reasonable assumptions. The Malaria Vaccine Initiative has estimated that a vaccine with 80% efficacy would prevent 8 deaths for every 1000 immunizations.

Additional investments by biotech firms, academic researchers and vaccine firms are needed to explore all possible scientific approaches to malaria vaccine development. A malaria vaccine would primarily target the developing country market (in addition to a small potential travellers and military market) so most of the development costs must be covered through the AMC in combination with “push” support. An AMC for malaria would need to be large enough, in terms of the guaranteed available market size, to attract additional investment in identifying candidates, establishing proof of concept and developing viable products. While proof of concept has been established for one vaccine against malaria, it is unclear whether the level of protection afforded by that vaccine meets the desired public health goals. An AMC would encourage development and production investment in second-generation products. Because significant supply capacity will be required to meet the developing world need, an AMC would, ideally, be large enough to encourage investment by several manufacturers.

Model results provide important insights about an AMC for an early-stage product:

- For early-stage products that require substantial R&D investment and face significant scientific risks, an AMC would be most effective if complemented by a package of “push” funding. The model results highlight the importance of push funding (direct R&D support) to reduce a manufacturer’s risk. The recent \$107 million grant by the Bill & Melinda Gates Foundation to MVI to support the investments of the GlaxoSmithKline mid-stage malaria vaccine is a significant example.
- The size of an AMC market should be designed to bring a market into a generally acceptable range; an AMC that results in manufacturers expecting a slightly negative risk-adjusted NPV may still be effective. Firms may still be attracted to this market if they have strong motivations to be good corporate citizens or see some other intangible benefit.
- The greater the time gap between successive products in the pipeline, the more challenging it is to find an AMC market size and price scenario that could support 2-3 manufacturers. If the AMC price is set too high, follow-on second and third generation products will not come online in time to enter the market. If the price is set too low, suppliers will not capture their required returns (as post-AMC supplier margins are low).
- The model indicates that an AMC for malaria of roughly \$5 billion with complementary push funding would be able to attract two manufacturers to the market.

**HIV/AIDS:** A vaccine against HIV/AIDS would be enormously cost-effective, given the tremendous burden of disease and the very high cost of treatment. However, it is difficult to provide accurate numbers of an appropriate AMC size given the uncertainty about the characteristics and price of a potential vaccine. IAVI has explored a number of scenarios in which they estimate that a minimal vaccine against HIV/AIDS that prevented 50% of infections for ten years, would, over time, avert about 210,000 infections a year. IAVI assumes that an AMC would accelerate the development of a vaccine by roughly five years.

The science of an HIV/AIDS vaccine is exceptionally difficult, and the failure of candidate vaccines thus far has underlined that multiple scientific pathways may have to be explored to accelerate progress. This will require additional investments by biotech firms, academic researchers and vaccine firms. An HIV/AIDS vaccine (though potentially with a different formulation) would likely have a global market with significant industrial country demand. Some question whether an AMC would have significant impact on early stage investment decisions given the uncertainty of the science. However others (most notably biotechs) believe an AMC would provide incentives to invest in early stage efforts to develop an HIV/AIDS vaccine, as it would increase the likely interest of vaccine manufacturers to license or purchase a vaccine candidate once proof of concept is established. There is broad agreement that, once proof of concept is established, an AMC is needed to provide critical incentives for firms to conduct multiple trials at different sites to evaluate the

efficacy of several candidates against different HIV subtypes in diverse populations with different patterns of HIV transmission. An AMC would also provide incentives to scale up production to meet developing country demand.

The modelling of an AMC for a high-risk, early-stage product like an HIV/AIDS vaccine provided some valuable insights:

- Given the high scientific uncertainty surrounding an HIV/AIDS vaccine and the lead time before there will be a marketable product, an AMC would be effective if coupled with increased “push” funding. “Push” funding is essential to advance the science needed for a vaccine; other non-economic benefits may also help to motivate investment in an HIV/AIDS vaccine.
- The model results indicate that an AMC commitment of roughly \$6 billion would establish a market that, when combined with a package of support for additional scientific work, would attract industry. This amount would signal strong donor commitment that, when combined with other non-economic motivations and with expanded push funding, would establish a viable market for an HIV/AIDS vaccine.

**Tuberculosis:** Approximately a third of the world's population is infected with *Mycobacterium tuberculosis* out of which roughly eight million come down with active TB every year, mainly in low-income countries. In Africa, a large proportion of TB "carriers" are co-infected with HIV, which dramatically increases the likelihood of degenerating from latent into active TB. The current BCG vaccine prevents serious complications of disseminated TB in children, but is not very effective at preventing pulmonary TB, the most common and most infectious form of the disease. Efficient drug therapy exists, but the treatment is long and case detection rates are low, making the development of a better vaccine an important goal. By 2006, at least six different TB vaccine candidates will have completed early clinical trials.

- Preliminary model results indicate that an AMC market of roughly \$6 billion would establish a market that, when combined with a package of support for additional scientific work, would attract industry.

	Rotavirus	HPV	Pneumococcal	Malaria	HIV/AIDS	Tuberculosis
Stage of development	2 licensed	2 late stage products	1 licensed and in use 2 late stage 2 dormant in pipeline	1 late stage 89 candidates* (29 early stage 60 pre-clinical)	30 early stage <sup>#</sup>	Several early stage
Estimated year vaccine available to AMC market	2008	2007-2008	2010	2016	~2016-2020	~2016-2020
Estimated size of AMC (nominal value - \$billion)	\$0.8-1.0 billion	\$0.8-1.0 billion	1.0-1.5	4.5-5.0 <sup>°</sup>	5.5-6.0 <sup>°</sup>	5.5-6.0 <sup>°</sup>
Measure of impact	3 deaths prevented per 1000 immunized	Informal estimates that ~65% of HPV disease would be prevented.	7 deaths prevented per 1000 immunized and 3.6 million deaths prevented by 2025 <sup>°</sup>	8 deaths prevented per 1000 immunized	210,000 - 700,000 infections prevented/Year <sup>^</sup>	

\* Malaria Vaccine Initiative, Advance Market Commitment for Malaria Vaccines, 12 September 2005; <sup>#</sup> IAVI website <http://www.iavi.org>, 2 November 2005; <sup>°</sup> AMC Commitment with complementary package of push support from NGOs, foundations and others; <sup>°</sup> PneumoADIP Concept Proposal for an Advanced Market Commitment to Accelerate Pneumococcal vaccine use in developing countries, 23 September 2005; <sup>^</sup> IAVI An Advanced Market Commitment for AIDS vaccine: Accelerating the response of industry, 14 October 2005.

#### IV. Cross-checking estimated AMC size for target vaccines

Determining the appropriate size of an AMC that will motivate industry investments is a challenging task based, necessarily, on a number of hard-to-estimate elements. Any methodology is fraught with uncertainty given the inherent uncertainty of vaccine development and imperfect information. Several different methodologies have been used by groups exploring AMCs. Each of these methodologies has its advantages and disadvantages but they all provide useful benchmarks against which the results of this study were cross-checked.

CGD<sup>24</sup> estimated the size of an AMC required to attract industry investment on the basis of an analysis of a sample of successful pharmaceutical products from 1990-1994. This analysis found that the average sale for these products was \$3.1 billion (NPV in 2004 prices). This measure was taken as an indication that an AMC size of \$2.3 billion, combined with a private market of around \$0.7 billion (both in NPV terms) can be expected to motivate firms to invest in the necessary R&D. It provides a useful benchmark about the general size of a market that would be considered attractive to the pharmaceutical industry.

IAVI<sup>25</sup> estimated that, taking into consideration the expected market in developed and middle-income countries, an AMC size of \$3.3 billion at the time of first sales would be needed.

The Malaria Vaccine Initiative<sup>26</sup> modelled market size for a malaria vaccine based on work by Boston Consulting Group. MVI's detailed demand model allows for country preferences for different products and includes a profitable military and travellers market for a vaccine with high efficacy. This model estimated that a total market size of \$5.2 billion nominal would be sufficient to attract second and third generation products. This figure is closely comparable to the CGD estimate.

The model used in this paper is tailored to each vaccine market and, in line with intuition, shows that a larger AMC commitment is needed for very early-stage, high risk products and a smaller AMC commitment is needed for late-stage products with known technologies and industrial country markets.

Fundamental scientific puzzles still bedevil efforts to design and develop vaccines against HIV/AIDS, TB and, some believe, even malaria. Solving these scientific puzzles and motivating investment in product development and production will require an AMC commitment that assures a future market. However, the AMC commitment must be complemented by a package of support that includes expanded "push" funding for research and promising public-private partnerships working to further vaccine efforts. This complementary push funding may come from NGOs, scientific institutions and foundations already supporting vaccine research and development.

It is reassuring to note that the results are all roughly comparable (when expressed in common units).

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<sup>24</sup> The Center for Global Development, *Making Markets for Vaccines: Ideas to Action*, 2005.

<sup>25</sup> IAVI, *An Advanced Market Commitment for AIDS vaccine: Accelerating the response of industry*, October 2005.

<sup>26</sup> MVI, *Advance Market Commitment for Malaria Vaccines*, September 2005.

## 4. SCOPE AND FUNCTIONS OF THE INDEPENDENT ASSESSMENT COMMITTEE (IAC)

### Summary

The IAC is a critical component of the AMC framework and will determine the credibility and perceived fairness of AMC decisions. The fundamental role of the IAC will be to assure that actions are aligned with AMC goals and assess whether they have been achieved. Given the nature of AMCs and the uncertainty of the underlying science, it is not possible to have a one-time definition of the operational objectives to achieve the AMC goals. Thus, an independent and credible process is needed to handle uncertainty, new information, and to incorporate changes if necessary.

The IAC will be responsible for the effective execution of core technical functions, notably setting TPPs based on required public health impact of new vaccines in developing countries; monitoring industry progress and impact of AMCs; reviewing and modifying the TPPs based on new overwhelming scientific evidence, if necessary; and determining when TPPs have been successfully met, triggering access to AMC funding. The IAC will minimize additional requirements beyond those showing public health impact in developing countries, relying on decisions of competent national regulatory agencies and the WHO prequalification processes as proof of vaccine safety, efficacy and immunity.

The composition of the IAC will be based on fair and transparent nomination and selection processes to ensure both its credibility and capacity to fulfil its responsibilities. IAC members will provide core technical expertise from a range of relevant fields. Lessons drawn from international health and non-health entities (e.g. WHO, EU, FDA, EMEA) show that issues like conflicts of interest and confidentiality are important but manageable.

The IAC may be structured in different ways, with advantages and disadvantages that can be assessed at a later stage. The two main options are to:

- Establish a parent IAC and, as needed, disease-specific working groups;
- Establish a one-time panel to set initial TPPs and focus the IAC on monitoring and verifying if products meet the TPP requirements.

The IAC will need transparent and efficient decision-making processes and procedures. Administrative support will be provided to the IAC by a secretariat which should be embedded in an existing entity or a consortium of existing entities. At an appropriate stage, discussions with existing entities should be carried out to determine the best possible fit.

### I. Introduction

The IAC and its functions are central to the credibility of the AMC framework. As the products donors commit to buy do not generally exist, the application of legally-binding contracts is not sufficient and must be complemented with transparent, fair and independent assessment processes. This paper summarizes the rationale, features and implementation options for an IAC. These findings are based on detailed analyses of existing mechanisms in which technical specifications are set and assessed by an independent entity, as well as consultations with diverse stakeholders.<sup>27</sup>

### II. The IAC: An essential component of a successful AMC

The IAC underpins the credibility of AMCs by ensuring that AMC operational objectives are set through a fair, independent and efficient process. The IAC will be responsible for overseeing AMC objectives and related data requirements. The diverse interests of stakeholders, including

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<sup>27</sup> Examples in the health field were researched in depth; comparable mechanisms in other fields such as military procurement and international regulation were also reviewed.

donors, the vaccine industry and developing countries, require that these objectives and data requirements be set transparently and efficiently so that they are perceived as credible, competent, and reasonable.

