Pandemic vaccine trials: expedite, but don’t rush

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Abstract
It has been proposed that the urgency of having a vaccine as a response to SARS-CoV-2 is so great, given the potential health, economic and social benefits that we should override the established steps in the research development process. In this article I argue that whilst there are some opportunities to expedite the production of a vaccine, it is a mistake to rush the research. We should retain the existing structures represented by clear and separate ‘phasing’ of trials. I offer three reasons for this view: the existing phases of trials is morally significant; rushing fails to appropriately weigh all of the relevant risks and benefits and consent is not sufficient for the justification of additional risk. Vaccines have played a central role in global health improvements and we should not endanger such achievements for an apparent short-term gain in response to a pandemic such as SARS-CoV-2.

Keywords
Research ethics, vaccine trials, SARS-CoV-2, risks and benefits

Background
The SARS-CoV-2 pandemic has resulted in millions of infections and hundreds of thousands of deaths across the globe. The absence of effective treatments and a preventive vaccine has meant that we have had to rely upon traditional public health measures, including physical distancing, closing borders and contact tracing, as our main response. The focus on reducing transmission through such
interventions has resulted in massive social and economic disruption, with a likely impact for decades to come. The number of people who have been infected, and whether or not they have longer term immunity, is unknown. In most countries, it is highly likely that the vast majority of the population remain immunologically naïve to SARS-CoV-2. The countries that have been most successful in keeping case numbers low are at the greatest risk of future infection. The existence of treatments for severe COVID-19 would be beneficial, but the only thing likely to allow a return to normal life is the prospect of an effective vaccine.

There are many different research groups across the world focused on producing a vaccine, and a number of early trials have been conducted (Mullard, 2020). The prospects for a successful vaccine are at the time of writing unclear. However, it has been proposed that an effective vaccine would be able to save so many lives and we should consider a number of different ‘shortcuts’ to speed up the research. In this article, I argue that whilst there is some opportunity to expedite the research process in developing a SARS-CoV-2 vaccine, we should not rush to drop key phases of the traditional stepped approach to research trials including during the development of new vaccines.

**Expedite, but don’t rush**

It has been argued that in an emergency, such as the present SARS-CoV-2 pandemic, it is so important to produce a vaccine quickly that we should consider modifying or dropping some of the established elements of the research process (Chappell and Singer, 2020; Smith et al., 2020). This argument for focusing on speed seems plausible to many because of the significant expected medical, social and economic benefits from an effective vaccine: preventing harm to most of the world’s nearly eight billion population and removing the burdens and costs of the traditional public health measures currently in place.

The implementation of the overall argument for modifications can take a number of different forms:

- Skipping animal studies prior to Phase I trials in humans;
- ‘combining’ Phase I and II trials;
- ‘combining’ Phase II and III trials;
- skipping Phase II trials altogether.

Producing an effective vaccine as quickly as possible is important, but such a vaccine should be both effective and safe. Where we can, we should expedite the research and production process. However, given the uncertainty about the real-world benefits and risks, especially in relation to SARS-CoV-2, we should resist the pressure to rush ahead with research. Otherwise, we risk being reckless or
I argue in this article that we have good reason to retain the current mechanisms for research, given what we know from our previous experience with vaccines, and we should resist the appeal for ‘shortcuts’ on the grounds of speed. A Phase I vaccine trial looks at baseline safety and issues relating to the body’s immunological response to the vaccine. The latter data are useful as a way to inform future decisions about the size, number and timing of doses. There is traditionally no focus on efficacy (which is why many Phase I drug trials are conducted on those without known disease). A Phase II trial looks at efficacy, often in a controlled environment. This is a relatively small-scale study demonstrating proof of concept, limited in numbers of participants. In Phase II vaccine studies, potential safety concerns will be an important outcome, but the main focus is demonstrating that the vaccine has sustained impact on the body’s immune system as a means of preventing infection. A vaccine that does not have lasting protective properties is of little use. A Phase III trial is used to scale up the exploration of efficacy in a larger group in the real world, with an importance given to close monitoring for any potential side effects. A Phase IV study is post-marketing and involves much larger real-world studies, perhaps in different social settings and in different populations. Phase IV studies can be ignored here as they do not delay the marketing of a product. However, safety is key to vaccine development and implementation and post-marketing surveillance for any side effects is vitally important (Destefano et al., 2018).

