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How Should the World Pay for a Coronavirus Disease (COVID-19) Vaccine?

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ABSTRACT

The potential health and economic value of a vaccine for coronavirus disease (COVID-19) is self-evident given nearly 2 million deaths, "collateral" loss of life as other conditions go untreated, and massive economic damage. Results from the first licensed products are very encouraging; however, there are important reasons why we will likely need second and third generation vaccines. Dedicated incentives and funding focused explicitly on nurturing and advancing competing second and third generation vaccines are essential. This article proposes a collaborative, market-based financing mechanism for the world to incentivize and pay for the development of, and provide equitable access to, second and third generation COVID-19 vaccines. Specifically, we propose consideration of a Benefit-Based Advance Market Commitment (BBAMC). The BBAMC uses health technology assessment to determine value-based prices to guarantee overall market revenues, not revenue for any specific product or company. The poorest countries would not pay a value-based price but a discounted "tail-price." Innovators must agree to supply them at this tail price or to facilitate technology transfer to local licensees at low or zero cost to enable them to supply at this price. We expect these purchases to be paid for in full or large part by global donors. The BBAMC therefore sets prices in relation to value, protects intellectual property rights, encourages competition, and ensures all populations get access to vaccines, subject to agreed priority allocation rules.

Keywords: Advance Market Commitment, COVID-19, global health, vaccines, value-based pricing.

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Introduction

The potential health and economic value of a vaccine for coronavirus disease (COVID-19) is self-evident given nearly 2 million deaths, morbidity associated with around 80 million cases,[1] the "collateral" loss of life as other conditions go untreated,[2] and massive economic damage, with consequential effects on livelihoods, health, and education.[3]

Governmental and global funding initiatives, including Project Warp Speed in the United States[4] and the Gavi COVAX Facility[5] with its partners the Coalition for Epidemic Preparedness (CEPI), United Nations International Children's Emergency Fund (UNICEF), Pan American Health Organization (PAHO), and the World Health Organization[6] are focused on, and investing billions in, speeding up the development, introduction, and global scale up of a first generation of vaccine candidates. As of mid-December, BioNTech/Pfizer and Moderna have Food and Drug Administration emergency authorization for use and are being deployed. There have been setbacks,[7] but other vaccine candidates are in phase 3 trials or have reported promising phase 3 trial outcomes and are making submissions to regulators.

Beyond the funding, alliances between manufacturers, small biotech and large pharmaceutical in the case of BioNTech and Pfizer, two large vaccine manufacturers in the case of GSK and Sanofi, and large multinational and large regional players in the case of AstraZeneca and Serum Institute of India, have helped speed development and ultimately scale up and roll out.[8-10]

The results from the first licensed products are very encouraging, although there is much about the virus we do not yet know.[11-13] However, there are important reasons why we will likely need second and third generation vaccines as well as additional first generation (ie, those in late stage development) successes to sustainably end the global pandemic. These reasons include[14] open questions about whether existing products stem transmission in addition to preventing symptomatic disease; the potential for mutation of the virus, as observed recently in the United Kingdom and South Africa[15]; unanswered questions about the duration of protection from existing products, potentially requiring vaccines with longer-term protection or regular booster shots; logistical challenges related to the "ultra-cold chain" and 2-dose regimens, both of which may be particularly acute in low- and middle-income countries; high unit costs and technologically complex manufacturing processes for the most efficacious vaccines thus far (BioNTech/Pfizer and Moderna); and the need for scale that cannot be achieved by any one manufacturer, even through licensing agreements, to reach the large global population outside of wealthy countries. Dedicated incentives and funding focused explicitly on nurturing and advancing second and even third generation vaccines are essential.

In this article, we propose a collaborative, market-based financing mechanism for the world to incentivize and pay for the development and provide equitable access to second and third generation COVID-19 vaccines. This is an advance market commitment (AMC) with pricing informed by health technology assessment (HTA).