The IAC ensures that AMCs will be managed efficiently and effectively in terms of public health impact. AMCs are designed to accelerate the development and introduction of needed vaccines in developing countries – the fundamental goal is the resulting public health impact in poor countries. The IAC will set TPPs for AMCs and define the data required to show that impact. The WHO prequalification process includes requests for information on public health utility, but does not define transparent public health goals or data requirements early on in the process. The early definition of TPPs, and the underlying emphasis on results, will assure that financial commitments will yield significant public health impact.

The IAC will provide the platform to adjust existing AMC product specifications as important new information becomes available. Given the nature of AMCs, particularly with respect to early-stage products where there is significant scientific uncertainty, the IAC is needed to provide a credible and transparent mechanism to assess new information and handle changes if they are required. It is important that the IAC should not, however, “raise the bar”, since the firms will invest on the basis of the TPPs originally defined.

### **III. Necessary features for an effective IAC**

An effective IAC requires clearly defined technical functions, credible composition, efficient and transparent decision-making processes and efficient administrative support for its actions and decisions to be perceived as independent, credible and fair.

#### **A. Clearly defined core technical functions**

IAC core technical functions include: (i) setting the TPPs based on required public health impact; (ii) setting the initial disease-specific TPPs; (iii) monitoring industry progress; reviewing and (iv) modifying the TPPs if overwhelming new scientific evidence warrants it (anticipated to occur rarely); (v) determining when TPPs have been successfully met and (vi) reporting.

##### *1. Defining generic requirements for TPPs*

The IAC should define TPPs to ensure that target products achieve a significant health impact in developing countries. Specifying performance goals rather than vaccine composition (in terms of serotypes, strains or clades) will reduce the risk of TPPs favouring, or being perceived as favouring, any one manufacturer’s product. TPPs should therefore be established based on required vaccine performance in terms of public health impact (e.g., levels of prevention of deaths and of cases) in the target population (e.g. infants and women) in developing countries. Candidate vaccines would be required to meet the current standards for licensing by competent national regulatory agencies such as the US Food and Drug Administration or the European Medicines Agency, and WHO prequalification. To ensure efficiency and avoid overlap, the IAC would accept the assessments of these competent regulatory agencies on vaccine safety, efficacy and immunity.

TPPs may also include a set of desirable (but not mandatory) attributes aimed at simplifying use in immunization programs and delivery systems in developing countries. These attributes may include, for example, fewer required doses, or standards to ensure stability and shelf life. Early experience with the development and introduction of polio vaccines demonstrated the importance of separate assessment of effectiveness in developing countries – the polio vaccine had to be reformulated to be effective in developing countries.

##### *2. Setting disease-specific TPPs*

Disease-specific TPPs must be developed for each AMC to set clear goals and data requirements for developers. The experience of the U.S. government with Bioshield, a program intended to fund both push and pull mechanisms for biodefense products, confirms the importance

of establishing clear TPPs. Despite spending authority of nearly \$6 billion, uncertainties about what would qualify for funding have led to a relatively muted industry response.

Once each set of disease-specific TPPs is defined by experts, an overarching review mechanism will be needed to ensure a consistent approach across AMCs. The IAC will have to find the right balance between setting highly desirable goals that may nonetheless be impossible to achieve and insufficiently ambitious goals that would fail to provide the desired health impact. TPPs also need to be perceived as neutral, unbiased towards any one manufacturer and justified by public health impact requirements. Consideration will be given to the differences for vaccines in early and late stages of product development. For example, for vaccines in early stages of development, TPPs will need to accommodate or encourage innovative new approaches.

### *3. Monitoring*

Periodically, the IAC will monitor progress towards achieving the TPPs. It will be responsible for determining whether, in light of significant or overwhelming new information, the TPPs for a given AMC should be modified.

It may also be useful to establish separate monitoring arrangements by an impartial entity, such as WHO or one of the existing Public Private Partnerships to assess the impact and effectiveness of AMCs, particularly as regards its effects on industry behaviour.

### *4. Modification of TPPs*

Specific elements of the TPPs may need to be modified, for example where significantly changed circumstances or scientific advances clearly indicate that initial TPPs are unachievable. Such modifications would be expected to occur only under exceptional circumstances, and only to lower TPP requirements. Increasing standards at a later date would be unfair to firms that invested on the basis of the initially-established TPPs. Modification of TPPs would be handled through a defined, transparent process that would be incorporated in AMC legal agreements and further developed, if necessary, by the IAC.

### *5. Determination that candidate vaccines meet the established TPPs*

The IAC will be responsible for determining whether candidate vaccines meet established TPPs. The IAC will assess candidates, reviewing information submitted by suppliers including proof of licensure and data, compiled according to appropriate standards, showing effectiveness in developing countries.

### *6. Reporting*

The IAC will provide regular reports that include progress and status updates of its activities. Appropriate mechanisms will need to be established to protect commercially sensitive and confidential information in all IAC activities.

## **B. IAC composition**

The composition of the IAC will be critical to its credibility and effectiveness. A fair and transparent nomination and selection process for committee members will be established, and appropriate mechanisms put in place to manage potential issues such as conflicts of interest and the need for indemnity of members. Experience and precedents from the workings of international health and non-health entities can be used as a basis for specific decisions and rules for IAC members and functions.

IAC members will provide the relevant expertise in the particular diseases for which AMCs are instituted drawing on knowledge about immunization practices, developing country health system issues, public health, vaccinology and vaccine development, manufacturing and commercialization, pediatric and internal medicine and economics.

A useful model for the IAC is the U.S. Advisory Committee on Immunization Practices (ACIP), whose recommendations determine U.S. government funding for vaccines. The ACIP does not set specifications for new vaccines, but does discuss potential public health utility and possible recommendations for vaccine use. ACIP's work feeds into the regulatory approval process for new vaccines as well as final decisions on inclusion in the U.S. Vaccines for Children (VFC) program.

ACIP composition and procedures may offer guidance on the composition and operating arrangements for the IAC. The ACIP is a broadly constituted body, "external" to the administration of the financial aspects of the VFC mechanism. It has expert voting members as well as a number of non-voting members who serve as liaisons to, and representatives of, various constituencies. For work on specific products it establishes specialized working groups, composed of parent committee members and additional specialists as needed. These working groups report back to the parent ACIP. As a result of the sensitivity of its decisions, the ACIP has developed procedures for handling situations where real or perceived conflicts of interest might arise.

### **C. Transparent decision-making processes**

The IAC must have authority and independence to perform its functions successfully. It will need transparent decision criteria (including voting rules) and procedures so that its decisions are recognized by all parties involved (e.g. countries, manufacturers, sponsors and the public health community) as fair, justified and independent.

## **IV. Implementation options**

An IAC may be structured in various ways to serve its purposes and functions. The main structural options include: (1) establishment of a parent IAC and, as needed, disease-specific working groups; or (2) the use of a one-time panel to set initial TPPs with the IAC responsible for ongoing functions. Irrespective of its structural arrangements, the IAC will collaborate with and rely on existing bodies and processes, such as national regulatory agencies and WHO prequalification processes, as much as possible.

### *Option 1: Parent IAC and disease-specific working groups*

A high level "parent" IAC would be set up together with specific product /disease working groups for each AMC disease. The parent committee would have authority over the working groups, providing guidance and ensuring consistency across recommendations. The working group membership would be selected with an emphasis on the expertise needed for particular diseases. This expertise would range from knowledge about scientific and manufacturing specifics to developing country demand for specific vaccines. This option meets the key needs of the AMC structure, but concerns have been raised about the efficiency and accountability of working groups.

### *Option 2: Panel to set initial TPP, IAC for ongoing functions*

An independent group, separate from an IAC, would be established on a one-time basis with responsibility for setting the TPPs for each AMC. Such groups could be convened, as needed, if they were also responsible for any modification of TPPs at a later stage. Given the need for product- and disease-specific expertise in setting TPPs, a separate group for each TPP would be necessary. This could create an oversight need to ensure consistency across TPPs. The IAC would be established separately, with primary responsibility for ongoing monitoring of progress and decisions on the eligibility of candidate vaccines. This option might allow greater involvement and influence of developing country scientists and program managers in determining product profiles best suited to developing country needs.

## 5. ENSURING EFFECTIVE EXECUTION AND PUBLIC HEALTH IMPACT

### Summary

The appropriate arrangements need to be in place to ensure that funds spent executing AMC's translate into delivery of vaccines and public health impact. Consideration must be given to:

- Country demand for vaccines, and the capacity for that demand to be realised – including through effective public financial management and procurement systems;
- The capacity to administer vaccines through effective health systems and vaccine programmes; and
- The sustainability of vaccine programmes in the context of recipient countries' public health strategies.

These issues are discussed both in general terms and with specific reference to uptake for vaccines against HIV/AIDS, pneumococcal and malaria.

Systems also need to be in place to ensure transparency and to avoid corruption – through diversion of finance or product. This may entail the inclusion of safeguards such as AMC procurement operating through a recognised agency subject to external audit. Collaboration with existing institutions operating at country level – such as UNICEF, GAVI and WHO – will allow the definition of appropriate implementation features.

### I. Introduction

A number of factors will affect the effective execution of AMC's and their impact on public health. These range from the ability of the recipient country (or donors on its behalf) to meet the co-payment (even one set at a low level); cases where the disease shows variations in different regions; and effective and transparent procurement and distribution channels. Complementary work has to be undertaken to ensure these factors do not inhibit uptake of effective vaccines and reduce the public health impact of immunization campaigns. These aspects are explored in more depth in the first part of the paper. The second part discusses these factors with reference to vaccines against HIV-AIDS, malaria and pneumococcal.

### II. Factors affecting uptake of new health technologies in developing countries

Push and pull mechanisms are designed to spur investment into vaccines for diseases mostly affecting low-income countries, enabling these technologies to be developed more quickly. However, for these technologies to have an impact on public health, they must be used by the target populations with the disease burden. The product must be demanded by governments and individuals, and a variety of health systems considerations need to be addressed, to enable such demand to result in actual product uptake.

Realistic estimations about uptake are important for many reasons. They allow industry to plan the scale of manufacturing; they help governments to plan their programming and operational systems for introduction of the technology; and allow governments and donors to develop sustainable financing strategies.

Inaccurate demand estimations can result in a misalignment between supply and demand. A vicious cycle can result, whereby uncertain demand leads to supply insecurity (shortage) and sometimes high prices and can make countries reluctant to introduce and scale-up the technology. The links between supply and demand are illustrated in the diagram below.

Introduction of new technologies in developing countries has been notoriously slow due to a variety of factors. Hep B and Hib vaccines are a prime example. The health need for these vaccines is greatest in the developing world, however, their introduction lags dramatically behind their uptake in developed countries. Fewer than 10% of infants in the world's 75 poorest countries routinely receive Hib vaccinations, nearly 15 years after their introduction in the developed world.

This example vividly shows that the development of new vaccines is only part of the story. In order to introduce new vaccines quickly after their development and to have maximum impact on



estimate uptake (making the case to industry and donors for enough supply and donors' resources to meet epidemiological need); whilst industry has the incentive to under-estimate in order to avoid over-production and wastage.

Distribution channels also need to be planned. This includes thinking about storage conditions, logistics, and drug management as well as information systems. People within the distribution chain may need to be trained.

If the product needs to be administered with the aid of a health care worker, human resource considerations come also into play. Health care workers in developing countries are typically short in supply and inadequately trained. These problems are exacerbated by weak incentive and support systems, international migration and the AIDS epidemic. These problems are likely to affect the timely roll-out of new vaccines. Similarly, attending to leadership and management capacity at the central and peripheral levels will be necessary to ensure smooth roll-out. These same considerations apply if the non-state sector, e.g. injectionists, pharmacists, traditional healers, and employers are to be involved in administering the new technology.

### **3. Scientific and regulatory**

Several types of uncertainties may remain even after Phase III: clinical trials as results in industrialised countries may not be capable of generalisation to the developing country context. This may be especially the case in situations where the targeted disease shows major geographical variations (e.g. Hib); diseases where the cause is incompletely measured with routine diagnostic tests (e.g. pneumococcal pneumonia); and infections for which major disease burdens results from their long term effects (e.g. HPV and Hepatitis B). Programmatic feasibility also needs to be considered, for example, could HIV vaccines feasibly be delivered to adolescent populations in developing countries?