Of course, where it is possible to expedite research we should do so, especially in a pandemic. There are a number of different options, without needing to blow up the established mechanisms for conducting research. These should all be explored and can be summarised as follows:

(a) Expediting research ethics approvals;
(b) expediting regulatory approvals;
(c) beginning manufacturing of promising vaccines ahead of trial completion.

First, we can expedite research ethics approvals. Criteria for the requirements for expedited review will differ according to the standard operating procedures for the relevant committee or the governance mechanisms within the particular national review system. Common grounds for expedited review are that the research is held to be low risk (which won’t be relevant here) or particularly urgent (which would be relevant). Such an expedited process may gain a few weeks of time per protocol.

Second, once the relevant trials have been conducted the process of licensure and other regulatory approvals might also be speeded up, if there is a commitment
to do so from the relevant bodies, as will surely be the case in relation to a vaccine for SARS-CoV-2.

Third, the most serious time constraint is the actual manufacturing process itself which may take many months. There have been recent proposals to begin manufacturing ‘promising’ vaccines before trials have been completed, so as to advance eventual delivery (Cohen, 2020). Altogether, these three measures may shorten the vaccine delivery process by a few months. This is where we should look to expedite processes to secure a safe and effective vaccine, not rushing through or skipping the different research phases.

In the rest of this article, I provide three reasons why a focus on speed as a priority, involving the modification or removal of different phases of the research trial process, is problematic.

Reason 1: the existing phasing of trials is morally significant
Reason 2: rushing fails to appropriately weigh all of the relevant risks and benefits
Reason 3: consent is not sufficient for the justification of additional risk in research

It is my contention that the existing system provides a better approach to balancing all of the relevant ethical considerations and should, therefore, remain in place.

**Reason 1: the existing phasing of trials is morally significant**

The urgency of the need and the size of the global population provide strong intuitive support for rushing the research process to develop an effective vaccine. In this section I explore why we have strong grounds to resist this move and stick with the current phased research development structures for pandemic vaccines.

There are a number of different versions of the general call to rush. One option is cutting out animal studies prior to human trials. This may be justified for a number of reasons: animal models are cruel and unnecessary as we have other in vitro methods of testing or such models do not replicate effectively what happens in humans (Singer, 1979). These are potentially good reasons not to conduct animal studies, but there is nothing special here about pandemic vaccine research. Chappell and Singer (2020) suggest that we should skip animal studies to speed things up. If there is any additional risk, they hold that it can be justified through individuals consenting to run that risk. I return to this argument later. Smith et al. (2020) propose a different route and argue in support of the current proposal from the World Health Organization (WHO) vaccine protocol group (World Health
This suggests that we should proceed straight from a Phase I study to Phase III studies in at least some sites whilst simultaneously conducting Phase II studies in other sites. In earlier iterations of the WHO vaccine protocol it was proposed to just ‘skip’ Phase II studies altogether.

Each version of the ‘skipping’ argument needs to be considered in detail, but my general point is that the phasing of trials has an important ethical justification. It is not merely that as we proceed through the phases, we gain greater epistemic certainty about the risk and benefit profile of the relevant intervention under study. We might achieve this because we have more people involved as participants, but this is not the primary purpose of phasing. Rather, the phases represent different steps in a process, with each phase having a different role, with different research questions to be addressed and different end points used to evaluate those research questions. The results cannot be homogenised across the phases. For example, a Phase I trial is not focused on efficacy, but a Phase II trial is. A product must, normally, succeed at Phase I before going on to Phase II. This is morally significant because Phase I includes a rigorous look at safety. In other words, meeting a safety threshold (Phase I) is a prior requirement to exploring efficacy (at Phase II). A Phase III trial is performed in much larger numbers of people than a Phase II. Phase II comes first as it seeks to demonstrate efficacy but does not expose so many participants to any potential risk. Once, through a Phase II trial, we have a demonstration of some efficacy, with no major side effects, we can then proceed on to a Phase III trial. It is only with a successful Phase III trial that a product can proceed to licensure.

