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Feature Article (essay)

A bioethical case against using human challenge trials for COVID-19

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Abstract

COVID-19 is a global health emergency for which vaccines are a key solution. A human challenge trial (HCT) is a way of studying vaccine efficacy where healthy volunteers are deliberately infected, in contrast to traditional phase III trials. Nearly 40 000 people worldwide have expressed willingness to participate in COVID-19 HCTs in hopes of accelerating vaccine development. This essay argues that HCTs may not only fail to deliver on this aim, but violate the bioethical principles of autonomy, beneficence, non-maleficence, and justice. For now, in the case of COVID-19, HCTs are inferior to tried-and-true phase III trials, which have already generated several vaccines at unprecedented speed.

Learning Points

1. COVID-19 is a global health emergency for which vaccines are a key solution.
2. The risks of human challenge trials for COVID-19 outweigh their benefits in terms of the bioethical principles of autonomy, beneficence, non-maleficence, and justice.

3. Since traditional phase III trials have generated COVID-19 vaccines at unprecedented speed, there is currently negligible role for human challenge trials for COVID-19.

Introduction

A human challenge trial (HCT) is a method of studying vaccine efficacy where healthy volunteers receive a vaccine or placebo before being deliberately exposed to an infectious agent [1]. Participants are quarantined in a clinical trials unit while researchers monitor their immune response and symptoms. In contrast, traditional phase III trials involve several thousand participants receiving a vaccine and being observed long-term to determine its efficacy [2]. HCTs began in the 1960s at the United Kingdom Common Cold Unit to investigate and cure low-virulence coronaviruses, and have contributed most of today's knowledge about these coronaviruses [3,4]. During the COVID-19 pandemic, nearly 40 000 people from 166 countries have volunteered to participate in HCTs through the organisation 1Day Sooner to help fast-track vaccine development [5]. In fact, a HCT called UK COVID Challenge led by hVIVO is now underway in the United Kingdom [6]. In theory, HCTs can accelerate vaccine development to save millions of lives. However, SARS-CoV-2 is a highly virulent coronavirus, unlike those studied previously, with the potential to cause severe disease and death with no current rescue therapy. Furthermore, phase III trials with wellestablished, less ethically contentious designs have already produced vaccines at unprecedented speed. This essay argues that HCTs for COVID-19 are not only redundant, but would challenge the bioethical principles of autonomy, beneficence, non-maleficence, and justice central to medical practice and research [7]. Therefore, despite ongoing public interest, HCTs are currently not scientifically or ethically justified for COVID-19 vaccine development.

Medical ethics deals with moral dilemmas arising due to conflicts between clinicians' duties towards their patients and their outcomes. Two main frameworks underlying medical ethics are utilitarianism and deontology. Utilitarianism is a branch of consequentialism which argues that an act is morally "good" if it leads to good consequences for the greatest number of people, or that "the end justifies the means" [9]. Conversely, deontology argues that people are not means but ends in themselves [10], so clinicians have a duty to respect patients' intrinsic rights. These duties and rights were elaborated by Beauchamp and Childress in 1979 as bioethical principles of autonomy, beneficence, non-maleficence, and justice [7]. Beneficence is a duty to promote wellbeing, non-maleficence is a duty to avoid causing harm, autonomy is a person's right to determine their own course, and justice refers to "fair, equitable, and appropriate treatment" according to patients' needs [7]. This essay will discuss how HCTs may breach these principles, and why the extensive planning required to make them ethically acceptable makes them less desirable than established phase III trials.

Discussion

A study respects participants' autonomy, their right to determine their own course, if they can give valid consent, where they are informed of the study's purpose, procedures, and potential benefits versus harms, given sufficient opportunity to ask questions, and have their understanding tested and documented [11]. However, it is challenging to fully inform participants when there are many unknowns surrounding COVID-19 and its long-term effects, particularly as new strains emerge [1]. Severe population risks posed by a pandemic may limit participants' ability to give uncoerced consent, and emergency circumstances risk deprioritising ethics as researchers rush or abbreviate consent procedures [12-14]. Offering monetary compensation, even in line with unskilled labour with comparable risk, becomes potentially exploitative if people participate out of a need for the money. This is especially true if HCTs are conducted in countries with higher background transmission rates which

tend to be poorer. Whilst advocates argue deliberate infection is more ethically acceptable in countries with already high natural transmission [1], participants from these countries are more likely to accept lower sums than in wealthier countries [15]. Whilst HCTs have the potential to generate important knowledge, this cannot take priority over the autonomy of participants and communities.

