

# COVID-19 human challenge studies: ethical issues

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COVID-19 poses an extraordinary threat to global public health and an effective vaccine could provide a key means of overcoming this crisis. Human challenge studies involve the intentional infection of research participants and can accelerate or improve vaccine development by rapidly providing estimates of vaccine safety and efficacy. Human challenge studies of low virulence coronaviruses have been done in the past and human challenge studies with severe acute respiratory syndrome coronavirus 2 have been proposed. These studies of coronaviruses could provide considerable benefits to public health; for instance, by improving and accelerating vaccine development. However, human challenge studies of severe acute respiratory syndrome coronavirus 2 in particular might be controversial, in part, for ethical reasons. The ethical issues raised by such studies thus warrant early consideration involving, for example, broad consultation with the community. This Personal View provides preliminary analyses of relevant ethical considerations regarding human challenge studies of severe acute respiratory syndrome coronavirus 2, including the potential benefits to public health and to participants, the risks and uncertainty for participants, and the third-party risks (ie, to research staff and the wider community). We argue that these human challenge studies can reasonably be considered ethically acceptable insofar as such studies are accepted internationally and by the communities in which they are done, can realistically be expected to accelerate or improve vaccine development, have considerable potential to directly benefit participants, are designed to limit and minimise risks to participants, and are done with strict infection control measures to limit and reduce third-party risks.

## Introduction

Coronaviruses are ubiquitous causes of respiratory infection in humans, and those causing symptoms of the common cold arguably constitute longstanding pandemics of low severity. Recent outbreaks of higher virulence coronaviruses (eg, those associated with severe acute respiratory syndrome [SARS], Middle Eastern respiratory syndrome [MERS], and COVID-19) have resulted in high numbers of deaths and disease, the institution of drastic public health measures, and more research on coronavirus vaccines. As of April 8, 2020, there are more than 100 vaccine candidates for COVID-19.<sup>1,2</sup>

Human challenge studies involve the intentional infection of research participants and can provide a powerful scientific method for the testing of vaccines and therapeutics and for studying host–pathogen interactions in small numbers of participants (ie, around 25–100 people). Such studies have been done with many pathogens, including low virulence coronavirus strains<sup>3–5</sup> and pandemic influenza virus H1N1.<sup>6</sup> Challenge studies generally have a good safety record; however, there have been rare cases of serious harms, such as myocarditis among influenza challenge study participants.<sup>7</sup> More virulent coronaviruses have not been investigated in human challenge studies, presumably in part because of a perception that these studies would pose unacceptably high risks to participants. Questions related to whether there are upper limits to research risks and what such limits might be or how they should be determined are unresolved.<sup>7–9</sup> The prospect of exceptionally great benefits (eg, in responding to a pandemic) in some cases justifying the higher risks has been suggested.<sup>9</sup> Human challenge studies with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with the appropriate strategies to minimise risk, might entail risks to participants below the commonly cited upper limits to risk.<sup>9,10</sup>

Animal challenge studies have been used to test coronavirus vaccines, but, to date, the generalisability of such studies to humans is poor.<sup>11,12</sup> Meanwhile, phase 1 research in humans of COVID-19 vaccines has been fast-tracked, including early testing of vaccines in humans without previous safety data in animals (NCT04283461).

Human challenge studies can result in considerable public health benefits by providing important scientific data regarding host–pathogen interactions (eg, correlates of protection) and the transmissibility of pathogens and by accelerating and improving vaccine development.<sup>7,13</sup> Human challenge studies can expedite vaccine development because these studies are often substantially smaller, shorter, and less expensive than other kinds of studies and thus enable the efficient selection of vaccine candidates for further investigation in larger studies (eg, field trials) or for monitored emergency use (with the ongoing collection of safety and efficacy data).<sup>13,14</sup>

Well designed human challenge studies have the potential to improve the efficiency of vaccine development, and thereby benefit public health sooner than would otherwise be possible (both during an epidemic and in interepidemic periods), and reduce the number of participants exposed to risk in the estimation of vaccine safety and efficacy. Thus, there is a compelling ethical rationale for doing such studies, at least in some cases.<sup>15–17</sup>

Nonetheless, human challenge studies are ethically sensitive and raise several controversial and unresolved issues in research ethics because some study designs can be perceived to involve high levels of risk for healthy volunteers, risks to third parties (eg, when the pathogen used to infect participants might spread to others), and high levels of uncertainty regarding the consequences of infection (especially with novel or neglected pathogens).<sup>7,8,18–20</sup> Furthermore, research during epidemics and pandemics can sometimes be controversial because of lower levels of

*Lancet Infect Dis* 2020;  
20: e198–203

Published Online  
May 29, 2020  
[https://doi.org/10.1016/S1473-3099\(20\)30438-2](https://doi.org/10.1016/S1473-3099(20)30438-2)

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community trust in research during such crises.<sup>21</sup> Thus, human challenge studies should be done to particularly high scientific and ethical standards to protect participants and preserve public trust in research and vaccines.