The phasing of trials is a pragmatic system designed to best assure the trade-offs between innovation and safety. Both of these are important in research and the current system attempts to evaluate the potential benefits and harms against a background of uncertainty. There is a danger of moving to an overall ‘emergency ethics’ approach, one that moves away from our usual practice of weighing different relevant moral considerations, to a focus only on presumed benefits. Careful, staged progression through the different phases of research provides the relevant balance. It may have some time costs, but overall it may turn out to be time efficient and, as we will see in the next section, we need to be very careful in assessing possible risks and benefits.

The existing system of phased trials serves as an important means of balancing benefits and risks. How many weeks will be saved by rushing through the research is an empirical matter. It is for the advocates of such an approach to convince us that such savings are real and that they are worth it. We are being asked to trade a slightly earlier access to a product of greater potential risk against being able to access a product that conforms to our normal risk-benefit protocols a few weeks later. The former approach essentially privileges supposed benefit over possible harm. Retaining the existing system, even in the face of a pandemic, is not a requirement to ensure
certainty before action, as uncertainty will always exist. It is, rather, about ensuring a balance between the different relevant epistemic and ethical considerations.

**Reason 2: rushing fails to appropriately weigh all of the relevant risks and benefits**

The argument for rushing the process is most easily justified by appeal to the size of the potential benefits. However, when we count potential harms and benefits, we need to take care. We need to ensure that we include all relevant considerations, we need to weigh them appropriately and we must consider the distribution of where any potential harms and benefits fall. One danger that we should avoid is to focus so much on the aim of producing an effective vaccine that we discount other relevant aims that might be damaged in pursuing this goal. For example, another relevant aim is to ensure trust by the community in other public health measures, for example, routine vaccination schedules. If a focus on producing an effective pandemic vaccine takes shortcuts, say, removes Phase II trials and then something goes wrong, this might damage public support for other vaccinations (or public health in general). The relevant risks to consider are not just those from the vaccine trial itself. For example, harms within a trial or with the post-marketing delivery of a pandemic vaccine are likely to damage trust in routine vaccination and may fuel anti-vaccination sentiment. Rigorous and phased trials (and post-marketing monitoring) are the best way to make sure that potential harms to research participants are reduced. Essentially, we need to ensure that we do not fall into cognitive biases that have long been discussed in psychological research, including the privileging of a short-term advantage over a more substantive future loss (Nisbett and Ross, 1980).

Uncertainty is central to research, but it is worth emphasising how little we know about SARS-CoV-2 as a novel virus and how little we know in general about coronaviruses as a group, despite experience with the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS). We currently have no effective vaccines to prevent any type of coronavirus. We can contrast this with our understanding of influenza if we were to be hit by an influenza pandemic. We have much greater understanding of influenza viruses, their impact on human health and the efficacy of previous influenza vaccines. This knowledge can form the basis for a new vaccine to respond to a novel influenza virus, almost certainly within six months. However, with SARS-CoV-2 we are starting from scratch and have extra grounds to be cautious in developing a vaccine. Many of the current candidate vaccines being developed involve new vaccine technology that has never been proven before in a successful vaccine (Mullard, 2020). Hopefully, at least one of these vaccines will prove effective and safe, but we should not just
assume that this will happen. For all of these reasons, skipping steps in the research development process in developing a SARS-CoV-2 vaccine is ill-advised.

Rushing through the research process, in the sense of skipping steps, did not happen in previous infectious disease outbreaks. For example, a vaccine was developed for Ebola, but that vaccine went through all of the appropriate trials (Agnandji et al., 2016; Henao-Restrepo et al., 2017; Kennedy et al., 2017). It is true that Ebola did not produce a global pandemic, but mortality rates for those infected were much higher (25%–90% according to World Health Organization, n.d.), so the urgency for a vaccine was great for the communities affected.

