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Commentary

COVID-19 vaccine development: Time to consider SARS-CoV-2 challenge studies?

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ABSTRACT

While a human challenge study holds the prospect of accelerating the development of a vaccine for the coronavirus SARS-CoV-2, it may be opposed due to risks of harm to participants and researchers. Given the increasing number of human deaths and severe disruption to lives worldwide, we argue that a SARS-CoV-2 challenge study is ethically justifiable as its social value substantially outweighs the risks. Such a study should therefore be seriously considered as part of the global research response towards the COVID-19 pandemic. In this paper, we contribute to the debate by addressing the misperception that a challenge study for the coronavirus would lower scientific and ethical standards for vaccine research and development, and examine how it could be ethically conducted. We also set out information that needs to be disclosed to prospective participants to obtain their consent.

1. Introduction

As the world struggles to control the COVID-19 pandemic, some researchers have proposed a bold agenda: using a 'challenge study' to deliberately infect individuals in order to accelerate vaccine development [1].

In the UK, a challenge study is already underway using related coronaviruses that cause milder disease [2]. A major limitation of this approach is that results using other coronaviruses might not directly apply to SARS-CoV-2, the coronavirus that causes COVID-19. So should challenge studies specifically using SARS-CoV-2 be considered?

This prospect has been characterized as a loosening or lowering of research standards [3]. However, challenge studies that are well designed and implemented can be ethically sound and safe for participants [4]. We believe that this option should at least be 'on the table', although further analysis is needed to establish whether such a study is scientifically and ethically justifiable.

If (as some characterise it) efforts against COVID-19 are akin to a war, and likely a long-drawn one, by the same analogy we should carefully consider what 'weapons' can be used, and how they should be deployed in an ethically acceptable manner. Here, we examine how SARS-CoV-2 human challenge studies could be ethically conducted, and some drawbacks and caveats.

2. Why challenge studies are done

Challenge studies have aided development of treatments and vaccines for malaria, influenza, typhoid fever, cholera and dengue [5]. Because these studies happen in a controlled environment, it is easier for researchers to study natural disease progression than it would be in the field. In traditional vaccine trials, a high-risk population is usually studied, but not everyone in that population is necessarily exposed, and risk may not be evenly distributed; people's exposure to infection may vary, and not everyone may be infected during the trial. This means that large trials with substantial follow-up time to accumulate enough cases are needed to test vaccine efficacy. A challenge study guarantees uniform exposure, so can be done faster with fewer participants. This approach could speed up vaccine development by eliminating ineffective candidates early on and accelerating field trials of the most promising vaccines.

3. The case for SARS-CoV-2 challenge studies

The urgency of the current pandemic gives substantial weight to challenge studies. As of 17 May 2020, more than 4.5 million

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COVID-19 cases and more than 307,000 deaths have been reported globally (see World Health Organization Covid-19 situation report). Those numbers will continue to rise, and there is great uncertainty concerning how many more cases, hospitalizations and deaths will eventually occur and how long the pandemic will last. The pandemic is expected to trigger a prolonged global recession that will further negatively impact the health and well-being of individuals worldwide.

SARS-CoV-2 challenge studies could enable three things: studying clinical progression, developing effective vaccines and testing candidate therapies. The latter is less imperative, as therapeutic trials are already taking place in existing patients. To study clinical progression, volunteers challenged with standardized virus doses would be observed to find out what proportion develop symptoms, how much virus it takes to cause disease, how long it takes for infected individuals to develop symptoms, how long individuals are infectious for, and what biomarkers are associated with more severe disease or more effective immune responses. These observations could help answer currently unresolved questions and aid policy decisions, such as whether quarantine durations are adequate, what criteria should be used to ensure that discharged patients are not infectious, the extent to which truly asymptomatically infected individuals are infectious, or whether recovered patients can later be re-infected.