This Personal View explores the ethical considerations relevant to coronavirus human challenge studies with a focus on the current COVID-19 pandemic. Early ethical analysis of COVID-19 human challenge studies is important because of the aforementioned complexities. In the 2015–16 Zika virus epidemic, the proposed human challenge studies were forestalled largely because of the conclusions of an ethics consultation that highlighted concerns regarding risk and uncertainty.<sup>19,22</sup> At the time, critics claimed that the ethics consultation had unnecessarily “slammed the door on progress”<sup>23</sup> because, according to Zika virus researchers, relevant risks could be adequately controlled and the potential public health benefits of human challenge studies with Zika virus could be considerable.<sup>22</sup> The apparent feasibility of field trials during the Zika virus epidemic was also considered a reason not to do human challenge studies with Zika virus;<sup>19</sup> however, the rapid resolution of the epidemic meant that field trials were unfeasible by the time vaccine candidates were ready for testing. It was argued by Shah and colleagues<sup>19</sup> that human challenge studies would be more ethically acceptable during interepidemic periods (when field trials would be unfeasible).<sup>24</sup> However, human challenge studies approved by ethics committees are increasingly being done in the context of high background transmission (ie, in endemic areas). The fact that prospective participants face background risks of infection might be salient to the ethical acceptability of the risks of human challenge studies (including during a pandemic).<sup>7</sup> Prospective consideration of COVID-19 human challenge studies might thus be crucial to ensure appropriate ethical analysis, policy making, and, possibly, study design during current and future pandemics.<sup>25</sup>

#### COVID-19 compared with other relevant diseases

Infection with SARS-CoV-2 is associated with consequences ranging from asymptomatic infection, to mild disease, to severe respiratory failure, and death.<sup>5,26</sup> SARS-CoV-2 emerged as a human pathogen in late 2019 and has since resulted in the COVID-19 pandemic.<sup>1,26</sup> Early reports from China estimated the overall COVID-19 case fatality risk to be 2–3%, with higher risks in older individuals (eg, 14·8% in those aged >80 years) and in those with comorbidities; the case fatality risk in health-care workers in China was 0·3%.<sup>27</sup> Estimates of the infection fatality risk (adjusted for asymptomatic cases) correlate with age, ranging from 0·007%–0·031% for people aged 20–29 years to 7·8%–10·1% for people aged 80 years and older.<sup>28,29</sup>

By comparison, SARS and MERS are associated with much higher overall population case fatality risks: approximately 10% for SARS<sup>30</sup> and 37% for MERS.<sup>31</sup> As a further (non-coronavirus) comparator, the 2009 H1N1 pandemic influenza virus was associated with a case

fatality risk of up to 0·1% in adults aged 20–64 years (and the infection fatality risk was probably substantially lower);<sup>32</sup> yet, early data in 2009 reported a case fatality risk for the overall population to be as high as 7%.<sup>33</sup>

#### Coronavirus human challenge studies

Human challenge studies involving coronavirus strains causing mild illness were done at the UK's Common Cold Unit from the 1960s to the 1990s.<sup>3</sup> Such studies were done safely, involved inpatient stays of up to 3 weeks,<sup>3</sup> and sometimes involved the testing of therapeutic interventions.<sup>4</sup> Coronavirus human challenge studies were reinitiated in early 2020 with mild strains,<sup>34</sup> and human challenge studies with highly virulent strains, including SARS-CoV-2, were proposed on March 31, 2020, by Eyal and colleagues,<sup>35</sup> and subsequently by others.<sup>36,37</sup>

Some might doubt whether viruses that are perceived to be associated with high risks of severe disease, such as SARS-CoV-2, are appropriate candidates for human challenge studies. However, such studies might arguably be ethically acceptable when there is a large public health threat associated with a particular pathogen (especially a pathogen for which no effective treatment or vaccine exists), relevant research risks can be adequately controlled or are similar to the background risk of infection in the community, and human challenge studies would accelerate vaccine development (relative to alternative study designs) or provide other considerable public health benefits. Because such studies warrant careful ethical scrutiny, analyses of ethical and scientific issues should inform policy development and possible study design.

