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Perspective

SARS-CoV-2 Human Challenge Studies — Establishing the Model during an Evolving Pandemic

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Human challenge studies (also called controlled human infection models), in which researchers intentionally administer an infectious agent to volunteers, have played major roles in vaccine and treatment development and in elucidation of pathogenesis and immunity. Such studies are not normally undertaken during a pandemic, however, and the potential risks and benefits of such research with SARS-CoV-2 in this setting have triggered widespread debate. While other commentators have made theoretical arguments for and against SARS-CoV-2 challenge studies, a consortium of academics, industry collaborators, and the British government (through the Human Challenge Programme of the U.K. Vaccines Taskforce) has now proceeded to address the technical and ethical considerations to enable such studies. The consortium's practical application of ethical principles against a backdrop of rapidly emerging evidence carries lessons for future outbreaks.

In early 2020, the World Health Organization established working and advisory groups to consider the rationale and ethical criteria for such studies and to issue practical recommendations, although feasibility was initially uncertain.[1,2] However, accruing clinical data revealed that Covid-19 was mostly mild or asymptomatic and self-limiting in young people (18 to 30 years of age) without preexisting health conditions.[3] This observation supported the decision to advance development of human challenge studies.

After extensive engagement of the public and prospective participants, establishment of a high-containment quarantine facility at the Royal Free London NHS Foundation Trust, manufacture of a challenge virus under Good Manufacturing Practice conditions, and multiple rounds of expert review, a study protocol was submitted for evaluation by the Specialist Ad Hoc Research Ethics Committee convened by the NHS Health Research Authority. This independent review process, undertaken from December 2020 through February 2021 for a study in seronegative participants and immediately afterward for one in previously infected volunteers, scrutinized the ethics of both these individual studies and the entire human challenge program, including issues raised by the evolving pandemic. Two key considerations emerged: the justification for such research and the management and minimization of risks.

Back when neither effective vaccines nor treatments were avail-

able for Covid-19, the potential scientific value of human challenge studies was evident.[4] The approval of several highly efficacious vaccines and the emergence of variants of concern (VOCs), however, raised questions about whether such studies were still needed and justifiable. Human challenge studies have features that cannot be replicated in natural infection studies. By eliminating confounders such as different viral strains and infectious doses, uncertain timing of exposure, and patient heterogeneity, investigators can identify protective host factors and immediate responses early during infection. By generating reliably high infection rates and permitting fine control of timing, challenge studies enable rapid direct comparisons of new vaccine candidates, revised regimens, and prophylactic, preemptive, or postsymptomatic treatments (see table).

The rollout of first-generation vaccines necessitated reappraisal of what role human challenge studies may still have in the pandemic response. Although speedy phase 3 vaccine efficacy trials were possible initially, dozens of vaccine candidates in earlier stages of clinical development now face uncertainty. With extensive public health measures and increasing vaccination, the feasibility of timely field efficacy trials is now unpredictable, and soon such trials may be impossible. Maintaining an unvaccinated placebo group is ethically questionable, and noninferiority trial designs require even more participants.

With uneven vaccine access, however, approvals of new vaccines and antivirals still need to be prioritized — and some as-yet-unlicensed vaccines (including inhaled and needle-free approaches) may offer major advantages. For new vaccines and antivirals, licensure based on immunogenicity or viral kinetics alone may be impossible, but human challenge studies could contribute efficacy data to complement larger-scale safety trials. This argument will become even stronger when challenge agents based on antigenically diverse VOCs are manufactured, allowing testing of cross-strain protection. Discussions are therefore ongoing with medicine regulators to establish the acceptability of this approach.

For human challenge studies to be acceptable, research risks must be appropriately managed and minimized. Development of SARS-CoV-2 challenge studies could not rely on extrapolation from existing respiratory virus challenge models. Instead, protocol-design decisions were based on emerging evidence; where data were incomplete, the most conservative approaches were taken.

