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Human challenge studies in the time of COVID-19: Pros and cons

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Can we speed up coronavirus vaccine development? A human challenge study, in which volunteers would be deliberately infected with coronavirus, could help in theory. In this article, two collaborators from the CTU Geneva explore the potential benefits and the risks associated with SARS-CoV-2 challenge studies.

COVID-19 poses an extraordinary global health menace for which new pharmacological therapeutics and vaccines are urgently needed. According to the World Health Organization's COVID-19 dashboard, as of 21 February 2021, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to over 110 million confirmed cases of COVID-19 and over 2.4 million deaths worldwide. Clinical trials have helped to find treatments, but just three therapeutics have been approved to treat COVID-19 so far: dexamethasone in the United Kingdom and Japan; Avigan (favilavir) in China, Italy, and Russia; and Veklury (remdesivir) in the United States, Japan, and Australia. Since July 2020, Veklury has had a conditional marketing authorisation

in Europe and it has also received a temporary authorisation in Switzerland, where the Swiss Agency for Therapeutic Products (Swissmedic) has decided to allow its temporary distribution to COVID-19 patients beyond those in clinical trials (see Swissmedic's website). However, none of these treatments are preventing people from getting sick and needing hospital care.

The best way to protect people's health is an effective vaccine. Among the hundreds of COVID-19 vaccines being developed around the world (Le et al. 2020), several have reported promising initial data, with some receiving authorisation for use and becoming available in some countries. But we are only at the beginning of vaccine development, and much work remains.

COVID-19 human challenge studies

In order to accelerate testing, researchers and institutions are exploring the feasibility and ethics of human challenge trials that could potentially support the development of vaccines and treatments to protect against SARS-CoV-2 infection. Human challenge trials deliberately expose healthy volunteers to infection in order to study diseases and test vaccines or treatments more quickly than a classical clinical trial. They have been used to understand and fight diseases such as influenza, malaria, typhoid, and dengue fever, and they have helped facilitate the licensing process of vaccines for cholera (Killingley et al. 2011; Haney et al. 2017).

One of the first COVID-19 human challenge studies will soon begin at the Royal Free Hospital in London since it has received final regulatory and ethical approval. In its first phase, researchers will try to identify a suitable dose of the virus SARS-CoV-2 that causes infection in healthy young people (aged between 18 and 30 years old). In a later phase, a vaccine candidate could be given to a group of healthy adults, who would then be exposed to the virus in a controlled environment. They would be closely monitored to see if the vaccine is successful in preventing infection and to identify any side effects (Kirby 2020).

Pros and cons of human challenge studies

Human challenge studies can speed up vaccine development, as it is easier to measure the effectiveness of a vaccine when participants are all exposed to the virus rather than waiting for natural exposure. A human challenge study takes months rather than years and involves fewer volunteers (usually around 25–100 people). In COVID-19 human challenge studies, these rapid results will help researchers focus on the most promising vaccines, because it is not possible to conduct conventional large-scale phase 3 studies for all candidate vaccines.

Over 38,000 people have signalled their willingness to participate in COVID-19 human challenge studies, and the UK government has invested 37.3 million euros to support such trials. However, purposefully infecting healthy volunteers with the virus SARS-CoV-2 raises ethical concerns, in part due to the unclear and developing risks of COVID-19. Previous human challenge trials involved diseases for which there was an extremely low risk of death or an approved rescue treatment. By contrast, COVID-19 has a significant mortality rate and there is no effective cure. Further, there is growing evidence that SARS-CoV-2 infection can cause long-term disabilities, as demonstrated by people experiencing "long COVID" (BMJ 2020). Some studies show that these sequelae can affect asymptomatic carriers and low-risk demographic groups. Based on these considerations, COVID-19 human challenges not only fail to provide any direct benefit for participants but also contradict the principle of non-maleficence. Besides objections for ethical reasons, scientific and practical limitations of the challenge model must also be considered. Since a challenge trial would include only young and healthy participants, the resulting data would not necessarily be generalisable to more vulnerable groups, such as older people or those with other health conditions.

Some vaccines, such as Oxford, Moderna, or Pfizer, have already received authorisation for use and

vaccination has started in some countries. Therefore, challenge trials will not actually help accelerate the current vaccine development timeline. However, even if these trials do not accelerate the development of the first vaccines, they may be important for second-generation vaccines. Second-generation vaccines are important because they will be needed to vaccinate people in low- and middle-income countries. In addition, they could potentially be administered orally, not require a booster, have fewer cold chain requirements, and cause fewer side effects. Challenge studies could also be key to studying how long immunity lasts (both from a vaccine and natural infection) and the extent to which infection by one strain is protective against another.

Conclusion

In conclusion, COVID-19 human challenge studies could accelerate vaccine development by helping to test multiple candidate vaccines. However, further discussion is needed to address critical issues. Consultation with scientists, research ethics committees, regulators, and potential volunteers will help to determine what degree of risk is acceptable and compensated by the estimated benefits.

Comment by Angela Huttner: "Recommending a human challenge study for SARS-CoV-2 remains a formidable challenge."

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There is perhaps an ethical and methodological argument to make for human challenge studies, but only under certain conditions. As outlined in the article, they should be employed for infections whose scope and duration of clinical manifestations are well established and for which highly effective rescue therapy exists. SARS-CoV-2 infection clearly does not fulfil these criteria. In addition, human challenge studies should be used only for infections that are expected to cause an actual clinical illness in volunteers and that are not already occurring at high frequency in the community.

The catch-22 of human challenge studies for SARS-CoV-2 is that, for ethical reasons, these trials must include volunteers who are relatively young and have no baseline medical conditions. These people are, however, the very ones in whom a SARS-CoV-2 infection is likely to be paucisymptomatic or asymptomatic. Therefore, clinical endpoints cannot be relied upon. While purely virological endpoints could be used instead (e.g. daily nasopharyngeal swabs for comparative viral kinetics), the vaccine's *clinical* effectiveness would remain poorly characterised. Regulatory approval requires more than virologic efficacy, as it should, given that severe COVID-19 appears to be driven primarily by the host's dysregulated cytokine responses and not upper respiratory viral replication per se.

There is a good deal of irony in performing a human challenge trial for a virus that is likely to produce few clinical events in its volunteers but is circulating and causing significant clinical morbidity and mortality in non-volunteers at the same time. Indeed, the high baseline prevalence of SARS-CoV-2 infections contradicts a key argument for human challenge trials: that induced infection is necessary because natural incidence is so low that thousands of trial participants would be necessary to observe just a few clinical events.

Given these paradoxes, recommending a human challenge study for SARS-CoV-2 remains a formidable challenge.

** The views expressed in this text are those of the author and do not necessarily reflect the position of the CTU Geneva.*

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