

ISSUES IN PUBLIC HEALTH

## Could human challenge studies for COVID-19 vaccines be justified in South Africa?

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Although human challenge studies (HCSs) have been widely employed in vaccine development for malaria, dengue, typhoid and cholera, the role of this research design in COVID-19 remains controversial. While the potential social value of HCSs in the context of a pandemic is clear, bioethicists are divided on the ethics, given that effective treatment for COVID-19 has eluded us to date. While compelling ethics arguments have been offered on both sides of the debate, scientific and regulatory complexities may not have been fully appreciated. Furthermore, accelerated development of efficacious vaccine candidates in traditional clinical trials has diluted some of the arguments in favour of HCSs. In low- and middle-income country settings, including South Africa, the need for robust patient care conditions for the conduct of HCSs, coupled with considerations such as perceptions of risk, consent processes, remuneration, vaccine hesitancy, fear of exploitation and access to vaccines, makes HCSs challenging to justify.

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Human challenge studies (HCSs) involve deliberate infection of healthy volunteers with infectious agents and have been an important research approach for ~300 years.<sup>[1]</sup> Historically, this research strategy has been used for centuries, dating back formally to the development of the smallpox vaccine by Edward Jenner in the late 1700s.<sup>[2,3]</sup> However, the concept of variolation (inoculation of smallpox material into people who had not experienced smallpox) dates even further back to Asia and North Africa.<sup>[4]</sup> Stories of inoculation practices used in China, Turkey, Africa and India prior to the 17th century found their way to the Royal Society in London via letters based on conversations held with African slaves in Britain and Europe, and from British officials working with the Dutch East India Company in India.<sup>[5]</sup>

Although research in the 18th century has been described as a 'cottage industry' where reliance on trial and error was all that could be done to establish efficacious interventions – a practice far removed from the randomised controlled clinical trials conducted by industry and academia today – Jenner had a keen scientific mind that he exercised well in his general practice in Britain. He had astute powers of observation, and while he did not have to submit his research ideas to regulatory bodies or research ethics committees, he and his peers conducted risk-benefit assessments on smallpox inoculations. The risk of dying from smallpox was 1 in 7 in the 1720s, while the risk of dying of deliberate inoculation was 1 in 100.<sup>[3]</sup> It was only in 1802 that more formal trials were organised in Vienna and Boston, where children were vaccinated and then deliberately infected with smallpox. Interestingly, the Jenner Institute at Oxford University has pioneered work on a COVID-19 vaccine.

Over the past 50 years, HCSs have become a unique research tool in vaccine development, with typhoid and cholera<sup>[5,6]</sup> being

good examples. Scientifically, HCSs could be of value because they potentially speed up vaccine development,<sup>[7]</sup> require fewer participants, so that there is less exposure to an experimental vaccine, and can be used to compare efficacy of multiple vaccine candidates and select the most promising vaccine for larger studies.<sup>[1]</sup> With COVID-19 specifically, HCSs may also be used to validate tests for immunity to SARS-CoV-2, to identify correlates of immune protection, and to investigate risks of transmission by infected individuals.<sup>[8]</sup>

For many fundamental reasons, HCSs are ethically and legally challenging. Deliberately infecting healthy adults with a virus may appear to be antithetical to ethical principles, especially the requirement to first do no harm. However, many argue that under certain conditions, such as pandemics, this may be acceptable. Nevertheless, careful study design is important to minimise harm. This design advantage can be achieved by recruiting young adults to whom COVID-19 poses least risk. It is known that in the UK, the risk of death from COVID-9 was <0.01% in those aged 18 - 39 years,<sup>[9]</sup> while this age group represented only 5% of hospitalisations.<sup>[10]</sup> In Africa, it would be important to establish which adults are at the lowest possible risk if they do contract COVID-19. In addition, specialised facilities and close monitoring would be necessary, as well as access to early supportive care including intensive care unit (ICU) beds, high-flow nasal oxygen and mechanical ventilation. In the context of COVID-19, the risks are especially high as there is currently no specific treatment and severe disease or death can occur in young adults. In Western Cape Province, South Africa (SA), 0.04% of adults aged 20 - 39 years with confirmed COVID-19 died during the first wave of infection.<sup>[11]</sup> In a study of 1 376 patients treated at district hospitals in the Western Cape from March to June