Regulatory standards and pathways may need to be developed if the product is path-breaking and regulators have limited familiarity with the class. Such standards and regulatory pathways can take time to develop. The WHO pre-qualification process may provide one opportunity for aligning regulatory standards in order to speed up registration and country level approvals. There is also the need for regulation and control once a product is on the market, so called post-licensure evaluation.

### **4. Programmatic and policy**

It cannot be assumed that public sector and individual demand will automatically arise in the presence of a new, safe, and effective vaccine and available financing. Since decision makers need to advocate spending scarce resources, they must be convinced of the disease burden in their own population and need to believe that the product can be feasibly and cost-effectively implemented. Once convinced, there are a variety of policy and programmatic interventions that need to be aligned, such as national treatment guidelines and the national Essential Medicines List.

Implementation policies and strategies will also need to be developed, notably identification of target populations, estimation of coverage rates, and how these are expected to change over time. Cost-effectiveness studies should be conducted to form the evidence base of the selected strategies. Policies on cost-sharing and financing will need to be agreed, as will methods of monitoring outcomes against pre-determined impact indicators.

Individual and community acceptance of new technologies may also need to be nurtured, in order to translate health need (latent demand) into actual uptake. Building such acceptance requires patient and community education and time.

International agencies, e.g. WHO, may need time to review the new vaccine in light of disease burden and to draft new treatment recommendations. The support of WHO, academics, and standard-setting organisations is crucial for the introduction and credibility of new vaccines, particularly in developing countries. Donors and country level decision makers both rely on key opinion leaders and WHO recommendations in deciding to support the new vaccine fully.

### III. Translating health need into uptake

The vaccine sector is characterized by an advanced knowledge of the system-wide barriers that come into play between epidemiological need and actual uptake. As a result, both the programmatic infrastructure and the institutions to address the barriers to uptake already exist.

The Global Alliance for Vaccines and Immunization (GAVI) has evolved a public-private partnership model - Advanced Development and Introduction Plans (ADIPs) aimed at reducing the lag between adoption of new vaccines in developed and developing countries. ADIPs have been developed for the Rotavirus and Pneumococcal vaccines which provide the means for early communication between firms and major purchasers on demand and supply, planning for vaccine delivery in developing countries, and assessing impact and cost-effectiveness of early introduction.

Although the specific features of the AMC vary according to the single disease, most of the demand side and health systems considerations for new vaccines are relatively similar.

The section below outlines what is known for specific technologies about other key variables affecting product uptake – e.g. willingness to adopt a new technology, willingness to pay and ability to pay as well as variables along the well-known AIDA continuum (Awareness, interest, demand and adoption).

## IV. HIV vaccine

### 1. Public sector demand

Three studies have estimated HIV vaccine uptake at *global level*, each with different coverage rate and vaccine characteristic assumptions, but a similar methodology of identifying coverage areas and target populations within those. The WHO/UNAIDS/IAVI study factored in how health systems and acceptability constraints would affect uptake, arguing that global uptake of an HIV vaccine would only be 20% of the health need (49 million treatments courses) for a low to moderate efficacy vaccine and 40% (260 million) for a high efficacy vaccine.

These studies share two primary weaknesses: a) price-elasticity was not fully examined and b) the time sequence for introduction was too optimistic; it was assumed that all countries would adopt the vaccine in year 1, whereas history has shown that some countries are fast adopters and others are slower.

Four studies have been conducted to estimate public sector demand for an HIV vaccine at *country level*. All of these studies follow a common approach: a) specify potential population groups that would benefit from the vaccine b) estimate the size of each group c) assess the potential coverage of each group and d) calculate the number of vaccines that the government would need to purchase to achieve this level of coverage. Estimated demand was based on simple vaccine characteristics, such as one dose with 100% efficacy and lifetime protection.

Studies in Brazil, Southern Africa and Thailand attempted to prioritise groups for vaccination on the basis of vaccine cost-effectiveness, in which cost was defined as related to vaccine cost and delivery and effectiveness was calculated as the number of infections (primary and secondary) averted by vaccination. Relative costs were adjusted to reflect difficulty in reaching different groups.

The four studies suggest that the number of HIV vaccine treatment courses needed in the initial “catch up” phase would be large if a broad targeting was followed, e.g. over 121 million courses in Brazil and 195 million courses in Southern India. Not surprisingly, a narrower targeting strategy, reaching only high-risk populations, would require far fewer courses, e.g. 9.6 million doses in Southern India, focusing on high-risk individuals and women receiving antenatal care services, and 1.3 million courses for 15-year old school students in Southern Africa.

These studies highlighted the importance of differences in epidemiological and behavioural patterns, health systems constraints to delivery, cultural factors and stigma associated with HIV and AIDS, as variables that can affect uptake. However, the studies do not seem to pay sufficient

attention to: 1) national system capacity to deliver vaccines and 2) managerial feasibility of the implied vaccination strategy (i.e. trying to reach several population groups simultaneously) as important factors affecting speed of uptake and coverage level. These studies also did not look at how the vaccine would be financed, including government of individual ability to pay.

## **2. Private sector demand**

All of the studies above assume that those who would potentially benefit from the vaccine would automatically be vaccinated. Experience from vaccination programmes and studies suggests this is a faulty assumption. Studies assessing private demand for a hypothetical vaccine, relying on willingness to pay technique and acceptability as well as analysis of the factors influencing such individual demand and acceptability, have found that people at higher risk have higher demand. Two of the five studies explored the effect of vaccine price and results were as one would expect: higher prices translate to reduced demand. In the same two studies, it was found that those with higher understanding of the vaccine had higher demand and willingness to pay. A surprise finding was that, even at zero price and 100% vaccine efficacy, some fraction of high risk populations may not take up the vaccine. This finding suggests that vaccine promotion campaigns may be required to boost individual demand.

## **V. Pneumococcal Vaccine**

### **1. The perspective of public sector decision makers**

A vaccine for pneumococcal pneumonia already exists, and more than 20 candidates are in various stages of development. This makes the survey work on factors affecting uptake more reliable.

The PneumoADIP Organization has conducted consultations with donors, EPI managers, regional advisors, new vaccine officers, and programme officers for immunization to understand their priorities when introducing new vaccines into the health system. Public demand was found to be most influenced by local disease burden evidence and vaccine efficacy evidence. Government/political opinion - that is, the vaccine's perceived importance as a government public health priority relative to other methods to prevent and control the disease - and need for critical studies - e.g. cost-effectiveness, and pilot introduction projects - were also ranked as important. Price and dosing schedule were less prioritised. It is likely that this is due to the perception that these factors could not be influenced.

Four major communication issues were found with the pneumo vaccine:

1) Decision makers at country level need to understand the vaccine – its efficacy, who should be its target population, etc. The PneumoADIP found that even educated EPI managers did not realise that the pneumococcal conjugate vaccine was intended for use on children as its primary target population.

2) Decision makers need to understand the level of disease burden in their local population. Global, aggregated information is not as persuasive as local information on burden of disease. This is consistent with surveys looking at interest in present and future vaccines against cholera, shigellosis and typhoid fever. Although public authorities had high interest in vaccines against typhoid fever and shigellosis for the general populations of these countries, the demand for a cholera vaccine was only for restricted populations at high risk.

3) People need time and opportunity to understand the implications of clinical trial data – the methods, the significance of results and the degree to which the results are replicable in their setting.

4) Decision makers need to be persuaded that vaccines are an investment; price becomes less an issue when quality of life benefits and full cost-effectiveness criteria are taken into consideration.

In the PneumoADIP Organization's survey work, the principal health systems factors that would prevent investment in new vaccines were operational aspects: dosing schedules, cold chain,

system capacity, and the importance of alignment with the EPI schedule, as well as lack of funds and/or funding without assured sustainability.

Public studies of EPI managers attitude revealed a mean “willingness to pay” of \$1.64 and median of \$1. At the start of the consultations, the managers stated that \$2 would be the absolute maximum WTP, however, during discussion, the group lowered their maximum to \$1. These results are consistent with the seven Asian country study cited above, which looked at vaccines against cholera, shigellosis and typhoid fever. In this study, maximum “willingness to pay” for new generation vaccines against these diseases was \$1 per dose.

## **2. Survey of donors’ knowledge and attitudes**

In surveys of international donors, PneumoADIP found inadequate knowledge of the principal causes of childhood disease burden. Although donors stated that reducing childhood mortality/morbidity, and improving neonatal care, were major priorities in their development assistant efforts, not one donor spontaneously mentioned pneumonia or meningitis as a major health priority in these groups. Donors identified HIV&AIDS, TB and malaria as the most common causes of child mortality. In actual fact, pneumonia and diarrhoea are the two leading infectious causes of childhood mortality, accounting for 19 and 17% of deaths respectively in children aged 1 month or more, and 26 and 3% of deaths in the neonatal period. But most donors perceived diarrhoea, pneumonia and meningitis as diseases of poverty linked to environmental factors – poor sanitation and overcrowding – rather than to specific vaccine-preventable pathogens. In short, PneumoADIP concluded that efforts to communicate the evidence on disease burden are needed if vaccines against the major killers are to be demanded by the public sector.

## **VI. Malaria vaccine**

In contrast to the situation with the pneumo vaccine, research has revealed a high level of awareness of malaria by individuals and government and a high interest in malaria vaccines, due to the view of malaria as a high-cost disease that is potentially fatal and impacts disproportionately on the poor. The current inadequacy of available treatments is another factor that leads to high interest in a malaria vaccine.

The product specifications demanded by developing countries are for child vaccines with efficacy in excess of 70% and limited to 3 or fewer doses. Adoption would be facilitated by a vaccine that can fit within the EPI, which is perceived as the only distribution system.

Adoption was seen to be dependent on new sources of funds from donors and support and co-ordination from existing international health agencies such as UNICEF, WHO and the World Bank, beyond what they can capably manage with their current structures and /or resources. Evidence of epidemiological need, product profile, price range, delivery costs, and level of commitment of public health authorities are other essential features to adoption.

Differences were found between the stated product preferences in Africa, Southeast Asia and South America; primarily, African decision makers had a lower efficacy requirement and a higher cost sensitivity versus other regions. Across all regions, the critical factors to facilitate uptake were similarly a threshold efficacy level, sustainable donor funding and advocacy, and the support of key influencers (opinion leaders, standard setting organisations, WHO, etc).

In terms of ability to pay, data from the Malaria Vaccine Initiative showed that malaria vaccine cost would only be a portion of today’s spending on malaria treatment and prevention. One scenario MVI modelled showed that, if one assumes that governments spend 10-30% of their health budget on malaria, then multiplying the \$6 co-payment for each treatment course times the population to receive the vaccine would result in 60% of total malaria spending. Since total vaccine expenditure would only be a portion of total current malaria spending on treatment and prevention), this suggests that a malaria vaccine cost of \$6 treatment is definitely possible, particularly if total spending on malaria continues its upward trend. This contrasts with the Hib experience, where

introduction of the Hib vaccine meant countries had to start spending multiples of previous aggregate expenditure on that disease.

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## 6. LEGAL ARRANGEMENTS

### I. Summary

AMC commitments from donors will be made via framework legal agreements; these will in turn be underpinned by financing and payment arrangements. For an AMC to be effective, these arrangements must be sufficiently binding to be fully credible in the eyes of the pharmaceutical and biotechnology industry: suppliers must be confident that the contractual obligations are legally enforceable, and that they are supported by appropriate financial commitments.

The specific contract provisions will be tailored for each AMC, while the framework and basic terms would be common to all AMCs. The legal structure<sup>28</sup> detailed in the Annex would be entered into among donors and suppliers. It can be easily adapted for contracts to be entered into by a third party, acting on donors' behalf, and suppliers. Governments of developing countries, while not party to the AMC agreements, would be involved as purchasers of vaccines subsidized by the AMC.

### II. Legal agreements

Groundwork for the legal structure and functional framework for AMCs has been thought through and laid out in the CGD study.<sup>29</sup> AMCs would be effected through two types of legal contracts that delineate core undertakings of donors and vaccine suppliers:

Framework agreement: In the first instance, donors would establish vaccine eligibility requirements and commit to a guaranteed price in an overarching framework agreement that would establish the AMC for a specific target vaccine. Suppliers would sign on to this framework agreement and assume certain reporting obligations that would assist in tracking progress toward potential target vaccines. The agreement would establish whatever administrative arrangements are needed to support the AMC before it becomes effective, including the terms of reference of the IAC that would make the core determinations about whether new vaccines meet the requirements specified in the framework agreement.