Given, as stated in the preceding text, that we know so little about this novel virus we need to take great care with developing a vaccine. We don’t know why only some people suffer a serious illness or even death as result of infection with SARS-CoV-2, whilst others suffer only mild or no symptoms. We don’t know what the medium- and long-term impact upon the immune system might be for those previously infected. We don’t know if those infected but with mild or no symptoms have any sustained natural immunity. We also don’t know how any vaccine will interact with the immunological impact of past infection, that is, how the bodies of those people who were previously infected will react to vaccination. Much will depend upon the nature of the candidate vaccine, but in the worst-case scenario vaccinating those previously infected with no or mild symptoms might actually prime full-scale COVID-19 in at least some people. This would be a disaster and vaccine trials have been discontinued in the past because of such reactions. An excellent recent example of this is the dengue vaccine (Dengvaxia) trial in the Philippines. (Halstead, 2018; Larson et al., 2019). Dengue is no doubt a complex case, because of the three different subtypes and the impact of previous infection on the course of disease, but we should note that we know a lot more about dengue than we do about SARS-CoV-2. I am not suggesting that such ‘priming’ will happen, but we need to take it seriously as a potential risk, especially given that we have had millions of people infected across the world and many have had mild or no symptoms.

Whilst it may be appropriate to produce a vaccine quickly as a way to save as many lives as possible and promote economic and social activity, we need to be aware of even rare side effects. If we are vaccinating potentially billions of people, a rare side effect may create many cases. Of course, even catastrophic side effects for some individuals might be ‘worth it’ for the global collective good. However, any such calculations are contentious and far from simple. It is reasonable to think we are in a poorer position to make an evaluation of any risks if we have skipped a phase of the research process. It is important to see that even if all phases are completed, a rare side effect might only emerge after licensure. For example, rotavirus vaccine can produce the rare side effect of intussusception\(^5\) that did not appear in the initial trials (Yih et al., 2014). Once an effective vaccine is released,
relevant pharmacovigilance needs to be in place, and some countries will require support for this because they do not currently have appropriate monitoring structures in place (Dawson, 2015). It is also possible that a vaccine impacts upon different populations and subgroups in different ways. For example, in the 2009 H1N1 pandemic there were a number of reports of young people developing the sleep disorder narcolepsy after being vaccinated (Partinen et al., 2014).

In this section I have focused on potential risks. Of course, most vaccines have an excellent safety record. My argument here is that we should not act in such a way that unnecessarily threatens the immense benefit to global health produced by routine vaccination, even if we suppose there is an advantage in the short term by doing so. Safety is essential to public support for vaccines and we should not act recklessly to threaten it.

**Reason 3: consent is not sufficient for the justification of additional risk in research**

Chappell and Singer (2020) argue that it is justifiable to expose fully informed individuals to the same level of risk that we already tolerate for those acting to reduce the overall level of harm related to SARS-CoV-2 (e.g. healthcare workers). They call this a principle of risk parity and argue that it should apply in relation to pandemic vaccine research. I will argue that their argument is problematic for two reasons. First, we need to take more care in making comparisons between cases. It is not just risk to the ‘volunteers’ in the cases that matters and once we factor in all relevant considerations there is no ‘parity’ between the cases. Second, consent cannot do the work that is required as a justificatory condition where we might choose to skip phases of research.

