

Evaluating use cases for human challenge trials in accelerating COVID-19 vaccine development

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Abstract

Recently, human challenge trials (HCTs) have been proposed as a means to accelerate the development of an effective SARS-CoV-2 vaccine. In this paper, we discuss the potential role for such studies in the current COVID-19 pandemic. First, we present three scenarios in which HCTs could be useful: evaluating efficacy, converging on correlates of protection, and improving understanding of pathogenesis and the human immune response. We go on to outline the practical limitations of HCTs in these scenarios. We conclude that, while currently limited in their application, there are scenarios in which HCTs would be vastly beneficial and, thus, the option of using HCTs to accelerate COVID-19 vaccine development should be preserved. To this end, we recommend an immediate, coordinated effort by all stakeholders to (1) establish ethical and practical guidelines for the use of HCTs for COVID-19; (2) take the first steps toward an HCT, including preparing challenge virus under GMP and making preliminary logistical arrangements; and (3) commit to periodically re-evaluating the utility of HCTs amid the evolving pandemic.

Keywords: Vaccine evaluation; COVID-19; Pandemic; Controlled Human Infection

Introduction

As of this writing on May 6, 2020, SARS-CoV-2 has swept across the globe, leading to almost 3.5 million confirmed infections worldwide and over 240,000 deaths.¹ While many clinical trials are underway for therapeutic candidates, vaccines are seen as humanity's best weapon against COVID-19. Ten initiatives have at least begun recruiting for phase 1 clinical trials of their vaccine candidates.^{2, 3} At least 115 other vaccine candidates are in discovery or pre-clinical stages of development across various institutions and companies.⁴ Organizations such as the Coalition for Epidemic Preparedness Innovations (CEPI) have advocated measures to shorten development times, such as conducting phase 1 clinical trials in parallel with animal testing and starting early scale-up of manufacturing capacity for promising candidates.⁵ Still, even with these urgent measures, in February the WHO optimistically projected 12–18 months until an effective vaccine could be approved for public use, with potential further manufacturing and regulatory delays until it is broadly accessible,⁶ although several initiatives have announced more aggressive targets.⁷

Historically, human challenge trials (HCTs) have played a useful and ethically defensible role in infectious disease research, providing crucial information about the nature of human-pathogen interactions.⁸ For example, HCTs have provided data on the efficacy of cholera vaccines prior to large field trials, while malaria human challenge models have been used for decades in drug development and gave early indications regarding the possible efficacy of RTS,S/AS01, the leading malaria vaccine candidate.^{9, 10, 11, 12, 13} They also have been used in the study of dengue, influenza, typhoid, norovirus, and other pathogens, and Zika challenge studies may be in development.^{14, 15, 16, 17, 18} In HCTs, a relatively small number of healthy volunteer participants are administered a vaccine candidate or a placebo. However, unlike in conventional trials, consenting HCT participants are then administered an infectious dose of pathogen, and the outcomes of this infection is tracked. By challenging participants with pathogens under close observation in a clinical setting, HCTs can provide a unique opportunity to assess efficacy of a vaccine candidate.

In the context of the SARS-CoV-2 pandemic, Eyal et al. suggested that HCTs could speed up COVID-19 vaccine development by several months.¹⁹ In the midst of a pandemic, they argued, even a modest acceleration in vaccine development could theoretically avert many deaths. This and similar proposals have sparked substantial dialogue by scientists and bioethicists about the ethical justification and practical utility of HCTs.^{20, 21, 22}

In this paper, we describe several potential use cases for HCTs in the current COVID-19 pandemic, the limitations of using HCTs in these scenarios, and their implications for deciding how to proceed with HCTs in assisting COVID-19 vaccination development.

Use cases for HCTs in COVID-19 vaccine development

We present three potential use cases for HCTs in COVID-19 vaccine development.

Evaluating efficacy

Eyal et al. proposed that HCTs, in combination with a large-scale short-term expanded phase 2 safety study, could be used to test for efficacy and replace comparably lengthy phase 3 trials.²³ With the necessary approvals in place, an HCT could theoretically take as little as two months to conduct, whereas a phase 3 trial—particularly one testing a vaccine candidate for which no correlates of protection are available—would likely take months longer to produce a reliable signal of efficacy and require far more trial participants. This is because the number of participants and the duration of a traditional phase 3 trial should be large enough to ensure that a sufficient number of participants have been exposed to the pathogen naturally, while in an HCT, exposure is guaranteed by the challenge.

One of the main advantages of HCTs is therefore that they could accelerate the licensure of an effective vaccine candidate. Indeed, there is precedent for licensing on the basis of HCT efficacy data. For example, HCT efficacy data in combination with conventional trials targeting safety and immunogenicity provided the basis for licensing the first FDA-approved cholera vaccine.^{24, 25} However, it remains unclear if an HCT together with an expanded safety trial would be sufficient for licensure of a COVID-19 vaccine.

As an alternative to Eyal and colleagues' suggestion of replacing phase 3 trials,²⁶ HCTs could be used in conjunction with them. In this scenario, HCTs could provide an early glimpse of efficacy in advance of phase 3 results. Phase 3 field trials would still be useful for demonstrating efficacy across the population—not just in healthy young volunteers—as well as revealing effectiveness under real-world conditions and the frequency of rare adverse effects of vaccination.