Guarantee and supply agreement: Participating suppliers that produce such a vaccine would be entitled to enter into a second-stage guarantee and supply agreement for their product. This would be a contract between donors, on the one hand, and any single supplier with a product that the IAC has determined meets the target product specifications under an AMC framework agreement.

Current versions of the general term sheets for the framework agreement and the guarantee agreement are attached in the Annex.

### III. Implementation

Two-stage pricing to ensure sustainability: The AMC agreements would also incorporate a two-stage pricing approach. Eligible suppliers would be guaranteed a higher price per dose for sales falling within the period and the financial envelope covered by the AMC. When the full amount of the AMC is spent on eligible treatments, suppliers would subsequently be obligated to continue to supply the vaccine at a lower cost-based price or to license other suppliers to do so.

Promoting competition: The framework agreement would be designed not to create a prize for the first supplier, but (like the markets do) to encourage development of superior second and third generation vaccines. This would be done by ensuring that the AMC period is lengthy enough, so that after one manufacturer has entered into a guarantee and supply agreement under the AMC it would still be worth the while of other manufacturers to continue work on target vaccines. Thus, separate AMC guarantee and supply agreements could be made with more than one manufacturer for different products tackling the same disease.

Taking new information into account: For an early-stage vaccine, the terms of the framework agreement, specifically the vaccine eligibility requirements, would be re-assessed periodically by the IAC

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<sup>28</sup> The term sheets were developed by [Covington & Burling] for the report of the Center for Global Development AMC Working Group; they have been revised and updated to reflect ongoing work on AMCs.

<sup>29</sup> CGD, *Making Markets for Vaccines: Ideas to Action* Report, September 2005.

to take into account additional information that becomes available. The terms of the agreement could be revised accordingly – although not to raise the bar in terms of the requirements for target vaccines.

Use of an intermediary organization: A possible variation of the legal structure proposed here is to include an intermediary entity between donors and manufacturers, acting on behalf of donors. Such an intermediary could manage donor commitments and provide a single point for AMC management and interaction, avoiding the confusion and transaction costs that would result from multiple donors and suppliers interacting directly. A financial institution acting as intermediary between donors and suppliers would help to ensure credibility with suppliers and might facilitate donors' financing arrangements.

Dispute resolution: Donors would be entering into a contract capable of legal enforcement. They would acknowledge that the transactions are subject to commercial law and agree to be subject to the dispute resolution and enforcement provisions in the agreements.

## ACRONYMS

ACIP	Advisory Committee on Immunization Practices
ADIPs	Advanced Development and Introduction Plans
AIDA	Awareness, Interest, Demand and Adoption
AMC	Advance Market Commitment
CGD	Center for Global Development
EMEA	European Agency for the Evaluation of Medicinal Products
EPI	Expanded Program on Immunization
FDA	Food and Drug Administration
GAVI	Global Alliance for Vaccines and Immunization
Hib	Haemophilus influenzae type B
HPV	Human Papilloma Virus
IAC	Independent Assessment Committee
IAVI	International AIDS Vaccine Initiative
IDA	International Development Association
MVI	Malaria Vaccine Initiative
PHA	Public Health Authority
TPP	Target Product Profile
VFC	US Vaccine for Children program
WHO	World Health Organization

## ANNEX

**Term Sheet for Advance Market Commitment  
Framework Agreement<sup>1</sup>**

1. **Parties:** One or more governmental grant-making entities (such as the U.S. Agency for International Development or the U.K. Department for International Development) or nongovernmental, grant-making organizations (each, a “**Funder**”)<sup>1</sup> and one or more pharmaceutical companies, biotech companies or emerging manufacturers<sup>2</sup> that will work within the Framework (as defined below) to develop eligible vaccine(s) (each, a “**Developer**”).
2. **Purpose:** Create a legally binding series of agreements that guarantees the developer(s) of a [*insert target indication*] vaccine that meets the requirements set forth in the agreements a specific price for each qualified sale of the vaccine in certain designated developing countries (the “**Framework**”).<sup>3</sup> The Framework Agreement will clearly state the goals and objectives of the Framework with regard to the target disease, the eligible countries and the affected populations.
3. **Benefits to Funders:** Fulfills the Funders’ statutory or regulatory mandates (or philanthropic mission, in the event Funder is a nongovernmental organization) by giving Developers an economic incentive to (a) select and implement R&D projects that are likely to lead to the development of one or more vaccines for [*insert target indication*], and (b) establish manufacturing capacity for production of such vaccines.
4. **Benefits to Developers:** Establishes a specific price (comprised of a Minimum Co-Payment (as defined below) by the purchaser and a guaranteed top-up payment by the Funders) for all eligible sales of a qualifying vaccine in developing countries that allows the Designated Supplier (as defined below) to cover, over the term of the agreements, R&D costs as well as manufacturing costs and to make an acceptable return on its investment. The guaranteed price will be based on a per-patient dosing regimen to provide the required prophylactic benefit and will be paid on all eligible sales up to the maximum number specified in the Guarantee and Supply Agreement. For example, if a course of 3 immunizations is required to provide the necessary immunity, the guaranteed price is \$20 and the maximum number of treatments is 250 million, then the Designated Supplier would receive the guaranteed price of \$20 only upon an eligible sale of all three doses comprising the course of treatment. If the Designated Supplier’s total eligible sales equal the maximum number of treatments, 250 or 750 million doses, then the Designated Supplier would be entitled to a guaranteed payment of \$5 billion.<sup>4</sup>
5. **Principal Responsibilities of the Funders:** Funders will (a) upon satisfaction of the conditions precedent set forth in Section 7, enter into the Guarantee and Supply Agreement (in the form attached to the Framework Agreement) with one or more Designated Supplier(s) (as defined below),<sup>5</sup> (b) fund the operation of the Independent Assessment Committee (as defined below) in accordance with budgeted amounts, (c) indemnify the members of the Committee for claims and losses arising out of the performance of their duties under the Framework Agreement and the Guarantee and Supply Agreement,<sup>6</sup> (d) retain the Administrators (as defined below) to administer the Framework in accordance with budgeted amounts, (e) maintain in strict confidence any confidential business information submitted to it by the Developers, and (f) agree to be bound by decisions of the Committee acting within the scope of its authority.
6. **Principal Responsibilities of Developers:** Each Developer will (a) provide confidential reports to the Independent Assessment Committee on the progress of its development efforts at the times specified by the Committee (it is contemplated that these reports will be high-level annual status reports at the outset and will increase in frequency and detail as the development efforts advance),<sup>7</sup> (b) provide such technical information as may be reasonably requested by the Committee in order to confirm that the conditions precedent set forth in Section 7 have been satisfied, and (c) agree to be bound by decisions of the Committee acting within the scope of its authority.

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<sup>1</sup> Notes are at the end of the document.

7. **Conditions Precedent to Obligations of Funders:** It will be a condition precedent to Funders’ obligation to enter into and perform their obligations under the Guarantee and Supply Agreement that (a) the vaccine meet the technical specifications and usability requirements outlined in Section 8 below and (b) the Developer of such vaccine agree to continue to supply such vaccine after the Maximum Guaranteed Amount (as defined in Section 7 of the Guarantee and Supply Agreement) has been exhausted.<sup>8</sup>
8. **Technical Specifications and Usability Requirements:** For a vaccine to meet the technical specifications it must, subject to Section 10, satisfy the approval, safety and efficacy requirements set forth in Schedule A.  
For a vaccine to meet the usability requirements it must, subject to Section 10, satisfy the dosage, means of delivery, storage, shelf life and other requirements set forth in Schedule A.
9. **Ongoing Supply Price Ceiling:** Each Developer of an Approved Vaccine (as defined in Section 12 below) that elects to enter into the Guarantee and Supply Agreement must agree to continue to supply such Approved Vaccine in Eligible Countries (as defined in Section 6 of the Guarantee and Supply Agreement Term Sheet) after the Maximum Guaranteed Amount has been exhausted at a price not to exceed the supply price ceiling set forth in Schedule A, as such ceiling may be amended by the Committee or the Developer as provided herein (the “**Ongoing Supply Price Ceiling**”).
- The Base Price (as defined in Section 3 of the Guarantee and Supply Agreement Term Sheet) at which an Eligible Country must purchase a Qualifying Vaccine in order to qualify for the price guarantee before the Maximum Guaranteed Amount has been exhausted shall equal the greater of (a) US\$1.00 (the “**Base Price Minimum**”) and (b) the Ongoing Supply Price Ceiling. Prior to entering into the Guarantee and Supply Agreement and from time to time during the term thereof, a Developer of an Approved Vaccine may agree to lower (but may not increase) the Ongoing Supply Price Ceiling.<sup>9</sup> If a Developer lowers the Ongoing Supply Price Ceiling, it may not then increase it without the approval of the Committee.
10. **Waiver of Conditions Precedent:** After the effective date of the Framework Agreement, the Independent Assessment Committee may (by a 2/3 vote of its members or at the direction of the Funders) (a) waive or modify the technical specifications or usability requirements in a way that does not materially increase the cost of performance for a Developer, (b) increase the Ongoing Supply Price Ceiling, provided that the Developer can reasonably demonstrate that its Manufacturing Costs (as defined in Schedule A) cannot reasonably be reduced below ninety percent (90%) of the Ongoing Supply Price Ceiling, or (c) decrease the Base Price Minimum, provided that, in each case ((a), (b) and (c)), the Committee determines that waiver, modification or increase would preserve the goals and objectives of the Funders, which will be set forth in the Framework Agreement.
- [For purposes of illustrating the foregoing, if a specification called for 60% effectiveness, the Committee could, by a 2/3 vote of its members, reduce the requirement to 50% effectiveness, but could not increase it to 70% effectiveness under this provision.<sup>10</sup>]
- To the extent a waiver is granted that is of general application, and is not specific to a particular proposed vaccine or Approved Vaccine, such waiver will apply to all Developers. For example, if the Committee determines that it would accept a specific decrease in efficacy in certain circumstances, it would be a general application waiver. If, however, a waiver is a result of a unique characteristic (or bundle of characteristics) of a proposed vaccine or an Approved Vaccine, it will not likely be a general application waiver. Nevertheless, the Committee will, wherever possible, structure waivers so that they are of general application and are not specific to a particular Developer or Approved Vaccine. Without disclosing specific confidential information of a Developer, the Committee will notify all Developers that have signed on to the Framework Agreement as to the terms of any general application waivers.

