# Human challenge studies for COVID-19 vaccines – reckless or resourceful?

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## Introduction

The ongoing Coronavirus Disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has completely disrupted all aspects of daily life. A return to normalcy is unlikely until a preventive vaccine is widely distributed for global use. In April 2020, a 12- to 18-month timeline for vaccine development was proposed by various global leaders.[1] Pharmaceutical companies, academic research facilities, and governments have all since been vying to develop a vaccine. The ongoing vigorous race against time for COVID-19 vaccine development has given rise to several questions about the feasibility, safety, ethics, logistics and other aspects of the process.

Given the imperative for speed, physicians, scientists, and politicians alike have argued in favour of accelerating vaccine clinical trials through adaptive measures.[2-4] Globally, vaccine developers have opted to conduct clinical trial phases in parallel to speed up COVID-19 candidate vaccine testing.[2,5] This has led to progression through vaccine development phases at unprecedented speed.[6]

One approach for rapidly testing vaccine safety and efficacy, and thereby accelerating vaccine development, is by using controlled human infection studies, which are often referred to as human challenge studies (HCS).[7] HCSs involve the administration of a candidate vaccine, followed by the deliberate infection of healthy volunteers with a laboratory strain of the pathogen for which the vaccine is being developed.[8] HCSs are promising as they have the ability to provide information about the efficacy of a vaccine before it is released for larger field trials and to the market.[9] In short, these trials decrease the number of participants needed to evaluate vaccine safety and efficacy and can allow the comparison of various vaccine candidates simultaneously.[8] Thus, HCSs are a valuable means to extract more information from vaccine trials and subsequently increase our knowledge of how to vaccinate against COVID-19.

However, these studies are ethically challenging as the deliberate infection of individuals may have severe deleterious outcomes, even within controlled environments. Their use within the context of the race to develop a COVID-19 vaccine has been the subject of several debates. One of the first calls to consider implementing HCSs for COVID-19 candidate vaccines came in March 2020, when Eyal et al. argued for the replacement of conventional, lengthy phase III testing of candidate vaccines with HCSs to accelerate vaccine development and therefore reduce the global burden of coronavirus-related mortality and morbidity.[10] On one hand, this cause has resonated with many globally as volunteers worldwide have opted to participate in HCSs should they be implemented.[11] Grassroots team "1 Day Sooner" has been advocating on behalf of COVID-19 challenge trial volunteers and has urged global vaccine researchers, developers, and governments to mobilize resources for COVID-19 HCSs.[11] On the other hand, some people have argued that HCSs are unwarranted, citing primarily the moral harm in the deliberate infection of individuals with a pathogen for which there is no cure.[12] As well, some have cited the long-term consequences of the novel virus as reason to avoid HCSs.[13]

In sum, the use of HCSs for the development of COVID-19 has been met with much controversy and has been the topic of contentious debate between researchers, politicians, and the public. This narrative commentary presents a discussion on the utility of human challenge studies in the context of a COVID-19 vaccine by weighing the risks against the benefits of using such a model. I argue that using HCSs presents a net benefit and that risks, while substantial, can be mitigated, making it essential that challenge trials be seriously considered by vaccine researchers globally.

## The case for challenge trials

A principal benefit of HCSs is their ability to generate vaccine efficacy data from a relatively smaller number of participants.[9] While conventional vaccine trials rely on participants being naturally exposed and infected after receiving a vaccine, all participants in HCSs are exposed to the pathogen of interest. This confers a key advantage to researchers as HCSs allow them to understand the role of the vaccine, if any, in altering disease outcomes within a controlled setting. In contrast, conventional trials rely on natural exposure of trial participants to circulating virus.[9] This becomes increasingly difficult within contexts with decreasing incidence of COVID-19 and among those who practice infection prevention measures such as physical distancing, public masking, etc. Paradoxically, as global efforts to control COVID-19 outbreaks have increased, we have slowed our ability to find results from conventional phase III trials. Conventional studies therefore compensate for this limitation by enrolling large numbers of participants, which not only presents greater logistical challenges, but also hampers trial progression and is not feasible where recruitment is difficult to achieve. Challenge trials, however, allow researchers to recruit far fewer participants to extract data of similar quality.[14] This model subsequently lends itself to a vaccine trial that progresses more rapidly, thereby enabling a vaccine to more quickly reach the market.