In either case, rapid indication of vaccine efficacy would provide clear advantages for COVID-19 vaccine development. Firstly, an early positive signal of efficacy from an HCT could crucially reduce the risk of producing a given vaccine candidate and encourage manufacturers to continue scaling production in advance of confirmatory phase 3 results, licensure, and widespread distribution.²⁷ Secondly, given the unprecedented level of risk and investment COVID-19 vaccine developers have already undertaken to push their candidates along the approval pathway, an early negative indication of efficacy from an HCT could signal to developers to abandon their candidate and “fail fast,” allowing time, funds, and other resources to be rapidly reallocated to more promising alternatives.²⁸ Challenge trials may also provide a platform to enable head-to-head comparison of different vaccine candidates.

Converging on correlates of protection (CoPs)

HCTs could also serve a function complementary to phase 3 trials by helping to identify and verify correlates of protection (CoPs) against disease endpoints. Once identified, CoPs could significantly expedite vaccine development efforts and the pathway to licensure.²⁹

A CoP is a biomarker generated by vaccination which correlates with protection against specific infection outcomes. For example, a titer of neutralizing antibodies over a set threshold could be a

CoP. Recently, many successful vaccines have been approved on the basis of specific CoPs set as surrogate endpoints, including vaccines against hepatitis B (hepatitis B surface antibody), H5N1 influenza (hemagglutination inhibition titer), and Japanese encephalitis (50% plaque-reduction neutralization antibody test).^{30, 31, 32, 33} If surrogate endpoints are used as the basis for licensure, there is no longer a need to wait for sufficient numbers of participants to be naturally infected to measure efficacy. In a population with low incidence of disease, this could reduce both the time and number of participants that are needed. Notably, this line of reasoning only applies to generating phase 3 efficacy and not safety data.

CoPs are typically identified in pre-phase 3 trials, animal challenge models, or observational studies. As of April 26, 2020, vaccine manufacturers such as CanSino and INOVIO had indicated the intention to look for secondary outcomes that might be important CoPs, such as titers of neutralizing antibodies and antigen-specific interferon-gamma (IFN- γ) cellular immune response in phase 1.³⁴ However, whether this will be sufficient to identify CoPs with high enough confidence to be used as primary endpoints for phase 3 remains an open question. While many vaccine-preventable diseases caused by viral infections have widely-accepted CoPs, finding a single measure of likely protection in the diverse human populations requiring vaccination is a daunting task. Some viruses, such as rotavirus, have no known CoPs despite years of searching.³⁵

HCTs may be useful for establishing CoPs for vaccine candidates if other methods fail. In the tightly controlled clinical setting of an HCT, there would be ample opportunity to collect diverse data on secondary endpoints and potentially establish causality between these secondary endpoints and protection. If an HCT successfully established CoPs, it could significantly accelerate the timeline to phase 3 efficacy data and licensure.^{36, 37}

Improving understanding of pathogenesis and the human immune response

Studies employing human challenge models could help us better understand the natural history of COVID-19, including the early stages of pathogenesis and the developing human immune response. Historically, human challenge models have elucidated critical features of infectious diseases that could not have been studied otherwise. For example, they have shed light on the evolutionary dynamics of influenza populations within a host, the dynamics of the immune response to common cold coronavirus 229E, and the role of *Plasmodium falciparum* gene expression changes in virulence.^{38, 39, 40}

In contrast to traditional clinical studies, a challenge model for COVID-19 would allow close observation of the participants prior to and from the point of vaccination and infection, in the absence of potentially confounding coinfection. This could help us resolve fundamental mysteries of COVID-19, such as the physiological basis for variation in disease severity, the progression of disease from the point of infection, the dynamics of the immune response when previously infected participants are exposed to the virus a second time, or the existence of a CoP.^{41, 42, 43, 44} In doing so, SARS-CoV-2 human challenges could provide insights that would form a bedrock for medical countermeasure development efforts more broadly.

HCTs may also have value in detecting vaccine-enhanced disease. Although there is not yet any evidence of vaccine-enhanced disease in COVID-19, there are historical examples of both vaccination and natural infection causing a pathology via an enhanced immune response in human subjects and animal models upon secondary infection. For example, primary infection with a Dengue virus serotype can elicit more severe disease pathology in humans who then become infected with a different Dengue serotype, through the proposed mechanism of antibody-dependent enhancement (ADE).^{45, 46}

Relevant to the current outbreak, animal models of SARS-CoV infection showed increased lung pathology after vaccination with whole SARS-CoV spike protein, although protection was achieved when vaccination was restricted to the receptor binding domain of the spike protein.⁴⁷ It is worth emphasising that the evidence for vaccine-enhanced disease in SARS-CoV is limited to *in vitro* and animal models, with the overall picture being that vaccination is protective. In humans, the clinical evidence for vaccine-enhanced disease in SARS-CoV is scant, and the evidence for SARS-CoV-2 even more so. As Eyal et al. propose, HCTs could be designed to minimize participants' exposure to vaccine-enhanced disease, with challenges occurring sequentially with over groups of incrementally increasing numbers of small groups of participants.⁴⁸

Limitations of using HCTs for COVID-19 vaccine development

HCTs could expose participants to significant risks

While HCTs could, in some scenarios, prove remarkably useful, they also could expose participants to relatively high risks. It will be important for volunteers, manufacturers, regulatory bodies, and other stakeholders to assess whether those risks are worth the potential benefit.