11. **Testing and Acceptance:** The Developer will submit the vaccine to the Independent Assessment Committee for testing and acceptance. The Committee will be responsible for making determinations with respect to whether a vaccine tendered by a Developer satisfies the conditions precedent set forth in Section 7, provided that the Committee will have the right to delegate this responsibility to one or more third-parties that it determines are qualified to make such determinations and are independent and unbiased.<sup>11</sup> The Committee will have the right to retain one or more consultants or rely on the actions of governmental or other third parties, such as the United States Food and Drug Administration or the European Medicines Agency, in making its determinations. The Committee will have authority to grant waivers of, or make modifications to, the application of specific technical specifications or usability requirements as provided in Sections 10 and 23.
12. **Designated Supplier:** If the Independent Assessment Committee determines that the conditions precedent have been satisfied (or if the conditions that have not been satisfied are waived or modified), then (a) the vaccine submitted by the Developer to the Committee will be deemed an **“Approved Vaccine,”** (b) the Developer of the Approved Vaccine will be deemed a **“Designated Supplier,”** and (c) at the election of the Designated Supplier, the Funders and the Designated Supplier will enter into the Guarantee and Supply Agreement promptly after the date of the final, written determination of the Committee.<sup>12</sup>
13. **Appointment and Composition of Independent Assessment Committee:** The Administrator, in accordance with procedures and guidelines to be set forth in the Framework Agreement, will from time to time convene one or more committees (each, an **“Independent Assessment Committee”** or a **“Committee”**), which should, to the extent necessary, be comprised of individuals with expertise in the following fields: (a) immunization practices, (b) public health, (c) vaccinology and vaccine development, manufacturing and commercialization, (d) pediatric and internal medicine, (e) social and community attitudes on immunization, (f) economics, (g) contract law and (h) the vaccine industry, in each case, as applicable, with developing country perspectives. The Framework Agreement will include procedures for the nomination and selection of members of each Committee (including the right of veto by representatives of the Donors, Developers and Eligible Countries) and rules for the ongoing participation of members, in each case that are designed to ensure that each Committee member is independent, unbiased and conflict-free and retains the confidence of the constituent communities<sup>13</sup>.
14. **Actions of the Committee:** [Each member of the Independent Assessment Committee will have one vote. Fifty percent of the members of the Committee, rounded up, will constitute a quorum. Except as provided in Sections 10, 21 and 23, all decisions of the Committee will be made by majority vote of the members at a meeting at which a quorum exists. If a specific institution is designated to serve as the Independent Assessment Committee, such as GAVI, then the Framework Agreement will provide that key decisions will require approval of the Board or Directors, or equivalent governing body. Procedures would need to be tailored to address the possibility of conflicts of interest and to provide for super-majority voting when required under the Framework.]
15. **Duties of the Committee:** The Committee will (a) seek to identify independent, unbiased and expert-qualified institutions and procedures to assist with determining whether a product meets the technical specifications and usability requirements and that can provide ongoing review of product safety and efficacy and manufacturing, (b) if necessary, designate Approved Regulatory Countries and Approved Manufacturing Countries (as defined in Schedule A) from time to time, (c) evaluate products presented by Developers to determine if they satisfy the conditions precedent, (d) at its discretion or at the direction of the Funders, (i) waive or modify the application of specific technical specifications or usability requirements pursuant to Section 10, (ii) increase the Ongoing Supply Price Ceiling, or (iii) decrease the Base Price Minimum, (e) if requested or as necessary, conduct multiple bilateral or multilateral meetings with Developer(s) in order to provide information about testing and acceptance procedures, waivers and modifications to the conditions precedent, market demand and supply forecasting, disease epidemiology and other relevant information,<sup>14</sup> (f) designate Approved Vaccine(s) and Designated Supplier(s), (g) after an Approved Vaccine has been designated, monitor the sales and use of such Approved Vaccine for ongoing compliance with the technical specifications and usability requirements set forth in Section 8 and decertify any vaccine that is not in material compliance with such specifications and requirements, and (h) determine whether the technical specifications and usability requirements set forth in Section 8 or the Maximum Quantity or Funders’ other payment obligations under the Guarantee and Supply Agreement

should be modified in whole or in part based on *force majeure* criteria pursuant to Section 23.

16. **Duties of Committee Members:** Each member of the Independent Assessment Committee will, in the exercise of its authority under the Framework Agreement, have the same fiduciary duties (including duty of care and duty of loyalty) as the director [of a Delaware corporation].<sup>15</sup>
17. **Administrator:** The Framework Agreement will provide for one or more institutions, such as the Vaccine Fund or the World Bank (each, an “**Administrator**”), to monitor and implement the Framework and to facilitate the performance of the Funders under the Guarantee and Supply Agreement, including, for example, to serve as a secretariat to govern the administration of the Framework, to convene from time to time the Independent Assessment Committee, to implement decisions of the Independent Assessment Committee, to manage the financial aspects of the Framework and the Guarantee and Supply Agreement (including the monitoring of Funder commitments and the allocation of those commitments across various vaccines, the investment of liquid assets, the disbursement of funds, the maintenance of appropriate records and accounts and the preparation of financial reports regarding the investment and use of funds), to report on the progress of the Framework to the Funders and to perform such other administrative, support and other tasks as may be set forth in the Framework Agreement or Guarantee and Supply Agreement or otherwise requested by the Committee or the Funders, subject to the approved budget for administrative expenses. The initial Administrator(s) will be designated in the Framework Agreement. The Framework Agreement will include procedures for the designation of additional or substitute Administrator(s).
18. **Actions of the Funders:** If there are multiple Funders, the Framework Agreement will include procedures for the Funders to make decisions relating to the Framework Agreement and the Guarantee and Supply Agreement.
19. **Budget:** The Framework Agreement will include a budgeting process to ensure that the reasonable expenses of the Independent Assessment Committee and the Administrators will be advanced by the Funders.<sup>16</sup>
20. **Addition of New Developers to the Framework:** During the period beginning on the effective date of the Framework Agreement and ending thirty-six (36) months thereafter, one or more entities may become parties to the Framework Agreement (*i.e.*, Developers) upon written acceptance of the terms of the Framework Agreement by such entity. Thereafter, additional entities may become parties to the Framework Agreement upon (a) written approval by the Committee if the new entity has technology or expertise that shows promise for the development of an Approved Vaccine, and (b) written acceptance of the terms of the Framework Agreement by the new entity; provided that no entity may become a party to the Framework Agreement with respect to a product after it commenced clinical trials for such product without the consent of the Funders.<sup>17</sup>
21. **Addition of New Designated Suppliers:** The Independent Assessment Committee may determine that a newly-developed vaccine satisfies the conditions precedent in Section 7, subject to (a) its waiver and modification authority, and (b) any existing general waivers, provided that no “generic” product will be eligible (*i.e.*, a product that (i) is the “same” as an existing Approved Vaccine (which determination will be made in accordance with the standards developed for determining sameness under the Orphan Drug Act in the U.S.) and (ii) substantially relies on data generated with respect to, or the regulatory approval for, an existing Approved Vaccine). Upon such a determination by the Committee, the Developer of the newly developed vaccine will have the right to become a party to the Guarantee and Supply Agreement, whereupon the Developer of the new vaccine will be deemed a “Designated Supplier” and the new vaccine will be deemed an “Approved Vaccine.” The addition of new Designated Suppliers and Approved Vaccines will, in each case, be subject to the original Maximum Guaranteed Amount set forth in the Guarantee and Supply Agreement. For clarity, the Framework Agreement is not intended to displace existing patent and regulatory exclusivity regimes.
22. **Reserved Rights of Developer:** Developer reserves all rights, and the Framework will not apply, to sales of any Approved Vaccine (a) outside the eligible countries identified in the Guarantee and Supply Agreement, and (b) in the military or travelers markets.

- 23. Force Majeure** In the event that there is (a) a substantial change in circumstances with respect to the [*insert target disease*] in the countries identified in the Guarantee and Supply Agreement, including its incidence, its characteristics or methods for its treatment or prevention, such that the technical specifications or usability requirements outlined in Section 8, or the Base Price Minimum or Ongoing Supply Price Ceiling set forth in Section 9, no longer achieve the original objectives, or (b) a substantial change in manufacturing technology for vaccines such that the Ongoing Supply Price Ceiling outlined in Section 9 is reasonably expected to exceed the [average] Manufacturing Cost of “Approved Vaccines” by more than [thirty percent (30%)], the Committee, if requested by the Funders, will have the right (by a 3/4 vote of its members), using the criteria set forth in Schedule B, to (a) modify the technical specifications or the usability requirements, as applicable, even if such modification increases the cost of performance by a Developer, (b) reduce the Maximum Guaranteed Amount or the Funders’ other financial obligations to reflect changes in the number of eligible countries or the incidence of untreated [*insert target disease*] in those countries, (c) decrease the Ongoing Supply Price, (d) increase the Base Price Minimum, or (e) terminate the Framework Agreement; provided that no such change shall have any affect on the rights and obligations of a Designated Supplier of an Approved Vaccine with respect to the Guarantee and Supply Agreement with respect to such Approved Vaccine that has been executed by such Designated Supplier prior to any such decision by the Committee. Unlike other decisions of the Committee, these decisions will be subject to judicial review by an appropriate forum to determine whether the Committee abused its discretion.<sup>18</sup>
- 24. Representation and Warranties:** The Framework Agreement will include standard representations and warranties of the parties, including representations and warranties by the Funders: (a) that they have authority to enter into the Framework Agreement and the Guarantee and Supply Agreement, (b) that, once executed, such agreements will be binding and enforceable in accordance with their terms, and (c) with respect to each governmental entity that is a Funder, that any sovereign immunity has been waived, and that all necessary appropriations or other approvals have been obtained to authorize, and that no further appropriations, approvals or authorizations are required with respect to, the financial commitments of that Funder.
- 25. Indemnification and Insurance:** The Funders [and the Developers each] will indemnify the members of the Committee, or if an institution is designated, such institution, as well as the Administrator(s), for claims and losses arising out of the performance of their duties under the Framework Agreement and the Guarantee and Supply Agreement.<sup>19</sup> In addition, the Funders will maintain director and officers insurance or equivalent policies for the benefit of the members of the Committee, any such institution and the Administrator(s).
- 26. Term and Termination:** The term will begin on the date that [ ] Developers have executed the Framework Agreement (the “Effective Date”) and, unless earlier terminated pursuant to Section 23 or this Section 26, continue until the [ ] anniversary of that date, unless the Guarantee and Supply Agreement has been entered into prior to such anniversary in which case the term will continue until the later of such anniversary and the expiration or earlier termination of the Guarantee and Supply Agreement.
- Funders will have the right to terminate the Framework Agreement (a) after the [ ] anniversary of the Effective Date if no Developer has commenced GLP toxicology studies for a product that shows reasonable promise to become an Approved Vaccine, (b) after the [ ] anniversary of the Effective Date if no Developer has commenced clinical trials for a product that shows reasonable promise to become an Approved Vaccine, (c) after the [ ] anniversary of the Effective Date if no Developer has commenced a pivotal clinical trial designed to demonstrate that a product meets the technical specifications and the usability requirements for an Approved Vaccine, (d) after the [ ] anniversary of the Effective Date if no Developer has filed an NDA or other comparable filing for a product that meets the technical specifications and the usability requirements for an Approved Vaccine, and (e) after the [ ] anniversary of the Effective Date if no Developer has entered into the Guarantee and Supply Agreement with respect to an Approved Vaccine.<sup>20</sup>
- 27. Remedies in the Event of Breach:** The Developers will have the right to pursue all available contract remedies, including damages, specific performance and other equitable relief.<sup>21</sup>

- 28. Dispute Resolution:** Any dispute arising out of or in connection with the Framework Agreement that is not settled by agreement of the parties shall be finally settled by arbitration in accordance with the United Nations' Commission on International Trade Law Arbitration Rules (the "UNCITRAL Arbitration Rules") in force on the date of the Framework Agreement. In the event of a conflict between the UNCITRAL Arbitration Rules and the terms of the Framework Agreement, the terms of the Framework Agreement shall govern.
- 29. Governing Law:** [New York law.]
- 30. Waiver of Immunity:** If a Funder is a sovereign, it will (a) acknowledge that the transactions are subject to private commercial law, and (b) waive sovereign immunity.
- 31. Other Provisions:** Other covenants, terms and provisions as requested by legal counsel to Funder or the Developers.
- 32. Exhibits:** Guarantee and Supply Agreement

## Schedule A to Term Sheet for Framework Agreement

### I Technical Requirements

#### A. Indication:

1. [TBD]

#### B. Target Population:

1. [TBD]

#### C. Efficacy Requirements

1. [TBD]

#### D. Duration of Protection

1. At least **\*\*duration to be specified\*\*** with no qualitative or quantitative exacerbation of subsequent disease

#### E. Interference

1. No interference with other pediatric vaccines

#### F. Regulatory Approval and Quality Control

1. Regulatory approval of a product[, with labeling that meets or exceeds the other technical specifications and usability requirements set forth herein,] in one or more of Canada, France, Germany, Italy, Japan, [Mexico], Spain, the United Kingdom, the United States, [others] and such other countries with regulatory standards and procedures that are at least equivalent to those in the foregoing countries, as the Independent Assessment Committee may designate from time to time (each, an **“Approved Regulatory Country”**). The Committee will have the right to remove any Approved Regulatory Country if its regulatory standards and procedures change after the effective date of the Framework Agreement or the date that it was approved by the Committee, as applicable.
2. Manufacture of product in one or more of Canada, France, Germany, Italy, Japan, [Mexico], Spain, the United Kingdom, the United States, [others] and such other WHO-qualified countries with regulatory standards and procedures that are at least equivalent to those in the foregoing countries, as the Independent Assessment Committee may designate from time to time (each, an **“Approved Manufacturing Country”**). The Committee will have the right to remove any Approved Manufacturing Country if its regulatory standards and procedures change after the effective date of the Framework Agreement or the date that it was approved by the Committee, as applicable.
3. In lieu of one or both of the foregoing requirements, the Committee may rely on an independent, unbiased, expert third party (*e.g.*, the WHO) to determine that the product meets or exceeds the other technical specifications and usability requirements set forth herein, and to ensure that the facilities where, and conditions under which, the product is manufactured are in compliance with Good Manufacturing Practices and other applicable international standards with respect to the manufacture, holding and shipment of vaccines, in each case throughout the term of the Guarantee and Supply Agreement.