2020, the mean age was 46.3 years and 58.5% were female.<sup>[12]</sup> New variants, such as the SARS-CoV-2 variant 501.V2, circulating during the second wave of infections since November 2020, may change the age distribution of cases, and this is currently being investigated.<sup>[13]</sup> Media reports, however, indicated that many younger South Africans had contracted the infection during the second wave.<sup>[14]</sup> Strategies to mitigate risks from an ethical perspective would include supporting valid informed consent, providing compensation for harm and burdens, providing efficacious treatment for infected participants, ensuring a reasonable likelihood of social benefit (access to vaccines), and a reasonable likelihood of faster development of vaccines relative to a conventional trial approach ('acceleration argument').

The World Health Organization (WHO) published guidance on the ethics of HCSs in May 2020 and listed eight criteria that must be met before these studies may be conducted:<sup>[15]</sup>

- Strong scientific justification must be provided.
- Risks and potential benefits must be assessed.
- Stakeholder engagement is essential.
- Co-ordination among researchers, funders, policymakers and regulators should occur.
- Site selection must ensure the highest clinical, scientific and ethical standards.
- Participant selection must minimise or limit risk, so young adults (18 - 30 years) or healthcare workers are preferable.
- Instead of regular research ethics committee (REC) review, a specialised independent committee comprising scientific and ethics experts, preferably at a national or international level, is advised. WHO collaboration with local or national RECs is advisable.
- Informed consent must be rigorous and include a test of understanding and ongoing discussions as new information emerges that may impact on the consent process.

In addition to these criteria, harm mitigation strategies include supportive care, including ICU access, long-term follow-up, and full compensation for any harms suffered. SA has a long history of clinical trials experience, but expertise in HCSs is limited. Clinical trial sites are established, but not at the standards required for HCSs. Limiting participation to young adults reduces risk but limits generalisability, as has emerged with the local AstraZeneca COVID-19 vaccine trials, where results could only be extrapolated to prevention of mild and moderate disease and not to prevention of severe disease.<sup>[16]</sup> While limiting HCSs to young people is not necessarily ideal, selecting healthcare workers could be problematic as they may be older and have comorbidities, so WHO criterion 6 for participant selection is not ideal. Likewise, criterion 3 requiring stakeholder engagement is important, but has not been optimally implemented during the current Johnson & Johnson vaccine rollout in the form of an implementation trial, causing confusion and conflict among healthcare personnel in the public and private healthcare sectors and inconsistent criteria being applied across trial sites during the phase 1 rollout. The constraints to achieving the site selection criteria and specialised independent ethics committee review in many African countries were not considered.

Finally, in assessing the relevance of the WHO approach to HCSs in SA, it is interesting to note that the WHO working group that developed these criteria had only one representative from Africa, from a Wellcome Trust-funded site in Kenya. The WHO report is therefore limited given minimal representation on the working group from other regions in Africa.

Globally, bioethicists argue both for and against HCS.

## Arguments for HCSs

Arthur Caplan<sup>[17]</sup> strongly advocates for HCSs based on the risk-benefit ratio. In his view, the benefits outweigh the risks, especially in the context of a pandemic. If society accepts the risks to healthcare workers exposed to COVID-19, we should accept the risks to healthy adult volunteers who participate with fully informed consent.<sup>[17]</sup> However, this argument does not adequately account for healthcare workers who also have personal protective equipment to protect them while treating COVID-19 patients. In a similar vein, Nir Eyal<sup>[18]</sup> supports the risk-benefit argument, taking illness and death during a pandemic into account as well as risks related to other interventions in regular healthcare. The net risk is important to consider, i.e. the risk of participating in an HCS 'minus the risk that the same person would face otherwise' in the community. He also argues that HCSs have an advantage because when the rates of infection decrease, traditional phase 3 trials are likely to experience recruitment and enrolment challenges. Finally, Caplan and Eyal both defend the 'acceleration argument', i.e. that vaccine efficacy results could be obtained faster in HCSs compared with traditional clinical trials, and in the context of a deadly pandemic, greater speed will ultimately translate into greater saving of human lives.