In human subject research, the risk–benefit ratio is usually favorable to the subject, and given greater weight than the potential good to the broader society.⁴⁹ HCTs do not provide a direct benefit to the subject's health and thus the risk–benefit ratio for participants leans toward the side of risk. However, in its analysis of regulatory considerations pertaining to challenge trials, the World Health Organization acknowledges that less strict standards could be justified on the basis of large societal benefit and urgent needs.⁵⁰ Still, an acceptable challenge model must only expose participants to a reasonable degree of risk and this risk should be minimized to the extent possible.

To minimize participant risks, HCT volunteers likely would be drawn from previously uninfected healthy young adults (e.g., under the age of 40; note that the ethical criteria laid forth by the World Health Organization estimate the likely age of participants as 18–30).⁵¹ Based on data from China, the overall infection fatality rate (IFR) for all 20–29-year-olds is thought to be between 1 in 10,000 and 1 in 1,000, and the IFR for 30–39-year-olds was found to be between 5 in 10,000 and 3 in 1,000.⁵² Similarly, estimates of IFR for these age groups across several Italian regions fall below 1 in 1,000.⁵³ This is somewhat higher than the risk of death from childbirth in the U.S., which is about 1.5 in 10,000, and roughly on par with the risk of death from kidney donation in the US, which is about 3 in 10,000, and liver donation, which is between about 1 in 1,000 and 5 in

1,000.^{54, 55} It is expected that actual risk of fatality among volunteers would be substantially lower, given that medical screening could ensure that volunteers exhibiting comorbidities are excluded from an HCT. The risk of severe disease (e.g., acute respiratory distress syndrome) may be one or two orders of magnitude higher than the risk of death, with as of yet unknown long-term consequences.⁵⁶

To reduce the effective risk posed to volunteers, both Eyal et al. and the World Health Organization suggest considering prospective participants' baseline risk of infection.^{57,58} The authors argue that selecting participants from those whose work or other circumstances put them at particularly high risk of acquiring COVID-19 infection in the normal course of life would reduce the *additional* risk being imposed by deliberate exposure. While this reasoning is compelling, it is unclear how stakeholders may incorporate it into existing bioethical decision-making frameworks. Furthermore, participants with a high baseline risk might systematically belong to vulnerable groups or be frontline healthcare workers making it ethically hard to justify including them in the study and removing them from providing healthcare provision in a pandemic.

To further reduce risks to volunteers, they should be provided state-of-the-art medical care. Indeed, many experts have expressed reluctance to pursue coronavirus HCTs in the absence of an effective therapeutic option.⁵⁹ It is worth noting that HCTs have been successfully conducted using other pathogens for which there is no therapy (e.g. attenuated challenge strains of dengue virus). Although the complications of severe dengue may be lethal, these trials were deemed acceptable on the grounds of a WHO disease management path which had been proven to reduce adverse outcomes.⁶⁰

As of this writing, several therapeutic candidates are in clinical trials and many more in discovery or in preclinical stages of development.⁶¹ These include antibody-based therapies, such as convalescent sera and monoclonal antibody treatments; antiviral compounds, such as remdesivir and favipiravir; and more generally repurposed compounds, such as hydroxychloroquine and azithromycin. Given the sheer number of therapeutic candidates under active exploration, it is quite possible at least one option will prove somewhat effective in the near future.⁶² However, a treatment's utility in mitigating risks faced by HCT participants would depend in large part on the details of the course of treatment. For instance, a therapeutic might only reduce the risk of the most severe outcomes, or only be effective if administered early in the course of an infection. The overall ethical picture may also depend on the cost and society-wide accessibility of effective therapeutics.

Another strategy for reducing risk to volunteers would be to use an attenuated form of SARS-CoV-2 as a challenge virus, which could be less likely to induce severe disease. However, this approach has several drawbacks. First, the results of an HCT conducted with an attenuated strain may be less easily translated to our understanding of a vaccine's efficacy in the context of community-acquired infections. In addition, attenuated strains of SARS-CoV-2 would necessarily require more time to design, produce, and validate than the wild-type strain. Attenuated strains may also have attributes that make them more or less difficult to manufacture at the scale and quality required for HCTs. For example, genome-wide modifications could unexpectedly hamper

the proof-reading activity of the virus's exoribonuclease, thereby decreasing genome stability and introducing genetic variation among the viral doses administered in an HCT. These factors would likely prolong the time it takes to get HCTs off the ground, or at a minimum add uncertainty to these timelines.

Unfortunately, the direct benefits of participating in any HCT would likely be minimal. Currently, studies by the 1Day Sooner research team are underway to understand the motivations of individuals who have already volunteered to participate in HCTs. One potential benefit to participants is the guaranteed high standard of care they would receive in an HCT, which may be greater than they would receive otherwise were they to fall ill with COVID-19, particularly if they would otherwise be seeking care in an overburdened healthcare system. Another benefit is that, even if a vaccine is ineffective, lower dose challenges may lead to less severe disease than normal exposures and protect participants from future SARS-CoV-2 infection due to immunological memory. Further, participants may be attracted to the possibility of receiving a potentially efficacious vaccine as soon as possible to avoid infection altogether.⁶³ However, based on preliminary data, it seems likely many volunteers would primarily be motivated by altruistic instincts, which come with their own payoffs. How these benefits are weighed in the ethical calculus surrounding HCTs remains an open question.

