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Nguyen, L.C., Bakerlee, C.W., McKelvey, T.G. et al. (11 more authors) (2020) Evaluating use cases for human challenge trials in accelerating SARS-CoV-2 vaccine development. Clinical Infectious Diseases. ciaa935. ISSN 1058-4838

https://doi.org/10.1093/cid/ciaa935

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

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Summary of the article's main points

Despite limitations, human challenge trials could accelerate a COVID-19 vaccine by providing signals of vaccine efficacy in as little as two months or by identifying surrogates of protection. Trial preparations would take many months and thus, should be started immediately.

Abstract

Human challenge trials (HCTs) have been proposed as a means to accelerate SARS-CoV-2 vaccine development. In this paper, we discuss the potential roles for such studies in the current COVID-19 pandemic. We present three potential use cases of HCTs: evaluating efficacy, converging on correlates of protection, and improving understanding of pathogenesis and the human immune response. We go on to outline the limitations of HCTs and conclude that, while currently limited in their application, there are scenarios in which HCTs would be vastly beneficial and, therefore, the option of conducting HCTs to accelerate COVID-19 vaccine development should be preserved. Thus, we recommend an immediate, coordinated effort by all stakeholders to (1) establish guidelines for the use of HCTs for COVID-19; (2) take the first steps toward HCTs, including preparing challenge virus 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; Human Challenge Trial

Introduction

As of May 17, 2020, SARS-CoV-2 has led to almost 4.5 million confirmed infections worldwide and over 300,000 deaths.[1] Vaccines are seen as humanity's best weapon against the virus. Organizations such as the Coalition for Epidemic Preparedness Innovations (CEPI) have advocated measures to shorten vaccine development times, such as conducting phase 1 clinical trials in parallel with animal testing.[2] Still, even with these urgent measures, in February the World Health Organization (WHO) optimistically projected 12–18 months until a vaccine could be available, with potential further manufacturing and regulatory delays,[3] although several initiatives have announced more aggressive targets.[4]

Human challenge trials (HCTs) present an opportunity to hasten vaccine development. In HCTs, healthy volunteers are administered a vaccine candidate, and then an infectious dose of pathogen. The outcomes of this infection are tracked, providing a unique opportunity to assess a vaccine candidate's performance.

Historically, HCTs have provided crucial information about human-pathogen interactions.[5] HCTs have demonstrated the efficacy of cholera vaccines prior to large field trials, while malaria challenges gave early indications regarding the possible efficacy of RTS,S/AS01, the leading malaria vaccine candidate.[6, 7]

Eyal et al. suggested that HCTs could speed up COVID-19 vaccine development by several months.[8] Even a modest acceleration, they argued, could theoretically avert many deaths. This and similar proposals have sparked substantial dialogue around HCTs.[9]

In this paper, we discuss three potential use cases for HCTs in the current COVID-19 pandemic, the preparatory steps needed to make them possible, and how to proceed while deciding whether to conduct HCTs for COVID-19 vaccine development.

Use cases for HCTs in COVID-19 vaccine development

In the context of the COVID-19 pandemic, HCTs could help evaluate vaccine efficacy, identify correlates of protection, and understand pathogenesis and the immune response.

Evaluating efficacy

HCTs could be used alongside an expanded safety trial to replace phase 3 trials, or in parallel with phase 3 trials to give an early indicator of efficacy.

Eyal et al. suggested that HCTs could be used to test for efficacy and, in combination with a large-scale short-term expanded phase 2 safety study, replace comparably lengthy phase 3 trials.[8] Phase 3 trials often take years and usually at least many months.[10] However, governments, vaccine manufacturers, and other stakeholders are currently moving to develop a vaccine at unprecedented speed.[11] The WHO Solidarity Trial expects to shorten the time to generate efficacy data from their trial to three to six months, if the trial is conducted in regions with high COVID-19 incidence or in high-risk populations such as healthcare workers.[12] Other stakeholders will likely conduct phase 3 trials with similar populations.[13] However, it might become harder to identify suitable populations at high risk of infection if COVID-19 incidence falls or fluctuates unpredictably due to social restrictions. Two studies in China examining the effects of the potential drug treatment remdesivir were forced to shut down when they were unable to recruit enough patients due to low disease incidence.[14]

With the necessary preparations and approvals in place, an HCT could take as little as two months to conduct and would require far fewer participants than a phase 3 trial due to viral exposure being guaranteed by the challenge. Therefore, HCTs could accelerate the licensure of a vaccine.