Additionally, candidate vaccines that have satisfied phase I safety and phase IIa dosage trials could be administered to volunteers who are subsequently challenged with the virus as part of a phase IIb trial to see how well the vaccine protects them as compared with a placebo or suitable alternative. Promising vaccines must eventually undergo large-scale testing in at-risk communities, but the process of assessing candidate vaccines prior to large phase III trials could be substantially accelerated by challenge studies [1,6].

It is difficult, if not impossible, to give a precise estimate concerning how much time could be saved in vaccine development through a challenge study. It is already very uncertain whether the US's goal of developing a vaccine within 18 months is feasible, given numerous logistical difficulties and the fact that most candidate vaccines will fail [7] And challenge studies themselves will take some time to establish, including production of a version of the virus that can be deployed in such a study.

But just as uncertainty about the feasibility of developing a vaccine within 18 months should not preclude extraordinary efforts already underway, it is worthwhile to now begin the process of preparing for a SARS-CoV-2 challenge study. Like other vaccine efforts, it is possible a challenge study would not result in an effective intervention. Nevertheless, making a vaccine available even a few weeks sooner than otherwise possible via a challenge study would save many lives and relieve pressure on strained health systems, and would have global social benefits, by allowing countries and economies to resume normal activity that much earlier.

4. Ethical concerns

4.1. Risks of harm to participants

Challenge studies pose substantial risks to participants and wider society. As of this writing there is no proven effective treatment for COVID-19. While the US and Japan have given emergency use authorization for Remdesivir, with more countries likely to follow suit, the underlying clinical evidence for its effectiveness remains limited, and at present it does not demonstrate lowered mortality [8]. Some have argued that a challenge study is inappropriate for any potentially fatal disease that lacks effective treatment [9]. One possibility is to begin preparing for challenge studies now, and only recruit subjects once there is a proven effective treatment. However, such a hard-and-fast rule is insensitive to actual risk levels that may be acceptable even in the absence of treatment.

Estimates of COVID-19 mortality and serious complications vary, with current symptomatic case fatality figures ranging from above 10% in France, Spain and Italy to around 0.1% in Singapore [10]. Case fatality figures may be over-estimates because they typically omit asymptomatic individuals who do not present for treatment.

More reflective of the risk of a challenge study would be the infected fatality ratio, which includes asymptomatic infections. For example, a French model has extrapolated from surveillance data to estimate an infected fatality ratio of 0.7% in that population [11]. And recent antibody testing suggests there may be even more asymptomatic infections than are confirmed due to limited testing [12]. Results from a serological study in residents of LA county imply an infected fatality ratio in that population of about 0.07% [13].

In addition, there is a clear age effect, with substantially lower mortality in younger individuals. In the French model, individuals age 20–29 were estimated to have an infected fatality ratio of 0.007% [11], which is roughly in line with the annual risk of dying in a traffic accident [14]. A SARS-CoV-2 challenge study would therefore likely recruit younger individuals, to minimize the risk of adverse outcomes. Results in this population may not generalize to older individuals and those with co-morbidities who would most benefit from effective vaccines. Nevertheless, this approach could accelerate progression of promising candidate vaccines to Phase III trials in high-risk groups.

Close monitoring for severe adverse reactions within the challenge study would also enable more rapid treatment. This would help lower the risk of harm compared with community transmission, where lack of detection of relevant symptoms could delay hospitalization. Careful participant selection and monitoring would minimize risks to the point where a challenge study's risks would be lower than other risky activity, such as the risk of death for front-line healthcare workers during the pandemic [15]. This suggests a COVID-19 challenge study's risks would be ethically acceptable—if there is substantial prospect of great social benefit.

4.2. Necessity and value

Justification for human challenge studies would need to rigorously demonstrate that the relevant knowledge could not be generated in a similar timeframe using less risky approaches.

By way of comparison, during the 2016 Zika virus epidemic, a challenge study was considered but ultimately rejected by a National Institutes of Health ethics panel, due to concerns about participant safety, third-party harms and social value [16]. At the time, it was believed that because the disease was widespread in certain regions, a more traditional design of testing a vaccine in the community could achieve similar social value as a challenge study without posing as many risks to participants as well as third parties, through for example male participants infecting female partners, with the disease then transmitted to fetuses.

