COMMENT

Immunological considerations for SARS-CoV-2 human challenge studies

Alexander D. Douglas and *Adrian V. S. Hill*

The ethics and practicalities of controlled human infection with SARS-CoV-2 have been widely discussed. Potential risks are clear. The case in favour hinges upon whether these risks can be mitigated to an acceptable, very low, level and whether the studies will provide substantial benefits that could not readily be obtained by other means. Here, we discuss the immunological considerations relating to each side of this balance.

Controlled human infection (CHI) models allow for the time, dose, route and strain of the infectious exposure to be controlled by the investigator. By eliminating the variability of community-based exposure, CHI enables hypotheses to be tested rapidly in small groups of individuals, independent of the prevalence of disease in the community. Furthermore, focusing on a small group of individuals in a defined time window permits an intensity of monitoring that is usually impractical in community-based studies, particularly in the pre-symptomatic period. As a result of these features, CHI studies of diseases including malaria, cholera and respiratory syncytial virus have made important contributions to our understanding of pathogenesis and development of vaccines and drugs[1]. CHI studies of endemic coronaviruses have yielded insights that are relevant in the context of the COVID-19 pandemic, notably that infection induces partial, but not sterile, immunity to re-challenge 1 year later[2,3]. The ethical and practical challenges for SARS-CoV-2 CHI studies have been reviewed elsewhere[4,5]; here, we address the immunological considerations for their implementation.

Design of SARS-CoV-2 CHI studies

Many features of study design for SARS-CoV-2 CHI will be similar regardless of the aim of an individual study. Key factors will include choice and manufacture of the challenge agent, volunteer selection and monitoring, and the use of antiviral therapy.

Infectious agents for CHI must be manufactured to high quality standards[6], a significant undertaking under biosafety level 3 conditions. Together with the desirability of comparability between studies at different centres, this makes it likely that, at least in early studies, only one, or very few, challenge virus strain will be used. Use of attenuated SARS-CoV-2 viruses has been considered, but over-attenuation could markedly reduce the value of a model. Use of a wild-type virus, in association with drug treatment (see below), is therefore favoured by many. There is, as yet, relatively little understanding

of the functional or immunological importance of SARS-CoV-2 sequence polymorphisms. There is thus little to argue for the selection of any particular viral isolate for CHI, although use of the now-dominant clade B1 and avoidance of culture-acquired mutations in the furin cleavage site of SARS-CoV-2 spike protein (which result in impaired membrane fusion) seem appropriate.

SARS-CoV-2 CHI is highly likely to be carried out in young, healthy, fully immunocompetent volunteers without risk factors for severe infection. Participants would be housed and monitored in containment facilities while infectious and, for most potential studies, would be SARS-CoV-2 seronegative at enrolment.

The first CHI study is likely to involve dose-ranging to find the minimum virus dose that achieves an adequate attack rate. Variability in whether exposed volunteers become infected is more common in CHI studies for respiratory viruses than, for example, for malaria. Low attack rates affect statistical power, necessitating larger studies, but the number of volunteers who can undergo SARS-CoV-2 CHI is likely to be limited by the scarcity of suitable facilities. Moreover, use of a higher dose to achieve an adequate attack rate may increase the risk of severe infection. The ability to achieve consistent infection, ideally with a low viral dose, is thus highly desirable. Beyond ensuring seronegativity of volunteers, the administration protocol is the main opportunity to promote consistency of infection. Intranasal administration of the inoculum in drops is most straightforward (intrapulmonary delivery is generally considered unacceptable on safety grounds) but results in short and variable contact time of the inoculum with the mucosa[7]. Repetitive low-dose inoculation and/or use of large-droplet spray devices for mucosal administration may improve consistency.

Access to an effective 'rescue therapy' is widely considered a prerequisite for CHI with a potentially lethal pathogen and has been a key obstacle to SARS-CoV-2 CHI so far. Data supporting the efficacy of the antiviral drug remdesivir, monoclonal antibodies and adjunctive

Jenner Institute, Nuffield Department of Medicine, University of Oxford, Oxford, UK.

✉e-mail: sandy.douglas@ndm.ox.ac.uk

therapies are accumulating, but controversies remain. We are not yet aware of peer-reviewed studies showing robust efficacy of a drug in mild infection, although antivirals are generally more effective when given earlier (during active viral replication and before the onset of severe immunopathology). Peer-reviewed demonstration of drug efficacy in early SARS-CoV-2 infection, for example for monoclonal antibodies[8], seems probable in the near future. Drug availability will bring with it the question of how the drug should be used. In our view, no volunteer in a SARS-CoV-2 CHI study should require 'rescue' from severe infection. Therapy must prevent the progression of mild symptoms or perhaps even prevent the development of symptoms at all. Very early treatment, limiting peak viral load and systemic dissemination, may or may not lower the risk of long-term sequelae, which are now recognized after even mild infection.