Chappell and Singer’s principle of risk parity assumes that any act that meets the required threshold of accepted risk in the circumstances is justified. Hence, if healthcare workers voluntarily take on a certain risk, why should research participants not be permitted to voluntarily take on the same amount of risk? The problem here is that the ‘comparison’ between cases is only looking at a narrow range of factors: the direct risk to the individual party consenting to the risk. However, as we saw in the previous section there are many relevant risks and benefits when we are looking at vaccine trials and we should take them all into account. If we are consequentialists, and I’ll assume here for the purposes of argument that we should be, then we should make sure we count all relevant potential consequences. Once we do this, there is no parity between the two cases. Chappell and Singer rely upon the great benefit of delivering a speedier vaccine (saving lives and restoring economic activity, etc.). But they never fairly consider the potential risks relating to both the participants in trials and the wider society through damage to vaccination programmes that I reviewed in the preceding text. Nor do they consider the
increased risk to the population that may be vaccinated with a vaccine that has not been through all of the usual assessment because of ‘skipping’ phases. Participants in trials may be able to consider the risks, but participants in pandemic vaccine programmes may not (given the numbers of people involved and the time, costs and difficulties of even attempted an informed consent in such circumstances). In Chappell and Singer’s ‘parity’ case, they also assume healthcare workers take on any risk involved in their caring roles voluntarily. This, in my view, fails to take into account how many healthcare workers’ roles involve identity issues relating to those roles and how little such roles are subject to negotiation and prior consent at the level of the individual. Being subject to risk in a professional role is just a different thing from being subject to the same amount of risk as a research participant. I don’t think that the principle of risk parity can provide the grounds for the relevant justification required as the comparative cases are not truly comparable. There is much to say about each of the three examples that Chappell and Singer (2020) discuss; in my view challenge studies are the most justifiable of these three, taking into account all of the relevant considerations. But justification for such a view will have to wait for another occasion.

Perhaps it is not the level of risk that does the work but the fact that those running the risk have consented to do so. This is a common view in bioethics and liberal societies more generally. However, an informed consent can by definition only be gained when we have the relevant information to be imparted, which must then be understood by the consenting party. We have good grounds to think that obtaining an informed consent within a research context is more difficult than often thought (Tam et al., 2015). This in turn provides grounds for caution if we are tempted to rely on individuals to protect themselves (Dawson, 2009). If we have skipped over some aspects of the phasing of research, as we saw earlier, we have reasonable grounds for being less certain about the nature of the relevant risks. We are also more generally ignorant of many aspects of the basic science relating to the virus, the impact of the virus upon the human body in terms of disease and the longer term immunological impacts. It is insufficient to seek to just inform relevant potential consenting parties that we are ignorant or uncertain about the relevant risks alone. If risks could in all likelihood be lower, if ‘skipping’ had not occurred, why should we think that consent alone is a sufficient justificatory condition? A stipulation that consent will provide the justification for additional and unnecessary risks that arise as a result of disrupted the normal research steps is not enough, even if such an informed consent is even possible. Again, as argued earlier, the phasing of research seeks to provide a relevant balance through both protection from harm and greater benefit through innovation. Seeking to gain an informed consent may be a necessary condition to justify the bearing of additional risk but it’s another thing to argue that it is in itself sufficient.
Conclusion
SARS-CoV-2 has had a huge impact on virtually everyone’s life across the planet. The existence of a vaccine, should one become available, would be a key piece in reducing the risk from the pandemic. However, we should not forget that the key interventions in the response so far have been public health measures particularly those related to physical distancing. Such measures are likely to continue to be our main source of protection for the foreseeable future. It would be excellent if we had an effective vaccine, but we should take care not to sacrifice other important considerations to produce one. An effective vaccine is a means to an important end: flourishing lives. We should take care to ensure we do not damage the end in promoting the means. Any vaccine should be produced quickly, but not at any cost. After all, only fools rush in.

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Notes
1. In this article I only focus on vaccine trials, but I think that at least some of these arguments could also be applied to research on treatments for COVID-19. I will leave that discussion for another time.
2. I will leave to one side the additional possibility that a narrative of ‘speed’ is used for political reasons, such as seems to be the case with President Trump’s pressure to deliver a vaccine as soon as possible for his own political reasons (Owermohle, 2020).
3. It might be that the traditional phases of trials need general reform because they are not appropriate. If this is the case, it would be good to see some arguments for such a view, so that it can be evaluated. I am focusing in this article only on the argument for a deviation from routine mechanisms specific to research contributing to responding to emergencies such as pandemics.
4. The use of animal models in coronavirus research is challenging (Gretebeck and Subbarao, 2015) but can be potentially important in terms of early efficacy and safety.
5. A complication in which one segment of the intestine ‘telescopes’ into another, causing an intestinal blockage.
6. See Dawson (2016) for discussion of different roles and related obligations.
Dawson

References

Agnandji ST, Huttner A, Zinser ME, et al. (2016) Phase 1 trails of rVSV Ebola vaccine in Africa and Europe. *New England Journal of Medicine* 374(17): 1647–1660.