Challenge trials have been used successfully in the past to generate information about a variety of diseases, most notably influenza,

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malaria, and dengue.[15] The first well-described challenge study on influenza was published in 1937.[16] Since then, several challenge study models have been employed in influenza studies, including some which led to the development of peramivir and oseltamivir, both of which are now widely used as antiviral medications.[14] The RTS,S malaria vaccine is another testament to the ability of HCSs to accelerate the development of vaccines. First approved for implementation in Malawi, Ghana, and Kenya in 2019, the challenge studies that preceded phase III trials for this vaccine were believed to have played a pivotal role in advancing malaria vaccine candidates along the development pipeline.[17,18] Yet another challenge study model evaluated the efficacy of dengue vaccine prior to larger scale testing, demonstrating that challenge trials can be highly useful in evaluating vaccine candidates before investing in large, yet potentially unsuccessful, clinical trials.[19] With a limited availability of resources such as clinical trial sites, HCSs have the strong potential to serve as an early checkpoint for vaccine trials, allowing researchers to focus resources on trials with early demonstrated success. Lastly, there is a strong track record for the success of HCSs in high-, middle-, and low-income countries, indicating that their use could be adopted in a variety of contexts during the COVID-19 pandemic.[7,8]

A corollary benefit of HCSs is that they allow researchers to identify correlates of protection at a level that is not possible outside of controlled conditions. Correlates of protection for COVID-19 have yet to be well characterized, and HCSs may constructively contribute to this growing body of knowledge. Researchers leading HCSs are uniquely positioned to assess molecular-level responses of study participants before and after they are infected with a challenge strain and HCSs for coronaviruses have previously been used to elucidate correlates of protection.[20] This granular level of analysis is not typically feasible in case-control or cohort studies and may improve the current state of knowledge on the immune response to COVID-19 infection.

## Logistical considerations

To be useful and in congruence with ethical standards, HCSs must be carefully planned and designed. Developing a "challenge model", which involves designing and producing an appropriate challenge strain and conducting dosing studies, is an involved and difficult process. Challenge strains must be developed with careful consideration and must be designed to generate a clinical response that is close to, but not more severe than the response associated with natural infection.[10] Next, dose-escalation studies, which are used to determine how much of the challenge strain of the pathogen should be administered to participants to induce a certain threshold of clinical disease, must be conducted before the HCSs can themselves be implemented. These preparatory measures can take weeks to months.[10]

Moreover, the overall process of conducting HCSs is demanding, and requires appropriately suited biosafety laboratories, consultation with scientists, ethicists, and clinicians, and procurement of appropriate facilities for monitoring and care of study participants, all of which could take substantial time to arrange.[13] Institutional review board approval represents another necessary, yet time-intensive, step that must occur before HCSs can be implemented. Therefore, given the time needed to prepare necessary preconditions for HCSs, challenge models must be developed sooner rather than later if we are to reap their full benefits.

## Ethical considerations

Noting both the ethically sensitive nature of challenge studies and the potential benefit they may confer in the process of COVID-19 vaccine development, the World Health Organization (WHO) developed a set of key criteria for the ethical acceptability of COVID-19 human challenge studies.[8] These eight criteria include scientific justification, assessment of risks and potential benefits, consultation and engagement, effective stakeholder coordination, intentional site selection, careful participant selection, unbiased expert review, and informed consent.[8] These criteria ought to be followed and fulfilled for any putative SARS-CoV-2 HCS to proceed.

Intentionally infecting a participant with a pathogen (i.e. the basic premise of challenge trials) is an apparent contradiction to the guiding medical ethics principle of non-maleficence. However, given the immense possible social benefits that could be reaped (i.e. a vaccine that reaches market sooner, enhanced understanding of the COVID-19 infectious process, etc.), certain precautions and conditions may allow us to mitigate ethical liability.

Firstly, it is imperative that any triallists who consider conducting HCSs are prepared to offer robust routine monitoring of study participants after they have been infected. In the case of advanced illness, researchers must be able to access state of the art therapeutic options and help the participant recover from disease.