Clearly, such pre-emptive treatment will require a study end point that can be evaluated very early in infection. In CHI studies of malaria vaccines, pre-symptomatic treatment of volunteers is now routine. In CHI studies of influenza vaccines, although pre-symptomatic treatment is not generally used, outcome is strongly predicted by early viral replication dynamics. Nasopharyngeal viral load may be an adequate end point for many SARS-CoV-2 CHI studies. Modelling anything but the mildest lower respiratory tract disease may not be possible.

To summarize, the need to ensure volunteer safety will permeate the design of SARS-CoV-2 CHI protocols. The risk to volunteers should be substantially lower than the risk associated with infection in an age-matched community cohort. The extent to which the safety measures affect the conclusions that can be drawn will need to be carefully evaluated for each study.

Value of SARS-CoV-2 CHI studies

The potential roles of SARS-CoV-2 CHI in studies of pathogenesis, viral transmission and therapeutics are well illustrated by the examples of existing CHI models for other pathogens[1,3]. Here, we focus on CHI studies to investigate natural or vaccine-induced immunity.

The use of SARS-CoV-2 CHI studies for vaccine development has attracted the most attention but merits critical examination. Leading candidate vaccines are already in phase III trials, which should provide efficacy readouts before SARS-CoV-2 CHI is available. For future vaccines, CHI will not replace the need for large-scale phase III safety and possibly efficacy data, including in high-risk subpopulations ineligible for CHI.

Instead, CHI may be used for 'enhanced phase I' vaccine trials, allowing for the early prioritization of future candidates, and for sub-studies within 'enhanced phase III' trials (for example, providing very rapid readout on the duration of protection or defining correlates of protection in subgroups chosen on the basis of measured immune responses). Rapid triage through 'enhanced phase I' trials could be very important if the current leading candidates fail. If, on the other hand, current phase III studies demonstrate efficacy (and ideally a correlate of protection, which would provide an alternative means of triaging future candidates), other difficulties may arise, again necessitating CHI studies. In the presence of a licensed vaccine and correlate, vaccines seeking to protect by novel, possibly superior, mechanisms would face difficulties in reaching field studies, particularly if the novel mechanism is difficult to assay (such as tissue-specific cellular responses induced by mucosal administration). Moreover, CHI studies may have value in areas of low disease incidence or if (once a somewhat effective vaccine is available) it becomes considered unethical to carry out a placebo-controlled field study.

CHI is also likely to be of value in exploring non-vaccine-induced immunity to SARS-CoV-2. Establishing the duration and immunological correlates of immunity induced by SARS-CoV-2 infection is of clear and urgent importance and could readily be addressed by CHI, as could the question of cross-protection against future antigenic variants of the virus. CHI in this context would be an accelerated and focused cohort study, with intensive immunological characterization before and early in infection, in a narrow population. By contrast, large field-based follow-up studies of naturally infected individuals could enable study of both reinfection in high-risk populations and risk of progression to severe disease if partial immunity is observed.

Finally, CHI studies should provide a rapid approach to screening new treatments for mild SARS-CoV-2 infection, such as monoclonal antibodies, with more established drugs on hand as back-up therapies.

Conclusions

SARS-CoV-2 CHI might generate crucial data in small numbers of subjects relatively quickly, but evaluations of its risk–benefit balance are changing constantly: knowledge about drugs and sequelae of infection, the urgency of answering particular questions, and the ability to answer them by other means are all evolving. Although we cannot yet know exactly which questions will be best addressed through CHI, preparatory work now will provide a new option in the community's toolkit to address the questions of the coming years.

1. Roestenberg, M., Hoogerwerf, M.-A., Ferreira, D. M., Mordmüller, B. & Yazdanbakhsh, M. Experimental infection of human volunteers. *Lancet Infect. Dis.* **18**, e312–e322 (2018).
2. Callow, K. A., Parry, H. F., Sergeant, M. & Tyrrell, D. A. The time course of the immune response to experimental coronavirus infection of man. *Epidemiol. Infect.* **105**, 435–446 (1990).
3. Tyrrell, D. A. J. A view from the common cold unit. *Antiviral Res.* **18**, 105–125 (1992).
4. Deming, M. E., Michael, N. L., Robb, M., Cohen, M. S. & Neuzil, K. M. Accelerating development of SARS-CoV-2 vaccines — the role for controlled human infection models. *N. Engl. J. Med.* **383**, e63 (2020).
5. Jamrozik, E. & Selgelid, M. J. COVID-19 human challenge studies: ethical issues. *Lancet Infect. Dis.* **20**, e198–e203 (2020).
6. Catchpole, A. P. et al. The manufacturing of human viral challenge agents for use in clinical studies to accelerate the drug development process. *BMC Res. Notes* **11**, 620 (2018).
7. Innis, B. L. et al. Convening on the influenza human viral challenge model for universal influenza vaccines, part 2: methodologic considerations. *Vaccine* **37**, 4830–4834 (2019).
8. Eli Lilly and Company. Lilly provides comprehensive update on progress of SARS-CoV-2 neutralizing antibody programs. *PR Newswire* https://www.prnewswire.com/news-releases/lilly-provides-comprehensive-update-on-progress-of-sars-cov-2-neutralizing-antibody-programs-301147631.html (2020).