#### Ethical considerations

##### Public engagement

Public engagement can help to assess the local acceptability of human challenge studies, maximise transparency by responding to any community concerns, and elucidate the potential effect of research on the community.<sup>38–40</sup> Engagement should therefore begin very early in the planning and design of COVID-19 human challenge studies, be done efficiently in light of the rapidly evolving pandemic, and continue during and after the research. Such activities should include dialogue between scientists, ethicists, prospective participants, and community representatives. Beyond these groups, international consultation (eg, with scientific bodies and policy making agencies) is also important.<sup>7,18</sup>

##### Public health benefits

The ethical acceptability of COVID-19 human challenge studies would be in part contingent on there being potential benefits (for public health or for participants) that outweigh the expected risks. Important potential benefits to public health include those arising from the acceleration of vaccine development, the development of more effective vaccines, and the improvement of relevant

scientific knowledge that can inform public health practice (eg, results regarding correlates of protection or the risks of transmission from asymptomatic individuals). Arguably, the benefit–risk profile of a particular study should also be considered by regarding its place in an overarching research programme,<sup>41</sup> compare favourably with alternative research designs, and be evaluated in terms of the generalisability of the findings (eg, estimates of vaccine efficacy) to relevant populations.<sup>7,16</sup>

The use of human challenge studies in the development of vaccines for SARS-CoV-2 is likely to have several benefits, including the opportunity to directly compare the efficacy of multiple vaccine candidates when doing multiple field trials might be less efficient or unfeasible. The benefits are likely to be higher when estimates of vaccine efficacy derived from such studies are generalisable to relevant populations and there is a clear pathway from human challenge studies to further testing and the timely regulatory approval, manufacture, and distribution of a novel vaccine. Furthermore, in interepidemic or interpandemic periods when field trials are unfeasible, human challenge studies might be the only way to test vaccine efficacy.

There can often be tensions between the scientific and public health aim to maximise generalisability and the need to protect participants, meaning that an appropriate balance must be sought between competing ethical considerations.

For example, the use of low-risk (eg, attenuated) challenge strains would reduce the risk to participants. This strategy, however, might require extended time for strain development and conflict with the need to select strains that are adequately similar to pandemic strains so as to produce results (eg, regarding vaccine efficacy) that are more relevant to public health priorities.<sup>16</sup>

Selecting participants at low risk of severe disease (eg, healthy young adults) would reduce the risk to participants. Nonetheless, such a strategy is also suboptimal because the results yielded might not enable confident estimates of vaccine efficacy in individuals at higher risk of disease (eg, older people [ $>60$  years] and those with comorbidities). However, if a vaccine for COVID-19 is subsequently approved for use, this strategy might at least enable the effective vaccination of individuals at lower risk to indirectly protect those at higher risk.<sup>42</sup> In any case, given the virulence of SARS-CoV-2 in older individuals and in those with comorbidities, the risks of human challenge studies would be more acceptable if such studies enrolled healthy young adults (eg, those aged 18–30 years), at least initially.

#### Potential direct benefits to participants

Although human challenge studies are often characterised as non-therapeutic research in which healthy volunteers do not directly benefit from study participation, there can sometimes be direct benefits to study participants. Although, payment of participants might be ethically

appropriate, payment is generally not considered a benefit that would offset risks.<sup>7</sup> However, potential direct benefits of being infected with SARS-CoV-2 in the course of human challenge studies would include participants being exposed to less infection-related risk than if they are infected in the community (eg, because of early diagnosis and medical care) and gaining immunity to future infection in the context of a high background risk (although more data are needed to clarify the degree and duration of immunity to SARS-CoV-2).<sup>16</sup> Participants might also benefit if they receive an experimental vaccine that turns out to be effective.

Participants' immunity, whether the immunity results from challenge infection or an experimental vaccine, might also benefit third parties, especially if health-care workers are recruited to participate in the studies, because this immunity might prevent health-care workers from becoming infected and subsequently infecting others.

#### Risks to participants

Participants in coronavirus human challenge studies might face risks associated with the challenge infection and, in some cases, the experimental vaccine (or other intervention). Such risks should be minimised—eg, via the restriction of participation in initial studies to healthy young adults and the provision of high-quality medical care, including intensive care, if required.