Push and Pull Framework

In the case of global diseases with attractive high- and middle-income country (HIC and MIC) markets, pharmaceutical companies generally invest in research and development (R&D) at risk; the expected buying power of these populations "pulls" vaccine candidates through development, manufacture, and delivery. Payers (governments or insurers) purchase vaccines that offer value, with prices reflecting value, competition, and the effects of negotiation. As a complement to these markets, since its establishment in 2000, Gavi has raised donor funding and bought these "global" vaccines on behalf of low- and lower-middle- income countries (LIC and LMICs), countries that would otherwise be largely ignored in manufacturing scale up and introduction planning, because of their limited financial resources.

Potential vaccines to prevent diseases, such as malaria, tuberculosis, and neglected tropical diseases, such as Leishmaniasis, and emerging infectious diseases, such as Ebola,[16] do not have a big enough expected market to attract private R&D investment funds. In these cases, governments and other funders design and finance "push" incentives; "pull" incentives; or some combination of the two to accelerate vaccine development and introduction. "Push" incentives reduce the costs of R&D borne by the vaccine developer, through co-financing, streamlining the development process, or partnerships. "Pull" incentives increase expected revenue contingent on successful vaccine development, for example by guaranteeing price, volume, or overall revenues.

The Bill and Melinda Gates Foundation and many bilateral donors fund product development partnerships in neglected disease areas, using push funding to build portfolios of candidates.[17] The challenge of selecting which candidates to back and providing the right incentives for development means that, at times, successful clinical development has brought products to market that subsequently see limited health system demand.[18]

There is therefore a robust global health debate as to the appropriate balance between push and pull incentives. A large enough market should, in theory, stimulate at-risk R&D investment by the private sector.[19-21] Pull mechanisms alone require larger up-front commitments and cross-organization coordination (although money is spent only once products come to market). Push funding, in contrast, can be done in marginal stages: by one funder acting unilaterally, and for one product or one development stage at a time.

Even when neglected disease vaccine development is financed with up-front push investments, market pull is still needed to cover manufacturing and distribution costs. Push investments should be used to stimulate initial research and development but only until a pull mechanism can incentivize the private sector to take on the remaining scientific and commercial investment risks. Push incentives should also aim to increase development competition (for example by identifying potential natural or synthetic antigens that might help prevent disease) rather than reduce competition by choosing lead candidates.

COVID-19: First Generation Vaccine Development

In the case of COVD-19 and the virus that causes it (SARs-CoV-2), CEPI, a public private partnership established in 2017 to accelerate R&D into innovation for epidemic and pandemic preparedness, moved quickly to expand its financing of early R&D candidates; several jurisdictions, notably the United States, China, Russia, the European Union, and the United Kingdom, also began push funding R&D by domestic universities and pharmaceutical companies. Estimates of COVID-19 "push" funding, in vaccine R&D and "at risk" manufacturing capacity, add up to around $10 billion.[22,23]

In the pandemic context, push funding for early R&D offers an important benefit: speed. But once vaccine candidates move beyond early-stage research into clinical development, push funders are necessarily required to "pick winners" that will progress into later-stage trials. The largest COVID-19 vaccine push initiative, US Operation WARP Speed, has already winnowed more than 100 possible candidates to 8 receiving government funding support, including Moderna, J&J, Novavax, Merck, Sanofi/GSK, and University of Oxford/AstraZeneca.[4] For COVID-19, the expected social returns of an effective vaccine are so high that additional push funding is being used to build manufacturing capacity to begin manufacturing at scale at risk (ie, before there is evidence of efficacy and safety to achieve regulatory approval).[24,25]

By mid-December 2020, many HIC governments have signed bilateral advance purchase commitments (APCs) with individual manufacturers for billions of doses of future COVID-19 vaccines. These APCs are contingent on products getting licensing approval. At the same time, Gavi, through its COVAX facility is racing to leverage a pool of donor and country health funds to sign APCs on behalf of high-, middle-, and low-income participating countries.[26,27]

Beyond this initial phase, we argue that a different push/pull balance will be needed for the longer term. Experts recognize that first generation vaccines, while of great importance, are not likely to be silver bullets. They also recognize and accept that much push funding will be bet on candidates that do not ultimately work.