A similar argument about lack of necessity could be made against SARS-CoV-2 challenge studies. However, the global harm wrought by COVID-19 in terms of effect on lives and livelihoods massively overshadows that of Zika. The risks, then, of a SARS-CoV-2 challenge study would be more easily outweighed by the social value of a challenge study that can substantially improve understanding of COVID-19 and accelerate vaccine development.

The public benefit of this acceleration, though, will depend on the COVID-19 pandemic situation in the coming months. The slowing of transmission via social distancing measures, and/or development of effective treatments may lessen the urgency of accelerated vaccine development. However, if successful treatments are found, a challenge study's risk profile will also substantially fall. Even if transmission is slowed, absent herd immunity or an effective vac-

cine, the possibility of a 'second wave' remains. In that case, challenge studies would become potentially even more advantageous over field trials because limited community spread due to social distancing would mean fewer naturally occurring cases that could be used to demonstrate a vaccine's efficacy. This scenario would bear some resemblance to the present situation for Zika, now that infection rates have fallen dramatically. Notably, this fall has spurred calls to revisit the prospect of a Zika challenge study, to improve the likelihood an effective vaccine will be in place should Zika ever resurface in large numbers [17].

4.3. Compensation

Challenge studies offer substantial monetary compensation; the ongoing coronavirus study pays participants GBP3500 [2]. Some ethical guidelines, such as those from the Council for International Organizations of Medical Sciences, hold that financial compensation should only be used to offset time and inconvenience in order to ensure people are not induced to participate against their better judgment [18]. This position has come under considerable scrutiny on a variety of bases, including scepticism that payment has a substantial distorting effect on judgment, and concern that such a policy results in underpayment, that is, paying subjects less than what would be fair or acceptable [4].

Even if payment is made to compensate for risks undertaken, this does not imply that compensation may be used to justify the risks and burdens imposed. Justification for a SARS-CoV-2 challenge study should depend solely on its prospective social benefits outweighing the risks.

4.4. Negative externalities

Even with appropriate participant selection criteria to minimize harms, fair compensation, and high-quality safety monitoring, the physical risks of a challenge study are substantial. How much risk should we allow individuals to undertake? Wartime analogies imply quite a lot; if individuals can volunteer to risk their lives on the battlefield, why not allow them to do so in the global fight against COVID-19? [19].

A key difference is the nature of potential negative externalities of a challenge study, as SARS-CoV-2 is highly infectious. Risk of community spread from participants can be mitigated by isolation and infection control measures. Participants would maintain their right to withdraw from challenge studies, but prevailing isolation and quarantine laws would apply to separate infected participants from the community even if they refused further observation and testing in the study.

Even with such measures, the possibility always exists of infecting research team members, despite adequate personal protective equipment, or, of individuals being infectious for longer than previously believed. But if research is key to pandemic response then researchers, like healthcare workers, should be allowed to bear the risks of conducting a challenge study as part of frontline work.

A further concern is that challenge studies could divert resources – medical personnel, equipment and other infrastructure – away from treatment centres and public health efforts that sorely need them. They should therefore be conducted in areas where healthcare systems are not overburdened and unlikely to become overburdened as the challenge study is undertaken.

4.5. Fair prioritization for treatment

Ill participants might have rightful claim to prioritisation for critical care resources like ventilators or recently developed treatments that are in short supply, analogous to the priority proposed for healthcare workers given their social contribution and the risks they undertake [20]. Such prioritisation, which is based on the principle of reciprocity, might come at the cost of non-participants, with consequent negative health effects.

To ensure fairer allocation and maximization of the medical utility of scarce resources, all patients needing critical care could be assessed equally based on short- and long-term survival prospects, with priority given to research participants only if they have equivalent prognoses and some prospect of benefit. However, any such prioritization would be subject to prevailing critical care triage or treatment policies in the relevant setting.