The critical component in determining study feasibility was estimating potential individual risk and identifying a sufficiently low-risk participant group. Data from early outbreaks in China indicated that asymptomatic and mild infection were common in young people, but the most relevant estimates of risk in our target population came from real-time access to U.K. data on clinical outcomes in previously healthy young adults infected in the community. These data suggested that careful volunteer selection, based primarily on younger age and absence of underlying health conditions, could render the model safe.

As an extra precaution, we used the QCovid algorithm[5] to estimate individual absolute risk for hospitalization or death, taking into account all relevant underlying factors. We could thus set a cautious inclusion threshold (equivalent to that for a 30-year-old with no risk factors, calculated as a 1:250,000 risk of death or 1:4902 risk of hospitalization) and provide individualized risk assessments for participants as part of informed consent. Since QCovid is based on population data, the risk of exposure cannot be disaggregated from the risk of severe outcomes, but we believe that the resulting potential for overestimating risk in certain groups is appropriately cautious for early model development, when the challenge infection's features are unknown. Using this risk score as an entry criterion may limit participant diversity, however, so once the model has proven safe, the score should be used only for participant information.

Although data on the relationship between inoculum size and disease severity are limited, it was logical to assume that higher doses might increase risk. Given the pathogenicity of SARS-CoV-2, it was ethically essential to start with the lowest possible amounts of inoculum, followed by careful dose escalation. In addition, to minimize the risk of severe Covid-19, virologic readouts rather than disease end points were targeted.

Some commentators argue that the lack of a guaranteed "rescue" treatment makes challenge studies problematic. Since the principal risk mitigation is participant selection, this gap should not be an absolute barrier. Furthermore, existing interventions (such as monoclonal antibodies) can significantly reduce the likelihood of progression of asymptomatic or mild Covid-19 to more severe disease. No drugs have undergone trials in early, presymptomatic

Scientific Rationale and Capabilities for SARS-CoV-2 Human Challenge Studies.

Focus	Potential Impacts	Practically Possible Only with Human Challenge Studies	Substantially Accelerated or Scientifically Improved by Human Challenge Studies
Vaccines			
Relative protective efficacy of SARS-CoV-2 vaccines	Using licensed vaccines as a benchmark, new vaccines can be directly and rapidly compared for prioritization. Field studies to determine relative efficacy would be unfeasibly large and subject to unavoidable confounding.	X	
Effect of vaccination on viral shedding from the nose (transmission blockade)	Preventing infection in the upper respiratory tract and viral shedding is critical to preventing transmission but cannot be practically assessed in field studies.	X	
Comparative efficacy of vaccines with different modes of action	Different vaccine platforms may induce distinct mechanisms of protection that are assessable only in a controlled study, given noncomparable immune readouts.	X	
Vaccine-mediated correlates of protection in immunized participants	Vaccine-induced markers that correlate strongly with protection from challenge infection can be validated as measures for vaccine licensure of new vaccine candidates in lieu of determining efficacy in a phase 3 trial.	X	
Nimble selection of optimal vaccine dose and dosing regimen, including heterologous combinations	Rapid attainment of data in small cohorts allows comparative analysis and avoids failed phase 3 trials.*		X
Booster-vaccine efficacy against variants of concern (VOCs)	Challenge viruses made using VOCs enable testing of homologous and heterologous protection.	X	
Immunity			
Innate immune, T-cell, and humoral responses that act during early SARS-CoV-2 infection	Immune responses start before any symptoms develop and are critical for protection but cannot be studied in natural infection (since patients are recognized only after symptom onset).	X	
Durability of natural and vaccine-induced immunity	In previously infected or vaccinated people, challenging at predefined time points clearly shows how long protection lasts, clarifying the need and timing for boosters or other interventions.	X	
Susceptibility to reinfection	By testing reinfection with SARS-CoV-2 in seropositive persons, researchers can immediately establish whether previous infection is protective.*		X
Host defense factors that mediate protection and viral clearance	Markers that differ between infected and uninfected participants can be used to calibrate and develop diagnostics, predictors, and new vaccines. Definition of correlates of protection in field studies is limited by confounding by uncontrolled viral and other factors.*		X
Antivirals and other treatments			
Durability of antiviral action as prophylaxis	Challenge infection at different time points after administration of monoclonal antibody or antiviral agents will determine how long they are effective.	X	
Rapid determination of efficacy of antivirals	Human challenge has a well-established role in antiviral evaluation and can use very small sample sizes to accelerate their development.*		X
Appropriate dosing for antivirals, next-generation monoclonal antibodies, and combination approaches	Rapid, small studies nimbly assess efficacy of dosing and regimen adjustments.*		X
Other			
Assessment of shed virus as a correlate of transmission during acute infection	Simultaneous assessment of viral titers in the respiratory tract, exhaled breath, air, and surfaces permits inference of transmission risk.	X	
Rapid testing of novel diagnostic tests	Sensitivity and specificity can be directly evaluated at known times after inoculation and correlated with measured viral titers.*		X