As stated in the WHO criteria for considering COVID-19 HCSs, risks must be evaluated for individual participants, society in general, and third-party contacts of participants when considering the ethical justifiability of HCSs for COVID-19 vaccines.[8] Though it can be argued that limiting initial HCSs to young healthy adults aged 18-30 years would substantially mitigate risk to volunteers of serious adverse events from COVID-19 infection, the broader social contexts of these volunteers ought to be considered during the decision making process. COVID-19 disproportionately continues to impact those who are older and immunocompromised.[21] Therefore, it would be critical to ensure that researchers conduct trials in facilities with sufficient capacity to distance and isolate participants such that there is no possibility of unintentional spread to community members who may be more severely impacted. As well, screening for prospective HCS participants must account for the risk that participation would pose to their third-party contacts. Accordingly, participants who regularly interact with groups at greater susceptibility of succumbing to COVID-19 may have to be screened out to minimize risk and mitigate ethical harm. Lastly, conducting HCSs where COVID-19 is endemic and already presents a high baseline risk of community transmission may increase the chances that direct benefit of HCSs outweigh net risks as potentially efficacious vaccines may impart immunity to individuals within high-risk regions.

Another point of ethical contention is that of collecting informed consent for COVID-19 HCSs. Because of how much is yet unknown about SARS-CoV-2 and COVID-19, including both short-term and long-term consequences, it may be difficult to obtain true informed consent from trial participants. However, this concern can be reduced by ensuring that participants are aware of all possible consequences of participating within such trials, including severe illness and death. This must be done in the written and spoken language of the participant. Additionally, after reviewing all risks of participating in such trials, participants should be asked to verbally summarize what risks they will be assuming by participating in HCSs to ensure full comprehension.

Participant compensation should be configured so as to reimburse volunteers for their travel and time, however, should not be large enough such that participants are financially incentivized to join HCSs or to overlook the possible risks of participating. Providing financial incentives that go beyond reasonable compensation would undoubtedly undermine informed consent and be inherently coercive and unethical.[22]

Ultimately, however, HCSs present a large social benefit on the premise that they may enable the acceleration of vaccine development. An overriding principle that would be necessary to ethically justify HCSs would be unbiased scientific justification that demonstrates how data collected from a potential challenge trial could accelerate the availability of a potential COVID-19 vaccine for the public (i.e. if studies with fewer risks could not generate vaccine efficacy result as accurately or expediently). This aim must be situated within a coherent overall strategy that seeks to improve the overall public health response to COVID-19.[8]

## Hurdles on the road to challenge trials

Despite the array of potential benefits of challenge trials, there are several limitations that ought to be discussed when considering their implementation. The most apparent of such limitations is the current lack of a rescue therapy. There are currently no Health Canada-approved treatments available for COVID-19, which would make conducting HCSs more problematic and ethically questionable. While remdesivir has been authorized for emergency use by the United States' Food and Drug Administration, it can not be used with confidence as a bona fide rescue therapy if a candidate vaccine does not produce immunity in an HCS participant.[23]

Proponents of HCSs and WHO have suggested that testing be done on healthy adults aged 18-30 to minimize overall risk of harm.[8,10,24] While this would be appropriate, given that the infection fatality ratio among 20-29-year-old persons is approximately 0.03%, there still remains an inherent risk when including younger participants in challenge trials without an available rescue therapy if an experimental vaccine is ineffective.[25] While HCSs have been beneficial for vaccine and therapeutics development in the past, the novelty of SARS-CoV-2 must be acknowledged. There is an inherent added risk associated with infecting participants with COVID-19 as compared to diseases for which HCSs have been used in the past such as influenza, malaria, and dengue. There is much that is still unknown about the pathogenesis and the long-term effects of COVID-19. The course of the COVID-19 pandemic has demonstrated that new evidence on SARS-CoV-2 is constantly emerging and it would be premature to say for certain that the impact of challenge trials would be limited within the parameters of the trial itself.