## Arguments against HCSs

Ruth Macklin,<sup>[19]</sup> a prominent bioethicist based at the Albert Einstein College of Medicine, disagrees with Caplan, Eyal and the WHO. While she acknowledges the public health imperative to save the most lives at the lowest cost (placing fewest research participants at risk), she argues that if there is no effective treatment available for COVID-19, such research is unjustifiable. She also raises concerns around the validity of informed consent, particularly considering that participants may be subject to the prevention misconception, i.e. believe in advance of the results that the vaccine is effective.<sup>[19]</sup> Kahn *et al.*<sup>[20]</sup> question the validity of the acceleration argument, i.e. whether it is true that HCSs can deliver reliable vaccine testing results significantly faster than designs more closely aligned with the traditional vaccine pathway. While HCSs are often justified in the context of limited spread of a pathogen in the natural environment, widespread exposure to SARS-CoV-2 during the pandemic has facilitated the conduct of traditional clinical trials. In fact, there are currently several vaccine candidates that, after phase 3 studies, have obtained emergency use authorisations and are in the process of being distributed *en masse* in several countries. In addition, various regulatory and logistic challenges would slow down the initiation of HCSs. These include selection of the most appropriate strain of the virus to use, manufacture of the strain in a BSL-3-certified laboratory that is compliant with Good Manufacturing Practice standards, obtaining regulatory approval from the Food and Drug Administration, and conducting dose-escalation studies.<sup>[21]</sup> Anna Durbin<sup>[22]</sup> estimates that it could take 9 - 12 months to set up an HCS, and a further 6 months to co-ordinate testing across multiple sites.

## Do the ethics arguments take all scientific concerns into account?

As a point of departure, ethics debates usually require a thorough interrogation of the science. In considering HCSs, it is important to consider model endpoints – will a disease model or an infection model be adopted? With an infection model, the endpoint is verification of infection, not disease. The malaria HCS is a prototype of this model. In a disease model, the endpoint is a specified clinical illness and is usually used when infection is difficult to measure. Enteric challenge models are an example of such a disease model.

Whether a disease or an infection model is chosen depends on the disease under discussion, the purpose of the model, the availability of treatment and the reproducibility of the model.<sup>[22]</sup> For COVID-19, the nasally administered inoculate is intended to produce mild upper respiratory tract illness, and viral shedding will be assessed.<sup>[23]</sup> It is also important that the endpoint chosen will not place the research participant at risk of severe disease. In dengue fever, for example, most infections are asymptomatic or mildly symptomatic. With COVID-19, progression from mild to severe disease is unpredictable even in young adults.

Choosing the appropriate challenge strain is also critical, as either a wild-type human strain or a recombinant strain can be selected. What happens when variants emerge while HCSs are already underway? During the second wave of infection in many countries, including SA, new variants have emerged.<sup>[13]</sup> It is important to know whether the strain will be transmissible to third parties because of viral shedding. The latter risk could be averted by ensuring adequate isolation after inoculation with the challenge strain.

Some ethics conversations overlook important scientific aspects of challenge models for COVID-19. In particular, the test population may not be immunologically representative of the target population if young volunteers are selected to participate in an HCS of a disease that adversely and disproportionately affects older people. It is a big assumption that HCSs will speed up vaccine development, and very problematic that the clinical disease spectrum is so huge. We currently have no idea whether the immune response in mild disease helps us at all with understanding the problematic immune manifestations in severe disease. Traditional clinical trials can set eligibility criteria to study mild and severe disease and enrol participants with a broad age range from young adults to older participants. Young adults are more likely to develop mild disease, while older participants are likely to develop more severe disease. HCSs enrolling young adults may improve our understanding of mild COVID-19 disease, but the ethics of such studies are questionable when the utility of such information for the prevention of severe disease is unclear, and when a small percentage of young adults deliberately infected in such trials may experience severe disease or even death.<sup>[7]</sup>