## II Usability Requirements

### A. Dosage:

1. [TBD]

### B. Route of immunization:

1. Any, provided conducive to use on a large scale in Eligible Countries as defined in the Guarantee and Supply Agreement

### C. Presentation:

1. Multi - dose vials

### D. Storage

1. \*\*to be determined\*\*
2. Two years shelf life

### E. Safety Requirements

\*\*to be specified, consistent with existing practices by UNICEF and PAHO\*\*

## III Ongoing Supply Price Ceiling

1. The Ongoing Supply Price Ceiling will be [TBD] , which amount will be adjusted on an annual basis to account for any changes in [the Producer Price Index for Chemicals and Allied Industries in the United States, or other similar index with respect to the country where the product is manufactured,] from the effective date of the Framework Agreement.
2. The Ongoing Supply Price Ceiling may be adjusted upwards or downwards based on the expected fully burdened cost of manufacturing qualifying vaccine products (without recapture of research and development costs) (the “**Manufacturing Cost**”).

**Schedule B to Draft Term Sheet for Framework Agreement**

**Criteria for Termination of Funders' Payment Obligations**

[Insert]

\* \* \*

## Term Sheet for an Advance Market Commitment Guarantee & Supply Agreement

1. **Parties:** Funder(s) and one or more Designated Suppliers.<sup>22</sup>
2. **Purpose:** Guarantee that the Designated Supplier(s) receive a specific price<sup>23</sup> for each sale of the Approved Vaccine if the sale qualifies as a Qualified Sale (as defined below) and the Approved Vaccine is purchased for use in an Eligible Country (as defined below), provided that the Designated Supplier commits to supply the Approved Vaccine to Eligible Countries as provided herein.<sup>24</sup>
3. **Principal Responsibilities of Funders:** Guarantor will, subject to Sections 7 and 13 below, irrevocably and unconditionally Guarantee that the price paid to a Designated Supplier will be not less than the price set forth in Schedule A (the **“Guaranteed Price”**) for each Qualified Sale of the Approved Vaccine up to the maximum number of sales specified in Schedule A (the **“Maximum Quantity”**),<sup>25</sup> provided that (a) the Base Price is not less than the greater of the Base Price Minimum and the Ongoing Supply Price Ceiling (as each may be adjusted from time to time pursuant to the Framework Agreement) (the **“Minimum Co-Payment”**), and (b) the Approved Vaccine is purchased for use in an Eligible Country. The **“Base Price”** is the amount actually paid, directly or indirectly, by the purchaser of the Approved Vaccine.<sup>26</sup>
4. **Principal Responsibilities of Designated Supplier:** The Designated Supplier will (a) use commercially reasonable efforts to create awareness of the availability of the Approved Vaccine in the Eligible Countries in order to meet the public health requirements in the Eligible Countries,<sup>27</sup> (b) establish manufacturing capacity in an Approved Manufacturing Country for the production of the Approved Vaccine to meet the public health requirements for the Approved Vaccine in the Eligible Countries as provided in Section 8,<sup>28</sup> (c) obtain and maintain regulatory approval from the applicable authorities in an Approved Regulatory Country and, with respect to manufacture, an Approved Manufacturing Country (or any substitute qualification determined by the Committee, such as prequalification by the World Health Organization (WHO)) for the Approved Vaccine,<sup>29</sup> and those facilities used in its production, as well as any local authorizations and approvals necessary to market and sell the Approved Vaccine in the Eligible Countries, including by complying with all adverse event reporting requirements and providing ongoing evidence of product and production safety and regulatory compliance, (d) provide the Committee with copies of all written communications to or from, including all filings or submissions to, and summaries of all oral communications with, the applicable regulatory authorities in the Approved Regulatory Countries and Approved Manufacturing Countries, and any other relevant regulatory agency, with respect to the Approved Vaccine and its manufacture, (e) in connection with the marketing, distribution and sale of the Approved Vaccine, comply with the U.S. Foreign Corrupt Practices Act and all other applicable law,<sup>30</sup> (f) provide information as reasonably requested by the Committee from time to time in order to confirm ongoing compliance with the technical specifications and usability requirements set forth in Section 8 of the Framework Agreement, (g) agree to be bound by decisions of the Committee acting within the scope of its authority,<sup>31</sup> and (h) continue to supply product to Eligible Countries to meet their requirements as provided in Section 8.
5. **Qualified Sale:** The sale of the Approved Vaccine for use in an Eligible Country will be deemed a **“Qualified Sale”** if it meets the criteria set forth in Schedule B, as modified from time to time by the Independent Assessment Committee. In the event of a conflict between a Administrator or the Funders and the Designated Supplier over whether a particular sale of the Approved Vaccine satisfies the criteria for a Qualified Sale, the matter will be resolved by arbitration.
6. **Eligible Countries:** Unless otherwise agreed by the Funders, only sales made for use in those countries that

are eligible for funding by the Global Vaccine Initiative and the Vaccine Fund, or any successor thereto, shall qualify for the Guaranteed Price (each, an “**Eligible Country**”). [The Eligible Countries as of the date hereof are listed in Schedule C.]

**7. Cap on Total Commitment and Termination of Commitment:**

The total payment obligation of the Funders pursuant to the Guarantee and Supply Agreement, including all payments and distributions to the initial Designated Supplier and any additional or replacement Designated Suppliers, will (a) not exceed, in the aggregate, [\$ \_\_\_\_\_] (the “**Maximum Guaranteed Amount**”), and (b) be subject to termination or modification by the Independent Assessment Committee pursuant to Section 23 of the Framework Agreement. Schedule C of the Framework Agreement sets forth the assumptions underlying the calculation of the Maximum Guaranteed Amount and the criteria for adjusting it if the number of Eligible Countries is materially reduced or a *force majeure* event occurs.

**8. Supply**

The Designated Supplier will supply the Approved Vaccines in Eligible Countries as provided herein during the Funding Term (as defined in Section 12) and, thereafter, for a period of ten (10) years, or such longer period as the Designated Supplier may determine (the “**Supply Term**”), at a price not to exceed (a) if the Designated Supplier has received total payments for the sale of the Approved Vaccine in Eligible Countries under the Guarantee Agreement together with the Base Price (the “**Gross Sales**”) in amounts, in the aggregate, greater than [fifty percent (50%)] of the Maximum Guaranteed Amount (the “**Minimum Gross Sales Amount**”), then the Ongoing Supply Price Ceiling, and (b) if the Designated Supplier has not received such amount, the Ongoing Supply Price Ceiling will be increased by [fifty percent (50%)] only until the aggregate Gross Sales for the Approved Vaccine equals the Minimum Gross Sales Amount, whereupon the increase in this clause (b) will cease to apply.<sup>32</sup>

Each Designated Supplier will be obligated to supply sufficient quantities of Approved Vaccine to meet the demand for such Approved Vaccine in the Eligible Countries based on a forecast to be reasonably agreed to by such Designated Supplier and the Administrator from time to time;<sup>33</sup> provided that in no event will a Designated Supplier be obligated to establish more manufacturing capacity to meet such forecast than it would for a comparable product with a similar market potential, which market potential shall be based on the Guaranteed Price and the Maximum Quantity; and provided further that a Designated Supplier shall not decrease such capacity (including by diverting Approved Vaccine for use outside Eligible Countries) after the Funding Term below its peak capacity during the Funding Term.<sup>34</sup> Notwithstanding the foregoing, a Designated Supplier will be relieved of its obligations with respect to an Approved Vaccine under this paragraph if, at any time after the third anniversary of the launch of such Approved Vaccine, the actual demand for such Approved Vaccine in the Eligible Countries is less than [ten percent (10%)] of the forecasted demand (other than as a result of a breach by such Designated Supplier of its obligations under the Guarantee and Supply Agreement).<sup>35</sup>

**9. Intellectual Property:**

The Designated Supplier will own all right, title and interest in and to the Approved Vaccine; provided, however, if the Designated Supplier fails to supply Approved Vaccine in the Eligible Countries as required in Section 8 during the Funding Term or the Supply Term or if the Designated Supplier meets such supply obligations, but such supply is not sufficient to meet the forecasted demand in the Eligible Countries and, in any event, within four (4) years prior to the expiration of the Supply Term, the Designated Supplier will grant Funders, or their designee, a non-exclusive, irrevocable, perpetual, license (with the right to sublicense) to make, have made, use, sell, offer for sale and import the Approved Vaccine solely for use in any Eligible Country, but Funders will not have rights to any other products and will have no right to sell Approved Vaccine outside the Eligible Countries or for use in the military or travelers markets in Eligible Countries. The Designated Supplier will provide such technology and material transfer and technical assistance as may be reasonably

requested by the Funders to transfer the manufacturing process for the Approved Vaccine to the Funders or their designee. The license grant will be royalty-free, unless the Designated Supplier has not been paid the Minimum Gross Sales Amount and is not in breach of the Guarantee and Supply Agreement, in which case such grant will be subject to a royalty of [ ] percent of net sales until such time as the aggregate royalty payments to the Designated Supplier equal the product of (a) [ ] percent, multiplied by (b) the amount, if any, by which the Minimum Gross Sales Amount exceeds the aggregate Gross Sales of the Approved Vaccine, whereupon such vaccine will be fully-paid and no further royalties will be due.<sup>36</sup>

- 10. Representation and Warranties:** The Guarantee and Supply Agreement will include customary representations and warranties for suppliers of pharmaceutical products, including conformity with product specifications and regulatory approvals, manufacturing in accordance with current good manufacturing practices or other applicable standards, and lack of infringement of third party intellectual property rights.
- 11. Indemnification and Insurance:** The Designated Supplier will defend and indemnify the Funders, the members of the Independent Assessment Committee (or, if an existing institution is designated to perform the responsibilities of the IAC, such institution), and the Administrator(s) from all claims and losses arising out of or related to (a) the use of the Approved Vaccine, including claims and losses for physical or mental injury (including death) and (b) infringement or misappropriation of intellectual property.<sup>37</sup> Each Designated Supplier will maintain such type and amounts of liability insurance, including, if appropriate, through a risk retention program, as is normal and customary in the industry generally, which will specifically cover the foregoing indemnification obligations.
- 12. Term:** The Guarantee and Supply Agreement will begin on the date that the first Designated Supplier executes the Guarantee and Supply Agreement and continue through such time as the Maximum Guaranteed Amount has been paid (the “**Funding Term**”), and, thereafter, until the end of the Supply Term, unless earlier terminated pursuant to Section 13.
- 13. Termination:** The Guarantee and Supply Agreement may be terminated by either party in the event of a material breach that is not cured within 30 days of notice thereof from the non-breaching party.
- In addition, Funders will have the right to terminate the Guarantee and Supply Agreement (a) with respect to a particular Designated Supplier in the event the Independent Assessment Committee determines that the Approved Vaccine of that Designated Supplier no longer satisfies the technical specifications and usability requirements set forth in Section 8 of the Framework Agreement, or (b) in the event of a force majeure event as determined by the Independent Assessment Committee as set forth in Section 23 of the Framework Agreement.<sup>38</sup>
- 14. Addition of New Designated Suppliers:** If the Independent Assessment Committee determines that a newly developed vaccine satisfies the conditions precedent in Section 7, subject to Section 10 of the Framework Agreement, and the Developer of the newly developed vaccine elects to become a party to the Guarantee Agreement, the Developer of the new vaccine will be deemed a “Designated Supplier”, the new vaccine will be deemed an “Approved Vaccine” and the new Designated Supplier will have the right to compete with the original Designated Supplier to make Qualified Sales of the new Approved Vaccine in the Eligible Countries under the Guarantee Agreement. The addition of new Designated Suppliers and Approved Vaccines will, in each case, be subject to the cap on Sponsor’s total commitment set forth in the Section 7.
- 15. Remedies in the Event of** The parties will have the right to pursue all available contract remedies, including

- Breach:** damages, specific performance and other equitable relief. In addition, if a Designated Supplier fails to meet its supply obligations with respect to an Approved Vaccine, other than as a result of a *force majeure* event, the Funders will be entitled to receive as liquidated damages, and not as a penalty, an amount equal to Gross Sales of Doses (as defined in Schedule B hereto) of Approved Vaccine for which payments were made under the Guarantee Agreement, less the Base Price.
- 16. Dispute Resolution:** Any dispute arising out of or in connection with the Guarantee and Supply Agreement that is not settled by agreement of the parties shall be finally settled by arbitration in accordance with the United Nations' Commission on International Trade Law Arbitration Rules (the "UNCITRAL Arbitration Rules") in force on the date of the Framework Agreement. In the event of a conflict between the UNCITRAL Arbitration Rules and the terms of the Framework Agreement, the terms of the Guarantee and Supply Agreement shall govern.
- 17. Governing Law:** [New York law.]
- 18. Waiver of Immunity:** [If a Funder is a sovereign, it will (a) acknowledge that the transactions are subject to private commercial law, and (b) waive sovereign immunity.]
- 19. Other Provisions:** Other covenants, terms and provisions as requested by legal counsel to Funders or the Designated Supplier.

