Explanatory note regarding "Proposal for funding and co-ordination mechanisms to maximize benefit / minimize cost / minimize risk from donor investment in COVID-19 vaccine development"

Note by the authors and origins of this piece: *This explanatory note was written in August 2022 to accompany publication in the Blavatnik School of Government working paper / policy brief series of an original note dated 7 March 2020.*

The March 2020 note was written by Dr Sandy Douglas (a vaccinologist in the University's Jenner Institute) and Dr Kate Orkin (an economist at the Blavatnik School of Government), with input from Professor Stefan Dercon (Director of the Centre for Study of African Economies) and Professor Adrian Hill (Director of the Jenner Institute). The ideas were developed in the last week of February 2020 and the written proposal evolved in discussion with entities in UK government and international donors over the following 10 days. The authors wish to make the original note available in the public domain, alongside explanation of the context and our ex-post reflections.

Summary argument

The paper's core argument was that finance (rather than development of new vaccine technology) was likely to be the binding constraint on the timing of broad and equitable global availability of COVID-19 vaccines. Stemming from this, the paper argued there was an urgent need and opportunity for funders to accelerate vaccine availability through strategic – but relatively modest – investment targeting critical market failures.

Outline and context of original note

At this point, most informed epidemiologists viewed a COVID-19 pandemic resulting in millions of deaths as virtually inevitable. A significant factor in the policy debate about whether 'lockdown'-like measures should be instituted was uncertainty about whether there was any viable 'exit route'. The initiation of mass vaccination programmes at the end of 2020 was not viewed as a credible possibility, with the most optimistic publicly-stated 'best-case scenarios' suggesting vaccines might become available in high-income countries in mid-2021. Significant government, philanthropic or international financial institution (IFI) investment in vaccine development had yet to materialise: the UK Vaccines Taskforce, the US Operation Warp Speed, and the international COVAX initiative were months away, and total investment which had been received by the Oxford COVID-19 vaccine programme was <£3m.

Our proposal brought together the perspectives of vaccinologists and economists. Douglas and Hill were optimistic that across a portfolio of existing vaccine 'platform technologies' (including Oxford's adenovirus vector approach but also others under development elsewhere) there was a high probability that clinical trials would demonstrate efficacy of a COVID-19 vaccine within 2020. They were concerned however that the technical grounds for this optimism, and the opportunities for

acceleration by removing bottlenecks, had not been appreciated by the policy-making community. They argued that manufacturing, rather than clinical trials, was likely to delay widespread availability of successful vaccines and that, based on basic epidemiological projections, every month by which vaccine availability could be accelerated would be likely to save over a million lives and provide very substantial economic benefit.

Because neither the technical processes of vaccine manufacturing nor the characteristics of the manufacturing market were well understood beyond a narrow community, opportunities for acceleration appeared likely to be missed. Contrary to discussion in some quarters about building new vaccine factories, Douglas and Hill felt that re-purposing existing facilities was likely to be the quickest route to secure adequate production capacity. Such facilities included so-called contract manufacturers, which operate within an almost-commoditised global biological medicine manufacturing market as subcontractors for drug developers, and vaccine suppliers focused on low and middle income countries (LMICs). Both of these types of manufacturer sit outside multinational pharmaceutical companies. Neither typically allocates its own capital to risky development of new vaccines, and neither was therefore likely to invest unsupported in delivering the fastest technically-feasible accelerated manufacturing of COVID-19 vaccines.

Major barriers were therefore that:

1. Contract manufacturing facilities were generally booked long in advance, and even after booking setting up a new manufacturing process in an existing facility has a long lead time.
2. The most promising manufacturers lacked access to capital and/or clear signals of a market (in advance of the success of clinical trials) to deliver what was technically feasible in accelerating manufacturing.
3. Multinational pharmaceutical companies seemed unlikely to prioritise financing large-volume, high-speed manufacturing of vaccines suitable for low and middle income countries (LMICs). Market failure in vaccine development for LMICs is widespread and well-recognised, as companies do not internalise the full societal benefit of the vaccines. In the case of COVID-19, this would be compounded by the need for speed and differentiation of approaches needed to serve high-income and LMIC markets.

Combining this technical and economic understanding led to a set of policy proposals which were then put to funders:

1. Up-front financial commitments designed to incentivise speed to billion-dose scale manufacturing, in parallel with rather than after clinical trials. This would need to be 'at risk' (i.e. before it was clear whether the vaccines would work).
2. De-risking by investment in a portfolio of different candidates, i.e. supporting all of the small group of programmes which could credibly deliver at speed.
3. Immediate World Bank, Gavi & WHO preparation for deployment, including in low and middle income countries.