### Will HCSs work in SA?

Most of the ≥40 000 human volunteers in (non-COVID-19-related) HCSs to date have been in high-income countries. While there is an ethical imperative to conduct HCSs in low- and middle-income countries (LMICs), when COVID-19 is rampant, it is important to consider many factors.<sup>[24]</sup> From an ethical perspective, one of the biggest challenges may be ensuring an authentic consent process that is not compromised by the lure of remuneration in low-income settings. If the risk of harm to third parties is to be mitigated by a prolonged period of isolation (~17 days) after deliberate infection, for example, the remuneration for time, inconvenience and other expenses is likely to be substantial in the context of socioeconomic disadvantage. While compensation for study-related burdens may be defensible in SA, as this is the norm for clinical trials, compensation for study-related risk-taking is more controversial. Some have argued that it is unfair to ask HCS participants to expose themselves to uncompensated risks for the good of society, and that they should be given 'danger pay'.<sup>[25]</sup> From their experiences of malaria challenge studies in Kenya, Njue *et al.*<sup>[26]</sup> argue that with appropriate information and investment in adequate community engagement to build trust, HCS participants can reason for themselves about how to balance risk and remuneration, using research remuneration to support what they value, such as school fees, debt, investments and

training. However, there are ethically significant differences between malaria and COVID-19 HCSs, in particular the fact that there are effective treatments for malaria and that COVID-19 HCSs require special care of participants that may be scarce in fragile health systems during a pandemic. For this reason, proceeding with HCSs in contexts such as SA requires a compelling scientific justification, a safety-enhancing research infrastructure, and participants who grasp the risks they face.

Concerns around justice also exist. Two considerations are important here – the implementation gap and vaccine uptake. The implementation gap – the gap between vaccine licensure and vaccine access – could be prolonged in LMICs.<sup>[7]</sup> Vaccines are currently being rolled out in the Global North, yet SA anticipates limited vaccine access in the first quarter of 2021. Once access is assured, uptake of the vaccine is important. SA has had a history of reasonable childhood immunisation coverage, reaching ~82% prior to the pandemic.<sup>[27]</sup> However, a recent Ipsos survey commissioned by the World Economic Forum has demonstrated that only 64% of South Africans would accept a COVID-19 vaccine.<sup>[28]</sup> While the validity of generalising these findings is unclear, vaccine hesitancy is growing in prominence in Africa.<sup>[29]</sup> Given the history of research-related exploitation in Africa, public trust in science, research and vaccines is waning and adverse outcomes could result in reputational harm to vaccine research and vaccine uptake in general.<sup>[30,31]</sup>

The benefits of HCSs for vaccine development will only be realised if there is a guarantee that there will be adequate uptake of the vaccine once it is available. We cannot justify HCSs by their benefits to society, in the absence of assurance that the LMICs that bear the risk burden will progress to availability of the vaccine for the whole population and will achieve adequate coverage.<sup>[7]</sup> High-income countries have bought up or are busy buying up vaccine stocks in advance.<sup>[32]</sup> This delay in vaccine access also undercuts the 'acceleration argument', since what good will it do for LMICs to speed up vaccine development by means of HCSs, if vaccine distribution will not be going at 'warp speed' for them?

### Conclusions

Although HCSs were proposed as an accelerated pathway to vaccine development early in the pandemic when the comparison with traditional clinical trial timelines was made, the speed with which recent traditional COVID-19 vaccine research has occurred has resulted in a few efficacious candidate vaccines that have emerged from phase 3 testing. In this context, the arguments that support HCSs based on urgency and speed have become less compelling. Unlike other diseases in which HCSs have been conducted safely, COVID-19 is immunologically complex and unresolved, there is no definitive treatment to date, and severity of disease outcome, including death, has not been consistent across the age spectrum. Enrolling younger participants only limits generalisability, as younger participants may be immunologically distinct from the elderly who are at higher risk. The AstraZeneca COVID-19 vaccine trial in SA is a prime example, where data on younger participants could not be extrapolated to the elderly who carry the risk of more severe disease.<sup>[16]</sup> Deliberate infection of healthy participants with a potentially lethal virus does not augur well in a global context of distrust of science and vaccine hesitancy. The alternative is an accelerated conventional vaccine development pipeline where regulatory bodies are balancing safety and speed. On the assumption that the vaccines being distributed now are beneficial, and since they are becoming available at warp speed, this expedited vaccine development confers the benefits of HCSs with fewer risks and fewer ethics complications. For these

reasons, along with the challenges with consent processes for research on less complex diseases than COVID-19, conducting HCSs in resource-poor countries appears to be an option of last resort during this pandemic.