Due to the relatively high burdens and uncertain risks HCT participants would face, extra attention would need to be paid to issues of informed consent, compensation, and participant rights.

Informed consent

Informed consent serves to safeguard a patient's autonomy—that is, their freedom to make decisions and take action based on their own reasons, values or beliefs—and protect them from potential harm.⁶⁴ Informed consent depends on the satisfaction of three conditions: adequate disclosure of the nature of a study and the participant's involvement, sufficient comprehension on the part of the potential participant, and the participant's voluntary choice to participate.⁶⁵

There are a number of challenges involving the informed consent process for any clinical trial. Research shows participants commonly have an incomplete or incorrect understanding of matters relevant to an informed decision to join a clinical trial.^{66,67} HCTs *must* implement an informed consent process that ensures individuals who enroll in the trial understand they will be intentionally exposed to an infectious pathogen *and* that this could cause them to get ill and suffer a certain level of disease symptoms. In disclosing information about a study to participants, research teams should thoroughly address the purpose of the research, the anticipated benefits and risks of the study to the participant, and any available alternative procedures. Challenge studies may require individuals to expose themselves to a higher level of risk than other trials and this should be emphasized throughout.⁶⁸

The informed consent process may take the form of multiple information sessions and discussions with opportunities to ask questions, written tests of comprehension, or psychological evaluations.^{69, 70} Empirical studies have shown that ensuring participants can access information and ask questions across a range of contexts enhances information retention and

comprehension.⁷¹ Previous controlled human malaria infection participants have been assessed on their understanding of the study, its key features, and its potential risks before consenting. Where individuals got any of the true/false questions wrong, research staff reviewed the question in detail until they were confident the individual understood the correct answer.⁷² As a result, participants in this trial reported a high overall level of understanding of the study, which is crucial to avoiding distorted judgment about risks. Despite this, it has been noted that research participants may require further education during the informed consent process to clearly distinguish risks from burdens.

However, it is not always best to provide as much information as possible. Inclusion of excessive or technical details, for example, may overwhelm even enthusiastic participants, potentially undermining the possibility of informed consent.⁷³

Previously established frameworks for evaluating human challenge studies argue that informed consent can be achieved by considering the following questions:

- Is there adequate information about the purpose of the research, procedures (including isolation), risks, discomfort, and lack of benefit?
- How will volunteers be provided with this information?
- Will there be adequate opportunity for questions and discussion?
- How will the capacity for making decisions and comprehension of information be assessed?⁷⁴

Crucially, establishing robust informed consent is not a sufficient criterion upon which to proceed with this research. One must also ensure that risks to subjects are minimized and reasonable in relation to the benefits they can expect, and that the selection of subjects is equitable.⁷⁵

A participant's right to withdraw

Some may argue that COVID-19 HCTs would be incompatible with the right of research subjects to withdraw consent from research participation at any time without penalty. That is, once infected with a challenge virus, volunteers could not necessarily withdraw during the containment period, as they may be a threat to the health of the broader public.^{76,77} This is consistent with the idea that there are limits to exercising rights when doing so could cause undue harm to others—for instance, studies involving experimental bone marrow transplantation require subjects to remain at the research facility after undergoing ablative chemotherapy, until transplantation and associated treatment have been completed.⁷⁸ Here, it is worth delineating between these participants' right to withdraw from continued receipt of study intervention or contribution to data collection and their continued confinement for public health purposes. HCT participants could still withdraw their consent from continued data collection and contribution, even if they could not leave the research facility immediately.⁷⁹ However, specific guidelines surrounding the limits on whether, how, and for how long participants can be kept in containment facilities following their withdrawal from research should be discussed among bioethicists and researchers. The restrictions surrounding participants' right to withdraw underscore the need for participants' emphatically informed consent prior to an HCT, particularly prior to challenge virus exposure.

Compensation

The question of to what extent clinical trial participants should be compensated is a contentious one, no less so when risks to participants are relatively high, as they may be in COVID-19 HCTs.⁸⁰ Clearly, trial participation should in no way *cost* participants money. Therefore, it should be considered an ethical obligation to ensure participants are reimbursed for all out-of-pocket costs such as travel expenses, childcare, follow-up care, and the like. However, the extent to which participants should be compensated for the time and burdens associated with their participation is less clear. We suggest that bioethicists and researchers convene to carefully discuss the virtues of compensation (e.g., fair treatment, paying respect to volunteers and enabling their participation) against its undesirable potential effects (e.g., undue inducement, encouragement of deception,⁸¹ skewing the participant pool), in order to arrive at recommendations for setting HCT compensation.⁸²

HCTs could expose society to relatively high risks

Another challenge facing the use of HCTs for COVID-19 vaccine development is that they may impose higher costs on society compared to traditional clinical trials. For example, in an ongoing pandemic, an HCT will require the use of scarce resources such as drugs, ventilators, and clinician time, potentially detracting from normal patient care. However, it is worth noting that traditional clinical trials may also impose significant opportunity costs, including the time of clinicians and participants. The net cost of an HCT will therefore depend in part on the extent to which it replaces other studies.