Concluding comments and ex-post reflections by the authors

It is difficult to be sure of the impact of this paper. The idea of at-risk investment in manufacturing was also being discussed elsewhere. The Financial Times reported on 5 March that Moderna was seeking government finance for scaled-up manufacturing, although Jeremy Farrar's book 'Spike' suggests this may have proven unsuccessful for at least the following two months. The Coalition for Epidemic Preparedness Initiative had invested in a portfolio of vaccines but had relatively limited resources and was not, to our knowledge, advocating immediate at-risk purchase of large-scale production capacity.

In some important respects, with hindsight, we were over-optimistic. It took several months longer than hoped to produce a billion doses of any vaccine, and costs both of development and producing each dose were higher than projected. Nonetheless the paper's core argument – for optimism regarding speed of vaccine development using existing technology, the likelihood of manufacturing as a binding constraint, and the importance of policy to overcome this – appears to have been valid.

The authors' impression was that the ideas expressed here were received by policy-makers and funders as being at least somewhat novel and persuasive. In April 2020, the UK government committed £65m to a plan one of us (SD) presented for at-risk manufacturing of the Oxford vaccine for UK supply (before the initiation of the first clinical trial of the product and before the University's partnership with AstraZeneca). The portfolio approach we proposed was echoed in the approach subsequently taken by the UK Vaccines Taskforce. UK policymakers and IFI representatives have said this proposal informed their drive for international co-ordination of financing for vaccine manufacture, initially through the March 2020 G20 Leader's Summit meeting and latterly through the establishment of the COVAX initiative. Beyond UK supply, Oxford implemented the at-risk internationally-distributed manufacturing strategy in its own programme, leading to an invitation to the Oxford team to present the model to the board of the World Bank. By the end of March 2020, Douglas and Hill had formed partnerships with four contract manufacturers and the largest LMIC vaccine supplier (Serum Institute of India). These early partnerships delivered over half of the more than 3 billion doses of the vaccine subsequently produced.

Sandy Douglas & Kate Orkin, 16 August 2022

Proposal for funding and co-ordination mechanisms to maximise benefit / minimise cost / minimise risk from donor investment in COVID-19 vaccine development

EXECUTIVE SUMMARY

The COVID19 epidemic creates a situation of unprecedented potential benefit of **speed** of availability of an entirely new medical intervention at huge scale. At current reasonable estimates of global COVID19 epidemiology, the marginal benefit of accelerated vaccine availability may well be in the range of **1m to 5m deaths averted**, and significant economic benefit, **for every month** timelines can be brought forward from current projections.

Current expectations, based upon accelerated but conventional vaccine development paradigms, suggest vaccine availability no sooner than 12-18 months, especially in LMICs. This document offers (1) vaccine developers' analysis of financial and non-financial constraints limiting speed of availability and (2) suggested structures to address these challenges, developed by economists. With these steps, we believe existing data on vaccine platform performance suggests a high probability (>80%) of achievable availability of an effective vaccine on a billion dose scale by c. October 2020, with *best-case* timeline as soon as June/July 2020, and at total cost <USD 1 billion. We estimate that this proposal could save 6-12 months versus timelines/mechanisms currently being proposed.

We suggest: (1) Immediate signalling of availability of capital on a scale pricing in benefits of speed and targeting billion dose manufacturing. (2) Encouraging progress towards this large-scale manufacturing in parallel with (rather than after) clinical trials. We believe cost-benefit may be optimized and risk minimized through immediate support, at this level of ambition, of a diverse initial portfolio, followed by structured down-selection of candidates as additional information becomes rapidly available in March-May. (3) Funding of a co-ordinated clinical trial infrastructure and preparation for prompt large-scale LMIC deployment are also likely to be beneficial.

CEPI (and its major donors), the World Bank, WHO and Gavi all have relevant expertise and joint scientific and economic analysis may assist identification and removal of constraints upon vaccine evaluation (trials), manufacture at scale, and deployment.

We provide an example (Annex 1) of our own CEPI-supported vaccine development programme's intended timeline combining accelerated clinical trials and manufacturing scale-up, including our analysis of financial and non-financial constraints at each point. This is intended to demonstrate feasibility of such acceleration; we believe a similar approach could equally be applied to other vaccine candidates.

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Note: Douglas and Hill are developing a candidate COVID19 vaccine. This proposal applies across any and all viable candidates.