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- Darton TC, Blohmke CJ, Moorthy VS, et al. Design, recruitment, and microbiological considerations in human challenge studies. *Lancet Infect Dis* 2015;15(7):840-851. [https://doi.org/10.1016/S1473-3099\(15\)00688-7](https://doi.org/10.1016/S1473-3099(15)00688-7)
- Morabia A. Edward Jenner's 1798 report of challenge experiments demonstrating the protective effects of cowpox against smallpox. *J R Soc Med* 2018;111(7):255-257. <https://doi.org/10.1177/0141076818783658>
- Rusnock AA. Historical context and the roots of Jenner's discovery. *Hum Vaccines Immunother* 2016;12(8):2025-2028. <https://doi.org/10.1080/21645515.2016.1158369>
- Gross CP, Sepkowitz KA. The myth of the medical breakthrough: Smallpox, vaccination, and Jenner reconsidered. *Int J Infect Dis* 1998;3(1):54-60. [https://doi.org/10.1016/S1201-9712\(98\)90096-0](https://doi.org/10.1016/S1201-9712(98)90096-0)
- Waddington CS, Darton TC, Woodward WE, Angus B, Levine MM, Pollard AJ. Advancing the management and control of typhoid fever: A review of the historical role of human challenge studies. *J Infect* 2014;68(5):405-418. <https://doi.org/10.1016/j.jinf.2014.01.006>
- Shirley DT, McArthur MA. The utility of human challenge studies in vaccine development: Lessons learned from cholera. *Vaccine* 2011;1:3-13. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3904492/> (accessed 22 March 2021).
- Giersing BK, Porter CK, Kotloff K, Neels P, Cravioto A, MacLennan CA. How can controlled human infection models accelerate clinical development and policy pathways for vaccines against *Shigella*? *Vaccine* 2019;37(34):4778-4783. <https://doi.org/10.1016/j.vaccine.2019.03.036>
- Deming ME, Michael NL, Robb M, Cohen MS, Neuzil M. Accelerating development of SARS-CoV-2 vaccines – the role for controlled human infection models. *N Engl J Med* 2020;383:e63. <https://doi.org/10.1056/NEJMp2020076>
- Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430-436. <https://doi.org/10.1038/s41586-020-2521-4>
- Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO Characterisation Protocol: Prospective observational cohort study. *BMJ* 2020;369:m1985. <https://doi.org/10.1136/bmj.m1985>
- Boulet AA, Davies M, Hussey H, et al. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis* 2020;ciaa1198. <https://doi.org/10.1093/cid/ciaa1198>
- Mash RJ, Presence-Vollenhoven M, Adeniji A, et al. Evaluation of patient characteristics, management and outcomes for COVID-19 at district hospitals in the Western Cape, South Africa: Descriptive observational study. *BMJ Open* 2021;1:e047016. <https://doi.org/10.1136/bmjopen-2020-047016>
- Tegally H, Wilkinson E, Giovanetti M, et al. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. *medRxiv* 2020 (epub 22 December 2020). <https://doi.org/10.1101/2020.12.21.20248640>
- Mlambo S. Stern warning to young people as new Covid-19 variant rocks SA during second wave. IOL, 18 December 2020. <https://www.iol.co.za/news/south-africa/gauteng/stern-warning-to-young-people-as-new-covid-19-variant-rocks-sa-during-second-wave-29c14b26-77bc-4b7c-b2ec-54a2f311895> (accessed 28 February 2021).
- 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* 2020;39(4):633-640. <https://doi.org/10.1016/j.vaccine.2020.10.075>
- Madhi SA, Baillie V, Cutland CL, et al. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. *medRxiv* 2021 (epub 12 February 2021). <https://doi.org/10.1101/2021.02.10.21251247>
