

# How Should the World Pay for a COVID-19 Vaccine?

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## 1. Introduction

This paper addresses the question of “How should the world pay for a COVID-19 vaccine?” It builds on work undertaken with Kalipso Chalkidou, Rachel Silverman and Ganesh Ramakrishnan from the Center for Global Development, and Hannah Kettler from PATH, and with Martina Garau and Marina Rodes-Sanchez from the OHE. All errors of fact, and analysis, and value judgements (especially those the reader may disagree with) are the sole responsibility of the authors.

The paper argues that there are two requirements to get the vaccine(s) we need:

(i) the right payment and financing mechanism

Creating a market for a vaccine with an advance market mechanism based on paying for value is the best way forward. We are currently locking ourselves into a COVID-19 paradigm of publicly funded development and manufacturing, with companies offering to price on a cost-plus basis. We do not think, for reasons we will discuss, that this is the best paradigm for both getting a vaccine and making it available at cost to poorer countries. We need to use something closer to the normal paradigm of paying for value and mobilising the private sector to invest at risk, in the expectation that they will get a return if they deliver the health gain that society wants. We need however to recognise the uncertainties around both demand and supply and so we propose a value-based (or benefit-based) advance market commitment (BBAMC) to cover all countries who wish to participate. Ideally this will build on proposals from the WHO for a vaccine pillar using a Gavi-led COVAX Facility.

(ii) the money to resource vaccine purchase

A serious commitment of money is needed on the part of high income countries (HICs) and donors, both to pay for vaccines for the nearly 50% of the world's population who live in low-income countries (LICs) and lower middle-income countries (LMICs) and to ensure that supply capacity is available to manufacture at scale for these population groups.

The paper is structured as follows:

- We set out the objective we are trying to achieve from a payment or financing mechanism in the COVID-19 context;
- We develop a framework for understanding what type of mechanisms work and how we can apply them to the COVID-19 vaccine effort;
- We outline the particular challenges of vaccine development for COVID-19;
- We focus on two proposed financing mechanisms: The Gavi COVAX Facility and the BBAMC;
- We propose some next steps – how the COVAX facility can be improved to increase the likelihood of getting useful vaccines and being able to supply them at scale;
- Finally, we think about some lessons for pandemic preparedness we can take from the COVID-19 vaccine race so far.

## 2. The Objective and Context for a Payment and Financing Mechanism

We are trying to achieve two things:

1. to get one or more vaccines that work<sup>1</sup>;
2. to give the world's population access to it. That means vaccines are:
  - developed and manufactured at speed;
  - manufactured at scale and delivered to populations across the world;
  - affordable to the low-income populations of the world and cost-effective<sup>2</sup>, i.e. a good use of scarce resources, in very different health care settings around the world.

### THE GLOBAL CONTEXT

The John Hopkins website (as at 26<sup>th</sup> July 2020) reports more than 16m people infected and more than 640,000 deaths (2). We also have a lot of "collateral" loss of life, as other treatable conditions go untreated because health systems are overwhelmed or because patients are too frightened of getting infected to seek medical help (3).

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<sup>1</sup> The WHO has set out a Target Product Profile (TPP) for a COVID-19 vaccine as at 9<sup>th</sup> April, updated (v3) at 29<sup>th</sup> April 2020. (WHO, 2020) (1)

<sup>2</sup> The paper does not discuss two important questions: "how do we establish the value of a vaccine?" and "how much of that value should go to the manufacturer?"

As well as the health costs, we also have massive economic damage, with consequential effects on people's livelihoods, and on their health and education. The World Bank is forecasting a much deeper global recession than occurred in 2008/9. The IMF has estimated loss of economic output of \$9 trillion<sup>3</sup> for 2020 and 2021 (4).

The case for a vaccine against COVID-19 appears overwhelming. We already know of the global health and economic benefits of vaccines (5). Immunization averts an estimated 2 to 3 million deaths every year. In the words of Bill Gates "Vaccines have saved more lives than any other tool in history. Smallpox, which used to kill millions of people every year, was eradicated with a vaccine. New vaccines have played a key role in reducing childhood deaths from 10 million per year in 2000 to fewer than 5 million per year today (6)."

### THE CORNUCOPIA OF SCHEMES TO SUPPORT COVID-19 VACCINE DEVELOPMENT

Not unsurprisingly, there are a large number of financing schemes underway or being proposed to reward and incentivise vaccine development, manufacturing and delivery. We distinguish between "push" and "pull" incentives to help understand them. Push incentives reduce the costs to organisations of research and development and of building manufacturing capacity, usually by helping to pay for these investments. Pull incentives help to guarantee one or more of prices, volumes, and revenues for a successfully developed product, so compensating for the possibility of the market not providing enough of an incentive.

A non-exhaustive list of the schemes is as follows:<sup>4,5</sup>

1. **The US Operation WARP Speed.** This aims to deliver 300 million doses of a safe and effective vaccine by January 2021 (11,12). Accelerated development is being achieved by direct federal government investment to support the clinical development of preferred candidates. There is also Federal government investment in manufacturing capacity at risk. 14 candidates were initially chosen from the 100+ candidates and this has now been reduced to five: Moderna; University of Oxford and Astra Zeneca; J&J; Pfizer; and Merck. Federal investment is also taking place to expand domestic supplies of specialised materials including glass vials. It is unclear what has been agreed in

<sup>3</sup> The AcceleratingHT proposal we consider later turns this into an estimated loss of \$375 billion per month.

<sup>4</sup> Proposals that we have not listed include: (i) Patent buy out proposals both from Elias Mossialos for the EU ("value-based purchases of intellectual property (IP) rights" (7) and from Hollis and Busby (8)) for a form of the Health Impact Fund – see <https://healthimpactfund.org/en/>. For a summary of theory on patent buy-outs see Kremer, 1998 (9); (ii) Yamey et al. Funding the Development and Manufacturing of COVID-19 Vaccines.(10);

<sup>5</sup> We have also seen proposals for compulsory licensing, which is permitted by international agreement under the TRIPS agreement of 1995 (clarified for use in Public Health in the 2001 Doha Declaration) but there are two big problems:

1. If you license something that you cannot manufacture, then you are no further forward. Proposals for compulsory licensing suffer from the need for investment in enough global manufacturing capacity such that someone is able and willing to supply you.
2. Talking about expropriating someone's intellectual property if they invest and succeed in developing a product, makes it less likely that they will invest. And the reality is that IP is not going to be an issue for LICs with COVID-19 vaccines. The UNAIDS initiative for a "[people's vaccine](#)" is responsive to advocacy demands but multinational pharmaceutical companies are [pushing back](#) against the idea of pooling intellectual property (IP) for fear of setting a dangerous precedent which will undermine future innovation. The World IP Organization (WIPO) Director General has stated that "[Focusing on access to non-existent vaccines, treatments or cures, rather than the encouragement of needed innovation, at this stage, may not only represent a misunderstanding of the sequencing of innovation and access, but also create a disincentive to investment in needed innovation.](#)"

terms of manufacturing and supply commitments by companies receiving funding or if any price or pricing policy has been agreed (13). Congress set aside \$10 billion in the CARES Act to fund this and related measures.

2. **The UK government.** While the UK government has pledged money to organisations like CEPI (see below), it is also supporting the development of national vaccine candidates providing direct R&D funding for two UK academic-led vaccine candidates, at the University of Oxford (in partnership with AstraZeneca), and at Imperial College London. It has also agreed to invest at risk in a manufacturing facility that can be used by AstraZeneca to manufacture the University of Oxford vaccine (14).
3. **The Coalition for Epidemic Preparedness (CEPI).**<sup>6</sup> CEPI launched a call in May to fund COVID-19 vaccine development and scale-up manufacturing capacity. It was specifically for vaccines that could be available for licensure in 12-18 months. They have 9 candidates, 7 of which are in clinical testing (as of 13 July). They are aiming to raise \$2 billion to support this. In addition, they are estimating that manufacturing scale up for the vaccine they support will cost \$1 billion.
4. **The WHO Access to COVID Tools (ACT) Accelerator** The WHO ACT Accelerator has three pillars relating to therapeutics, testing and vaccines (15). Investment cases for all of the pillars were launched on the 27<sup>th</sup> June with a call for \$31.3 billion of funding across the three pillars, of which \$3.4 billion has already been pledged (16). The vaccine pillar will be the responsibility of CEPI and of Gavi. The COVAX Facility, which we discuss in more detail below, is the model that is being proposed to pool vaccine procurement, mainly for 'Gavi eligible', LIC and LMIC countries.
5. **AcceleratingHT.** The AcceleratingHT Initiative (17) is an academic initiative led by Michael Kremer, the Nobel prize winning economist and a key driver behind the establishment of the concept of and practical application of the Advance Market Commitment (AMC) (which we discuss below). The AcceleratingHT initiative is focused on speeding up the manufacture and delivery of any approved vaccine. They propose to do this in two ways: i) Manufacturing capacity is built speculatively for vaccine candidates in advance of any regulatory approval for sale of the vaccine; ii) "Excess" manufacturing capacity is built such that all global need is supplied in a short window of time. The logic for the initiative is to address perceived market failure that "vaccine firms do not capture all of the gains from early supply and so produce slower than optimally"<sup>7</sup>. It does not address vaccine development, as benefit calculations are "conditioned on approval of a vaccine". They argue for innovation in clinical development, but their proposal is not intended, in itself, to achieve this. A social cost-benefit calculation is made, using the IMF estimate of \$375 billion monthly loss to the world economy due to COVID-19. The economic and health benefits of this justify public "at risk" investment in manufacturing capacity for potentially successful vaccine candidates. They propose a \$137bn investment in manufacturing capacity for 18 vaccine candidates of which \$92 billion is push funding of manufacturing capacity. The balance is pull funding, a commitment to buying the products manufactured<sup>8</sup>.