URGENCY OF COVID19 VACCINE DEVELOPMENT AS GLOBAL PUBLIC GOOD

Deaths from COVID19 may occur at a mean rate of 1m-5m per month over the remainder of 2020 (total 10m-50m), based upon models suggesting infection of up to 70% of global population in an early wave of infection. Timing of peak death rate is unclear but may be as soon as June. Beyond this wave/peak there is increasing concern that the virus will continue to transmit at a lower level in the population, posing an ongoing threat to those not previously infected. Development of a vaccine will remain of the utmost urgency even if it is not possible to realise maximum benefit from development before the peak of the epidemic; beyond the peak, >=30% of global population are likely to remain under threat of recurrent waves of infection.

Expected impact is highest in LMICs. Mortality in LMICs may exceed that seen in the early stages of the epidemic, due to weaker capacity for containment and treatment. Previous modelling of impact of a flu pandemic suggested annual expected losses of 1.6% of national income for LMICs, as compared to 0.3% for HICs.[1]

VACCINE DEVELOPMENT LANDSCAPE

COVID19 vaccine availability:

1. Requires clinical development of a new product but is feasible: Unlike for flu pandemics, there is no proven 'template' COVID19 vaccine. However as demonstrated for Ebola in 2014-16, development of vaccines against transient epidemic infections is significantly simpler than development of vaccines against long-term infections (HIV, TB, malaria). There are similarities between Ebola and COVID19 in that there was encouraging pre-epidemic data from primate studies[2].
2. Starts from a position of availability of 4-10 plausibly useful vaccine 'platform technologies', partly nurtured by CEPI, but without one candidate having clear dominance at present.
3. Faces a capital and manufacturing scale-up challenge: for most if not all candidates, there is no large-scale manufacturing process / facility established within well-capitalised corporations. Large company interest in epidemic preparedness has historically been low due to low commercial return. Instead, many COVID19 vaccine developers are relatively small biotech companies or not-for-profit/academic entities. Arguably most relevant expertise exists within such entities rather than large corporations, but nonetheless some developers lack in-house trial and/or large-scale manufacturing capacity: these developers are thus assembling consortia of partners to advance their candidates (Figure 1).

We therefore believe that, in the current situation, there is high risk of development of an effective vaccine with sub-optimal speed, but risk of failure to develop an effective vaccine at all is low (c. 10-20%, on a 2-year timescale). The critical challenge is therefore one of acceleration.

[1] Fan, V., Jamison, D. and L. Summers. 2018. Pandemic Risk: How Large are the Expected Losses? Feb 1 96(2): 129–134. Fan VY, Jamison DT, Summers LH. The Loss from Pandemic Influenza Risk. In: Jamison DT, Gelband H, Horton S, Jha P, Laxminarayan R, Mock CN, et al., editors. Disease Control Priorities. 3rd ed. Volume 9 Washington: World Bank; 2018: 347-358.

[2] For COVID19, the relevant primate data relates to another coronavirus, MERS. It is also noteworthy that the studies in primates involve deliberately overwhelming infection, and so success in these studies suggests excellent vaccine performance – in Ebola, 'real world' protection was easier to achieve than in primates.

PROPOSED PROCESS: Please refer to Figure 1 & Table 1 alongside description of this proposal.

Immediate needs: seed funding to capital-constrained leading programmes, and clear visible prospect of further funding:
Problem: CEPI has identified and allocated funding to leading programmes, but as above, some leading programmes remain critically constrained by lack of working capital. This is slowing progress, lowering ambition, and increasing risks of failure.
Proposal: Ideally within the coming week, (1) Immediate identification of capital-constrained programmes among CEPI's portfolio, and immediate allocation of additional funding of USD 10m to each such programme. (2) Clear statement offering line-of-sight for developers and their contractors through to the possibility of competitively allocated milestoned financing of the order of ~USD 100 million per candidate, starting from early April, and potential for additional financing thereafter. This will trigger a level of ambition not seen hitherto, in particular by providing developers with credibility in discussions with potential manufacturing partners.

Clinical trial financing and co-ordination:
Situation/ problem: (1) Maximum clinical trial financing needs (i.e. for a successful candidate proceeding through increasingly large trials) are in our view <USD 60m for a successful candidate. There is however a need for urgent **acceleration of decision-making** on trial financing. (2) Some developers have strong technologies but limited access to clinical trial expertise.
Proposal: (1) We estimate that clinical trial progress (as distinct from manufacturing scale-up) at maximum possible speed requires total disbursement (across all programmes) of <USD 100m by early April and an additional <USD 200m from early May; this would be sufficient for Phase III evaluation of at least five candidates. Below, we outline a possible mechanism for allocation of such finance. (2) An internationally integrated clinical trial programme could evaluate multiple candidates as they progress (an 'adaptive platform trial', on the template of smaller Ebola treatment trials). This will benefit candidates produced by developers lacking optimal clinical trial expertise, but we suggest that, to avoid risk of excessive rigidity, it is funded *as well as* trial funding to developers with in-house trial expertise.

