Should We Allow the Use of Human Challenge Vaccine Trials for COVID-19?

Jordan Tassone

In response to the ongoing pandemic, scientists around the world acted to develop vaccines. The deployment of COVID-19 vaccines has significantly reduced the physical and economic health impacts of the SARS-CoV-2 virus. However, in the clinical trial stages of these vaccines, some researchers proposed using 'human challenge trials' where participants are deliberately infected with the virus in a laboratory. Although such studies have helped scientists create treatments/preventions for smallpox, cholera, and yellow fever (McPartlin et al., 2020), their use remains controversial regarding COVID-19. This essay will investigate four key factors to determine if such trials are ethical, and if they should be used in response to COVID-19.

Informed consent is a fundamental ethical consideration in any scientific research and is of significance in human challenge trials (HCT). Informed consent refers to a participant's willingness to partake in the study, having knowledge of all details, including risks, of the research. Those opposed to conducting HCT for a COVID-19 vaccine suggest that since the virus is novel, it is impossible to obtain informed consent from participants (Bramble, 2020). While HCT have been conducted for other respiratory viruses like influenza and respiratory syncytial virus, these diseases are well understood (Weijer, 2020). Individuals favouring HCT for COVID-19 would have commenced

studies in early 2020, before the discovery that SARS-CoV-2 can cause strokes and myocarditis, including in young adults. Nevertheless, informed consent remains possible, researchers would simply advise volunteers of the possibility they may suffer unknown side-effects. If informed consent required awareness of all risks that could possibly result from a clinical trial, not even traditional vaccine trials could take place. Another argument against HCT for COVID-19 is that participants cannot give informed consent, since they lack knowledge of what it is like to experience severe illness (Bramble, 2020). HCT would only select young adults (18-30) with no pre-existing health conditions. It is hypothesised that even if participants were informed of the very-low risk of severe complications, volunteers could not truly consent to the trial as they have never experienced this risk first-hand. Nonetheless, the same can be said of any other clinical trial unrelated to COVID-19, where participants with no experience of severe illness can still provide consent. Exemplifying this reply is trials for new medications for the treatment of depression, anxiety, and insomnia. Therefore, informed consent should not act as a barrier in preventing the use of HCT in response to COVID-19.

Another ethical consideration in scientific research is voluntary participation: an individual's decision to join the trial without external influences. An issue with the use of HCT in developing a COVID-19 vaccine is it may lead to the exploitation of disadvantaged groups. Clinical trials occasionally offer financial incentives to participants (Sulmasy, 2021). This incentive is more persuasive to those enduring economic hardship, thereby exposing disadvantaged individuals to a greater risk of harm for society's benefit. To counter this, participants should only volunteer for purely altruistic reasons. Similarly, people in high-risk professions will be more inclined to participate in the trial since they are more likely to believe their infection to be inevitable. Again, this would further perpetuate the vulnerability of certain groups of society for the benefit of others. However, this could be avoided by conducting HCT in regions with zero/extremely controlled community spread. Such trials may also be carried out in areas with high

community spread, where everyone has a similar probability of infection irrespective of occupation. As voluntary participation is achievable in HCT, it should not prevent scientists from using such trials in developing a vaccine for SARS-CoV-2.