<sup>6</sup> CEPI's mission is to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks and was developed as a collaboration between the Wellcome Trust and the Gates Foundation in 2017. Before COVID-19, it had given grants to teams developing vaccines for MERS, Nipah and Lassa specifically, and grants for developing vaccine technology for rapid development against unknown pathogens in general.

<sup>7</sup> This and other quotes are taken from the presentation Incentive Design to Accelerate a COVID-19 Vaccine, available at <https://drive.google.com/file/d/1JPNiV7LGnSUUDcXY0sK3VdgpJnR2XH2t/view>.

<sup>8</sup> We note that a related proposal by Snyder et al. (18) uses a model by Chaturvedi et al. (19) to argue for an advance purchase pull mechanism to incentivise both late stage development and manufacturing. Using a demand function that combines health impact (with a DALY valued at 3xGDP per capita) and economic impact, but with reserve prices below maximum benefit, they end up with an optimal ex ante expected award of \$11.6 billion per successful candidate. With a 30% chance of success this is \$37.7 billion ex post.

6. **The Gates Foundation.** The Gates Foundation's priorities and approach has been reported in an internal White Paper which advocates for a mix of funding totalling \$38 billion to \$74 billion (20). This includes: a \$2 billion push for CEPI to support vaccine development; \$12 billion push to scale up capacity to manufacture bulk vaccine and package it; and \$24 to \$60 billion in grants to cover procurement costs to assure suppliers of low- and middle-income country market demand. The White Paper states that: "The scope and urgency of the current pandemic is also such that at-risk decisions to scale manufacturing capacity will need to be made early in the R&D process, which will in turn require assurances of demand and availability of funding for procurement to pay for finished products."
7. **The EU proposal.** The EU is proposing<sup>9</sup> use of its joint procurement powers to secure sufficient production of vaccines in the EU and thereby supplies for its Member States through Advance Purchase Agreements (APAs) with vaccine producers via its Emergency Support Instrument (ESI) which will comprise (i) right to buy a specified number of doses at a given price in a given timeframe in return for (ii) funding part of the upfront costs faced by them. There is EUR 2.7bn available under that scheme. Early engagement between the EMA and manufacturers is already underway.<sup>10</sup> The Commission acknowledge that "the failure rate of vaccine development is high. There is a very real risk that none of the supported candidates will be successful. However, the value of earlier access to a vaccine is enormous, in terms of lives saved and economic damage avoided. This makes the risk worth taking. This proposed framework is therefore an insurance policy, which transfers some of the risk from industry to the public authorities in return for assuring Member States equitable and affordable access to a vaccine, should one become available."<sup>11</sup>
8. **Gavi COVAX Facility.** As we noted in the WHO Accelerator, Gavi is proposing a Gavi Advance Market Commitment for COVID-19 Vaccines (Gavi COVAX AMC) (21). Relabelled a "COVAX Facility"<sup>12</sup> this is a "pull" design complementing CEPI's push funding for promising vaccine candidates. We discuss this proposal in detail later.
9. **The BBAMC.** The global health policy team at CGD have, together with several of us from the Office of Health Economics, and Hannah Kettler from PATH, developed a concept we refer to as a benefit-based advance market commitment (BBAMC). We discuss this in detail later.

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Average ex post program spending is \$110.4 billion on 2.9 successful vaccines with an average of 2.2bn doses and an average price of \$50 per dose. In this scenario, net health and economic benefits total \$2.8 trillion.

<sup>9</sup> EU Strategy for COVID-19 vaccines. Published 17<sup>th</sup> June 2020. Available at

[https://ec.europa.eu/info/sites/info/files/communication-eu-strategy-vaccines-covid19\\_en.pdf](https://ec.europa.eu/info/sites/info/files/communication-eu-strategy-vaccines-covid19_en.pdf)

<sup>10</sup> The Joint Action will involve a central procurement process giving all member states the option to purchase vaccines through this route. It avoids competition between member states and increases EU leverage when negotiating with industry. Vaccine policy remains the responsibility of member states. It goes on to say:

- APAs can include other "relevant conditions (such a production capacity in the EU, possible availability of production facilities for the manufacturing of other vaccines or medicines in case of failure, or liability arrangements.)"
- Once a vaccine is successful member states can acquire under the terms of the APA.
- Allocations between member states would be according to a "population -based distribution key."

The Commission will enter into an agreement with participating member states to formalise their reciprocal commitments.

<sup>11</sup> We can note that in respect of global initiatives, the "Commission is ready to support the development and operation of an inclusive international COVID-19 procurement mechanism that facilitates early and affordable access to vaccines and other tools for all who need it across the world. With sufficient scale and scope, such international mechanism could become the world's insurance policy against pandemics".

<sup>12</sup> It has the full title "The COVID-19 Vaccine Global Access Facility". See COVID-19 Vaccine Global Access (COVAX) Facility. Discussion Document 11<sup>th</sup> June 2020. Gavi.

Before we discuss these different initiatives in more detail, we should reflect briefly that a lot of money is being proposed to be spent. Over \$230 billion in total. Much of this is duplication. We can, however, compare that with the IMF estimate of economic damage alone, which is \$375 billion *a month*.

### 3. A Framework for Understanding What Works and Applying it to Getting a Vaccine for COVID-19

#### **PUSH VERSUS PULL INCENTIVES**

We have distinguished between push incentives which reduce the costs to organisations of R&D and of building manufacturing capacity, and pull incentives which seek to compensate for the possibility of the market not providing enough of an incentive to “pull” through R&D and manufacturing capacity investment. To understand what is needed in the case of getting a COVID-19 vaccine, it is helpful to explore the use of push and pull incentives in different settings.

#### **R&D INCENTIVES IN HIGH-INCOME COUNTRY MARKETS**

In the market for a vaccine in a high-income country (HIC) pharmaceutical companies research and develop, at risk, vaccines for diseases affecting HIC populations. They do this with the expectation that, if the vaccines work, they will be able to sell them to HIC health care systems. Payers (whether governments or insurers) will buy if they offer value. There may, of course, be competition and there may be negotiation on price. There will be academic research in understanding the disease, and in understanding whether different approaches to developing a vaccine are possible. This has the effect of reducing the costs of pharmaceutical industry research and development by reducing likely failures, which is a major source of cost. We can think of this as early stage “push” which, although not direct funding, potentially reduces costs for all companies. But buying power in the market “pulls” investment through development, manufacture, and delivery.

#### **PUSH AND PULL FUNDING IN LOW-INCOME COUNTRIES**

Introducing these same vaccines to low-income countries (LICs) is more difficult because many of these countries do not have money to buy vaccines. Hence the creation of The Vaccine Alliance, known by the shorthand Gavi, buying on behalf of LICs. Buying power from Gavi (in this case from donors funding Gavi) pulls investment through<sup>13</sup>.

Some diseases do not have a big enough HIC disease burden to provide an R&D incentive to invest. Malaria and TB are good examples. There are other neglected tropical diseases, like Leishmaniasis and Chagas disease, that attract even less investment. Vaccines for pandemics (such as Ebola) and for biological warfare agents (such as Anthrax) also fit into the same economic category. Here we see both “push” and “pull” funding.

#### **PUSH VS PULL**

There has been a debate as to the appropriate balance of push (which reduces R&D costs and failure rates, so reducing scientific risk) and pull (creating the market and so reducing commercial risk). There is no reason why a large enough market will not stimulate R&D risk taking investment by the private sector. The question has been, in the global health

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<sup>13</sup> Two other policies have been key: (i) differential pricing, so prices paid are close to manufacturing cost – returns on R&D are obtained from HICs and some MICs and (ii) organising Gavi’s procurement programme to reduce the time period between launch in HIC markets and vaccines being available in LICs.

arena, what is the most cost-effective use of donor resources? The reality has been that budget constraints rather than efficiency may have held sway. A pull commitment requires a bigger up-front commitment and more cross-organisation coordination, even though it does not have to be spent immediately – we have to wait for the products – whereas push can be done one bit at a time.

A benefit of push funding in a pandemic for which we were not prepared is, of course, speed. The problem however, is that once the push funding goes beyond investment in the early stage public good of creating knowledge about disease mechanisms, it involves the donor picking winners.

An example of the problem of ‘picking winners’ is with product development partnerships (PDPs). The Gates Foundation set up PDPs in neglected disease areas in order for them to develop portfolios of pipeline products. It sought to deal with the product selection challenge by expecting the PDPs to behave as venture capitalists with a social purpose, i.e. to build a portfolio of candidates that offered potential. They ‘invested’ the capital at risk and were seeking to leverage the private sector to help deliver value. But the consequence has been some challenges in making sure that products that do get to market are taken up and used by governments. This is because the emphasis is on “what can we push through to market?” rather than “what do health systems actually want, or are able, to use?”