To sustain a portfolio of candidates to address the longer term needs for COVID-19, credible pull incentives for development (in addition to manufacture and scale up) are needed to attract more private capital, harness greater industry expertise, and reduce the R&D price tag and risks borne by taxpayers.[28] While ultimately, pull incentives need to be paid out, if designed correctly, the private sector will bare more of the risks and costs of failure, leaving the public sector spending more on successes.[29] In designing a pull incentive, we argue for an approach that also gives the MICs and their population needs a "seat at the table" alongside the HICs.[30] Although the LMICs and LICs will likely require donor funding support, pull for future generation products can bring Gavi/COVAX in early to make sure these countries' needs are also represented. Working together, a credible pull mechanism will send a clear market signal.

AMC Versus Advance Purchasing Commitments: Promoting Competition

The AMC is a pull mechanism offering a guaranteed market for products meeting preagreed specifications but not for any individual product, creating room for competition.[31-33] The AMC was

first introduced in 2009 for a "late-stage" pneumococcal vaccine that a number of manufacturers were already developing for HIC target populations. The objective of the pneumococcal vaccine AMC was to motivate manufacturers to invest in manufacturing capacity scale up and product introduction in LICs, shortening what was then a typical 10- to 15-year delay between first launch in HICs and introduction in LICs. Since the pneumococcal vaccine AMC was launched, more than 150 million children have been immunized, saving an estimated 700 000 lives.[28,34-37]

Kremer and others have argued that the AMC mechanism maybe most efficient when used to drive R&D as well as manufacturing and delivery.[21,31,38] A 2005 report[31] modelled an AMC for an early-stage malaria vaccine: funders (buyers) would lock in a guaranteed price for a certain volume, thereby delivering a return on R&D and avoiding the problem of time inconsistency when buyers push for lower prices once R&D is sunk, or developers seek higher prices because of the absence of alternative suppliers.

The terms APC and AMC are often used interchangeably in the literature but should be differentiated: APCs contract an individual company/a specific product, whereas an AMC offers a global market commitment but not a commitment to any particular company or product. Manufacturers with products would naturally prefer to secure APCs in advance of product approval. However, APCs only make sense from the payer's perspective when there is an imperative to preemptively secure access to a scarce resource, as in the COVID-19 pandemic.

Guaranteeing volumes via APCs comes, however, at a high cost to payers. To mitigate the risk of product failure and ensure access to at least one vaccine, payers will need to contract for much larger volumes than they need, betting on a number of different suppliers. For example, Canada has been reported to have purchased enough to vaccinate its population 5 times over.[39] Existing APC agreements for COVID-19 have also lacked clarity on how price is to be determined, including how much is paid up-front and cannot be recovered if the candidate fails, and whether and how pricing accounts for governmental and philanthropic push investments. APCs risk governments choosing who to back in a way that distorts the development portfolio in favor of late-stage candidates or products deemed to be most promising.[11,40–42] If future markets are pre-empted with APCs, then products at an earlier development stage or ones with less well-established platforms, will be crowded out. Kremer et al[38] explored whether buyer contracting is more efficient using APCs or a framework AMC. They find that, while a well-designed APC is more efficient for late-stage candidates, an AMC is efficient for early-stage candidates. In this context, competition (more than 3 or 4 developers as is the case with COVID-19 vaccines) is very important in improving efficiency in terms of speed of entry, quality of the vaccine, and potential for price competition.

Using HTA and Cost-Effectiveness to Create a Benefit-Based Advance Market Commitment (BBAMC)

To design an AMC funders must set clear, ex ante vaccine price and quality standards, crucial parameters that determine the shape and power of the pull incentive. Up until now, the AMC model (both the pneumococcal vaccine AMC and those proposed in the literature for COVID-19),[43-45] do not address the important issue of differentiating the reward to reflect quality differences between products.