Manufacturing scale-up:
Background: Impact at global scale requires ambition to manufacture at least at 100m – 1bn dose scale. Manufacture at extremely large scale is technically feasible for most candidates, and potentially extremely cheap. We estimate that, at >100m dose scales, **most candidates under current development could be produced for <USD 0.10/dose**. Biological products like vaccines are frequently made by contract manufacturing organisations (CMOs): it is unlikely that any new large-scale vaccine manufacturing facility will be (or needs to be) built to tackle the outbreak. Instead, manufacturing capacity can be rented. Some such capacity is idle; some could be re-allocated from less urgent use.
Problems: (1) Due to resource constraints, few if any programmes are targeting the billion dose scale necessary for global benefit. There is currently limited understanding of constraints upon scale of manufacture of most candidates. Billion dose scale is not necessarily dramatically harder than 10m dose scale, and may provide significant economies of scale. *Early* process development suitable for this scale will be relatively low in cost. Once the fixed costs of preparation are paid (as necessary for any market), marginal cost of provision for LMICs will be low. However preparation appropriate to the maximum achievable final scale must start now. (2) For some if not all of the leading candidates, lead-times for manufacturing at large scale (a number of months) are such that manufacturing time (rather than clinical trial timelines) is already likely to be the constraint which determines timing of availability of vaccine.
Proposal: (1) **Performing clinical trials and manufacturing scale-up in parallel**, rather than in sequence, for those programmes for which availability time is likely to be constrained

by manufacturing lead times (i.e. *not* those with slow trial plans and/or very rapid manufacturing methods). (2) To support this, we suggest allocation in early April of funding to such programmes, **targeting manufacturing at the greatest possible scale as soon as possible**. Early stages of this work will include **identification of what this maximum achievable scale is for each candidate** i.e. the binding non-financial constraints, and refinement of achievable timelines. We estimate cost significantly <USD100m for any one programme in April-May, likely back-loaded. Although this work must be initiated in advance of trial results, later stages could be abandoned and costs reduced for example if a candidate's trial results are poor. (3) Immediate central procurement e.g. by Gavi of options contracts for large-scale vial filling, from June. This may be a binding constraint on deployment, and can be allocated at a later date to the most promising candidates.

Proposed funding and delivery structure (covering both trials and manufacturing)

Problems: (1) Neither simple market mechanisms not existing contract structures for vaccine financing (advance market commitments to incentivise long-term investment e.g. in factories) are likely to deliver optimal outcome in the current situation, especially for LMICs. The over-riding need is for short-term capital. (2) Only vaccine developers (not vaccine buyers) have the detailed understanding of candidates' production processes which are necessary to contract with manufacturing partners (CMOs). (3) CEPI is playing an critical and valuable role, but may benefit from additional financial and technical support in view of the magnitude of the COVID19 problem and the complexity of the economic and contracting challenge it poses.

Proposals:

(1) Substantial investment by states/donors, structured to minimise risk. We propose a process as illustrated in Figure 1 and Table 1. This would involve:

A) Allocation by early April of milestoned financing for April-May up to a maximum potential spend of c. USD 160m per plausible candidate, covering both trials (<USD 60m) and, for candidates for which manufacturing lead times are a constraint, manufacturing scale-up (<USD 100m). We anticipate proposals for such a call will come from consortia led by vaccine developers, who will themselves have secured manufacturing and other capacity propositions from a range of subcontractors (Figure 1). For some candidates this funding would be likely to include either initiation of large-scale manufacture within this period, or initial down-payments upon CMO capacity from June onwards. Although we propose prioritisation of 'keeping options open' by maintaining a broad portfolio, milestoning means that later stages will be contingent upon emerging information (see Table 1 legend). Some candidates will fail and so the later payments will only be received by the most promising candidates (Table 1). We therefore estimate total actual spend from this allocation, across all candidates, is likely to be <USD 500m.

B) Additional funding to the most promising programmes would likely be required in late May, to secure large-scale manufacturing from June onwards: at this point, the number of candidates in sufficiently competitive and pro-LMIC positions to merit ongoing donor funding is likely to be quite small. By this stage for-profit developers of such promising candidates may expect commercial return, but not-for-profit developers may be able to undertake billion-dose manufacture for USD 100-200m.