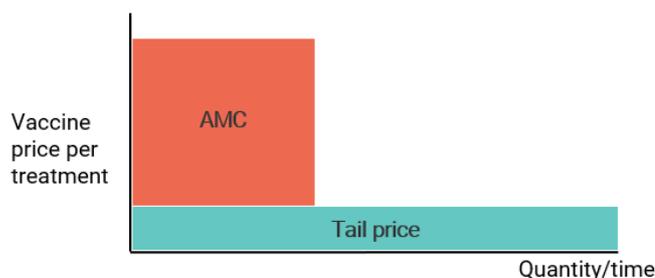
On the other hand, pull funding is less used by donors, arguably for the reasons we set out above. However, pull funding has previously been used in the context of global health pandemic preparedness. In the case of Ebola, development of the Ebola vaccines up to 2014 was led by governments because of the national security concern about the bio-weapon threat Ebola posed. Vaccine candidates were then licensed or acquired by companies (Merck, Janssen and GSK) during the early stages of the 2014 West Africa Ebola outbreak. Gavi promised an advanced purchase commitment for any vaccine in at least phase 1 during the 2014-16 outbreak. The pull mechanism used by Gavi in 2016 ensured that there was a stockpile of vaccine candidates ready for a subsequent outbreak in 2019. At the start of this outbreak, stockpiled doses were licensed for compassionate use, and trials were jointly funded by multiple donors. At the end of 2019, a Gavi pull fund of \$173m (to run from 2019-2025) was established to fund a stockpile of 500,000 doses, to be made available free-of-charge to the low- and middle-income countries affected (22).

### THE ADVANCE MARKET COMMITMENT (AMC)

The most well-established pull funding mechanism is the advance market mechanism (AMC). The AMC was conceived as an idea to promote research and development for both early stage and late stage products (23). The first use of the AMC mechanism was for a “late stage” pneumococcal vaccine already developed for HICs. The key objective was to shorten the typical 10-15-year gap before the vaccine was available in LICs (24). \$1.5 billion was raised towards the AMC from 5 donor countries plus the Gates Foundation. Initially two suppliers, GSK and Pfizer, were given AMC contracts. Companies could see the \$1.5bn market commitment and the pressing need for the vaccine. Hence, they had a high expectation that they would be contracted to supply (25). The Serum Institute of India has now joined, (after 10 years and considerable support from funders to be in a position to join the AMC) with a pneumococcal vaccine that secured a share of the AMC in the most recent tender (26)<sup>14</sup>.

<sup>14</sup> The remaining \$167m that had not been allocated was recently transferred to the Gavi COVAX AMC pot.

Commitments ensured that manufacturers had to provide the pneumococcal vaccine at a price no higher than \$3.50 per dose (referred to as the tail-price ceiling) which was paid by the GAVI general fund<sup>15</sup>. Manufacturers also received a \$3.50 'top-up subsidy' on the first 21% of doses in each contract which was paid through the \$1.5 billion AMC fund, i.e. they were paid \$7 per dose for these initial doses. We illustrate this in Figure 1.



**FIGURE 1: ILLUSTRATIVE SCHEMATIC FOR THE PNEUMOCOCCAL VACCINE AMC PRICING SYSTEM.**

SOURCE: Adapted from MVI Advance Market Commitment for Malaria Vaccines (2005)

The AMC used a Target Product Profile (TPP) to ensure that participants met a certain quality standard. The TPP was, however, used as a qualifying threshold instead of a tool to differentially reward better quality vaccines. There was, however, a quality difference between the two vaccines. The planned co-payment from countries was dropped, and for this reason, most countries requested the superior, Pfizer, vaccine as there was no differential in price faced by the country.

Overall, the mechanism was effective. More than 150 million children have been immunised, saving an estimated 700,000 lives (24).

The essence of the AMC pull concept was originally intended to:

1. Create a market for a new vaccine with guaranteed advance market commitments, i.e. not initially to any specific company, unlike advance purchase contracts.
2. Ensure entry into the scheme requires meeting a minimum TPP
3. Guarantee (to the companies) a price above cost to provide a return on innovation
4. Guarantee (to the buyers) a tail price close to marginal cost once appropriate returns on R&D and manufacturing investment have been made.
5. LICs supplied at the tail price (which in practice is paid for by Gavi donors)

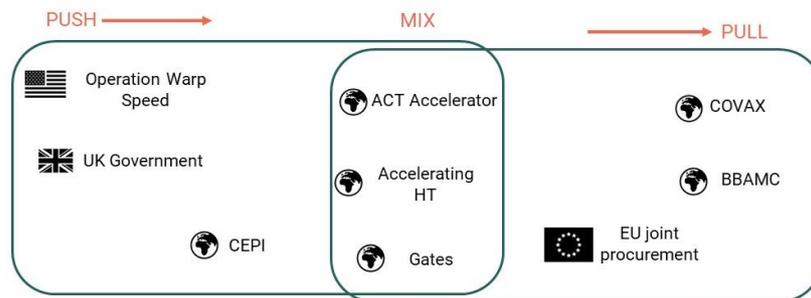
We want to argue that AMC style pull mechanisms are better than reliance on push, because it means that those making the investment only get a return if the product is

<sup>15</sup> The tail price ceiling, intended to be an upper limit, initially became the de-facto price as both companies set the price at the ceiling for the first two tender rounds. This has now changed. The Serum Institute price, for example, represents a 43 per cent reduction from the initial Gavi tail price of \$3.50.

successful. But, as noted, there are occasions on which the need for speed means that some initial push funding is required.

More generally, we can note that Kremer and others have argued that the AMC mechanism may be most effective when it is promoting research and development as well as manufacturing and delivery (23,27,28). The key difference is in the nature of the contract between the buyer (in this case pooled by Gavi) and the vaccine developer. In the 2005 report (23) an early stage AMC for a malaria vaccine was modelled with an initial framework agreement in which the funders (buyers) guaranteed a price for a certain volume. Chalkidou et al. (2020) set out such an AMC in which each buyer makes a price and volume commitment which is aggregated by the organising secretariat (29). Kremer et al. 2019 (28) find that a framework AMC is more efficient than bilateral supply commitments for early stage candidates (i.e. where development as well as manufacturing capacity expenditure is needed) when there is enough competition (more than 3 or 4 developers). The AMC did not envisage bilateral contingent contracts conditioned on a product being invented, of the sort that we have for COVID-19 vaccines. This is important as we argue that schemes creating an Advance Market Commitment for COVID-19 vaccines provide the most useful buying mechanism for us to consider.

We now group the COVID-19 proposals in Figure 2 according to whether they are push, pull, or a combination.



**FIGURE 2: SCHEMATIC SHOWING THE ARRANGEMENT OF COVID-19 SCHEMES OFFERING PUSH FUNDING, PULL FUNDING OR A COMBINATION OF BOTH.**

Two of the proposals, the GAVI COVAX and the BBAMC, are proposing an AMC-style pull incentive. We compare these two proposals in Section 5 below. But in order to design the right AMC for the COVID-19 vaccine, we have to understand the specific challenges in developing and manufacturing a COVID-19 vaccine, and they are very different to the pneumococcal challenge. We discuss these in the next section.

## 4. Challenges of COVID-19 Vaccine Development

There are three main challenges relevant to the race for a COVID-19 vaccine.

### **FIRSTLY, IT IS NOT EASY TO GET A VACCINE. FULL STOP.**

We don't have a COVID-19 vaccine. And we might never have one. If we look at the top 3 infectious killer diseases in the world, despite a lot of donor and private investment:

1. We don't have a vaccine against HIV, despite looking for one since the 1980s (more than 30 years ago) (30,31). The first large HIV vaccine trial reported results in 2003, 17 years ago.
2. We only recently got a vaccine against malaria. A major achievement after more than 20 years of development (32), but unfortunately it has limited effectiveness (33,34).
3. And we still only have the old BCG vaccine for TB despite years of trying to get a new one (35).

Of course, it is a bit circular – if we had effective vaccines that were widely available, they would not be the top 3 killer infectious diseases, and these are not infectious diseases with close similarities to COVID-19. If we look at diseases that are more closely related to COVID-19, like SARS and MERS, however, we do not have vaccines for these coronaviruses either. There are several virus-specific challenges including (36,37):

- Coronaviruses do not generally naturally induce long-term immunity.
- The vaccine needs to generate immunity in older people which is difficult.
- There may be safety concerns with coronaviruses around vaccine-induced enhancement of antibodies to achieve immunity.

If it is possible to overcome these specific challenges, there is a possibility with all vaccines that safety issues emerge after the vaccine is licensed. This happened recently with a Dengue vaccine where life threatening safety problems were only discovered after a million children in the Philippines had been vaccinated<sup>16</sup>.

Once we accept the inherent uncertainty around safety, the significant scientific barriers to vaccine development make it hard to get portfolio diversification. This raises the question as to how diversified the global COVID-19 vaccine candidate portfolio is? Shnaydman and Scannell have explored this (41). Based on their work, Scannell writing in the FT on May 10th (2020) contrasts (39):

- on the one hand “a bunch of mediocre vaccines, each with a mere 10 per cent chance of working, but they were likely to fail for entirely different reasons.” If we put 20 into trials and they are all independent, the likelihood of failure is 0.9<sup>20</sup> (= 0.12158), i.e. we have an 88% chance of success.
- with “a set of excellent vaccine candidates, each with a 40 per cent chance of working, but all likely to fail for the same reason. Here, we would be stuck with a 60 per cent chance of failure no matter how many we tried.” An example of this might be if they are all aiming at the same target and it turns out not to be the right one.