In addition, HCTs pose the unique risk of accidentally releasing contagious pathogens into the surrounding community. Extensive measures—from the design of the biocontainment facility in which participants are isolated to the protocol for judging whether participants can be allowed to leave isolation—should be structured to minimize this risk. In addition, the team leading an HCT should consult the local community well beforehand, soliciting input and opening channels of communication.⁸³

Finally, in rushing to conduct HCTs to evaluate COVID-19 vaccine candidates, the biomedical community may risk deleterious outcomes that could set back the field of human challenge research significantly. Recent research using human challenge models has yielded valuable insights for the control of influenza, dengue, and other infectious diseases, and an overly hasty or mismanaged COVID-19 trial could risk the gains from many other future HCTs.⁸⁴

Data from HCTs may not translate to the field

HCTs may face limitations in providing data that clearly translate to real-world settings. Historically, certain human challenge models have been shown to produce results that are generally predictive of performance in the field. For instance, the efficacy of the RTS,S vaccine candidate in protecting against malaria in studies using a *P. falciparum* sporozoite challenge model was partly borne out in subsequent field studies,⁸⁵ and the typhoid conjugate vaccine's efficacy in a challenge model was predictive of efficacy in the field.^{86, 87} Conversely, candidates that performed poorly in this challenge model also failed to confer broad protection in the field.⁸⁸

However, results from challenge studies do not always match results from field studies. For example, a malaria vaccine candidate that failed to show effects on parasite growth in a blood-stage *P. falciparum* HCT successfully diminished parasite growth in larger field studies.⁸⁹ The relevance of challenge model-derived data to the real world will depend on several factors.

First, as discussed above, the strain of virus chosen for an HCT could affect how well its results generalize in the field, with wild-type strains likely offering more applicable results and attenuated or otherwise engineered strains offering less applicable results.

Second, the mode of administering the challenge virus in an HCT, along with the dose administered, could affect the general applicability of HCT results. Various potential routes of pathogen administration have been proposed or used in past HCTs. These include inhalation of aerosolized virus, intranasal instillation via droplets, oral administration, mosquito bites, and intravenous or subcutaneous inoculation.^{90, 91, 92, 93, 94, 95} The chosen method of administration can affect the severity of the infection and the nature of the immune response. For example, in challenge studies of influenza, inhalation of aerosolized virus is thought to result in a more severe infection in the lower respiratory tract, with an immune response and natural history distinct from the type of upper respiratory infection that is observed after administering virus intranasally.⁹⁶ Unfortunately, our current understanding of SARS-CoV-2 transmission is limited. Transmission via respiratory droplets has been well established,⁹⁷ but the evidence remains mixed on the possibility and prevalence of fecal-oral transmission, spread via aerosolized particles, or fomite transmission.^{98, 99, 100} And even with perfect knowledge, the choice of administration method would depend on its resemblance to routes of community-acquired infection, its relevance to intended clinical endpoints, and the risk it poses to participants. As new information arises about SARS-CoV-2's routes of infection, challenge models may have to morph in significant ways to provide efficacy signals predictive for real world conditions.

Third, in an HCT, the timing of the viral challenge relative to vaccination is the same across all patients. By contrast, in traditional efficacy trials—as in the potential real-world use of a vaccine—the timing of exposure to the virus relative to vaccination is highly variable. This may contribute to a gap between HCT and real-world settings if the efficacy of the vaccination depends on the time between vaccination and infection.

Fourth, it may be difficult to generalize from vaccine efficacy in pre-screened healthy young people to its efficacy across the broader population, since responses to vaccination can depend on age, immune status, comorbidities, nutrition, microbiota, history of infection, genotype, and other factors.^{101, 102, 103} That said, traditional phase 3 studies are not perfect in this regard, either. For example, a phase 3 study of the BCG vaccine against COVID-19 in Australian health care workers excludes children, pregnant or breastfeeding women, and individuals known or suspected to be infected with HIV.¹⁰⁴

Fifth, it is unclear whether field-relevant clinical endpoints are practically or ethically feasible to test in the context of an HCT. From the perspective of participant risk, it is desirable to choose the minimum infectious dose of challenge virus required to induce mild disease in most

participants, leaving the remaining minority of participants uninfected. However, it is possible that vaccine candidates will more effectively abrogate severe disease than mild illness, as has been seen with influenza vaccine candidates.¹⁰⁵ If such candidates were tested in HCTs with mild disease as its primary endpoint, their efficacy against severe disease may go undetected. On the other hand, while using a higher infectious dose of challenge virus to target severe disease as an endpoint for HCTs could improve the utility of their efficacy results, it would pose considerably greater and perhaps impermissible risks to participants. If using severe disease as an HCT endpoint, the availability of effective therapeutic options would become even more important for participant safety. Choosing appropriate endpoints for a challenge model would be the central time-consuming challenge of dose-finding studies.

