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Essay

Why we (probably) must deliberately infect

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In a recent article preprint,[1] Nir Eyal, Marc Lipsitch, and Peter Smith note that we could speed up trials of a novel coronavirus (SARS-CoV-2) vaccine by deliberately infecting volunteers. After 'normal initial safety, vaccine dose finding, and immunogenicity studies',[2] appropriate subjects would be carefully informed of the risks of infection associated with the experiment and be given the opportunity to participate. The authors believe that 'in the circumstances of a devastating global pandemic', the studies they propose 'may be an acceptable way to bypass Phase 3 testing, and speed the licensure of efficacious vaccines'.[3]

* Professor of Law, Brooklyn Law School. For helpful comments, I thank Elizabeth Amann, Jonathan Baron, Nir Eyal, Govind Persad, Jeremy Sperling, and an anonymous peer reviewer.

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1 Nir Eyal, Marc Lipsitch & Peter Smith, *Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure*, JOURNAL OF INFECTIOUS DISEASES (forthcoming).

2 *Id.* at corrected proof p.1.

3 *Id.* If a human challenge study demonstrated efficacy, 'an expanded placebo-controlled study would be conducted in the field, involving at least 3000 vaccinated persons, primarily for short-term safety assessment, but also to gather further evidence on immunogenicity'. *Id.* at corrected proof p.2. This larger study would not involve deliberate infection and would include the elderly and other groups in greater danger. *Id.* I express no opinion about the non-challenge experimental regime the authors recommend but recognize that these other aspects of testing must also be chosen wisely in order to maximize the value of human challenge studies.

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I argue that the authors could make a far stronger claim. Given reasonable empirical assumptions, deliberately infecting volunteers is not only 'acceptable' but ethically mandatory (subject to some qualifications). Those empowered to fund, organize, and run vaccine trials would be acting impermissibly from a moral perspective if they had the opportunity to significantly speed up the identification of a safe and efficacious vaccine but failed to do so because of unnecessary hand-wringing over the ethics of allowing volunteers to be deliberately infected.

Human challenge studies have often been performed in modern times to improve our understanding of minor illnesses (such as the common cold) and to investigate vaccines for more serious but treatable illnesses (such as malaria).[4] They have not been commonly used to fight diseases like COVID-19, which has been associated with high levels of morbidity and mortality and is not yet well understood. Because standard vaccine trials would require thousands of subjects and take a long time for a substantial percentage to be exposed to the novel coronavirus, particularly if social distancing measures remain in place, trials where humans are deliberately infected can dramatically reduce the number of subjects needed and the amount of time required to assess vaccine efficacy.

Such considerations recently led 35 members of Congress to send a letter to the heads of the Department of Health and Human Services and the Food and Drug Administration urging the acceleration of COVID-19 vaccine research by, among other methods, 'potentially [using] challenge trials'.[5] They note that 'our situation in this pandemic is analogous to war, in which there is a long tradition of volunteers risking their health and lives on dangerous missions for which they understand the risks and are willing to do so in order to help save the lives of others'.[6]

Many considerations support the use of human challenge trials (most of which Eyal and colleagues discuss). The first and most obvious is that COVID-19 presents a threat to global health of a magnitude unprecedented in recent generations. The disease has sickened millions and killed hundreds of thousands. It has also been a tremendous burden on healthcare systems, a burden that in some places has reduced the quality and availability of treatment for non-COVID-19 illnesses.[7] Finding a vaccine sooner would reduce morbidity and mortality. Moreover, quarantine and social distancing measures mitigate contagion but have tremendous societal costs, reducing the freedom of billions of people. They also cause or exacerbate unemployment, substance abuse, domestic violence, and mental health disorders.[8]

Second, the risks to volunteers in the proposed human challenge studies would be limited. Subjects would be healthy, relatively young, and from places where the virus already poses a serious risk of infection. They would be duly informed about the risks and unusual nature of the trial. Special testing could ensure that subjects

4 Jon Cohen, *Studies That Intentionally Infect People with Disease-Causing Bugs Are on the Rise*, SCIENCE, May 18, 2016.