**Schedule A to Draft Term Sheet for Guarantee and Supply Agreement**

**Guaranteed Price and Maximum Quantity**

A. Guaranteed Price.

The Guaranteed Price is [*Insert Guaranteed Price*], and is based on an assumed Minimum Co-Payment of \$6. If the Minimum Co-Payment is changed (as provided in the Framework Agreement), then the Guaranteed Price will be adjusted upwards or downwards by adding an amount equal to the adjusted Minimum Co-Payment less \$6. By way of example, if the initial Guaranteed Price is \$24 and the Minimum Co-Payment is (1) increased to \$8, then the Guaranteed Price will be increased by \$2 (\$8 minus \$6) or (2) decreased to \$1, then the Guaranteed Price will be decreased by \$5 (\$1 minus \$6).

C. Maximum Quantity (of vaccine in Doses).

\* \* \*

**Schedule B to Draft Term Sheet for Guarantee and Supply Agreement**

**Criteria for Qualified Sales**

**A. Buyer Criteria.**

1. Buyers Included. Qualified Buyer include (a) UNICEF, (b) WHO, (c) Pan American Health Organization, (d) any individual Eligible Country that is purchasing for the benefit of the public sector or local non-profits, and (e) and any other buyer approved by the Independent Assessment Committee.
2. Buyers Excluded. A pharmaceutical company, acting directly or indirectly through one or more intermediaries, will not qualify as a Qualified Buyer.

**B. Sales Criteria.**

1. Course of Treatment. A single course of treatment, regardless of the number of individual immunizations, required to provide the desired efficacy and duration of protection will be deemed a single “Dose” and will constitute a single sale. For example, if 3 immunizations over a period of 2 years are required to achieve the desired efficacy and duration of protection, then the sale of all 3 immunizations, one Dose, will be required to constitute a Qualified Sale.
2. Bundled Sales. In the event that the Designated Supplier bundles the sale of the Approved Vaccine to a purchaser with the sale or licensing of another product or service of the Designated Supplier or its affiliates, the Designated Supplier will reasonably assign prices to (allocate revenue amounts between) the Approved Vaccine and such other products or services sold or licensed by the Designated Supplier or its affiliates to the purchaser, in accordance with the terms set forth in Exhibit B1 in order to ensure that the Designated Supplier has attributed a reasonable and equitable portion of that sale to the Approved Vaccine.
3. No Top Up. The Designated Supplier will not seek or receive any additional compensation or value for the sale of the Approved Vaccine in an Eligible Country other than compensation from the purchaser in the form of the Base Price and the compensation from the Funders under the terms of the Guarantee and Supply Agreement; provided, however, that the Designated Supplier may seek and receive additional compensation or value if (a) additional Funders are added to the Guarantee and Supply Agreement by amendment, or (b) approved by the Administrator, or its designee, in writing.
4. Use in an Eligible Country. If the Approved Vaccine is purchased for use in a particular Eligible Country, the Designated Supplier must have a reasonable expectation that the Approved Vaccine will actually be used in such Eligible Country. For purposes of illustrating the foregoing, if UNICEF, as it presently operates, certifies that a country has certain requirements for the Approved Vaccine, then the Designated Supplier will have a reasonable expectation that such requirements of the Approved Vaccine will actually be used in such country.

**C. Other Criteria.**

*[Insert other criteria]*

\* \* \*

**Schedule C to Draft Term Sheet for Guarantee and Supply Agreement**

**Eligible Countries**

Afghanistan	Congo, Republic of	Lao PDR	Senegal
Albania	Côte d'Ivoire	Lesotho	Sierra Leone
Angola	Cuba	Liberia	Solomon Islands
Armenia	Djibouti	Madagascar	Somalia
Azerbaijan	Eritrea	Malawi	Sri Lanka
Bangladesh	Ethiopia	Mali	Sudan
Benin	Gambia	Mauritania	Tajikistan
Bhutan	Georgia	Moldova	Tanzania
Bolivia	Ghana	Mongolia	Timor Leste
Bosnia & Herzegovina	Guinea	Mozambique	Togo
Burkina Faso	Guinea-Bissau	Myanmar	Turkmenistan
Burundi	Guyana	Nepal	Ukraine
Cambodia	Haiti	Nicaragua	Uganda
Cameroon	Honduras	Niger	Uzbekistan
Central African Republic	India	Nigeria	Viet Nam
Chad	Indonesia	Pakistan	Yemen
China	Kenya	Papua New Guinea	Zambia
Comoros	Korea, DPR	Rwanda	Zimbabwe
Congo, Democratic Republic	Kyrgyz Republic	São Tomé	

\* \* \*

## Notes to the Annex

<sup>1</sup> The Framework and Guarantee Agreement term sheets are designed to accommodate a variety of Funders, despite the fact that there are substantial differences between governmental and nongovernmental organizations in areas such as funding capacity and ability to contractually commit to the Guarantee Agreement. Alternatively, an intermediary such as the World Bank or the Vaccine Fund, could enter into the Framework and Guarantee Agreement on behalf of various Funders.

Because traditional commercial mechanisms for ensuring compliance, such as letters of credit or escrow arrangements, could be unattractive to potential Funders as they would result in increased transaction costs and unnecessarily tie up funds that could be made available for more immediate opportunities, the Framework Agreement was structured as a bilateral contract. Once one or more Developers sign on to the Framework Agreement, the financial commitment of the Funders would become binding, and, in the event of a default by the Funders, the Developers would be able to pursue standard contract remedies, such as money damages and specific performance, to enforce their rights.

<sup>2</sup> The Framework and Guarantee term sheets do not discriminate among potential Developers and are designed to allow participation by pharmaceutical companies, biotechnology companies and emerging manufacturers.

<sup>3</sup> Each Framework Agreement will establish a specific price for qualified sales of an Approved Vaccine, by supplementing the “floor price” (*i.e.*, Minimum Co-Payment) paid by a vaccine purchaser (e.g., UNICEF) with a certain fixed payment to be made by the Funders. The Framework Agreement is not intended to displace, and indeed is specifically designed to work with, existing procurement systems. The Framework is sufficiently flexible that it can work within any procurement system, provided that the Minimum Co-Payment is tendered.

<sup>4</sup> The price guarantee should be “per course of treatment” rather than “per dose.” This approach provides incentives to ensure that all doses of multiple dose vaccines are administered, and encourages the development of vaccines requiring fewer doses where scientifically possible.

<sup>5</sup> Until a vaccine is approved under the conditions set forth in Section 7 of the Framework Agreement term sheet, the Funders are only required to commit to the Framework Agreement, and fund the functions of the Independent Assessment Committee. Once an Approved Vaccine is identified, the Developer has the right, and the Funders the obligation, to enter into the Guarantee Agreement with respect to that product. In other words, the Funders will not be required to pay for a vaccine unless and until a qualifying product is approved and the Developer agrees to make that product available to all Eligible Countries at a sustainable price after the price guarantee has been exhausted.

<sup>6</sup> Indemnification is deemed to be particularly important to attract qualified members to serve on the Independent Assessment Committee.

<sup>7</sup> Developers may provide confidential information to the Independent Assessment Committee in two circumstances. First, Developers would submit progress reports to the Independent Assessment Committee during the term of the Framework Agreement. These reports will provide a way to evaluate the effectiveness of the mechanism during the research and early-development periods. These reports, if not promising, may provide the basis for the Funders to withdraw from the Framework Agreement under Section 26 of the term sheet. Second, for those Developers seeking to participate at a later date, the Framework Agreement requires some evidence that the Developer has a technology or expertise with scientific promise for the development of an Approved Vaccine.

<sup>8</sup> Although the Framework Agreement is designed to create an enforceable bilateral contract between the Developers and the Funders, the Funders would not be obligated to enter into the Guarantee Agreement until a product is tendered that meets certain minimum technical specifications, such as approval of both the product and its manufacturing process by a qualified regulatory body and certain safety, efficacy and use requirements.

<sup>9</sup> The Ongoing Supply Price Ceiling is designed to ensure that an Approved Vaccine will continue to be available at an affordable price once the Maximum Guaranteed Amount has been exhausted. However, because we cannot know today the actual cost of manufacturing an Approved Vaccine, the Framework establishes a mechanism that is designed to incentivize Developers to invest in cost-effective vaccine manufacturing technology and to protect Funders from paying for expensive vaccines. The Framework links the Ongoing Supply Price Ceiling to the Base Price, which is the minimum co-payment that is necessary to trigger the Funders’ obligations under the price guarantee. If the Base Price for an Approved Vaccine is high, Eligible Countries (and donors) will be less likely to purchase that Approved Vaccine, which means that the Funders’ price guarantee will not be triggered. The Developer is, therefore, able to effectively lower the Base Price, and thereby increase market demand, by agreeing to supply the product at a lower price once the Maximum Guaranteed Amount has been exhausted. Thus, the Framework mirrors the conditions in markets in the developed world by allowing Developers to compete based on price.

<sup>10</sup> Because the Developer should be assured that the Funders cannot change the rules of the game after the Framework Agreement is entered into, technical requirements cannot be changed to increase the burden of those requirements unless there is a significant change in circumstances with respect to the disease that would significantly reduce the need for a vaccine or undermine the specifications, such as a dramatic decrease in disease prevalence, a significant change in disease transmission or progression or a major advancement in treatment. As noted below, these types of changes would be subject to judicial review. Technical requirements may be decreased, however, at the discretion of the Independent Assessment Committee or the request of the Funders.

<sup>11</sup> To avoid inefficiencies and reduce administrative costs, the Framework Agreement permits the Committee to rely on third parties and their procedures, such as the World Health Organization and its prequalification process.

<sup>12</sup> As noted above, the Framework Agreement is designed to be self-executing with respect to the Funders, providing the Developers with the right to enter into the Guarantee Agreement on the terms specified in the Framework Agreement. The Framework Agreement is also designed to permit more than one Developer to receive funds under the Guarantee Agreement. The Framework Agreement distinguishes between those Developers who are second because they are simply copying the First Developer's vaccine and those who are second because their independent research program happened to take longer.

<sup>13</sup> Alternatively, the Framework Agreement could designate an existing institution, such as GAVI (provided that its mandate was expanded), to serve as the Independent Assessment Committee.

<sup>14</sup> It is contemplated that the Developers would have the right to consult with the Independent Assessment Committee, much the same way that companies consult with the FDA in the United States, to discuss the design of clinical trials, the structure of drug approval applications, the country or countries in which such drug approval will be sought, the possibility of granting waivers and other issues relating to the approval of an Approved Vaccine.

<sup>15</sup> The duties of a corporate director under Delaware Law are the duty of loyalty, the duty of care and the duty of good faith. The duty of loyalty requires the director to place the corporation's interests above his or her own. The duty of care requires the director to act with certain minimum level of skill and deliberation. The duty of good faith requires that a director not act with bad faith, or engage in intentional misconduct.