Finally, HCTs may also prove less effective than clinical trials for monitoring potential adverse effects from the vaccine. If adverse events are rare—e.g., with an incidence of 1/100 or less—then the small number of participants in an HCT may be unable to detect them. Also, HCTs would be conducted over a compressed timespan, and might be unable to detect adverse long-term effects. For example, vaccine-enhanced disease has been observed years after vaccination. Children in the US who received doses of a particular measles vaccine in the 1960s, for instance, experienced vaccine-enhanced disease during measles outbreaks 2–14 years after vaccination.¹⁰⁶ Likewise, the vaccine-enhancement observed in historical respiratory syncytial virus vaccine studies arose approximately one year after initial vaccination, and similar time-lagged enhanced disease responses have occurred in consecutive infections with different dengue serotypes.¹⁰⁷ It might be that this is simply because of delayed exposure, but it is also possible that these effects only show after sufficient time passed between vaccination and infection. In that case, vaccine-enhanced disease occurring on a similar timeline for SARS-CoV-2 vaccines would arise outside the bounds of an HCT, rendering them ineffective for monitoring such adverse events.

Developing a COVID-19 challenge model may take a long time

The practical utility of HCTs in testing efficacy, evaluating CoPs, or serving other purposes will depend critically on how quickly they could be prepared and conducted. Some initial preparatory steps include:

- Convening experts and stakeholders to develop HCT protocols
- Coordinating with vaccine manufacturers to design multi-arm trials, if possible/desirable
- Gaining approval from institutional review board (IRBs) and regulatory bodies
- Establishing partnerships with clinical researchers and institutional sponsors
- Reserving and/or building clinical biocontainment facilities in which sufficiently large trials could be conducted
- Securing access to ventilators, therapeutics, and other equipment required to provide the highest standard of care to participants in case of severe disease

For the sake of speed, these steps could be done in parallel to the extent possible. Beyond these tasks, the three main time-consuming steps—apart from vaccine production and initial clinical

trials—are manufacturing challenge virus, conducting dose-finding studies, and conducting the HCT itself.

Manufacturing challenge virus

Unlike the production of virus for animal challenge studies, challenge virus for HCTs must be produced under good manufacturing practice (GMP). Only a handful of manufacturers in the US and UK are equipped to safely and securely produce GMP-grade challenge virus for COVID-19 HCTs. The longest stage of manufacturing is establishing a standardized and documented protocol for production, which produces consistently high-quality material free of adventitious agents. From there, virus stocks must be produced and stored, which would take at least a few weeks.

Experts have provided varying estimates on the time it would take to produce virus stocks. Some have suggested that in an ideal world this would take between three and six months, while others have said producing the virus in as little as a month may be realistic. Amidst the economic disruption caused by a pandemic, supply chain problems could lengthen the expected time to completion. The urgency with which this process is treated might also have an influence on timelines. On the other hand, the timeline to having usable challenge virus could be shortened considerably if GMP-grade wild-type or attenuated virus were already in production for uses other than HCTs. This may be the case, since producing a high-quality supply of the virus is necessary for creating certain classes of vaccines. One example is Long Island-based Codagenix, who have a codon deoptimised virus production pipeline, and who have partnered with the Serum Institute of India to develop a COVID-19 vaccine.¹⁰⁸ Alternatively, if these processes have not been developed and tested to GMP standards, doing so for an HCT could reduce other manufacturing timelines later on.

Notably, any GMP-grade virus created for human challenge must be validated in animal models and FDA-approved prior to dose-finding studies.¹⁰⁹ This includes verifying that the virus causes disease as expected in animal challenge models, without unexpected toxicity. This validation process would likely take at least two months to complete.

Dose-finding studies

Before HCTs can be performed, the infectious dose to be administered in virus challenges must be determined. This typically is done via an escalation study, in which a very small number of participants (perhaps five) are initially administered a very low dose of virus.¹¹⁰ This initial dose could be inferred from animal challenge models and past human challenges with other viruses.¹¹¹ Participants would be followed for several weeks in a biocontainment unit to assess the presence and severity of any resultant infections. They would be released from isolation once no longer infectious.

If fewer than about 60% (precise threshold might vary) of individuals reached the desired clinical endpoint, the dose would be elevated and the experiment iterated with a new group of participants until successful. This dose then may be verified in multiple independent tests with a larger number of participants to establish reproducibility of the induced symptom complex. This verification step

could potentially be done in parallel at multiple sites.¹¹² Experts have also provided varying estimates of the time it may take to complete a dose-finding study for a COVID-19 challenge model, ranging from two to six months.^{113, 114, 115}

Like HCTs themselves, dose-finding studies carry appreciable risks for volunteers that should be weighed carefully before advancing. As discussed above, risks to volunteers in dose-finding studies will vary as a function of several factors, including the targeted clinical endpoints. All practical measures should be taken in dose-finding studies to minimize risk to participants, such as priority access to the best available medical care and pre-screening on the basis of risk factors such as age, sex, and medical exclusion criteria. The same community consultation and society risk assessments that are carried out for HCTs would need to be carried out for dose-finding studies as well.

It is worth noting that regulatory requirements for infectious dose-finding studies vary from country to country.¹¹⁶ In the US, the FDA regulates challenge virus as a biologic drug, and any dose-finding studies require an Investigational New Drug (IND) application to proceed. Meanwhile, in at least some European countries, the challenge virus is considered a Non-Investigational Medicinal Product (NIMP), and dose-finding studies may require fewer regulatory approvals than in the US.