- Caplan A. Is it ethical to give someone coronavirus to create a vaccine? Yes. *Boston Globe*, updated 14 May 2020. <https://www.bostonglobe.com/2020/05/14/opinion/is-it-ethical-give-someone-coronavirus-create-vaccine-yes/> (accessed 26 January 2021).
- Eyal N. Why challenge trials of SARS-CoV-2 vaccines could be ethical despite risk of severe adverse events. *Ethics Hum Res* 2020;42(4):24-34. <https://doi.org/10.1002/eahr.500056>
- Macklin R. Human challenge studies for a COVID-19 vaccine: Ethical quandaries. *The Doctor's Tablet Blog*, 15 May 2020. <https://blogs.einsteimed.org/human-challenge-studies-for-a-covid-19-vaccine-ethical-quandaries/> (accessed 25 January 2021).
- 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):28538-28542. <https://doi.org/10.1073/pnas.2021189117>
- Steenhuysen J. Exclusive: U.S. to make coronavirus strain for possible human challenge trials. *Reuters*, 14 August 2020. <https://www.reuters.com/article/us-health-coronavirus-vaccine-challenge-idUSKCN25A1EL> (accessed 25 January 2021).
- Durbin A. Challenges in conducting human challenge studies: Policy perspectives from India and the United States. *Ethics in Clinical Research Webinar* 3, 2020. <https://nbmworkshops.com/nbmWebinarClinical3.html> (accessed 22 October 2020).
- Levine MM, Abdullah S, Arabi YM, et al. Viewpoint of a WHO Advisory Group tasked to consider establishing a closely-monitored challenge model of COVID-19 in healthy volunteers. *Clin Infect Dis* 2020;ciaa1290. <https://doi.org/10.1093/cid/ciaa1290>
- Jamrozik E, Selgelid MJ. Human infection challenge studies in endemic settings and/or low-income and middle-income countries: Key points of ethical consensus and controversy. *J Med Ethics* 2020;46(9):601-609. <https://doi.org/10.1136/medethics-2019-106001>
- Grimwade O, Savulescu J, Giubilini A, et al. Payment in challenge studies: Ethics, attitudes and a new payment for risk model. *J Med Ethics* 2020;46(12):815-826. <https://doi.org/10.1136/medethics-2020-106438>
- Njue M, Kamuya D, Njuguna P, et al. Ethical considerations in controlled human malaria infection studies in low resource settings: Experiences and perceptions of study participants in a malaria challenge study in Kenya. *Wellcome Open Res* 2018;3:39. <https://doi.org/10.12688/wellcomeopenres.14439.2>
- Baletta A. Dramatic drop in SA's immunisation rates. *Spotlight*, 24 June 2020. <https://www.spotlightnsp.co.za/2020/06/24/dramatic-drop-in-sas-immunisation-rates> (accessed 16 December 2020).
- Baletta A. What we know about vaccine hesitancy in South Africa. *Spotlight*, 7 October 2020. <https://www.spotlightnsp.co.za/2020/10/07/what-we-know-about-vaccine-hesitancy-in-south-africa> (accessed 16 December 2020).
- Moodley K, Rossouw T. What could fair allocation of an efficacious COVID-19 vaccine look like in South Africa? *Lancet Glob Health* 2021;9(2):E106-E107. [https://doi.org/10.1016/S2214-109X\(20\)30474-5](https://doi.org/10.1016/S2214-109X(20)30474-5)
- Dawson L, Earl J, Livezey J. SARS-CoV-2 human challenge trials: Too risky, too soon. *J Infect Dis* 2020;222(3):514-516. <https://doi.org/10.1093/infdis/jiaa314>
- Richards AD. Ethical guidelines for deliberately infecting volunteers with COVID-19. *J Med Ethics* 2020;46(8):502-504. <https://doi.org/10.1136/medethics-2020-106322>
- Oxfam International. Campaigners warn that 9 out of 10 people in poor countries are set to miss out on Covid-19 vaccine next year. *Press release*, 9 December 2020. <https://www.oxfam.org/en/press-releases/campaigners-warn-9-out-of-10-people-poor-countries-are-set-miss-out-covid-19-vaccine> (accessed 25 January 2021).

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