(2) In addition to the funds, vaccine development expertise & development programme insight of **CEPI**, there may be roles in this process for: the funds and economic expertise of the **World Bank**; the regulatory function and potential clinical-trial co-ordinating function of **WHO**; the implementation expertise and national government vaccine purchasing partnerships of **Gavi.**

(3) Rapid pre-implementation multi-source review of this proposal, or anything based upon it, to mitigate concern of optimism bias.

FIGURES

Figure 1: Relationship of vaccine developers to contractors within consortia bidding for funds

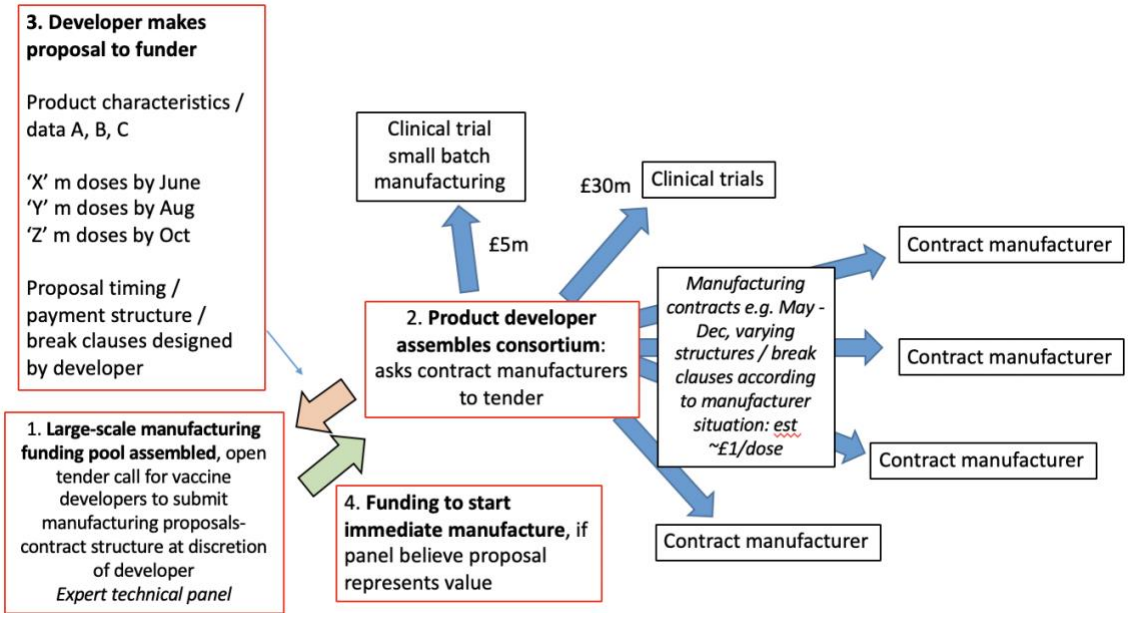

Figure 2: Possible progress of hypothetical candidates through proposed funding process

Progress will be accompanied by rapidly improving information upon which to base later funding. The following illustrates the relationship between types/ sources of information and possible timing of information availability.

1. Safety & efficacy: platform's track record (now); animal studies (April); clinical trials (May)
2. Manufacturing scalability & cost: nature of process (now); lab-scale yield data (March); scale-up progress and quotations (April onward); identification of binding non-financial constraints e.g. materials (April)
3. Deployment practicality: route, number of doses, storage temperature (largely inherent to platform, known now).

Vaccine: Developer	**Mid-March round (seed funding)**	**Early April allocation, immed spend (large trials & manufacture scale-up)**	**Early April allocation, milestone-dependent**	**May round**
A: >1bn corp. 1	Not financially constrained	Not needed	Not needed	Looks promising but commercial focus on HICs
B: >1bn corp. 2		Availability time constrained by trial, not manufacturing, do not fund manuf. now	Not needed	Too slow. Terminate.
C: >1bn corp. 3		20m (some indep. funding)	70m, milestone not hit	Terminated.
D: Small biotech 1	10m	20m (some indep. funding)	30m	Looks promising but complex delivery, not suitable for LMICs
E: Small biotech 2	10m	30m	70m	Promising. 150m for 1bn doses for LMICs.
F: Small biotech 3	10m	Not viable, terminate.	Terminated.	Terminated.
G: Not-for-profit 1	10m	Weak data, 5m	10m, milestone not hit	Terminated.
H: Not-for-profit 2	10m	30m	70m	Promising. 150m for 1bn doses for LMICs.
I: Not-for-profit 3	10m	30m	70m	Disappointing trial result.
Total allocated	60m	135m	320m	300m
Total spent	60m	135m	240m	300m