The HCT itself

We estimate that an HCT for COVID-19 would take at least two months to complete. Our estimate includes:

- At least two weeks in isolation to screen volunteers for prior infection and other potential exclusionary health factors.
- At least two weeks after vaccine/comparator administration to allow for an immune response. This vaccination step may take longer if multiple consecutive doses must be administered.
- At least four weeks after viral challenge to observe attainment of mild infection endpoints, observe and resolve infections reaching more severe endpoints, and document the end of viral shedding from the respiratory and gastrointestinal systems.

The number of participants required to complete an HCT with sufficient statistical power to provide useful efficacy data would be determined by the attack rate of the challenge virus, the vaccine's efficacy, and the targeted clinical endpoints. Unfortunately, depending on the biosafety level required for isolating participants infected with COVID-19, it might be impossible to conduct the HCT with all participants in the same place at the same time. For example, isolation units used for influenza challenge studies typically have fewer than 40 beds (B. L. Innis, personal communication, May 4, 2020). Therefore, if a hundred or more participants are required, an HCT may need to make use of multiple biocontainment units simultaneously, or be performed sequentially on smaller cohorts, which would extend the timeline to completion. Alternatively, new biocontainment units with sufficient capacity could be built.

Taken together, virus manufacturing, verification of vaccine performance, and dose-finding studies would take no fewer than five months, and likely longer. Our best estimate is that, at maximum speed, manufacturing would take one month, challenge virus validation and approval two months, and dose-finding four months, for a total of seven months. The very earliest efficacy data from an HCT could be available is several weeks after the conclusion of dose-finding. If approached with due urgency, this relatively rapid timeline may be possible, but countervailing forces could lengthen it substantially. The path to an HCT will involve dozens of players, including researchers, regulators, health care providers, manufacturers, volunteers, community members, and policy-makers. Active coordination will be necessary to synchronize all the moving parts and minimize lags arising from interdependencies among these players.

Of course, the time it takes to achieve HCT results is only important to the extent the earliest vaccine candidates move quickly through phase 1, 2, and 3 trials. And currently, in the midst of the pandemic, governments, vaccine manufacturers, and other stakeholders are moving to develop an effective vaccine at unprecedented speed. For example, the first participant in a phase 1 clinical trial for the Moderna vaccine candidate, mRNA-1273, was dosed just 63 days after Chinese authorities released SARS-CoV-2's genome sequence.¹¹⁷ Moderna's CEO aims for the company to begin phase 2 trials in late spring and phase 3 in summer or early fall.¹¹⁸ The company suggested the vaccine ultimately could be available under emergency use authorization as soon as fall 2020. Meanwhile, the CanSino Biologics candidate has begun a phase 2 trial early based on preliminary phase 1 safety data.¹¹⁹ This phase 2 trial is also projected to be complete in fall 2020. The INOVIO Pharmaceuticals candidate appears to be following a comparable timeline. Researchers at the University of Oxford indicate as a best-case scenario to have efficacy results from phase 3 trials for their vaccine candidate as soon as this fall.¹²⁰

To accomplish these ambitious goals, vaccine makers are pursuing a number of time-saving strategies apart from HCTs, such as parallelizing steps that are typically run in series. This exposes the companies to far higher risks of wasted resources and funds if a vaccine candidate fails. For example, before final data was available for their phase 1 trials, CanSino Pharmaceuticals began its phase 2 trials, and Moderna—with the support of the US Biomedical Advanced Research and Development Authority (BARDA)—has already begun producing vaccine doses for phases 2 and 3.¹²¹ Moderna also began recruiting participants for its phase 1 study before showing the candidate's efficacy in animal challenge models, instead choosing to run the animal tests and clinical trials in parallel.¹²²

Beyond parallelization, vaccine makers are expected to take other steps to accelerate vaccine timelines if possible. They are likely to conduct large-scale phase 3 trials in regions with high COVID-19 incidence,¹²³ or in high-risk populations such as healthcare workers or family members of infected individuals. With relatively high disease incidence, less time would be needed to observe whether the vaccine effectively prevents infection at the chosen endpoints. Already, thousands of health care workers in the Netherlands and Australia are being recruited to participate in phase 2/3 trials testing whether the tuberculosis-targeted BCG vaccine confers protection against COVID-19.^{124, 125} However, it might become harder to identify suitable populations at high risk of infection if COVID-19 incidence continues to fall or fluctuates

unpredictably due to social restrictions. For example, two studies in China examining the effects of the potential drug treatment remdesivir were forced to shut down because they were unable to recruit enough patients for their trial due to low disease incidence.¹²⁶

Given the breakneck pace of clinical trials for the current phase 1 vaccine candidates, it is highly uncertain whether HCTs could be set up soon enough to accelerate their development. However, if none of these vaccine candidates proves effective, HCTs may prove useful for candidates currently at earlier stages of development, especially if COVID-19 incidence declines.

The societal benefits are potentially large, but deeply uncertain

Accelerating a widely-available and effective vaccine, whether by using HCTs or some other means, has the potential to prevent a great number of additional infections. This would yield both direct benefits, such as averted deaths, and indirect benefits, such as a boost to economic productivity. While a concrete estimate of the magnitude of these benefits would strengthen the case for using HCTs, these kinds of predictions can be misleading.¹²⁷

In planning during the current COVID-19 pandemic generally, efforts at prediction are complicated by many deeply uncertain and changing factors, such as the actions of governments, SARS-CoV-2's transmissibility under various climatic and social conditions, the safety and efficacy of different vaccine candidates, the risk of reinfection, and the availability of effective treatments.