He and, separately, McDonnell et al. (40) have argued that the current portfolio may contain too much emphasis on candidates with ease (speed) of development. This bias is exacerbated by the dependence on substantial push funding which requires funders to

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<sup>16</sup> Dengue is a virus for which vaccine development has been complicated by the natural history of the disease. There are four serotypes of dengue that co-circulate in endemic areas. The majority of dengue infections cause Dengue Fever (DF) characterised by mild, flu-like symptoms. Dengue infection can also cause much more serious Dengue Haemorrhagic Fever (DHF) and the risk of this haemorrhagic form of the disease increases if someone has had a prior infection by a different serotype. In 2017, 1 million children in the Philippines were given a Dengue vaccine, Dengvaxia produced by Sanofi. It took years to discover that the vaccine increased the risk of DHF particularly in sero-negative children (38).

pick winners. The understandable but unhelpful bias for 'quick winners' is demonstrated by CEPI's funding calls for candidates that can be developed in 12-18 months.

Analysis of the COVID-19 portfolio demonstrates this. Shnaydman and Scannell modelled the portfolio as of April 2020 and found "based on our crude parameterization, there is a ~40% chance that no vaccine is approved within 18 months, a ~67% chance that no more than one vaccine is approved, and a ~93% chance that no more than two vaccines are approved."(41)

Funders are not the only ones picking winners, with a number of high-income governments pursuing a 'vaccine nationalism' approach. On this point, Scannell adds "Diversification is also undermined by therapeutic nationalism whether in a weak form (such as the well-intentioned backing of national winners) or a strong one (a bias to supplying the domestic market)."

We also have CEPI, the Wellcome Trust, and the Gates Foundation involved in investment decisions. But, as Scannell puts it "If we look at the Covid-19 front-runners, individually rational choices may have concentrated risk in terms of the vaccine platforms that are being used and the specific pieces of viral machinery targeted. ... An overt move towards diversity is necessary, even if individual projects look less attractive". Shnaydman and Scannell emphasise this, stating that "governments and/or agencies such as CEPI or BARDA "should ideally support a portfolio of projects that balances, among other things, speed to market, vaccine platform risk, vaccine-specific risk, clinical trial capacity, regulatory capacity, and manufacturing capacity."(41)

We need to consider the possible consequences of being in an environment where the key R&D funding decisions not being made by biotech and pharmaceutical companies thinking of the returns they can get from developing and introducing an effective vaccine, but by international agencies and governments concerned about speed of development, ease of manufacture or (understandable) political preference. The private sector does not always get the balance right, but this approach may not lead to an optimal portfolio.

We may find that none of the lead candidates are successful or meet all requirements, so that more clinical development is needed. The timelines in that case will go out well beyond 2 years. But it is possible that one or more of the lead candidates delivers a vaccine. It is important to be optimistic.

As of the 14<sup>th</sup> of July, there were 23 candidates in clinical development and 140 candidates in preclinical evaluation (42). These vaccines are being developed by a range of different types of organisation. This includes academic led groups (e.g. Oxford, Imperial), small biotech companies (e.g. Moderna, Inovio), and large multi-national pharmaceutical companies (e.g. GSK/Sanofi). Crucially they cover 9 different vaccine technologies ranging from established technologies, like adenovirus-based vaccines, to novel technologies, like mRNA vaccines (43). Of the 23 candidates in clinical development, 8 are being developed by Chinese teams and 4 by teams based in the USA. The remaining 12 are being developed by teams based in the UK, Australia, Japan, Korea, Canada, Germany and Russia.

## SECOND, MANUFACTURING SCALE UP IS HARD

The world needs this vaccine quickly at an unprecedented speed and scale. There is already a shortage of supply for established global vaccines and only a small number of large-scale and established vaccine manufacturers. Vaccine manufacturing is challenging and expensive for a number of reasons (44):

### High process variability

- Vaccine manufacturing is predominantly based on biological not synthetic processes which are highly variable<sup>17</sup>.
- Because of this potential variability there is also high regulatory complexity<sup>18</sup>.

### Long lead-times

- Lead times can vary from 6 months (for egg-based influenza vaccines) to 3 years (pentavalent combination vaccines (45)) and demand for vaccines is usually estimated 3 years in advance to allow for managing production.
- New vaccine technologies could theoretically lead to vaccines being produced much quicker because of the smaller amounts of antigen needed and the possibility for fully synthetic manufacturing processes (46).

### High up-front and ongoing costs

- Facilities in HICs can cost between \$50M and \$500M depending for example, on the vaccine and the complexity of the process, and the level of automation<sup>19</sup>.
- Vaccine production platforms are diverse. While components in the process may be common (for example bioreactors, filters, chromatography, fill and finish) the arrangement of components in the process may be different and the scale of each component may vary, which all lower fungibility. Adapting a bioreactor for a different vaccine may be technically possible but will be time consuming. For example, combination vaccines are usually manufactured across several facilities and then combined later (45).

While COVID-19 highlights the transformation in vaccine development<sup>20</sup> that has taken place in the last few years, the specific requirements for a COVID -19 vaccine further complicate the manufacturing challenge:

<sup>17</sup> The raw materials for vaccines are also often produced through biological processes potentially adding additional variability. To ensure consistency, highly skilled workers and strict Quality Control (QC) are needed.

<sup>18</sup> Changes to manufacturing processes (e.g. new raw materials, new equipment etc) usually require regulatory approval and may require clinical trials. This means there is a trade-off between speed to market and optimising the manufacturing process to save costs over the long life of the vaccine in the market. In addition, Manufacturers who want to sell through pooled procurement mechanisms (e.g. PAHO/UNICEF) also must go through WHO prequalification.

<sup>19</sup> While up-front costs can be lower in low resource settings, other ongoing costs can be higher (e.g. cost of importing raw materials, cost of paying highly skilled expat employees). Raw materials are usually expensive and scarce.

<sup>20</sup> This transformation centres around the development of platform technologies that are more generalisable than traditional vaccines and some of those platform technologies allow for fully synthetic vaccines. These two breakthroughs, platform technologies and synthetic vaccines, along with preparedness investment in coronavirus vaccines from CEPI, enabled the COVID-19 pipeline to be filled with potential candidates just weeks after the genome was shared with the world.

1) Platform technologies allow a 'plug and play' approach to vaccine development, where the core vaccine is standardised, and the disease specific component can be added very quickly. This means that one platform can be the backbone of lots of products. This is exemplified by Janssen's AdVac technology which is being trialled for COVID-19 but which is also the backbone of their licensed Ebola vaccine and phase II HIV candidate.

2) Synthetic vaccines such as RNA/DNA vaccines that can be manufactured using synthetic RNA/DNA synthesis techniques. These processes now rely much less on the biological processes fundamental to other vaccine types. This means that there is a potential to manufacture billions of vaccines very quickly to satisfy global demand. However, ~70% of the global vaccines are produced by developing country vaccine

We need vaccines at unprecedented speed: Normally ‘we’ accept a longer wait for delivery of innovation (certainly for low- and middle-income countries). Even in HICs, we often trade off taking time negotiating price versus the health gain we could get from immediate use. This is usually because there are competing claims on the health budget. Companies therefore have time to build up manufacturing capacity and the innovator has an incentive to ensure that it has enough of a drug or vaccine available to be used when payers decide to adopt. In some cases where we do need an instant response we can stockpile – as we now do with Ebola vaccine and with Anthrax vaccine.

There are no related vaccines: There are no existing coronavirus vaccines, so there is no manufacturing capacity to rapidly repurpose for COVID-19. If we were in the middle of a H1N1 pandemic, manufacturing capacity would not be as much of a challenge given existing capacity and technology for seasonal influenza vaccines (47).

There is large diversity of vaccine platforms in the COVID-19 pipeline: Given low fungibility of vaccine manufacturing, the diversity of vaccine technologies is a barrier to rapid scale up (43). The pipeline contains candidates covering 9 different vaccine technologies and there is very low fungibility across them. Building manufacturing capacity at risk that is entirely ‘platform agnostic’ is not possible, therefore it will either be extremely expensive, or require some ‘hedging’ (i.e. picking) of winners.

There is little experience globally in manufacturing using novel vaccine platforms: Expertise is not widespread for manufacturing novel vaccines using mRNA and DNA based platforms (e.g. mRNA/DNA/VLP based). There are likely to be very few low- and middle-income country manufacturers who have the expertise or capability to manufacture these vaccines and the companies developing these vaccines (mainly small biotechnology companies) are not experienced in working with manufacturers outside of HICs.

We want companies to start manufacturing the vaccine before they know if it works. Hence the buying mechanism has to cover both a mechanism for getting vaccines developed, *and* a mechanism for getting them manufactured.

### THIRD, DEMAND IS UNCERTAIN

It could be argued that it is obvious that there is a market for a COVID-19 vaccine in enough HICs and UMICs to ensure a market incentive for private investors – especially with the push funding already invested. While the demand is potentially large in the very short term, however, it is much more uncertain in the middle-long term.

Like its cousins MERS and SARS, COVID-19 could simply die out. Alternatively, herd immunity could build over time whilst the vaccine is being developed. Governments initially keen to vaccinate their whole population might become less committed to buying a vaccine. The economic recession could lead to drastic cuts in aid and domestic healthcare budgets that lead governments to shirk earlier commitments, while other technological breakthroughs (e.g. a cost-effective “cure”) could undermine the anticipated

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manufacturers. The expertise for manufacturing these very novel vaccines is very limited globally, but especially with developing country manufactures, many of whom are unable to develop other complex vaccines such as combination vaccines using traditional technology. Therefore, while these transformations make it theoretically possible to develop and manufacture significant quantities of vaccine quickly, there are other practical barriers which add complexity. The commercial and IP ‘baggage’ that platform vaccines bring means that the traditional access paradigm based on IP sharing to supply low and middle-income markets is more costly for developers and the complexity of these novel vaccine technologies means that in practice the pool of manufacturers able to manufacture this vaccine is much smaller.

size and nature of a vaccine market. These uncertainties become more pronounced the longer it takes to develop a vaccine.