Chappell RY and Singer P (2020) Pandemic ethics: the case for risky research. *Research Ethics* 16(3–4). DOI: 10.1177/1747016120931920

Cohen J (2020) Pandemic vaccines are about to face the real test. *Science* 368(6497): 1295–1296.

Dawson A (2009) The normative status of the requirement to gain an informed consent in clinical trials: comprehension, obligations and empirical evidence. In: Corrigan O, Liddell K, McMillan J, et al. (eds) *The Limits of Consent: A Socio-Legal Approach to Human Subject Research in Medicine*. Oxford: Oxford University Press.

Dawson A (2015) Ebola: what it tells us about medical ethics. *Journal of Medical Ethics* 41(1): 107–110.

Dawson A (2016) Civic, professional and personal obligations in public health emergency planning and response. In: Arras J, Jennings B, Barrett DH, et al. (eds) *Public Health Emergency Response*. Oxford/New York: Oxford University Press.

Destefano F, Offit PA and Fisher A (2018) Vaccine safety. In: Plotkin SA, Offit PA, Orenstein WA, et al. (eds) *Plotkin’s Vaccines*. Philadelphia, PA: Elsevier, 1584–1600.

Gretebeck LM and Subbarao K (2015) Animals models for SARS and MERS coronaviruses. *Current Opinions in Virology* 13: 123–129.

Halstead SB (2018) Safety issues form a phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine. *Human Vaccines & Immunotherapeutics* 14(9): 2158–2162.

Henao-Restrepo AM, Camacho A, Longini IM, et al. (2017) Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!). *Lancet* 389(10068): 505–518.

Kennedy SB, Bolay F, Kieh M, et al. (2017) Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. *New England Journal of Medicine* 377(15): 1438–1447.

Larson HJ, Hartigan-Go K and de Figueiredo A (2019) Vaccine confidence plummets in the Philippines following dengue vaccine scare: why it matters to pandemic preparedness. *Human Vaccines & Immunotherapeutics* 15(3): 625–627.

Mullard A (2020) COVID-19 vaccine development pipeline gears up. *Lancet* 395(10239): 1751–1752.

Nisbett R and Ross L (1980) *Human Inference: Strategies and Shortcomings of Social Judgment*. Englewood Cliffs, NJ: Prentice-Hall.

Owermohle S (2020) White house pressure for a vaccine raises risk the U.S. will approve one that doesn’t work. *Politico*, 15 June. Available at: https://www.politico.com/news/2020/06/15/pressure-coronavirus-vaccine-risk-approval-316094 (accessed 25 June 2020).

Partinen M, Kornum BR, Plazzi G, et al. (2014) Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination. *Lancet Neurology* 13(6): 600–613.

Singer P (1979) *Practical Ethics*. Cambridge: Cambridge University Press.

Smith MJ, Emanuel EJ, Thome B, et al. (2020) Ethical conditions for accelerating COVID-19 vaccine research.

Tam NT, Huy NT, Long NP, et al. (2015) Participants’ understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. *Bulletin of the World Health Organization* 93(3): 186–198.
World Health Organization (2020) *An International Randomised Trial of Candidate Vaccines Against COVID-19*. Geneva: WHO. (Draft of 28 May 2020). Available at: https://www.who.int/publications-detail/an-international-randomised-trial-of-candidate-vaccines-against-covid-19 (accessed 22 June 2020).

World Health Organization (n.d.) Frequently asked questions on Ebola virus disease. Available at: https://www.who.int/emergencies/diseases/ebola/frequently-asked-questions (accessed 22 June 2020).

Yih WK, Lieu TA, Kulldorff M, et al. (2014) Intussusception risk after rotavirus vaccination in US infants. *New England Journal of Medicine* 370(6): 503–512.