Our two month estimate includes:

- At least two weeks in isolation to screen volunteers for prior infection and other exclusionary health factors,
- At least two weeks after vaccination to allow for an immune response, and possibly longer if administering multiple consecutive doses,
- At least four weeks after viral challenge to observe and resolve infection endpoints and document the end of viral shedding.

There is precedent for licensing on the basis of HCT efficacy data: such data, in combination with conventional trials measuring safety and immunogenicity, provided the basis for licensing the first FDA-approved cholera vaccine.[15] However, an HCT replacing a phase 3 trial would at least have to be accompanied by an expanded safety trial, which would take additional time and might still not suffice for vaccine licensure. At a minimum, post-licensure trials would be necessary to continuously evaluate the vaccine's efficacy and safety.

Instead of replacing phase 3 trials, HCTs could be used in conjunction with them to provide an early glimpse of efficacy in advance of phase 3 results. This could allow manufacturers to reallocate time, funds and other resources from less to more promising candidates.[16] Phase 3 trials would still be useful for demonstrating efficacy across the population under real-world conditions and the frequency of any rare adverse effects of vaccination. Challenge trials may also enable head-to-head comparison of different vaccine candidates.

Converging on correlates of protection

Correlates of protection (CoPs) are biomarkers that correlate with protection against specific infection outcomes. HCTs could be used to identify or verify CoPs against disease endpoints. If in phase 3 trials CoPs are used as surrogate endpoints instead of clinical endpoints, this could expedite licensure.[17] Vaccines that have been approved based on CoPs include vaccines against hepatitis B, H5N1 influenza, and Japanese encephalitis.[18, 19, 20]

CoPs are typically identified in animal challenge models, observational studies, or early clinical phases. Some vaccine manufacturers have signaled their intention to look for secondary outcomes that might be important CoPs.[21] However, finding CoPs is a difficult task. Some viruses, such as rotavirus, have no known CoPs despite years of searching.[22] HCTs could help establish CoPs for vaccine candidates if other methods fail, since the controlled clinical setting of an HCT provides greater opportunity to reveal links between secondary endpoints and protection. If an HCT established links that were causal, secondary endpoints could be used to accelerate the progress of many different candidate vaccines. Notably, CoPs could only accelerate the generation of efficacy data and not safety data.

Improving understanding of pathogenesis and the human immune response

Studies employing human challenge models (HCMs) could help us understand the natural history of COVID-19, including early stages of pathogenesis and the human immune response. HCMs have elucidated features of infectious diseases that could not have been studied otherwise, such as the evolutionary dynamics of influenza populations within a host and the dynamics of the immune response to common cold coronavirus 229E.[23, 24]

A COVID-19 HCM 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 resolve the physiological basis for variation in disease severity, the disease's progression from infection, or the immune response upon re-infection.[25] They could thereby provide insights that would form a bedrock for medical countermeasure development efforts more broadly.

HCTs may also have value in detecting vaccine-enhanced disease. For example, animal models showed increased lung pathology after vaccination with whole SARS-CoV spike protein.[26] Notably, the evidence for vaccine-enhanced disease in SARS-CoV is limited to in vitro and animal models, with vaccination appearing protective overall. 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 over small groups with incrementally increasing numbers of participants.[8]

However, in contrast to a conventional clinical trial, an HCT may be unable to detect adverse events that are rare or have delayed onset. For example, time-lagged enhanced disease responses occurred in consecutive infections with different dengue serotypes.[27] This may simply be from delayed exposure, but it is also possible that these effects only appear if sufficient time has passed between vaccination and infection.

Limitations of HCTs

All these approaches are limited by the extent to which data gathered from HCTs can be generalized to the field. Historically, some human challenge models have produced results that

are generally predictive of performance in the field,[28] while others have not.[29] The generalizability of HCT results depends on several factors.