The main way HCTs achieve their proposed benefit of advancing vaccine development faster than phase III trials is in settings of low transmission, where natural infection rates are too low for larger trials to progress [11]. However, with the widespread transmission of COVID19, phase III trials have successfully generated several vaccines at record speed, which has rendered HCTs redundant in the COVID-19 vaccine development effort. It is unclear whether organisations such as the United States Food and Drug Administration would even consider HCT data in licensing decisions, with policies mandating late phase clinical trials involving thousands of participants including those who are elderly and have comorbidities [16]. Researchers also need up to two years to agree on an HCT model, develop and manufacture a challenge strain, gain approval for human use, and conduct dose-escalation studies to determine the target dose to elicit the minimum level of illness required to determine primary outcomes. This process may be too slow for a global health emergency [16]. To be ethically acceptable, low risk challenge strains must be used in healthy young adults to have the lowest possible risk of severe complications [8], but this could produce results less applicable to higher risk groups infected with higher risk strains [1]. There are no guaranteed direct benefits to participants apart from a vaccine possibly being effective. So far, vaccines have mainly been effective in preventing severe symptoms rather than transmission [17], although volunteers may overestimate benefits due to the "preventative misconception" that infection will confer some immunity regardless [18]. HCTs ultimately offer marginal benefits compared to phase III trials but pose substantial risks.

HCTs pose several unique harms compared to traditional trials. In their defence, HCTs incorporate harm-minimising measures such as only infecting 10-50 participants compared to several thousand in phase III trials, and only recruiting healthy young adults more likely to develop self-limiting disease but who would be monitored, isolated, treated, and compensated [18]. Despite this, participants would still incur several risks without direct benefit such as invasive procedures, frequent bodily fluid sampling, and extended quarantine. Furthermore, participants may still develop severe disease (particularly with emerging strains [18]) or longterm consequences such as stroke [19], respiratory deficits [1], and "long COVID" [20]. There have not yet been any human deaths in HCTs, thanks to the availability of rescue therapies, so COVID-related deaths in HCTs without reliable rescue therapies could erode public trust in vaccine research. Although HCTs have previously been conducted on influenza, which lacks rescue therapy, COVID-19 is 10 times as lethal [21]. Supporters have argued that healthy young adults should be able to consent to HCTs as they can for kidney donation, since COVID-19 infection carries the same mortality of 0.01% [13,22,23]. However, a well-understood procedure which has been performed for decades with a high success rate is not readily comparable to deliberate infection with a poorly understood virus. HCTs are also unique in putting third parties at risk of unintentional transmission from participants, which could trigger man-made outbreaks [1]. Even if HCTs were conducted, larger trials would still be needed because adverse effects, such as cerebral venous sinus thrombosis and immune thrombocytopaenic purpura linked to the Vaxzevria (AstraZeneca, University of Oxford, UK) vaccine, may only emerge once thousands have been vaccinated [18]. HCTs offer limited social and scientific benefits despite substantial risks compared with

alternative trial designs, and their benefits are further diminished by the time and resources required to mitigate their risks.

Vaccination helps achieve justice by protecting whole populations from disease and reversing negative social and economic impacts. HCTs indeed have the potential to rapidly evaluate several hundred vaccines and weed out less promising candidates before investing in larger trials. However, HCTs are logistically difficult, time-consuming, and expensive to conduct ethically and justly. Years of planning is required to develop a challenge strain, address ethical concerns, then rigorously justify the need for HCTs in protocols, trial registers, and articles [16]. Extensive dialogue needs to occur between all stakeholders (for example, scientists, ethicists, prospective participants, community representatives, other countries) regarding design, standards for data collection and dissemination, community acceptance, and how results will affect future research, practice, vaccine licensure, and manufacturing [1]. Shortcutting these procedures risks eroding public trust and fuelling hesitancy if vaccine development is considered too hasty [18]. Once approved, HCTs themselves would require enormous resources including suitable sites, trained staff, personal protective equipment, emergency medical services, regular staff testing, and purpose-built facilities to contain the virus in an enclosed environment with single negative pressure, filtered, externally vented rooms with separate wastewater systems. Countries with high background transmission where HCTs would be conducted tend to have strained health systems, so HCTs may divert scarce resources away from their pandemic response [24]. Furthermore, these communities may face higher transmission risk due to systemic injustices (for example, increased incarceration, overcrowding, limited access to medical care) [24], which HCTs could be seen as exploiting. Whilst HCTs are well-intentioned, the practical reality of conducting them may undermine the pursuit of justice in the COVID-19 pandemic.