The pneumococcal AMC used a target product profile (TPP) to ensure products met a minimum quality standard; qualifying vaccines would be entitled to a uniform "ceiling" AMC price for a pre-determined share of the doses Gavi, on behalf of donors, committed to in a multiyear supply agreement. The TPP represented a qualifying minimum threshold; in the case of the pneumococcal AMC, it was not a tool to differentially reward vaccines based on efficacy or other valuable characteristics. For COVID-19 vaccines, Snyder et al[43] propose an AMC to speed late-stage development and manufacturing where the AMC price set would be based on cost disclosure using a model by Chaturvedi at al.[46] Their proposal does not address differential quality. Conti and Sharfstein also propose a cost-based AMC.[44] Bach and Trusheim[45] likewise propose an AMC with a minimum quality threshold to be set, and then ask for manufacturer bids to supply. In our view the AMC design needs to be developed to promote competition based on quality and on cost-effectiveness.

COVID-19 vaccines are likely to vary dramatically in efficacy profile and other key characteristics and therefore in health and economic value. A cost-based pricing approach could encourage manufacturers to focus on meeting only minimum efficacy hurdles and may even result in the pursuit of higher cost and more capital-intensive technologies.[47] In contrast, a value-based pricing approach could be designed to reward vaccine efficacy and manufacturing efficiency while ensuring affordability as prices will reflect local constraints. We propose consideration of a Benefit-Based Advance Market Commitment (BBAMC),[29,30,48,49] itself adapted from an earlier AMC proposal designed to drive R&D for new tuberculosis treatments.[50,51] The BBAMC uses HTA and value-based pricing to guarantee overall market revenues, not revenue for any specific product or company.

The feasibility of such an approach depends on our addressing two immediate challenges: how to assess the value of a vaccine,[52,53] and how much of the value should be allocated to the developer in the form of a value-based price, which is important from both an incentive and a societal outcome perspective. Critical issues for consideration in assessing value include the adverse health externalities of infection, including the "fear of contagion"[54,55]; the insurance value of having a vaccine available[56]; the impact on patients without COVID-19 of an overwhelmed health system unable to treat them; and the macroeconomic, social, and psychological impact of nonpharmaceutical interventions (eg, social distancing and school and business closures).

Smith et al,[57] Beutels et al,[58] and Smith et al[59] argue the assumption, which underpins most economic evaluation, of being at the margin (partial equilibrium analysis) hinders pandemic impact assessment, and a broader analytical approach is needed to assess pandemic impact and, by implication, the potential benefit of a vaccine. Neumann et al[60] and Cohen et al[61] argue that while analyses should be conducted from both a health system and societal perspective, this does not mean manufacturers should capture the entire societal benefit of a vaccine, diagnostic, or therapy. We share this view. Although it is important to assess the full health and economic burden of COVID-19, the health and economic benefits of an effective vaccine are sufficiently high that we do not need to wait for calculation of the "full" vaccine value. The objective of a value-based pricing regimen is not to maximize the potential gains to developers but to create incentives for socially optimal R&D investment. In this case, although some have argued for high prices,[62] developers do not need to capture the entirety of health and social benefits of a pandemic vaccine to have sufficient incentive to invest their own private capital,[63] nor are companies expecting such high returns.[64] Prices based on the health benefits alone, taking account of externalities as conventionally modelled in vaccine economic evaluation, should likely provide sufficient incentive.

A preliminary design for an BBAMC for a COVID-19 vaccine could work as follows:

(1) Early HTA establishes a value-based price based on the WHO TPP.[65] The WHO TPP offers a range of minimum and more desirable attributes, including efficacy rates. It can therefore be used to set a minimum entry requirement and also to assess a range of values and therefore prices. Country-specific HTA leads to differential pricing based on expected health benefit and ability to pay for a new product. There is an inherent perverse incentive, however, for countries to understate their ability to pay for the health gains of a vaccine in order to pay less. A third party, pro-rata, assessment of value and willingness to pay may therefore be needed to establish ex ante prices linked to the TPP.
(2) Based on the early HTA results and ex-ante prices, each country would lock in a total revenue (price × volume) based advance commitment; these commitments would range between a minimum and maximum level based on different efficacy (and therefore price) scenarios. An at-launch assessment would evaluate vaccine performance against the TPP to calculate the appropriate "locked in" revenue commitment, giving both parties protection from opportunistic behavior. Price competition would be encouraged but would not alter that total revenue commitment, increasing volumes purchased over time as illustrated in Appendix 4 of Chalkidou et al.[50]
(3) The AMC will be the aggregation of individual commitments. Commitments must be guaranteed by a third party, such as the World Bank, a regional development bank, or, in the case of a major HIC, an independent central bank. A credible mechanism is needed to signal to industry that the AMC will be honored. If countries renege, the guarantor would pay developers.
(4) The BBAMC will offer value-based advance market commitments (country-specific prices for country specific guaranteed volumes) to developers that meet the minimum effectiveness threshold (as per the WHO TPP). This incentivizes follow-on innovators to stay in the game, as early licensed vaccines may not meet all needed criteria in terms of efficacy; method of administration; cold chain and other distribution needs; or safety profile. Late failure of front-running candidates or safety risks may also require restricting vaccine use or even market withdrawal. If and when multiple vaccines are licensed, they will compete for market share within the guaranteed revenue pool, as in a normal vaccine market. The vaccine that best meets the preferred product characteristics for a payer will receive both a higher price and a greater volume share of the total revenue commitment. However, competing vaccines could lower prices to get more of the market.
(5) To ensure that the public does not pay twice for a vaccine, pricing can account for push funding (for R&D or manufacturing) by adjusting either the price or the size of the AMC made by each country. Only push funding for successful vaccine candidates should count against countries' market commitment. Governments backing the "wrong" candidates have not partially met their commitment. This will add to the incentive for governments to choose carefully and leverage cross-government collaboration (eg, via CEPI) to spread risk.
(6) To balance providing expected returns on investment with payers' need to manage budgets, the value-based price will only be paid for a preagreed proportion of the guaranteed commitment, to a preagreed maximum volume or a preagreed time period. Beyond this, developers will supply at a "tail-price,"[66] which will be a heavily discounted price (eg, a 70% discount), designed to mimic post patent-expiration generic pricing.
(7) Participation of HICs and MICs will clarify global market size and build a powerful Gavi COVAX AMC that is more than a vehicle for donor aid to buy vaccines for LICs.
(8) The poorest countries (LICs and LMICs) would not pay a value-based price but the tail-price from day 1. Innovators must agree to supply them immediately at the tail price, or to facilitate technology transfer to local licensees at low or zero cost, to enable them to supply at this price. As Gavi proposes, we expect LIC and LMIC purchases to be paid for in full or large part by donors. This both protects intellectual property rights and ensures all populations get immediate access to vaccines, subject to agreed priority allocation rules.
(9) Allocation rules of some form will need to be developed to ensure manufacturers are able to distribute product across commitment-making countries. This process can build on national and supranational bodies, notably the WHO.[67-71]
(10) Effective governance arrangements will be needed across 4 key parties: (1) payers (eg, governments, international bodies, and donors); (2) the guarantor(s) who will sign agreements with the payers and provide credible commitments to the market; (3) the secretariat/coordinator, funded by a small levy on the buyers; and (4) the vaccine developers who register to participate in the scheme and agree (in contracts with the guarantor) to supply vaccines at the preset value-based prices. Developers will contract with payers to supply requested quantities at these prices.

It is beyond the scope of this article to illustrate how this might work in practice, but more detailed discussion is available in the report proposing an AMC for new tuberculosis drugs.[50,51]

Anticipated Concerns with This Proposal

We anticipate four concerns with our proposal. First, the BBAMC uses ex ante estimates of the expected value of a vaccine with associated expected volumes. These are likely to be highly uncertain. The market for a vaccine may erode, for example, if herd immunity builds up over time or new therapeutic advances make the disease easily treatable. Locking countries into honoring ex ante commitments may therefore lead to unnecessary expenditure. We nonetheless argue that it is preferable for the developer to absorb R&D risk and for the country to absorb the population health risk. This distribution of risk reflects the respective strengths of the parties, developers understand development risk and countries understand their populations.