First, the timing of viral challenge relative to vaccination is the same for all patients in an HCT but highly variable in real-world use. This may prove problematic if the effects of the vaccination depend on the time between vaccination and infection.

Second, the method of administration can affect the nature of infection and the immune response. For example, in influenza challenge studies, inhalation of aerosolized virus is thought to cause more severe, lower respiratory infection compared to intranasal instillation.[30] For generalizability, the mode of administration should mirror routes of community-acquired infection, while balancing the model's relevance to intended clinical endpoints and the risk it poses to participants.

Third, it is unclear whether field-relevant clinical endpoints are ethically feasible to test in 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, possibly using an attenuated challenge virus strain to achieve this result. However, it is possible that vaccine candidates will more effectively abrogate severe disease than mild illness, as has been seen with influenza vaccine candidates.[30] If such candidates were tested in HCTs with mild disease as its primary endpoint, their efficacy against severe disease may go undetected, along with associated CoPs. Additionally, if attenuated or otherwise engineered virus strains were used, they might generally offer less applicable results. If using wild-type virus strains or using severe disease as an HCT endpoint, the availability of effective therapeutic options would become an even more important consideration for participant safety.

Fourth, it may be difficult to generalize from results in pre-screened healthy young people to the broader global population, since responses to infection and vaccination can depend on age, immune status, comorbidities, infection history, genotype, and other factors.[31, 32] That said, traditional phase 3 studies are not perfect in this regard either, as they often exclude subsets of the population such as children and pregnant women.[33]

Preparatory steps needed for an HCT

HCTs' practical utility depends 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,
- Gaining approval from institutional review boards and regulatory bodies,
- Establishing partnerships with clinical researchers and institutional sponsors,
- Securing access to ventilators, therapeutics, and other equipment to provide the highest standard of care to participants in case of severe disease.

For the sake of speed, these steps could be partially parallelized. Beyond these, the three main time-consuming steps—apart from vaccine production and initial clinical trials—are manufacturing challenge virus, conducting dose-finding studies, and potentially preparing clinical biocontainment units.

Manufacturing challenge virus

Before HCTs are possible, a challenge virus must be produced under good manufacturing practice (GMP), which only a handful of manufacturers in the US and UK are equipped to do. The first manufacturing steps—contracting a production facility, securing raw materials and

establishing a standardized protocol for production of high-quality material free of adventitious agents—typically take one to two months when there are no supply chain problems. From there, virus stocks must be produced and stored, which would take at least several weeks. After production, the facility needs to conduct release testing, which usually takes at least three to four months. (B. L. Innis, personal communication, May 9, 2020) Finally, the virus must be FDA-approved prior to dose-finding studies.

This timeline could be shortened if GMP-grade virus was already in production for other uses, such as for a live attenuated vaccine. Otherwise, starting production for HCTs could hasten other manufacturing timelines later on.

Dose-finding studies

Before HCTs can be performed, the infectious dose to be administered in challenges must be determined, typically via an escalation study. In escalation studies very few participants are initially administered a very low dose of virus. This initial dose could be inferred from animal challenges and human challenges with other viruses.[34] Participants would be followed for several weeks in a biocontainment unit to assess the presence and severity of any resultant infections. This process would be repeated until some proportion of participants have reached the desired clinical endpoint. This means dose-finding studies carry appreciable risks for volunteers that must be weighed carefully. Experts estimated that a dose-finding study for a COVID-19 challenge model would take two to six months. (personal communications - currently seeking permission to cite them by name).

It is worth noting that regulatory requirements for infectious dose-finding studies vary.[35] In the US, any dose-finding studies require an Investigational New Drug application to proceed. Meanwhile, in at least some European countries, challenge virus is considered a Non-Investigational

Medicinal Product, and dose-finding studies may require fewer regulatory approvals than in the US.

Preparing clinical biocontainment units

Depending on the biosafety level required for COVID-19 HCTs, it might currently be impossible to conduct an HCT with sufficient participants in the same place at the same time. For example, isolation units used for influenza challenges typically have fewer than 40 beds (B. L. Innis, personal communication, May 4, 2020). Therefore, if more participants are required, HCTs may need to use multiple biocontainment units simultaneously with great logistical effort, or be performed sequentially in smaller cohorts, which would extend the timeline to completion. Alternatively, new biocontainment units with sufficient capacity could be built.