It is also crucially important to approach such trials with caution and consequently be cognizant that data obtained from such a study may not be perfectly generalizable to the larger population.[25] Should this be the case, candidate vaccines will require further field testing to ensure efficacy in high-risk populations, which would extend time taken for clinical testing. However, even in this case, HCSs would be useful for high-risk populations for several reasons. Based on results from the HCS, researchers may be able to identify the most effective candidate vaccines in the development pipeline and focus resources towards its development. As well, the evidence collected from HCSs on correlates of protection will inform larger field trials on which efficacy data are critical for successful COVID-19 immunity. Even in a worst-case scenario, a vaccine effective only on low-risk individuals would be beneficial as it could impart a level of herd immunity that would curb spread of SARS-CoV-2 from low-risk groups (young, healthy individuals) to high-risk populations (older or immunocompromised individuals).[26]

Despite their efficacy, vaccines have increasingly been met with skepticism, with individuals citing rationale grounded in religious, moral, and political reasoning.[27] The unprecedented speed of vaccine development in the context of COVID-19 has heightened public apprehension about vaccine safety.[28] Within this context, it is possible that HCSs could pose a risk to public understanding of safe vaccine development. Those who oppose HCSs have cited that serious adverse events, should they occur during an HCS, jeopardize public reputation and belief in science.[29]

## Recommendations and conclusions

Reconciling the concerns raised above with the urgent need for a vaccine is indeed a difficult task. Each additional day without a vaccine leads to more COVID-19 associated deaths and contributes to the ever-increasing psychosocial and socioeconomic impacts stemming from the COVID-19 pandemic and related interventions such as closures and lockdowns. COVID-19 challenge trials currently present an ethical grey area and there is much to be discussed and deliberated before they are implemented. Even if well-designed trials have high social value and include thoughtful, informed consent from volunteers, there are still many reasons to remain vigilant. Evolving evidence will play a vital role in justifying the moral feasibility of human challenge studies in a COVID-19 context. Consolidating the standards postulated by WHO with the considerations presented above, it is evident that HCSs may lead to an immense social good when risks are sufficiently mitigated. The main benefits of HCSs in COVID-19 vaccine development are:

(i) candidate vaccine(s) may be accelerated through the development pipeline,
(ii) fewer participants would need to be enrolled in studies to attain results on safety and efficacy, and
(iii) an increased understanding of the correlates of protection for COVID-19.

Among the most stated arguments against HCSs are:

(i) the lack of a rescue therapy,
(ii) risks due to the novelty of the virus and its potential long-term effects,
(iii) difficulty in generalizing study results to broader populations,
(iv) exacerbation of mistrust in science should adverse events arise.

Nonetheless, I argue that the benefits of HCSs presently outweigh the risks. While there is no rescue therapy for COVID-19, routinely monitoring patients and ensuring access to the best available care will greatly mitigate the chances of serious adverse events occurring within the already low-risk population that would be eligible to participate in HCSs (i.e. young healthy adults). Although it is true that much is still unknown about SARS-CoV-2 and its long-term impacts, uncertainty is characteristic of most experimental trials in which new therapeutic approaches are tested. In fact, even within the context of COVID-19 vaccines, candidate vaccines using novel platforms are being tested in human populations (e.g. see Moderna's mRNA-1273 vaccine). The point of utmost importance, however, is that our current state of knowledge on SARS-CoV-2 is made aware to potential participants

and informed consent is collected with the knowledge that there may be long-term consequences associated with COVID-19 infection. Since the challenge trial results may not themselves be generalizable to high-risk populations, it is recommended that HCSs are followed by large-scale short term expanded safety field trials before being submitted for licensure.[10] Learning about vaccine efficacy within younger, low-risk populations will be beneficial on the path to developing safe and effective COVID-19 vaccines, but further testing is needed to validate results in wider populations. Lastly, the risk of HCSs contributing to public mistrust in science can be mitigated by ensuring that clear and transparent communication occur at all stages of HCS development. This includes public educational outreach to help communities hosting HCSs understand the aims of the trial, including all potential risks. As well, regular stakeholder and community participation before, during, and after HCSs will be critical to ensuring that communities are involved in shaping how such studies are conducted within their localities.