Gavi is aiming to procure 2 billion doses by the end of 2021 plus an 'emergency stockpile' of 200 million doses with a focus on supplying vaccines for 20% of a country's population, prioritising health care workers and other vulnerable groups in eligible low- and lower-middle income countries (48). However, it does not yet have funding commitments from donors that would enable it to make these procurement commitments.

## 5. Exploring the Proposals for an AMC: The Gavi COVAX AMC and the BBAMC

We are seeing an outbreak of vaccine nationalism with countries going it alone and seeking to make deals on price and volume, using push funding to get access rights. We see willingness to take away intellectual property rights, such as threatening compulsory licensing. Whatever means are deemed necessary to get citizens access to a vaccine. Whilst this is an understandable political response it may be self-defeating:

- Countries may find that backing the national vaccine 'horse' is not successful. Indeed, we have argued that not cooperating on developing a global portfolio may increase the risk that the vaccine portfolio is unbalanced and no vaccines succeed;
- Most countries are not funding their own vaccine candidates, have no manufacturing capability and don't have the buying power to get to the front of the queue on their own.
- Threatening to seize intellectual property makes it less likely that we get a vaccine as it will discourage at-risk private investment in vaccine development.

In contrast, getting global or regional coordination or consistency of approach will send clearer signals to developers about demand (both prices on offer and volumes needed). While there has been a significant delay in global coordination, things are starting to change with the WHO ACT vaccine pillar and regional initiatives such as the EU joint procurement proposal. At a minimum we need a coordinated response for vaccine provision for the 3.7 billion people (50% of the global population) who live in LICs or LMICs<sup>21</sup> that makes vaccines for these populations available at cost, without undermining the intellectual property rights of those developing the vaccines. We need to pull vaccines through the pipeline to complement the push funding going into R&D and manufacturing. Our assessment is that this is best done through an advance market commitment (AMC).

In this section of the paper, we set out: The elements of the Gavi COVAX Facility and the BBAMC concept; and then, in the next section consider how the Gavi COVAX Facility could incorporate elements of the BBAMC to become a more effective tool to deliver vaccines.

<sup>21</sup> Of the world's population 9% (~705 million) live in low-income countries, 40% (~3 billion) live in lower-middle income countries, 35% (~2.7 billion) live in upper-middle income countries and 16% (~1.2 billion) live in high-income countries (49).

## THE GAVI COVAX FACILITY

The COVAX Facility is a pull mechanism<sup>22</sup> intended to complement CEPI push. In other words, it has been designed to provide a pull mechanism for vaccines that are recipients of CEPI push funding for either clinical development or to create manufacturing capacity. The COVAX pull is not intended to motivate risk capital for either development or manufacture. It involves “two types of pull mechanisms”:

- **“manufacturer-specific contingent volume guarantees to** procure vaccines that meet the agreed WHO Target Product Profile”.
- **“a market-wide demand guarantee**, i.e. an AMC. The discussion document states that “in addition to securing supply, the COVAX Facility intends to support a continued pipeline of improved products coming to market.” and that “pull incentives generally encourage successful development and focus on addressing commercial risk.”

The emphasis is, however, on the short term “manufacturer-specific volume guarantee”, rather than the longer term “market-wide demand guarantee”. Explicitly, “the pull instrument will be structured as a market-wide demand guarantee, out of which multiple manufacturer-specific volume guarantees will be made. For the initial period (2021-2022), the majority of this market-wide demand guarantee will be issued as volume guarantees on specific products to individual suppliers. For the later phase (after 2022), it is expected that the majority of the guarantee would remain unallocated, allowing introduction of improved products over time.” This may reflect the perceived importance of getting bilateral guarantees to buy certain volumes, but it neglects the need to get more candidates coming through.

We can note that, whilst in principle “all countries are invited to participate<sup>23</sup>”, it is primarily a scheme aimed at LICs and LMICs. Donor financial support for LICs and some LMICs would be available via Gavi<sup>24</sup>. It is essential that this population is addressed, but this leaves out the significant number of middle income and high-income countries that are unable to support national vaccine candidates who will be at the back of the queue for bilateral deals. It is also important that HICs with candidates and bilateral agreements are able to join. This will help to shape an overall market and to establish rules about the priorities for the allocation of vaccine supplies. Gavi state that these would follow WHO policy recommendations. Some negotiation may be necessary to get more countries on board.

So how will it work? The financing structure, legal agreements and governance mechanism have still to be developed but the Facility will negotiate with manufacturers for volumes and prices via an Expression of Interest. It looks as if there would be legally binding commitments made by Gavi to purchase from specific manufacturers. These

<sup>22</sup> Our comments are based on the COVID-19 Vaccine Global Access (COVAX) Facility. Discussion Document 11<sup>th</sup> June 2020. Gavi.

<sup>23</sup> Self-financing HICs and UMICs would “make a binding financial commitment to purchase doses” and make some up front “down-payments against future vaccine supply” which “will enable the Facility to enter into advance purchase commitments for future vaccine supply” The UMICs would have access to multilateral development bank (MDB) loans to support their participation. It is “a risk management mechanism” designed to allow countries “to enter a joint pool for securing and procuring vaccine doses” and “reducing risk for manufacturers concerned about investing without assured demand.” The working assumption is that some countries will have bilateral agreements with manufacturers. But these candidates may fail. Access to the Facility would come on top of bilateral agreements for both countries and manufacturers.

<sup>24</sup> Seed funding from OECD country ODAs of USD \$500m was pledged at the 4th June launch. Much more is needed.

would be backed by commitments made to Gavi by purchasers such as UNICEF, PAHO and individual countries<sup>25</sup>. It is possible that the EU could be another regional grouping operating under the scheme. However, it does not create a market. To do this Gavi would need to be guaranteeing an overall market size given the country commitments on its “book”, not making large contingent volume commitments to each individual manufacturer.

The downsides of the COVAX Facility as currently proposed are:

**1. It does not incentivise development.** It assumes that the push funding model via CEPI (and others) can deliver a vaccine of the required quality. According to Annex D, the CEPI worst case scenario is that one vaccine hits the target. With 9 candidates, 1/9 is over a 10% probability of success which is twice what a recent NBER paper calculated that public sector push has achieved in previous emerging infectious disease research investments.

**2. It does not incentivise development of better vaccines.** It is cost-based rather than value-based. Pricing will “be negotiated under the expectation that manufacturers seek minimal returns in the near term” [i.e. cost-based] and “there could be a flat price from manufacturers” which will take into consideration any other direct financial support received by manufacturers” (i.e. push funding). There is no value-based pricing but the paper says that “Beyond the near term, pricing would evolve to a traditional tiered pricing approach<sup>26</sup>” (presumably around a weighted average cost price). There is no differential reward for better vaccines. Indeed, there is no mention of using HTA to assess the value of any vaccine to participating COVAX countries. As long as (all or some part of) the WHO TPP is met then a cost-based price is paid. But success is not linear. A vaccine that achieved the WHO TPP lower end of 50% efficacy (and which is apparently not necessarily

<sup>25</sup> “Upon availability of doses, vaccines will be procured via **existing procurement mechanisms** (eg UNICEF Supply Division, PAHO Revolving Fund, EC, individual country procurement mechanisms).” It is not clear what this means, but it may mean that these groupings agree the commitments on behalf of their members and are legally responsible to Gavi for honouring them.

<sup>26</sup> It is worth setting out the pricing proposals in some detail. The note states that “the Facility will adopt the following **pricing principles**:

- Vaccine prices may reflect **the range of cost of goods (COGS), vaccine profiles, developer and manufacturer profiles, levels of support received and risk incurred** during development.
  - Vaccine prices may reflect different **time periods in the disease evolution and associated variations in market conditions and commercial opportunity**. This acknowledges the broad willingness from suppliers to consider the vaccine as a global public good in the short-term, to meet global requirements for priority populations, and to evolve later to a more market-based approach. Given the pressing public health need, it is expected that manufacturers would seek **minimal returns**. Such a model could provide incentives to as wide a range of countries as possible to join the COVAX Facility for the short-term period, while establishing a blueprint for a future lower price for LICs/LMICs.
  - Vaccine prices may be tiered, reflecting countries’ varying **ability to pay**.
  - Both the Facility and suppliers are expected to adhere to **transparency principles**. The Facility will expect from manufacturers to provide full visibility on other external funding received and will provide countries with the pricing of all participating vaccine candidates’ (to the extent that such information can be shared).
- Based on these pricing principles, the Facility proposes a **mixed pricing approach that will evolve over time**:
- Short-term period to reach priority populations and control the pandemic: **A flat pricing strategy (with firms able to set their own price, which then applies across countries participating in the Facility) will be encouraged**, given existing bilateral agreements between a number of countries and manufacturers and broad expectations to price the vaccine as a global good during the short-term period. Such a pricing structure should incentivize broad country participation in the Facility. However, some manufacturers may prefer tiered pricing; **the Facility will accommodate that request** if the price levels offered for each tier are considered suitable. If a flat pricing strategy is proposed by manufacturers, **a cross-subsidization mechanism may be applied** to establish differential pricing charged to countries to account for varying ability to pay.
  - **Beyond this initial short-term period, the market is expected to evolve towards a traditional, market-led, tiered pricing approach** (noting that the Facility, itself, will be time-limited).

the WHO TPP's efficacy floor—see Footnote 3 above) would require unrealistic assumptions to achieve immunity in countries such as the USA(50).