Second, the BBAMC will have different prices in different countries; manufacturers may be tempted to supply higher-value markets first, or to prioritize countries that have not signed up to the AMC. Countries may have used push funding to obtain pre-emptive purchase rights in many of the APCs being announced. Participating countries will need to agree to a set of allocation rules that reflect WHO allocation principles but also the reality of existing agreements by participating countries or regional groupings. These rules will need to recognize that different prices are being paid in different markets, but these considerations do not override the preagreed allocation mechanism. Countries participating in the joint effort will be weighing the increased overall probability of success and lower prices versus a more risky and expensive unilateral approach where, if successful (lucky), they could jump the line to vaccinate their own populations.

Manufacturers do not have to participate in the AMC; however, participation should be made conditional on their preagreement to make certain quantities available to participating countries.

Third, it could be argued that it is too late to do it now. Several large countries and regional groupings are unlikely to participate and instead continue pursuing bilateral APCs, although they may help to fund Gavi purchases of vaccines for LICs and LMICs. We argue that this is not in their collective interests, not least because it reduces the portfolio diversification needed to increase the overall probability of finding effective second and third generation vaccines. The greater the participation, the more likely it is that private sector capital in both HICs and MICs will be motivated to invest in vaccine development.

Furthermore, building on the suboptimal but perhaps politically justifiable current situation with bilateral deals, several of us have set out how the Gavi COVAX Facility and the EU Procurement Joint Action could be adapted with elements of the BBAMC to make them more effective.[72] It is important to recognize the need for an effective market for follow-on vaccines, and a BBAMC will provide that. The Gavi COVAX Facility recognizes the importance of moving from APCs to a second market-based stage, including use of AMC tools,[73] but there is more it can do expressly to signal it is interested in rewarding value.

Fourth, some may argue that other "pull" proposals offer more attractive alternatives. These include patent buy out proposals,[20,74] and a form of the Health Impact Fund.[75] We argue that an AMC best fits 5 key design requirements set out by Towse and Kettler[76]: (1) a viable price setting mechanism; (2) getting the quality needed; (3) need for competition to encourage improved follow-on products; (4) timely access for low income populations; and (5) credibility with industry. It is harder for "prize" type pull mechanisms to accommodate follow-on products and avoid suboptimal winner-take-all outcomes. The BBAMC may also be more acceptable to industry, as it provides a guaranteed market, albeit with important social obligations, but does not challenge intellectual property rights or supplant the normal workings of the market in other disease areas.

Three Lessons for Future Pandemic Preparedness

The aftermath of the COVID-19 pandemic will offer an opportunity to strengthen global preparedness in expectation of another pandemic; it is a matter of when and not if. The H1N1 pandemic led WHO to maintain influenza vaccine capacity[77] while Ebola outbreaks led to establishment of CEPI.[78] Informed by the analysis in this paper three additional steps are needed as we look forward.

First, we need to build in advance, as a complement to CEPI's rapid platform for early-stage push funded research, a market based pull mechanism to finance vaccine development, manufacturing, and procurement. The BBAMC is, in our view, a powerful mechanism to use, creating a market to stimulate competition and using an HTA-driven value-based price to incentivize quality, which cost-based approaches are not able to do.

Second, lessons from the implementation of the Equal Allocation Framework that WHO, Gavi, and other partners have built to facilitate the allocation of COVID-19 vaccines[69,71] should inform global international allocation rules for future pandemic priority products. This will be difficult and may involve accepting that countries hosting successful candidates get preferential access.

Third, the global community should establish in advance robust financial commitments by HICs, other donors and multilateral institutions to pay for LIC and LMIC vaccines in a pandemic scenario, potentially triggered by a preset hurdle (eg, a WHO pandemic declaration).

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