4.6. Informed consent

Due to the substantial risks involved, special care should be taken concerning the information conveyed during the informed consent process and participants assessed to ensure they truly understand what they are undertaking [4]. Box 1 details essential information for potential participants to understand. The content of this list reflects generally accepted informational components of informed consent relating to benefits, risks, procedures and other consequences of enrolling in the challenge study. This list is not exhaustive, and omits elements of informed consent like information on marketability of resultant products or data confidentiality policies that, while important, do not raise particularly unique issues for a SARS-CoV-2 challenge study.

Box 1 : Essential information in the informed consent process for a SARS-CoV-2 challenge study.

Information	Details
Risks of contracting COVID-19 and mortality.	Based on existing observational data, broken down to the extent feasible by age range and other relevant factors. Uncertainties around these estimates should be conveyed, along with the possibility that the rates among challenge study participants will substantially differ.
Nature of COVID-19 and treatment.	Spectrum of disease presentation and severity, prognosis, and type of symptomatic treatments and supportive care available (e.g. invasive mechanical ventilation for critically ill cases)
Prospects for success.	Explanation of the study's aims and prospects for benefiting society, of sufficient derail that participants can adequately assess whether the social value of the study is worth its substantial personal risks. In the interest of transparency, this should include forthright information on the very real possibility that candidate vaccines will

(*continued on next page*)

Study procedures.	Length of stay, type of facility, amenities available, visitation from family possible and alternatives, follow-up procedures, etc.
Risks of experimental vaccines/ treatments.	Phase I safety data should already be available when a challenge study commences.
Potential for re-infection and negative consequences of acquiring antibodies.	Information on what is known about the duration of immunity, both from natural infection and from vaccination, acknowledging that there could be a risk of re-infection, even if patients receive the vaccine; along with the theoretical potential that antibodies could make re-infections worse by facilitating virus entry into cells.
Requirements for mandatory isolation.	Participants may withdraw from the study at any time, but would still have to remain in isolation per local policies. Data gathered up to point of withdrawal may be retained if local laws allow so, especially in light of the substantial public interest in retaining as full and unbiased a dataset as possible.
Priority for treatment, or lack thereof.	Depending on whether such priority is agreed to by relevant local healthcare institutions, with the caveat that such policies are outside the control of the research team and could be subsequently changed.
Compensation.	Including information on whether payment will be pro-rated in case of early withdrawal.
Post-trial entitlements.	E.g., access to future vaccines or experimental therapies.
Alternatives to participation.	Other options, if available, to help fight COVID-19: e.g., participation in Phase I clinical trials for COVID-19 treatment and non-challenge vaccine trials; social distancing; good hygiene/ frequent hand-washing.

A difficulty with obtaining adequately informed consent is that much information about COVID-19, including actual mortality risk and infectiousness after recovery, is still highly uncertain, and models have been rapidly adjusting since the early days of the pandemic. Uncertainty, however, does not preclude adequate informed consent; phase I safety trials, for instance, by definition have an uncertain risk profile. Advances in community testing and subsequent modelling of COVID-19 will help reduce this uncertainty and improve upon the informed consent process for a potential challenge study. But as long as the probable range of risks is acceptable (as argued above), uncertainty does not preclude the provision of adequate informed consent.

5. Conclusion

The stakes of a SARS-CoV-2 challenge study are high due to the risks of harm to participants. There may be devastating repercussions for all other human challenge studies if one or more volunteer participant(s) were to experience significant adverse outcomes or even death from intentional exposure to COVID-19. A SARS-CoV-2 challenge study should not just be well-designed with appropriate safeguards to minimize risk, but its inherent risks and its justification – seeking to more quickly reduce the human toll of the pandemic as a global good – should be communicated to the public to minimize potential fallouts. We have argued that challenge studies could be ethically conducted without lowering of scientific and ethical standards—they merit serious consideration as the human toll of the COVID-19 pandemic continues to grow.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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