Although many young adults infected with SARS-CoV-2 are asymptomatic, some infections cause more severe disease. For individuals aged 20–29 years, the estimated risk of admission to hospital for treatment is 0.6%–1.0% and the infection fatality risk is 0.007%–0.031%.<sup>28,29</sup> More data are needed for more accurate estimates; however, these values include young adults with comorbidities who would be excluded from human challenge studies. There might nevertheless be rare severe outcomes (eg, potentially fatal respiratory failure requiring ventilation) or lasting harms (eg, long-term respiratory deficits) among participants in human challenge studies.<sup>7,43</sup> Although these risks might be higher than those associated with many modern human challenge studies, such risks might be considered acceptable if COVID-19 human challenge studies have considerable expected benefits, the risks in question do not entail a major net increase in risk (in light of background risks of infection), and there is long-term follow-up of participants and full compensation for any research-related harms. SARS-CoV-2 challenge studies might thus be ethically acceptable (especially when participants already face a high background probability of infection), even in the absence of specific or curative treatment. The use of attenuated strains that could provide data equally as useful as the data provided by wild-type strains and the use of proven specific treatments (if developed) could further reduce risks to participants, but developing such strains or treatments could take a long time and thus detract from the acceleration of vaccine development that is enabled by challenge studies.

### Background risk

Another important consideration for human challenge studies is the background risk of infection faced by potential participants. Individuals who are highly likely to be naturally infected with a pathogen during an epidemic (eg, in some cases, health-care workers) might face a smaller increase in risk related to participation in human challenge studies than the general population. The existence of background risks has been judged to be one consideration in favour of the ethical acceptability of early yellow fever challenge studies,<sup>9</sup> proposed Zika virus challenge studies,<sup>19</sup> and human challenge studies in endemic settings more generally.<sup>7</sup>

However, the contribution of background risk to assessments of research risk is controversial.<sup>7</sup> One reason for concern is that background risks of infection are sometimes due to injustice (eg, when a higher probability of infection is caused by poverty or policy failures, such as those that leave health-care workers with inadequate personal protective equipment). A second reason for concern is that where background risks are high, although the marginal risk of participation in human challenge studies might be low, the absolute risk of infection might be high nonetheless. For instance, because yellow fever is associated with a case fatality risk of 15–50% (ie, much higher than COVID-19),<sup>44</sup> the early yellow fever challenge studies, which were done in an endemic area (with a high background risk),<sup>10</sup> had a high absolute risk of infection. Early yellow fever studies are still widely regarded as being ethically acceptable, not only because of the high background risk of infection, but also because the results led to public health benefits and the volunteers provided proper informed consent.<sup>9,10,45</sup> Subsequent yellow fever studies were, however, disbanded after three deaths among study participants.<sup>10</sup>

Risk minimisation is thus important for human challenge studies, even in the context of high background risk. With appropriate risk minimisation (eg, careful titration of viral dose, early diagnosis, and optimal medical care if required), some healthy participants in human challenge studies might face little (if any) additional risk related to experimental infection. However, because COVID-19 has placed a strain on health-care systems, challenge studies (and other research) might be unfeasible or inappropriate during an epidemic, in part because scarce resources need to be prioritised for clinical care. Therefore, for such studies to be approved, decisions about the optimal timing and location of human challenge studies would be crucial.

### Self-experimentation

It is conceivable that researchers might volunteer for COVID-19 human challenge studies during the current pandemic alongside other volunteers. This occurrence raises questions regarding the degree to which self-experimentation increases the permissibility of high-risk human challenge studies. The Nuremberg Code posits

that high-risk studies might be more acceptable when researchers themselves serve as volunteers. However, this suggestion, which was appealed to in vindication of early yellow fever studies,<sup>9</sup> might be controversial, in part because clinical and research staff might feel pressure to participate.<sup>7</sup> Whether the willingness of researchers to undergo the risks of challenge infection would justify exposing other research participants to higher risks is also unclear.<sup>25</sup> In any case, so long as all participants provide adequate informed consent and other research ethics criteria are met, high-risk human challenge studies might be justified whether or not they include self-experimenting researchers.