<sup>16</sup> A Funder's obligation to reimburse the Independent Assessment Committee is subject to the requirement that its expenses be reasonable. A Funder may want to give further consideration to mechanisms that would permit it to regulate the cost of the Committee without compromising the Committee's independence.

<sup>17</sup> These procedures were intended to strike a balance between, on the one hand, permitting companies with promising technology or relevant expertise to participate in the Framework and, on the other hand, discouraging free riders who would operate outside the Framework and sign on only at the last minute. If companies do not sign on the Framework, the agreement would lose its binding effect. Moreover, it would be difficult for the Funders to monitor the success of the Framework, particularly with respect to research and early development, without the periodic reporting by the Developers required under the Framework Agreement. Funders may wish to strike a different balance, such as allowing companies to join the Framework up until the commence pivotal trials.

<sup>18</sup> The Framework Agreement for an early stage vaccine could be in force for a decade or more before a vaccine candidate is presented for final review to the Independent Assessment Committee. Accordingly, a force majeure provision permitting the Committee, at the request of the Funders, to alter the Framework Agreement based upon extraordinary events has been included. The force majeure clause would void or alter the Framework Agreement in the event of major changes to technology, disease epidemiology, etc. that make a vaccine either inappropriate or unnecessary or that would require a change in the specifications that would be more burdensome to the Developers. These determinations require the approval of a super-majority of the Committee and are subject to judicial review.

<sup>19</sup> It is contemplated that this indemnification will be similar to that which is provided to officers and directors of corporations. Accordingly, the indemnification of the Independent Assessment Committee may exclude intentional misconduct or actions that are conducted in bad faith or for personal gain.

<sup>20</sup> The Funders have the right to terminate the Framework Agreement if certain interim milestones have not been achieved in a timely manner. This provision is included to provide the Funders with an early out if the Framework does

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not appear to be stimulating productive research and development activities. This would permit Funders to pursue other, more-promising opportunities.

<sup>21</sup> Funders may wish to consider liquidated damages provisions to bolster the credibility of their commitment.

<sup>22</sup> The Framework and Guarantee Agreement term sheets are designed to accommodate a variety of sponsors, despite the fact that there are substantial differences between governmental and nongovernmental organizations in areas such as funding capacity and ability to contractually commit to the Guarantee Agreement. The Guarantee Agreement term sheet permits a single Funder, multiple Funders or a system where a lead Funder parcels out participations to sub-Funders. Alternatively, an intermediary such as the World Bank or the Vaccine Fund, could enter into the Framework and the Guarantee Agreement on behalf of various Funders.

<sup>23</sup> The Guarantee Agreement provides for a price guarantee, rather than a minimum quantity guarantee. The Guarantee Agreement is designed so that price for each Qualified Sale could vary. For example, a higher payment could be made in the early years to permit the Developer to recapture R&D costs and capital investments in manufacturing capacity more rapidly, with lower payments in the later years.

Because Developers are ultimately driven by profits, rather than sales, the anticipated cost of goods will be an important factor for any potential Developer in deciding whether to participate in the Framework. Notwithstanding the total size of the Maximum Guaranteed Amount, if the price per Dose is low (*i.e.*, the Maximum Quantity is high) relative to the anticipated cost of goods, then the Developer will not likely be motivated to participate in the Framework. The risks for the Developer are both that the Maximum Guaranteed Amount will not generate a sufficient return on its investment and that, once the guarantee has been exhausted, it will be obligated to supply at the Ongoing Supply Price for a loss.

As discussed in note 9, the Framework mitigates some of the risk of high cost of goods for the Developer with respect to the ongoing supply price, by permitting the Committee to adjust upwards the Ongoing Supply Price Ceiling. The Guarantee Agreement also alleviates some of the risk with respect to the Guaranteed Price by automatically adjusting the Guaranteed Price to reflect changes in the Ongoing Supply Price, and therefore, the Minimum Co-Payment. In other words, the Funders' financial commitment, or top up, under the Guarantee Agreement with respect to each course of treatment remains fixed, but the Guaranteed Price (*i.e.*, the total payment to the Designated Supplier) varies. For example, if the initial Guaranteed Price of \$24 is based on an initial Minimum Co-Payment of \$6, then the Funders would be obligated to pay \$19 per course of treatment, regardless of any change to the Minimum Co-Payment, but the Guaranteed Price paid to the Designated Supplier would change based on changes to the Minimum Co-Payment (which would result from changes to the Ongoing Supply Price). So, if the Ongoing Supply Price increased (*e.g.*, as a result of higher than anticipated Manufacturing Costs), the Guaranteed Price would increase.

Alternatively, the Guaranteed Price could be fixed, so that the payment to the Designated Supplier would be set and the financial commitment of the Funders would change based on changes to the Minimum Co-Payment. For example, if the initial Guaranteed Price of \$24 is based on an initial Minimum Co-Payment of \$6, then the Designated Supplier would receive \$24 per course of treatment, even if the Ongoing Supply Price, and therefore the Minimum Co-Payment, changes. In this scenario, the Guaranteed Price would not increase to reflect increased Manufacturing Costs, but the amount that the Funders would be obligated to contribute to the Guaranteed Price would be decreased based on an increase to the Ongoing Supply Price and, therefore, an increased Minimum Co-Payment. Similarly, a reduction in the Ongoing Supply Price would decrease the Minimum Co-Payment, subject to the Minimum Base Price, and, therefore, increase the amount that the Funders would be obligated to contribute to the Guaranteed Price.

<sup>24</sup> Vaccine must be made available to all Eligible Countries on a first-come, first-served basis. A Developer may not select a few Eligible Countries where it wishes to offer the vaccine. Moreover, as discussed below, a Developer may not cease to supply vaccine once the price guarantee is exhausted.

<sup>25</sup> The Maximum Quantity and the Guaranteed Price can be set to yield desired revenue. Price guaranties are on a per treatment—*e.g.*, course of immunization—basis, rather than a per dose basis.

<sup>26</sup> The Minimum Co-Payment concept, together with the Minimum Base Price floor, was introduced to create an incentive to help ensure that qualifying vaccines are not wasted and that payments are not made for unusable vaccines. If countries, or other donors, are required to make a minimum investment in an Eligible Vaccine, then there is greater likelihood that appropriate quantities of the vaccine will be procured and that those quantities will be administered. This also provides additional safeguards that donor funds will not be wasted on a vaccine for which there is no market. Depending on the particular disease at issue, it may take many years to develop an Eligible Vaccine, which may utilize as yet unidentified technology. Intervening events, such improvement in treatment options or the development of entirely new vaccine technologies, may render a technically adequate vaccine unnecessary or unattractive. Similarly,

unforeseen characteristics of an Approved Vaccine, such as medically harmless but culturally unacceptable side effects, which would not have been addressed in the technical specifications, may render an otherwise safe vaccine unsuitable in certain countries. The co-payment requirement helps ensure that the advance market commitment will be used for Approved vaccines that actually meet the requirements of the Eligible Countries.

<sup>27</sup> Although the Designated Supplier has responsibility for generating awareness of the availability of Approved Vaccines in Eligible Countries, Funders must also share in this responsibility.

<sup>28</sup> It is critical that the Designated Supplier have adequate manufacturing capacity to meet the ongoing needs of the Eligible Countries, not just the Maximum Quantity of product. In addition, as noted below, consideration needs to be given to the contract remedy if the Designated Supplier fails to establish adequate manufacturing capacity, or otherwise meet its supply requirements, under the Guarantee Agreement, particularly once the Guaranteed Price has been exhausted. Section 15 of the Guarantee Agreement includes a proposal for liquidated damages, but other options are available.

<sup>29</sup> To avoid inefficiencies and reduce administrative costs, the Framework Agreement permits the IAC to rely on third parties and their procedures, such as the World Health Organization and its prequalification process.

<sup>30</sup> Compliance with the Foreign Corrupt Practices Act was imposed to alleviate concern that illegal payments might be used to generate demand. Obviously, the purpose of the Advanced Markets mechanism is to generate orders for vaccines that will be used, not to simply to generate orders for vaccines.

<sup>31</sup> There is a tension between the need for certainty in the determinations of the Independent Assessment Committee and the need for some review. Court review was deemed impractical in most circumstances. Instead, the goal is to create an Independent Assessment Committee that would be viewed as independent and impartial by all participants in the Framework, but which is subject to review if it exceeds or abuses its authority, and with respect to certain critical decisions, such as a decision to alter or terminate the Funders' payment obligation in the face of a force majeure event, as described in note 38 below.

<sup>32</sup> The Guarantee Agreement requires that the Developer continue to make Approved Vaccines available even after the Funding Period expires at a price not to exceed the Ongoing Supply Price Ceiling. If there are multiple Developers, the Ongoing Supply Price Ceiling will be increased for a limited time for any Developer that does not receive a certain minimum percentage of the Maximum Guaranteed Amount during the Funding Term, which amount is defined as the Minimum Gross Sales Amount. The increase will cease to be effective, and the cap will return to the predetermined amount, once the Developer's aggregate sales equal the Minimum Gross Sales Amount. The Minimum Gross Sales Amount is intended to be a rough proxy for a return on the Developer's investment in the Eligible Product, but cannot exceed 100% of the Maximum Guaranteed Amount. The cap will be set forth in technical specifications in Appendix A to the Framework Agreement, and may be modified, in the discretion of the Independent Assessment Committee, as provided in Section 10 of the Framework Agreement.

<sup>33</sup> Because it will be difficult to establish the supply requirements in advance, the Guarantee Agreement provides that the Designated Supplier and the Administrator will agree on a forecast. However, a Designated Supplier may be concerned that the Administrator would establish aggressive supply requirements that would not be realized. As an alternative, the Guarantee Agreement could provide a mechanism for the Parties to determine an appropriate forecast or this could be referred to the Committee or an independent expert. Another option would be for the Funders to guarantee the forecast or a portion thereof in addition to the price. While this would shift some risk to the Funders, the forecast would be established once the Approved Product had obtained regulatory approval.

<sup>34</sup> The capacity requirements are designed to permit a Designated Supplier to establish capacity to supply Approved Vaccine outside the Eligible Countries without unfairly diverting such supply from the Eligible Countries. Other metrics could be used to provide similar protection, such as requiring that a Designated Supplier establish a dedicated facility to supply Approved Vaccine for Eligible Countries.

<sup>35</sup> This provision is included to protect Designated Suppliers in the event that forecasted demand for an Approved Vaccine is not realized.

<sup>36</sup> If the Designated Supplier of an Eligible Vaccine fails to meet its supply requirements under the Guarantee Agreement, it would be required to grant the Funders, or their designee, a non-exclusive, royalty-free (except as necessary to provide the Designated Supplier with the Minimum Gross Sales Amount, as described above) license to

exploit the Eligible Vaccine only in Eligible Countries. Although less than ideal, this is intended to make the relevant technology available to the Funders if the Designated Supplier breaches its obligations under the Guarantee Agreement. Because this provision may not provide much of an incentive not to breach, especially if a Designated Supplier has already received the Maximum Guaranteed Amount and because, even with this license, there could be a disruption of supply, the term sheet also includes a liquidated damages provision in Section 15.

<sup>37</sup> Indemnification is deemed to be particularly important to attract qualified members to serve on the Independent Assessment Committee. It is contemplated that this indemnification would be similar to that which is provided for directors and officers of corporations.

<sup>38</sup> A *force majeure* provision permitting the Independent Assessment Committee to alter the Guarantee Agreement based upon extraordinary events has been included. The force majeure clause would permit the Committee to void or alter the Guarantee Agreement in the event of major changes to technology or disease epidemiology that render a vaccine either inappropriate or unnecessary. For example, if advances in other technology substantially reduced the incidence or transmission of the target disease in Eligible Countries, then the Funders financial obligation would be reduced accordingly. As noted in Section 7 of the Guarantee Agreement term sheet, Schedule C would include criteria, such as assumptions underlying the Framework Agreement, to guide the Independent Assessment in taking any such extraordinary action, which as noted in the Framework Agreement term sheet, would be subject to judicial review.