Awareness of the reasons individuals may volunteer for HCT is crucial in determining if such studies are ethical. Over 38,000 people agreed to participate in HCT for COVID-19 through the organisation 1Day Sooner, one of which was Lena Jewler. Jewler stated her choice to participate was to contribute to a greater good (Bloomberg Quicktake, 2021). This may be due to the lack of opportunities for people to contribute to a wider cause as a member of Western society (Bramble, 2020). Participation in challenge trials could be viewed as emblematic of the absence of opportunities people have to help others. Approving HCT is problematic, as some believe it inclines us towards pursuing an individualist culture, unwilling to change the underlying societal structures that provide one with greater chances of acting selflessly. Although Western societies are characterised by their individualistic nature, there are sufficient opportunities for one to act selflessly. Sperm donation, volunteer work and surrogacy commonly occur in Australian communities, and are of low medical risk. Moreover, HCT is analogous to live organ donation – a regular practice in Western societies. This act of medical altruism carries similar risks to that of COVID-19 HCT. The difference in fatality, hospitalisation, and long-term harm rates between COVID-19 and live organ donation is statistically insignificant (Jayaram et al., 2022). This subsequently indicates we should enable HCT, since society has already accepted the act of live organ donation. Those critical of HCT may reply that live organ donation is dissimilar to HCT; we cannot justify the use of HCT through such an analogy. Organ donors provide significant help to one person, while challenge trial volunteers eliminate a small risk of infection/fatality to a larger group. However, the kind of benefit in live organ donation and challenge trials are identical: a reduction in death and morbidity. As the presumption that Western societies do not provide adequate opportunities for altruism is false, approval of HCT in developing a

COVID-19 vaccine will not further perpetuate an 'individualist culture'.

A favourable risk-benefit balance must be obtained for HCT. An important benefit of HCT is their elimination of confounding variables which typical Phase III vaccine trials cannot. These include different viral strains – which was of particular importance in this pandemic as it was known before 2020 that coronaviruses mutate frequently – and uncertain timing of exposure, which was also important regarding COVID-19 as scientists could use HCT to examine how vaccines affected the incubation period for SARS-CoV-2 (Rapeport et al., 2021). Furthermore, despite the global use of currently approved vaccines, HCT is necessary for future vaccine generations (Eyal et al., 2021). Due to the increasing and ongoing prevalence of COVID-19 in populations around the world, HCT is the only type of trial that can accurately test whether current/future vaccines prevent infection as well as the durability of natural and vaccine-induced immunity). This is exceptionally important due to the requirement of a cold chain to distribute approved mRNA vaccines and unaffordable pricing of vaccines for under-developed countries. The benefits of HCT indicate a favourable risk-benefit ratio for participants and the community. However, objections have been proposed in response. One reply is the long-term health risks of COVID-19 outweigh the benefit one gains by contributing to science. This is an inadequate reply, as the principal risk-mitigation strategy is participant selection. According to one UK study, selecting only 20–29-year-olds for HCT maintains a risk of death approximately 0.00031% per participant (Eyal et al., 2021). Another response is to question the results obtained through HCT, whether they are truly beneficial given they may not be generalisable to the wider population. However, immune-bridging studies in higher-risk groups are always conducted after HCT, irrespective of participant demographics. Although the issue of generalisability is not prevalent in traditional vaccine trials, HCT is still a more efficient process even accounting for such follow-up safety studies. A third common response is to examine whether if it is really in one's best interest to participate

in the study. Those opposed to HCT declare it is unethical to justify using participants from vulnerable communities and high-risk occupations on the basis that their infection is 'inevitable'. It would be immoral for authorities to rely on assailable groups, who they let down by failing to protect them from transmission of SARS-CoV-2, to participate in HCT. Nevertheless, as referenced in the voluntary participation discussion, this could be addressed by only holding HCT for COVID-19 in populations with either high community transmission, or extremely low/zero community transmission of the virus. Additionally, critics of HCT overlook mental health in analysing the benefits of participation. The threat of catching COVID-19 and/or passing it on to loved ones was, and still is, a very real threat to many across the globe. This fear of COVID-19 infection/transmission is a recognised anxiety disorder (Taylor & Swan, 2022). HCT could treat this anxiety. Participants would receive a high standard of medical care in the unlikely event of complications, and they would no longer worry about transmitting the virus since they would isolate until they are no longer infectious. All this being considered, it is evident the benefits of HCT outweigh the risks.

Notwithstanding widespread ethical concerns regarding the use of HCT in developing a cure for SARS-CoV-2, the above analysis nullifies such fears. I believe human challenge trials should have been used to diversify the portfolio of potentially approved vaccines at the beginning of the pandemic, as well as supporting their ongoing use in the maintenance of an ongoing low fatality and hospitalisation rate.

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