**3. It is not at all clear that a market is being created that reduces risk for both countries and (successful) manufacturers.**

Although it takes the pragmatic view that countries will sign manufacturer specific bilateral deals outside of the COVAX Facility, it is not at all clear that a market is being created that reduces risk for both countries and (successful) manufacturers outside of these bilateral deals. Instead we seem to have a series of bilateral agreements (termed “advance purchase commitments with manufacturers”) within a framework set out by Gavi and at prices negotiated by Gavi. Gavi does not seem to be playing the role of an intermediary that is making a market by holding a “book” of country commitments to purchase vaccine and a corresponding “book” of offers to supply volumes with timelines, contingent on obtaining a product licence and meeting the WHO TPP criteria. Holding a book may be the intention, but it is not conveyed in the text as written. Gavi should be guaranteeing an overall market size given the country commitments on its “book”, not making large volume commitments to each individual manufacturer. Not unsurprisingly it goes on to say “it may be the case that volume guarantees cover volumes in excess of the targeted demand in order to hedge the Facility against failure of certain vaccine candidates. Appropriate financing instruments or risk transfer solutions will need to be considered to ensure that no unfunded liabilities arise from this approach and that financial losses would be minimised should vaccine candidate success rates be significantly different from their anticipated levels.” This comes close to saying that if there is over supply (we fortuitously have a lot of successful vaccines and manufacturing capacity pre-built for them) then suppliers cannot necessarily expect their contracts to be honoured. If this is the case, then the bilateral contracts will be of limited value. It would, we argue, be more sensible to recognise this problem by committing to guarantee prices and minimum volumes for the *market* rather than give separate guarantees for individual products which may not in practice be met. Developers then know that while prices and minimum volumes for the market are guaranteed, they have to compete for market share. We would argue that this is a more credible offer for both buyers and sellers.

The benefits of joining for self-financing countries (i.e. HICs and UMICs not expecting donor funding support) are also unclear. Gavi state that “Fully self-financing countries that join the Facility before early deals with manufacturers are concluded (date to be determined) will be able to access the ring-fenced volume for self-financing countries, while those that commit after this point would not have this assurance.” On the one hand, it makes sense to have a cut-off, to avoid a situation in which countries wait to see if the vaccine candidates they have priority supply deals with succeed, and if they fail, only then choose to join the international pooled market arrangement. An alternative would be for countries to enter COVAX offering commitments that excluded their bilateral deals. They might seek to self-insure against development failure by committing to buy more than they might need. Alternatively, they could be offered some form of associate status, whereby they supported the COVAX Facility by providing information on their own bilateral deals and expected volume requirements, but did not formally join the COVAX market commitment.

## THE BBAMC

The BBAMC<sup>27</sup> is based on the MVAC proposed for new drugs for TB, and in turn is an adaptation of the pneumococcal AMC with some important adaptations, the most important of which are that:

- (i) It uses value-based pricing rather than the cost-based AMC with a single price and purchaser.
- (ii) It is designed to stimulate R&D (as well as manufacturing) investment.

The benefit-based advanced market commitment (BBAMC) in our view builds on the strengths of the COVAX<sup>28</sup> proposals:

1. It incentivises both the clinical development of a vaccine as well as manufacturing supply investments. The BBAMC proposal is distinct in its focus on “pull” incentives for product development. We do not assume that current push funding mechanisms will necessarily be sufficient to bring the portfolio of safe and effective vaccines we need to market. The challenges inherent in vaccine development have largely been overshadowed by an emphasis on the need to scale up manufacturing rapidly<sup>29</sup>.
2. We are, however, likely to need complementary push investment to bring forward at risk manufacturing capacity investment by companies<sup>30</sup>. This can be accommodated.
3. We are likely to need a number of different vaccines. Assuming more than one vaccine proves sufficiently efficacious, the vaccine that best meets the preferred product characteristics (as detailed in the WHO Target Product Profile or TPP) would

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<sup>27</sup> A summary of the BBAMC in slide form can be accessed <https://www.cgdev.org/sites/default/files/BB-AMC-May-2020-ppt.pdf> . Additional material includes:

- “Leave No One Behind: Using a Benefit-Based Advance Market Commitment to Incentivise Development and Global Supply of COVID-19 Vaccines” available at <https://www.cgdev.org/publication/leave-no-one-behind-using-benefit-based-advance-market-commitment-covid-vaccine>
- “The Race for a COVID-19 Vaccine: An Overview of Current Proposals and Our Contribution in Bringing in the Missing Middle” available at <https://www.cgdev.org/blog/race-covid-19-vaccine-overview-current-proposals-and-our-contribution-bringing-missing-middle>
- “In the Race to Develop A Vaccine For COVID-19, Is A Pull For R&D Essential Or Optional?” available at <https://www.cgdev.org/blog/race-develop-vaccine-covid-19-pull-rd-essential-or-optional>

<sup>28</sup> And also a manufacturing push such as from CEPI or from Accelerating HT

<sup>29</sup> Attracting in private capital invested at-risk, but with manageable risk and the prospect of a commercial return. This needs to be done through pull funding. Push funding for early stage research can indeed be cheap and efficient; but the costs and risks grow for funders. There is also a risk of funders pursuing the sunk costs fallacy - “we’ve paid for it so far, let’s just keep going” leading to “we paid for it to be developed so now we ought to buy and use it.”

<sup>30</sup> We need manufacturing capacity to be built at risk. This can be done through a higher price for early entry. But this risks complicating setting a value-based price for the vaccine, and may incentivise accelerated development and introduction of a vaccine that is easier to manufacture, but less effective. We are therefore likely to need push investment to bring forward at risk capacity investment by companies. We set out how this can be accommodated in our BBAMC model.

receive a greater share of the total revenue commitment<sup>31</sup>. There would be competition, as in a normal vaccine market. To achieve this, we need to create an AMC rather than a network of conditional bilateral contracts.

4. Rewarding companies with prices that reflect value rather than cost is key. To this end, the TPP can be used not just to set a minimum entry requirement, but also as a basis for assessing value and therefore price.
5. Attracting HICs and MICs as well as LICs is key and not optional, building an advanced commitment that is not just funded by donor aid. This brings clarity on the size of a very uncertain overall global market. Of course, the poorest countries would not pay a value-based price but the tail-price. This both protects intellectual property rights and ensures populations get access to vaccines.
6. There is differential pricing as the advance commitments are built on value assessments done by national payers that are based on products' expected health related benefit and countries' health budgets which impact ability to pay for a new product.

As with the COVAX Facility

1. Push funding can be taken into account by either adjusting the price or adjusting the size of the advance market commitment made by the country<sup>32</sup>.
2. Low income country and lower middle-income country contributions should be met with donor support through Gavi.
3. Allocation rules of some form will need to be developed to ensure manufacturers are able to distribute product across the countries making up the commitment

In our view, for reasons we set out above, significant commercial uncertainty remains around demand in the medium to long-term and an AMC is needed. In our mind, credible pull incentives for development, alongside research push, are needed to further de-risk the development process for both payers (governments and donors) and suppliers (industry and investors), to crowd in private investments reducing the cost to HICs taxpayers, to share the risk of development between the government and the companies, and to inject payer accountability to the process. In particular, we are likely to need a number of

<sup>31</sup> In terms of target performance, companies are working towards the fairly widely defined WHO Target Product Profile (TPP), without explicit incentives to address market or population specific needs, including differential safety, effectiveness and cost-effectiveness of different vaccine profiles in different populations and geographies. But such performance attributes may well make all the difference in how quickly and effectively we can control the pandemic. The BBAMC mechanism would allow inclusion of more than one product meeting minimal TPP requirements. Provision will be made for a product offering more suitable characteristics for implementation in different contexts and populations. It also takes account of the likelihood that the first vaccine to get a product license may not meet all needed criteria (in terms of overall efficacy, or method of administration or safety) and multiple vaccines may ultimately be necessary to address challenges of efficacy and tolerability in sub populations or to address field conditions. The value assessment element of the BBAMC allows for the same product or indeed different products to command different prices and hence market share across different country contexts and epidemiological realities as they may meet local needs at differing levels (perhaps because of a differential safety profile; their effect on younger versus elderly multi-morbid populations; the need for cold chain; or administration complexity).

<sup>32</sup> Push funding (R&D push or manufacturing capacity push or both) for successful vaccine candidates only could count against a countries market commitment. Governments backing the wrong candidates have not partially met their commitment. It does not count. This will add to the incentive for governments to choose carefully and also to consider cross-government collaboration. Alternatively, early R&D push and early manufacturing push are taken into account in the arrangements for locking in value ex ante. This is an area that will need further discussion, but which can in principle be incorporated in a BBAMC.

vaccines. Therefore, it needs to be a value-based price rather than cost-based to incentivise the development of better vaccines and to avoid incentivising high cost low quality vaccines at the expense of lower cost, but better quality, ones. Current speed-focused models imply a winner-takes-all approach, especially to those who are not in the lead and there is little discussion of what would happen to second (and perhaps better performing or safer) entrants.