Taken together, virus manufacturing and dose-finding studies would take at least five months, and likely longer. We estimate that, at maximum speed, manufacturing, validation and FDA approval of the challenge virus would take four months, and dose-finding four months, for a total of eight months. Given these timelines, it is unlikely that HCTs will support testing of the vaccine candidates currently in phase 1 or beyond. However, if approached with due urgency, they could help accelerate the development of vaccine candidates in earlier developmental stages. The path to an HCT will involve dozens of players, and active coordination will be necessary to minimize lags arising from interdependencies among them.

Ethical considerations

HCTs come with appreciable risks to study participants, research staff, and wider society. It will be important for volunteers, manufacturers, regulators, and other stakeholders to assess whether those outweigh the potential benefit.

The risk to participants has been discussed extensively in other pieces.[36] It should be minimized by selecting volunteers with low risk of severe disease outcomes, providing state-of-the-art medical care, carefully selecting the virus strain and mode of administration, and carefully deciding whether a placebo group should be included.[37] HCTs must implement an informed consent process that ensures participants understand they will be intentionally exposed to an infectious pathogen, and that this could cause them to get ill and suffer disease symptoms, including uncertain long-term effects.[38] Participants must understand that, once exposed to the virus, they will only be allowed to leave the study facility when they no longer pose a risk to others, even if they decide to withdraw from the data collection aspect of the trial. Further, bioethicists and researchers should carefully weigh the virtues of compensation (e.g., paying respect to volunteers, enabling their participation) against its potential undesirable effects (e.g., undue inducement).[38]

HCTs also involve potential negative consequences that are less direct. HCTs could unintentionally expose trial personnel to the virus, or accidentally release virus into the surrounding area, both of which could lead to wider outbreaks. Teams leading HCTs should consult the local community and other relevant stakeholders well beforehand and take all necessary measures to minimize these risks.[36]

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 challenges has yielded valuable insights for the control of influenza, typhoid and other infectious diseases, and an overly hasty or mismanaged COVID-19 HCT could risk the gains from future HCTs.[39, 40]

Conclusion

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 offer distinct advantages due to the speed and richness of the data they could generate. However, practical and ethical considerations constrain the range of scenarios in which HCTs could actually influence vaccine development timelines. For example, even if HCTs were pursued immediately, it is unlikely they could provide efficacy data on the current phase 1 vaccine candidates soon enough to be useful.

Nevertheless, there are still many scenarios in which the benefits generated by HCTs would likely outweigh their risks. For example, it is quite possible that we will reach the end of 2020 without any of the vaccine candidates currently in clinical trials having shown efficacy, but with one or more drugs having proven effective against severe COVID-19, and a range of vaccine candidates in early developmental stages. In such circumstances, it could make sense to run a large, multi-arm HCT of, say, a dozen vaccine candidates in parallel with a multi-arm phase 3 trial. This could provide both rapid efficacy data to 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 such scenarios, we recommend an immediate, coordinated effort by all stakeholders to 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. The WHO and the NIH

have already started this process. (Notably, this could provide useful guidance in the event of future pandemics as well.)

2. Taking the first practical steps toward HCTs, including preparing challenge virus 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. periodically conducting a systematic re-evaluation, and adjusting course based on the progress of the pandemic and 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.

Funding

This work was supported by 1Day Sooner. The publication fee as well as part of the salaries of some of the authors are funded by 1Day Sooner.

Conflict of interest

All authors, with the exception of Thomas Darton, are affiliated with the research arm of 1Day Sooner, a non-profit 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.

Acknowledgements

We are indebted to the feedback and insights provided by Bruce Innis, Luciana Borio, Richard Gorman, Heather Youngs, Chris Somerville, Pooja Panigrahi, Randall Kincaid, Richard Bruns, Kendall Hoyt, and Christian Kleinedam who have been most generous with their time. Being mentioned here does not imply endorsement of any parts of our work.

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