### Uncertainty for participants

In addition to risks, infection with novel or neglected diseases might be associated with high levels of uncertainty. Unexpected adverse events might occur and participants should be warned that risk estimates might not include such outcomes and be fully compensated for any harms. Importantly, levels of uncertainty regarding so-called familiar pathogens are often higher than they seem and might increase the scientific benefits of human challenge studies because such studies might reveal important new findings that can help to reduce risk to future participants in larger studies or improve clinical and public health practice.<sup>7</sup>

### Risks related to experimental vaccines

Although vaccines are usually associated with very low risks, experimental vaccines might not protect participants and, in some cases, might even increase the severity of disease among those who are subsequently infected. These outcomes have occurred, for example, for vaccines against respiratory syncytial virus<sup>46</sup> and dengue virus,<sup>47</sup> in some cases resulting in small numbers of deaths among participants in vaccine research. This kind of danger might apply to coronavirus vaccines, because vaccine-enhanced disease has been observed in animal challenge studies with coronaviruses.<sup>12</sup>

Vaccine-enhanced disease could result in high risks to participants in both human challenge studies and vaccine field trials. Challenge studies are arguably a superior way of evaluating the risk of vaccine-enhanced disease compared with field trials because smaller numbers of participants are vaccinated and challenged at a time and participants receive closer monitoring and more immediate medical care than would be available in a field trial. However, if vaccine-enhanced disease is rare, human challenge studies enrolling small numbers of participants might not reveal it.

### Risks to third parties

The potential for third-party risks should be a key consideration in the ethical evaluation of human challenge studies.<sup>7,18</sup> If high-risk strains are used, there would be strong ethical justification for strict infection

control measures, including stringent use of protective equipment by research staff and isolation of participants while contagious; public health law might require such measures, even if participants choose to exercise the right to withdraw from research. Low-risk strains might sometimes warrant strict infection control because of the potential for mutation (resulting in higher risks) and because some local communities might not accept even low third-party risks.

### Alternative trial designs

In the current pandemic, one might think that doing vaccine field trials without human challenge studies would be preferable because field trials are particularly feasible where incidence is high, the feasibility of field trials could be increased by innovative designs (eg, ring vaccination), human challenge studies might need to be followed by field trials in any case (whether or not regulators are willing to approve a vaccine for monitored emergency use on the basis of human challenge studies alone), and considerable time might be required to develop challenge strains and establish human challenge studies.

Such proposals are worth considering but face several practical and ethical difficulties. First, if more than one or two SARS-CoV-2 vaccine candidates become ready for efficacy trials, then multiple (parallel or sequential) field trials would plausibly require tens of thousands of participants and take many months or years to complete. Second, in such cases, human challenge studies would be by far the most feasible way of providing comparative efficacy estimates, which would help to identify more efficacious vaccines.<sup>48</sup> Third, vaccine-enhanced disease would be problematic in small numbers of volunteers in human challenge studies, but might cause even greater harm and controversy in large field trials.<sup>47</sup> Fourth, public health policies in many jurisdictions might suppress transmission to the point where field trials are unfeasible. Finally, site selection for field trials raises justice concerns. The burdens of field trials done during COVID-19 epidemics would be concentrated where public health policies are weakest and disease incidence highest. Furthermore, the largest benefits of mass vaccination (after a vaccine is shown to be efficacious in a clinical trial) would primarily accrue to populations other than those in which field trials occur because large numbers of individuals in these populations would have been infected during the peak of the epidemic (ie, at the time of the field trial). Ultimately, ethical assessments of the potential benefits and risks of human challenge studies compared with alternative trial designs by local and international decision makers should be made in light of the best available empirical data and models of the expected harms and benefits of different proposed research programmes.

### Conclusions

COVID-19 poses an extraordinary global health threat for which vaccines are urgently needed. Among other

benefits, COVID-19 human challenge studies could accelerate vaccine development, helping to test multiple candidate vaccines. More ethically acceptable study designs would involve young healthy participants in inpatient settings with immediate access to high-quality health care and strict infection control measures. All risks should be minimised to the extent that risk minimisation would not unduly compromise potential research benefits. Consultation with scientific experts, prospective participants, and the wider community will help to determine the extent to which residual risks are acceptable and outweighed by the expected benefits.

#### Contributors

EJ wrote the first draft of the manuscript. MJS and EJ conceived the study, edited the manuscript, and approved the final version for publication.

#### Declaration of interests

EJ and MJS report grants from the Wellcome Trust.

#### Acknowledgments

Our ethical analyses in this paper were informed by a project supported by the Wellcome Trust (210551/Z/18/Z). The funder of the study had no role in the writing of the manuscript or the decision to submit for publication.

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