A BBAMC for a COVID-19 vaccine would work in the following:

1. **Early health technology assessment (HTA) establishes a value-based price on the assumption that the TPP was met<sup>33</sup>:**
  - a. The price would be “locked in” to provide overall market predictability.
  - b. The early HTA assessment would enable the size (price x volume) of each country’s advance commitment to be identified.
2. **The AMC is the aggregation of the individual commitments.**
  - a. These need to be guaranteed by a third party (such as the World Bank). This may be difficult in the case of a major HIC. However, a credible mechanism is needed to ensure that advance market commitments are honoured.
  - b. The BBAMC will offer value-based entry market commitments (country-specific tiered prices for guaranteed volumes) to developers that meet the minimum effectiveness threshold (as per the WHO TPP) as an incentive to keep many different potential innovators in the game post launch. This would hedge risk against late failure of one or more early candidates and against the possibility of safety risks after widespread deployment requiring restricted use or withdrawal from the market of the first entrant.
  - c. To access the purchase commitment, the successful innovator must agree that any volumes beyond the guaranteed commitment pool—up to a pre-agreed maximum or for a pre-agreed time period—will either receive a heavily discounted price (e.g., a 70 percent discount), close to cost (plus a margin), or be made available to local licensees.
3. **A mechanism to deliver manufactured vaccines around the world:**
  - a. As a condition of accessing this guaranteed market, governments would require the successful innovator(s) to license their vaccines out to other suppliers at low or zero cost, helping facilitate widespread scale-up across to LICs.

In addition, effective governance arrangements will be needed<sup>34</sup>. It is beyond the scope of this paper to illustrate how this might work in practice, but this information is contained in

<sup>33</sup> This would also determine the vaccination strategy, i.e. the volumes required. The resulting value-based price could be adjusted downwards for relevant public push R&D and manufacturing funding (depending on the arrangements governing the funding)

<sup>34</sup> There are four key parties, (i) the governments who make commitments (ii) the guarantor who will sign agreements with the governments and so provide credible commitments to the market (iii) the secretariat / coordinator, who will be funded by a small levy on the governments, and (iv) the developers who will register to participate in the scheme and agree (in contracts with the guarantor) that they will supply vaccines at the

the MVAC report proposing an AMC for new TB drugs which is accessible via both the CGD and OHE websites (29,51).

We summarise in Table 1 below a comparison of the COVAX Facility and the BBAMC.

**TABLE 1: COMPARING THE COVAX FACILITY AND THE BBAMC**

Attribute	COVAX	BBAMC
<b>Incentivise private capital to invest in development</b>	No, push needed	Yes, but compatible with push
<b>Incentivise private capital to invest in manufacturing capacity</b>	No, push needed	Yes, but separate push needed also
<b>Contingent Advance Purchase contracts</b>	Yes	No
<b>Advance Market Commitment</b>	No (Phase 1 is not a market commitment, planned Phase 2 includes unspecified market commitment)	Yes
<b>Incentivise follow-on vaccines</b>	Only if AMC component put in place	Yes, a major objective is to have more than one vaccine
<b>Countries to participate</b>	LICs, LMICs but HICs, MLICs welcome	HICs, MICs, LICs (via Gavi) to give overall market commitment
<b>Quality hurdle</b>	WHO TPP	WHO TPP, with a minimum and maximum for setting value-based prices
<b>Cost-based Pricing</b>	Yes, flat price (allows for other options after first 12 months)	No, except for the LIC/ LMIC tail-price
<b>Value-based pricing</b>	No	Yes, using HTA to assess value
<b>Differential pricing</b>	Reference to tiered pricing	Yes, prices reflect local HTA and affordability results
<b>Account taken of push funding</b>	Yes, in price	Yes, in price, or reduced volume commitment
<b>Donor support for LICs / LMICs</b>	Yes	Yes
<b>Prioritising allocations of vaccines</b>	Secretariat	Pre-agreed, implemented by the Secretariat

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pre-set value-based price. Subsequently they will contract with governments to supply specific quantities at this price.

## 6. Putting it all Together: A Tale of Two Paradigms

We have a clash of paradigms that is inhibiting our ability to design the right buying and funding mechanisms and in particular to move from cost-based bilateral conditional contracts to value-based advance market commitments.

### CURRENT BUSINESS PARADIGM

As we set out above, the current business paradigm for pharmaceuticals, including vaccines, for HICs, is that the market pulls products through. It is a spot market (where product is usually bought and sold for immediate delivery or with short term contracts – perhaps as long as a vaccination cycle) characterised by an expectation on the part of the private sector that investment at risk will lead to a return if a product that improves health is delivered, in part because price will reflect value rather than cost. Although the determination of value may be disputed.

By contrast, for LICs, tiered or differential pricing delivers drugs and vaccines developed for HICs at or near cost, but donor support is needed to buy them – donor led-pull. For diseases without a HIC market then donor push and pull is needed. However, with the exception of the pneumococcal-AMC, (and some stockpiling, for example of Ebola vaccine) which we have discussed above, the emphasis has been on push.

In MICs, including those graduating from Gavi and Global Fund support, we have seen a growth of spot purchasing (including short term contracting) but there is still an expectation of tiered/ differential pricing, and a desire not to pay above cost if possible. There is, arguably, no credible mechanism to develop drugs and vaccines for which there is no HIC market, other than to push fund domestic institutes and companies.

For MICs arguably we are moving (slowly) towards (at least for upper-middle income countries) markets that look more like HIC ones. The emphasis on paying cost-based prices, and not paying for value is changing with the growth of HTA or value assessment in many MICs, but there is a lack of expectation on the part of global and local companies that R&D investment will be rewarded with prices that reflect value. Arguably we need a stage of advance market commitments of the sort we have set out in the BBAMC to get these markets working in a way that they can transition to an HIC style spot market. There will still be an issue of income per capita in terms of ability to pay value-based prices that are high enough to reward R&D, but as we showed with the MVAC proposal for new TB drugs, there is enough of a market in MICs to reward R&D investment, if it can be mobilised through the right mechanism.

Both the COVAX Facility and BBAMC can involve HICs and upper-middle income countries. The R&D based industry will understandably be very concerned about encouraging a new way of doing business that could become the new normal which is not a viable business model for them to research, develop and deliver profitable innovative vaccines for the future. The BBAMC was derived from the MVAC proposal for new TB drugs and was explicitly intended to be a transitional mechanism to a spot market where MICs paid value-based prices for new drugs which enabled companies to get a return on their R&D investment.

### THE COVID-19 PARADIGM

We are in a COVID-19 paradigm characterised by:

- Government direction and intervention in all sectors of the economy, reflected in the vaccine hunt by (i) push support for early and late stage development and (ii) for

manufacturing with (iii) contingent procurement options as part payment for the push funding.

- Companies exercising corporate social responsibility and recognising that resources need to be committed without a necessary expectation of profit. This is reflected in the vaccine hunt by statements by some companies that vaccines will be supplied at cost for the first year (i.e. the pandemic period)<sup>35</sup>.
- Donors identifying the need to find substantial resources to enable LICs to buy the vaccines and other health technologies they will need to tackle COVID-19.
- MICs falling through the gaps with most not in a position to push fund vaccine candidates or manufacturing capacity.
- A current lack of global coordination and commitment (in sharp contrast for example to the handling of the 2008 economic crash).

We should pause at this point and note that there is not one global vaccine industry, but three (i) the large multinational R&D-based vaccine manufacturers who have about 80% of the value of the global vaccine market but only 20% of the volume (ii) the Developing Country Vaccine Manufacturers (DCVMs) and (iii) small HIC biotechs and niche manufacturers. The last two groups have the other 20% of the value and deliver 80% of volume primarily manufacturing large volumes of established vaccines at low cost. As we saw, DCVMs from China have COVID-19 vaccines in clinical development. Many DCVMs are able to manufacture under license. They offer a potential route to enable a COVID-19 vaccine to be manufactured at scale around the world.

The R&D based industry is not necessarily going to want to manufacture billions of doses of a new vaccine to supply at cost. That is not their core business. Innovators' willingness to take-on responsibility for global manufacturing may therefore be limited, so they may well welcome initiatives by Gavi and Gates Foundation and others to invest in manufacture aimed at LICs and lower-middle income countries, and recognise the need to "hand-off" manufacture of their products to others, subject of course to addressing quality of manufacture concerns and competitive issues (some technologies are proprietary).

What is missing in the present COVID-19 paradigm, is a recognition of the need:

1. **for greater global co-operation** and a move away from vaccine nationalism or every country for themselves.
2. **to get private capital mobilised to address the challenge.** The pharmaceutical industry has to provide a return to investors; its commitment to a "charitable" enterprise is likely to be far lower than its investment in a project with high profit potential (52). As Craig Garthwaite put it "to develop the science we need to get us out of the pandemic, we must convince biotechnology firms that we will pay for the value they create. We can't just hope that they will follow the better angels of their nature and risk tens of millions of dollars with little hope of a return." (52)

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<sup>35</sup> The R&D based industry are very aware that in the current pandemic with economies under pressure, all businesses (whether in pharmaceuticals or any other sector of the economy) have to do what society expects, whether they make or lose money from it. Society looks to the academic science base and to the private sector industries' research and development skills for treatments and vaccines to tackle COVID-19. Hence the substantial investments being made and some R&D-based companies stating that they will supply, at least initially, on a "not-for-profit" basis. This commitment has to be time limited, as private investors expect a return. The sector cannot commit large amounts of capital without making profits.