For example, reinfection with SARS-CoV-2 may be possible and pose unknown health risks. In this case, a relatively early vaccine could stifle the harms caused by future waves of infection or an endemic form of the pathogen.¹²⁸ On the other hand, if humans develop immunity post-infection, as antibody-studies indicate in rhesus macaques,¹²⁹ and if immunity lasts for several years, as it does for SARS-CoV and MERS-CoV, then a high number of prior infections will curb the number of new infections.^{130, 131} In this scenario, if the spread of the virus is uncontrolled in the near future, the benefits of accelerating a vaccine may be relatively lower.

Even without the possibility of reinfection, spread may be controlled in ways that make vaccine timelines critical. In countries that manage to suppress the virus for only a limited time, an accelerated vaccine might prevent or extenuate a subsequent wave of infection. In countries that successfully suppress the virus until a vaccine is available, benefits of vaccine acceleration may come from enabling governments to safely end suppression efforts and alleviate the economic burden these efforts impose.¹³²

The respective probabilities of these scenarios will likely vary substantially by country, and there are many epidemiological possibilities beyond those discussed in this paper. For instance, future treatment availability and potential climatic effects on the transmission of the virus are further points of uncertainty that influence the overall benefits from accelerating vaccine availability.

Given these factors, the value of accelerating COVID-19 vaccine development might be very large, saving thousands or even millions of lives, but it might also be relatively small if a vaccine

takes very long to develop. It seems likely, however, that many of these uncertainties will be clarified in the months leading up to the launch of any HCTs, allowing for adaptive decision-making. Planning should focus on how to make decisions given the current deep uncertainty — and having the option of pursuing HCTs is valuable in many possible scenarios. Crucially, the societal value of HCTs depends on how quickly they can be developed, conducted, and generate results. Early planning and preparation is therefore particularly valuable.

Conclusions

In this paper, we presented three potential use cases for HCTs in accelerating COVID-19 vaccine development: evaluating efficacy, converging on CoPs, and improving understanding of pathogenesis and the human immune response. In each of these, HCTs appear to offer distinct advantages, particularly related to the speed and richness of the clinical data they could generate. However, practical and ethical considerations—as well as inherent limitations to HCTs—constrain the range of scenarios in which HCTs could actually move the needle on vaccine development timelines. For example, even if HCTs were pursued immediately, it is highly uncertain whether they could provide efficacy data on the current phase 1 vaccine candidates soon enough to be useful. Soberingly, even if HCTs were used to great effect, accelerating vaccine development by one month or more, the benefit of this acceleration is difficult to predict given its dependence on myriad political, epidemiological, and technological factors.

However, there are still many scenarios in which the benefits generated by HCTs months from now would likely outweigh the associated risks. Imagine, for example, it is January 2021. Disappointingly, none of the vaccine candidates that have completed phase 2 trials have presented compelling efficacy data, nor have clear correlates of protection been identified.¹³³ While significant testing has been performed in animal challenge models, promising results in these studies have failed to translate to humans. Fortunately, an affordable repurposed drug has shown significant therapeutic effectiveness against moderate to severe cases of COVID-19, leading to a lower fatality rate and stabilized healthcare systems worldwide. Stringent social distancing and quarantine measures have led to the virus's containment in many countries, but fears remain that imported cases will spark outbreaks in the large fraction of the population that remains susceptible. Absent clear alternatives, the WHO recommends conducting a large multi-arm HCT of a dozen up-and-coming vaccine candidates in parallel with a multi-arm phase 3 trial.¹³⁴ The WHO hopes the HCT will provide both rapid efficacy data that can be used in down-selecting candidates and rapid confirmation of any CoPs indicated in phase 2 trials.

To preserve the option to implement HCTs in scenarios such as this, we recommend an immediate, coordinated effort by all stakeholders to address the considerations outlined in this manuscript and make the necessary preparations. These include:

1. Convening experts to discuss the ethical and practical considerations associated with HCTs for COVID-19, concluding in a set of recommendations and guidelines for their use

in the present pandemic and their role in the licensure process (which, notably, could provide guidance that is broadly useful in the event of future pandemics, too),

2. Taking the first practical steps toward an HCT, including preparing challenge virus under GMP and making preliminary arrangements with volunteers, vaccine developers, regulators, academic institutions, and clinical researchers to run HCTs in situations where they are expected to be highly useful,
3. Keeping informed of the evolving situation, periodically conducting a systematic re-evaluation, and adjusting course based on the progress of the pandemic and the outcomes of the first drug and vaccine trials.

HCTs have the potential to considerably shorten the COVID-19 pandemic, saving many lives and enabling economies and societies to return to normality. But we must act now to ensure this opportunity is not missed.

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Conflict of interest

All authors, with the exception of Thomas C Darton, report affiliation with the research arm of 1Day Sooner, an organization whose mission is to advocate on behalf of volunteers interested in participating in human challenge trials that would accelerate effective COVID-19 vaccine development.

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