Conclusion

COVID-19 is a global health emergency for which vaccines are a key part of the solution. Governments and communities have placed high urgency and expectations on vaccine development, perhaps with the erroneous belief that “anything is better than nothing”, which risks deprioritising human safety and wellbeing in research [24]. HCTs are a way of evaluating vaccine safety and efficacy by deliberately infecting a small number of participants with a low-virulence challenge strain of SARS-CoV-2. Despite ongoing public interest in HCTs, they have a limited role to play in the COVID-19 pandemic considering traditional phase III trials have already generated several effective vaccines. Furthermore, when examined against the four principles underlying contemporary medical ethics – autonomy, beneficence, non-maleficence, and justice – the ethical risks of HCTs would arguably outweigh their benefits for the COVID-19 pandemic. HCTs would not be impossible to conduct ethically, but the time it would take, considering that we already have several vaccines, means they have been left in the dust.

References

[1] Jamrozik E, Selgelid MJ. COVID-19 human challenge studies: ethical issues. Lancet Infect Dis. 2020;20(8):e198-e203.

[2] Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. J Infect Dis. 2020;221(11):1752-6.

[3] Callow KA, Parry HF, Sergeant M, Tyrrell DAJ. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect. 1990;105(2):435-46. [4] Higgins PG, Phillpotts RJ, Scott GM, Wallace J, Bernhardt LL, Tyrrell DA. Intranasal interferon as protection against experimental respiratory coronavirus infection in volunteers. Antimicrob Agents Chemother. 1983;24(5):713-5.

[5] 1Daysooner. COVID-19 human challenge trials. [Internet]. 2020. Available from: https://1daysooner.org.

[6] hVIVO Services Limited. UK COVID Challenge United Kingdom: hVIVO Services Limited. [Internet]. 2020. Available from: https://ukcovidchallenge.com/covid-19-volunteertrials/.

[7] Beauchamp TL, Childress JF. Principles of biomedical ethics. 6th ed. NY: Oxford University Press; 2009.

[8] World Health Organization. Key criteria for the ethical acceptability of COVID-19 human challenge studies. [Internet]. 2020. Available from: https://www.who.int/ethics/publications/key-criteria-ethical-acceptability-of-covid-19humanchallenge/en/.

[9] Sinnott-Armstrong W. Consequentialism. In: Edward N. Zalta, editors. The Stanford Encyclopedia of Philosophy. Summer 2019 ed. Stanford (CA): Stanford University; 2019.

[10] Kant I. Groundwork of the metaphysics of morals: a German-English edition. Cambridge (UK): Cambridge University Press; 2012.

[11] Bambery B, Selgelid M, Weijer C, Savulescu J, Pollard AJ. Ethical criteria for human challenge studies in infectious diseases. Public health ethics. 2016;9(1):92-103.

[12] Singer P, Chappell R. Pandemic ethics: the case for experiments on human volunteers. DC: Washington Post. 2020.

[13] Chappell RY, Singer P. Pandemic ethics: the case for risky research. Res. Ethics. 2020;16(3-4):1-8.

[14] Smith M, Emanuel E, Thomé B, Upshur R. Ethical conditions for accelerating COVID19 vaccine research [version 1; peer review: 1 approved, 1 approved with reservations]. Wellcome Open Res. 2020;5(249).

[15] Lamkin M, Elliott C. Avoiding exploitation in phase I clinical trials: more than (un)just compensation. J Law Med Ethics. 2018;46(1):52-63.

[16] Deming ME, Michael NL, Robb M, Cohen MS, Neuzil KM. Accelerating development of SARS-CoV-2 vaccines — the role for controlled human infection models. N Engl J Med. 2020;383(10):e63-e.

[17] Brown CM, Vostok J, Johnson H, Burns M, Gharpure R, Sami S, et al. Outbreak of SARS-CoV-2 infections, including COVID-19 vaccine breakthrough infections, associated with large public gatherings - Barnstable County, Massachusetts, July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(31):1059-62.

[18] Kahn JP, Henry LM, Mastroianni AC, Chen WH, Macklin R. For now, it's unethical to use human challenge studies for SARS-CoV-2 vaccine development. Proc Natl Acad Sci U S A. 2020;117(46):28538-42.
[19] Fifi JT, Mocco J. COVID-19 related stroke in young individuals.Lancet Neurol. 2020;19(9):713-5.
[20] Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. BMJ. 2020;370:m3026-m.
[21] McPartlin SON, Morrison J, Rohrig A, Weijer C. COVID-19 vaccines: should we allow human challenge studies to infect healthy volunteers with SARS-CoV-2? BMJ. 2020;371:m4258-m.
[22] Jayaram A, Sparks J, Callies D. Justifying the risks of COVID-19 challenge trials: the analogy with organ donation. Bioethics. 2021:10.1111/bioe.12889.
[23] Kortram K, Ijzermans JN, Dor FJ. Perioperative events and complications in minimally invasive live donor nephrectomy: a systematic review and meta-analysis. Transplantation. 2016;100(11):2264-75.
[24] Wibawa T. COVID-19 vaccine research and development: ethical issues. Trop Med Int Health. 2021;26(1):14-9.