Specifically there are three ways in which the COVAX Facility could be improved by a shift of paradigm which we set out in the next section.

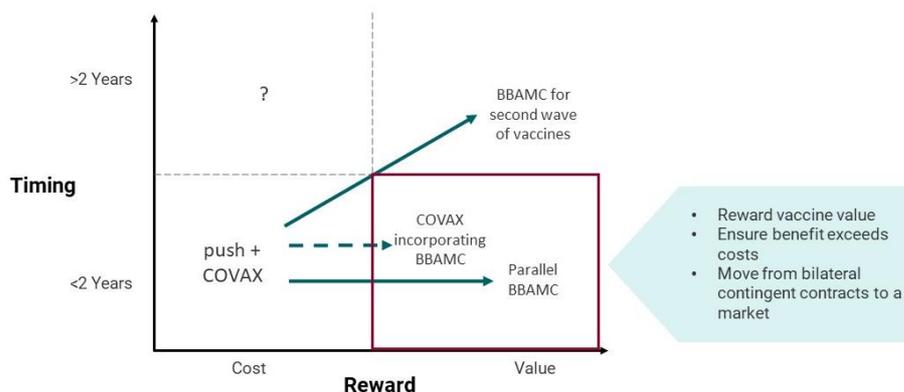
## 7. Moving the COVAX Facility Towards a Benefit-Based AMC

The challenge for the current proposals notably the COVAX Facility is threefold:

1. **Reward Vaccine Value.** This is to avoid countries getting locked into purchasing low-efficacy vaccines. Deals with manufacturers should incorporate value assessment. At a minimum, the deal is only valid or commands a higher price if a vaccine meets WHO target product profile characteristics based on modelling against epidemiological, health system delivery and demographic characteristics. Ideally price/total deal amount for vaccines scale progressively with vaccine effectiveness
2. **Ensure Benefits Exceed Costs.** This is to avoid countries rolling-out low-efficacy vaccines because of the sunk cost fallacy (“we paid for them, so we may as well use them”) even though the costs of roll-out exceed the benefits. We need to ensure use of a vaccine in any patient group passes the “do benefits exceed the cost?” challenge. We need to ensure health technology assessment (HTA) is conducted before rolling out a vaccine (even if the vaccine price is a sunk cost) and also use HTA processes to ensure accountability and due process around vaccine adoption decision-making.
3. **Move from Bilateral “Deals” to Market Commitments.** This is to avoid countries being locked into purchasing low-efficacy vaccines even if better vaccines become available; bilateral deals crowd out private sector investment in other promising candidates and lower the overall probability of successful vaccine development. This can be done by:
  - Beyond or instead of bilateral deals, maintain “pull” for R&D by committing; unallocated pool of funds to a market-wide advance commitment;
  - Link value of commitment to vaccine performance through an HTA process;
  - Clearly communicate that countries will be open to procuring any effective vaccine in years 2-3 and will respect IP/pay prices commensurate with product value.

### HOW DO WE MOVE THE COVAX FACILITY TOWARDS A BBAMC?

It could be argued that timing is key here. If manufacturers and governments and international funders are already “locked” into push funding and contingent advance purchasing contracts, then it is too late to step back and change the buying mechanism at least for the current leading vaccine candidates. We illustrate this point in Figure 3, using greater or less than 2 years to have a vaccine, as an indicator of how radical the changes can be.



**FIGURE 3: SCHEMATIC OF THE CHANGES TO THE COVAX FACILITY NEEDED TO INCORPORATE THE BBAMC**

It is feasible to introduce a BBAMC for a potential second wave of candidates but also to implement incremental change to current proposals and mechanisms in place.

We have three non-mutually exclusive options:

- Add elements of BB AMC to existing deals; moving you right along the X axis (COVAX incorporating BBAMC)
- Run a parallel BBAMC, a belt and braces approach, in which countries already committed to bilateral deals can also join. This can be moving us to value and can sit to the right of the first option.
- Scope out/scale up a BBAMC for post first launches, i.e. a second wave of development. COVAX becomes a BBAMC scheme.

### THERE ARE POTENTIAL CHALLENGES

- Advance market commitments are based on ex ante estimates of the expected value of a vaccine with associated expected volumes. These are likely to be highly uncertain. Locking countries into honouring these commitments may lead to unnecessary expenditure if, for example, COVID-19 were to disappear, or become easily treatable. However, current arrangements involve countries and donors making large push commitments, taking on development risks. It is unclear exactly what commitments are being entered into in the bilateral contingent advance purchase contracts, but it is likely that there is some commitment to buy, i.e. they are not pure option contracts whereby the buyer can choose to exercise the option but may choose not to. Our assessment is that it is better for the *developer* to take on R&D risk and for the *country* to take on the population health risk (i.e. the volume risk). This distribution of risk reflects the respective strengths of the parties – developers understand development risk and countries understand their populations. Two further points:
  - It is possible that countries seek to “free ride” in their estimates of ex ante value, in which case some sort of pro-rata assessment of value and willingness to pay will be needed to establish the ex ante prices linked to the TPP;
  - It would of course be possible to base price and volume on an “at launch” HTA as is usually done for a new treatment or vaccine. However, this may give rise to opportunistic behaviour on the part of either the countries or the manufacturers,

with one seeking low prices and the other high prices. By locking in price based on how the vaccine performs at-launch against an ex ante assessment of value in relation to the amount of the TPP met, both parties have some protection from opportunistic behaviour.

- Deciding which markets are supplied first and in what quantities will be a major challenge for manufacturers of a COVID-19 vaccine in any setting. The AMC will have different prices in different countries and manufacturers may be tempted to supply higher value markets first. It is also possible that they may decide to prioritise supplying countries that have not signed up to the AMC. Countries may have used push funding to obtain pre-emptive rights to be supplied – in effect this is the price of the option to buy the vaccine if it works. There are three different but related issues here:
  - allocation rules as between countries participating in the AMC will need to be agreed as part of agreement to participate. They will need to reflect WHO allocation principles and also the reality of agreements already entered into by participating countries or regional groupings;
  - these rules will need to recognise that different prices are being paid in different markets, but that manufacturers do not allow these considerations to override the pre-agreed allocation mechanism;
  - manufacturers do not have to participate in the AMC. However, if they do participate, then this could be made conditional on them pre-agreeing certain quantities available, recognising however, that there is no commitment on the part of the participating countries to buy any particular vaccine, only a commitment to buy in total towards the total market value commitment.
  - It is important to recognise that some major countries are likely not to participate directly, but to continue to pursue bilateral arrangements – although they may help to fund Gavi purchases of vaccines for LICs and LMICs. This is regrettable, and we would argue, not in their interests. It remains the case that a facility for LICs and LMICs is needed, many UMICs are being ignored in all discussions, and HICs would also benefit from participation. The greater the participation, the more likely it is that private sector capital in both HICs and MICs will be motivated to invest.

We need also to go back to the money. A COVAX Facility cannot work, whether or not it is adapted to have elements of a BBAMC, without donor resources to ensure low income country populations are able to access vaccines when (and if) they are successfully developed.

## 8. Three Lessons for Future Pandemic Preparedness

When another ‘disease X’ pandemic emerges, it is clear that we need to avoid some of the mistakes that are currently being made with COVID-19. In particular, with preparation it may be possible to avoid the government push/industry cost-pricing paradigm we are in with potential negative consequences for the composition of the global portfolio and engagement of private capital.

Firstly, while preparedness for a repeat of an H1N1 virus-based pandemic was built up with WHO monitoring and seeking to maintain influenza vaccine capacity, a more

comprehensive set of market mechanisms now need to be developed. CEPI has worked, and shown that we can get early stage research underway very quickly and get candidates into the pipeline quickly, in part because of genuine innovation in vaccine technology over the past 20 years. But we also need to build market mechanisms in advance, i.e. plan for a (benefit-based) AMC.

Secondly, distributive issues will always be an issue in a pandemic and work can take place in advance to get countries to sign up to a realistic set of rules (which may include an element of vaccine nationalism, i.e. countries that host successful candidates get some preferential access.)<sup>36</sup>

Thirdly, the financing arrangements to pay for LIC vaccines and for some LMICs could be pre-agreed and automatically triggered by a pre-set hurdle (e.g. WHO declaring a pandemic).

Finally, let us not forget that COVID-19 is causing a global health and economic disaster and wish success to all of those in academia and in industry involved in researching, developing, or planning the manufacture of a COVID-19 vaccine.

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<sup>36</sup> There are three different and conflicting principles of justice (53)

1. Rights based – Government A has a contract for the vaccine, it has a right to that vaccine for its citizens
  2. Desert based – Government B has funded the research and the capacity that has enabled this vaccine to be developed and produced - it deserves to access that vaccine for its citizens
  3. Needs based – Government C has a highly vulnerable population - it needs that vaccine for its citizens
- We can prioritise health care workers on all three principles. We could make trade-offs e.g. using a variant of Nord's person trade-off (PTO) approach. How many of your country's vulnerable citizens are you prepared to sacrifice so that health care workers in another country can get the vaccine? This gets us into principles of global justice, beyond social justice in terms (primarily) of scope (54). The point is that we need to be having these discussions and going beyond bland statements or lists of priorities that exceed conceivable short-term supply availability and so do not provide a basis for serious trade-offs. Note that there is a Human Right to Health literature, that approaches this issue from a different perspective (55).

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