* It may be possible to partially infer or determine answers to these questions using other study designs, but only if community transmission is ongoing.

SARS-CoV-2 infection, but to further reduce risk, we included safe, well-tolerated antivirals as preemptive therapy to be given early after the confirmation of infection. Though efficacy in this setting was uncertain, caution argued for antiviral use in case evidence-based assumptions about disease severity proved inaccurate. This approach was designed to be responsive to new data, however, and discontinuation of automatic preemptive treatment of infected participants, once the model was shown to be safe and well-tolerated, was embedded in the protocol to avoid confounding by treatment.

Still, some risks remain. The greatest unknowns relate to "long Covid" (i.e., late complications or protracted disease). Although cases have been reported, data from the U.K. Office for National Statistics and the COVID Symptom Study provided reassuring evidence implying that persistent symptoms beyond 3 months were rare in young adults after mild disease. Nevertheless, careful follow-up, specialist referral, and compensation to cover inability to work are important components of the study design. To ensure that the existence of risks that are less well quantified is understood, the study's informed consent process balances participant understanding with comprehensive detail, reiterating at multiple points key facts about potential consequences and the right to withdraw from the research even after inoculation.

Although the scientific justifications for such research remain unchanged despite pandemic surges, limitations in clinical capacity can affect the conduct of challenge studies, which requires access to specialist support in the rare event that a participant needs higher-level care. Investigators should consider this possibility in advance to avoid allowing the study's operational needs to negatively affect other patients' treatment. Collaboration with government and the NHS has assisted in prioritizing limited resources and determining optimal timing. Implementing challenge studies during a pandemic wave might also affect public health messaging when social distancing and lockdown measures are being emphasized. This potential conflict highlights the importance of ongoing public engagement.

Our experience thus far indicates that a SARS-CoV-2 human challenge research program can be developed as part of the pandemic response. Its establishment has relied on broad collaboration (established before the pandemic through the Human Infection Challenge Network for Vaccine Development) that provided the varied expertise, broad consensus, and funding required. This approach accelerated both challenge-virus manufacture and the ethics review process, ensuring that study design was informed by real-time scientific data. With SARS-CoV-2 continuing to cause major outbreaks globally and improved vaccination and treatment still necessary, the ethical arguments for human challenge studies remain compelling, despite the changing nature of the pandemic.

Disclosure forms provided by the authors are available at NEJM.org.

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1. Jamrozik E, Littler K, Bull S, et al. Key criteria for the ethical acceptability of COVID-19 human challenge studies: report of a WHO Working Group. Vaccine 2021;39:633-40.
2. Levine MM, Abdullah S, Arabi YM, et al. Viewpoint of a WHO Advisory Group tasked to consider establishing a closely-monitored challenge model of coronavirus disease 2019 (COVID-19) in healthy volunteers. Clin Infect Dis 2021;72:2035-41.
3. Kuiper VP, Rosendaal FR, Kamerling IMC, Visser LG, Roestenberg M. Assessment of risks associated with SARS-CoV-2 experimental human infection studies. Clin Infect Dis 2020 November 29 (Epub ahead of print).
4. Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. J Infect Dis 2020;221:1752-6.
5. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ 2020;371:m3731.

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