In addition to the past successes of HCSs with influenza, malaria, and dengue, many of the criteria outlined by the WHO for COVID-19 HCSs have been followed by previous HCSs.30 A recently published review examining HCSs in low- and middle-income countries (LMICs) identified 13 case studies published from 1992-2018 and determined that studies largely utilized multi-stakeholder engagement to design and execute studies, coordinated with institutional review boards from high income countries, and placed a key focus on ensuring informed consent by providing multiple information sessions and conducting tests of understanding.30 Furthermore, these studies designed exclusion criteria that intentionally reduced risks to participants and took intentional approaches to mitigating future harm. These studies were valuable as they demonstrated that HCSs can safely and ethically be conducted in LMICs. Previous success in conducting HCSs in both HICs and LMICs while fulfilling many criteria the WHO has postulated for COVID-19 HCSs demonstrates that WHO criteria can be met if HCSs for COVID-19 candidate vaccines are adequately prepared.7 This requires firm commitment from vaccine developers and national research programs.

By September 15, 2020, only one vaccine developer had expressed interest in considering HCSs (Oxford University/AstraZeneca).[31] As of October 30, 2020, select federal governments have committed to advancing the development of HCSs for COVID-19 vaccines. For instance, Imperial College London, funded by the United Kingdom government and supported by hVIVO (a clinical research organization) have began preparations to conduct HCSs in January 2021.[32] Additionally, the Belgian national government and the United States' National Institute of Allergy and Infectious Diseases (NIAID) have made seed investments in preparing for HCSs.[33] However, other vaccine developers and federal governments have remained silent on the matter.

This narrative commentary presents an argument for the adoption of HCSs based on the literature selected to inform the review, representing a key limitation in its methodology. Nonetheless, its aim is to outline some of the critical considerations necessary in deciding whether to advance with the use of HCSs. Although this commentary echoes ideas posited in recent months by some clinicians, scientists, and bioethicists, it further urges that advancement in the serious consideration of HCSs by vaccine developers is needed to prevent further loss of life and extended economic hardship.[22,24] Given the logistical and ethical considerations outlined above and the time and resources necessary to appropriately and morally conduct HCSs, I urge vaccine researchers and developers to begin developing challenge models before additional time is lost so HCSs will be available and ready to implement if necessary. If challenge models are not seriously considered and pursued right now but are deemed necessary in later months, we will have placed ourselves at a significant disadvantage not having mobilized their development earlier.

Scientists have encouraged an emphasis on cooperation and coordination within the context of vaccine development for COVID-19.[34] Coordination of collaborative networks between bioethicists, clinicians, scientists, policy makers, vaccine developers, government officials, and cultural leaders will need to continue to assess the clinical, cultural, political, and logistical feasibility of HCSs. As well, meaningful public engagement should inform the development of any HCS. Furthermore, researchers participating in HCSs must be committed to collaborating on protocols and openly sharing results to maximize benefits and expediate the clinical testing process. With these values in mind, the planning of HCS trial designs, development of safe and characterized challenge strains of SARS-CoV-2, and recruitment of interested volunteers should continue so that when HCSs are needed, there is no delay in initiating the studies. Although being insufficiently cautious can be harmful, so too can being overly cautious. Given the egregious toll that COVID-19 has had on global health, it is important that we consider approaches that we may not otherwise consider.

The usefulness of challenge trials may not be optimal during some current late phase III trials (i.e. the ongoing trials by AstraZeneca, Moderna Inc., Sinovac), but HCSs could nonetheless offer useful data that complement findings from phase III trials. Although the HCS approach may not make it feasible to accelerate the deployment of the first COVID-19 vaccine, given the array of vaccines currently in phase III clinical trials, it may hasten the development of subsequent vaccines. While one of the first developed COVID-19 vaccines may demonstrate high safety and efficacy, it is entirely conceivable that the first developed vaccine(s) may only be moderately effective or not effective.[35] In this scenario, HCSs will be able to help researchers contrast vaccine efficacy between a licensed and candidate vaccine. In an arena where billions will need to be vaccinated to reduce the burden of SARS-CoV-2, multiple vaccines will likely be needed. Facilitating HCSs that contribute to the accelerated development and subsequent deployment of any of these vaccines will be nothing short of a global health victory.

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