5 Letter from Bill Foster et al, to Alex M. Azar II, Secretary, Department of Health and Human Services, and Stephen Hahn, M.D., Commissioner, Food and Drug Administration, Apr. 20, 2020.

6 *Id.*

7 Denise Grady, *The Pandemic's Hidden Victims: Sick or Dying, But Not from the Virus*, N.Y. TIMES, Apr. 20, 2020.

8 *See, e.g.*, Samantha K. Brooks et al, *The Psychological Impact of Quarantine and How to Reduce It: Rapid Review of the Evidence*, 395 LANCET P912 (2020); Amanda Taub, *A New Covid-19 Crisis: Domestic Abuse Rises Worldwide*, N.Y. TIMES, Apr. 6, 2020.

properly understand the potential risks and hoped-for benefits of the experiment.[9] Doing so would increase our confidence that participation is rational and not swayed by transient impulses. Testing could also ensure subjects understand their rights to cease participation in the experiment at any time, as well as their obligations to remain in isolation until they are no longer dangerous.

Subjects would receive a carefully measured dose of the virus. Because amount of viral exposure seems to affect symptom severity,[10] the dose would hopefully lead to even lower rates of mortality and morbidity than are seen for people of similar age and circumstances infected in the wild. Subjects who develop COVID-19 would receive state-of-the-art care and benefit from any treatment advances that occur by the time the trials are conducted. There may even be ways to reduce risk further by, for example, using weak strains of the virus or altering the virus to make it weaker.[11]

Third, as Eyal and colleagues note, it is possible that volunteering could represent a net benefit to volunteers under certain assumptions. For example, if most subjects are eventually going to be exposed to the virus anyhow, subjects can develop immunity to the disease with a controlled viral dose, receive top-notch medical care, and not have to fight for limited ventilators and medical staff. Most of those who do develop the disease (and the corresponding at least temporary immunity it likely confers) will be able to return to their normal lives sooner than they otherwise would. And, of course, if a trial has identified an efficacious vaccine, subjects who did not receive placebo would be the first to benefit.

If volunteering confers a net benefit to the health and well-being of subjects and speeds the search for a vaccine, then there are no obvious reasons not to require human challenge trials. Challenge trials would not be merely morally permissible but morally obligatory, as all else being equal, we must take actions likely to dramatically reduce pain and suffering over actions likely to do so less dramatically. This is particularly so when the actions directly or indirectly invoke the use of public or charitable funds and resources. The only significant ethical issues arise when we think volunteers are likely to experience a net reduction in their health or well-being as a result of their participation. Then, we face familiar ethical questions about how much risk we should allow altruistic volunteers to take for the greater good.

Ethicists who take a consequentialist approach focus on the expected societal benefits of human challenge trials relative to the expected societal costs. Josh Morrison and Sophie Rose, founders of a group that has already recruited thousands of COVID-19 human challenge volunteers, pose the benefits this way: if 'one-sixth of the world's population is infected each year and a vaccine could prevent 0.5 per cent of those infected from dying, one month's faster vaccine deployment would represent close to a half-million lives saved. Speeding up the process by a single day could save nearly 20,000 people'.[12] By contrast, they point to a study estimating the infection fatality rate

9 I thank Jonathan Baron for the suggestion.

10 Joshua D. Rabinowitz and Caroline R. Bartman, *These Coronavirus Exposures Might Be the Most Dangerous*, N.Y. Times, Apr. 1, 2020.

11 Jon Cohen, *Vaccine Designers Take First Shots at COVID-19*, Science, Apr. 3, 2020, at 16. Risk might be reduced even further if only viral fragments are needed.

12 Josh Morrison & Sophie Rose, *Infect Us With the Coronavirus. It Could Speed Up a Vaccine.*, Wash. Post, Apr. 27, 2020.

in China at about 3 in 10,000 for 20–29 year olds and 8 in 10,000 for 30–39 year olds,[13] and the risks would likely be lower still for volunteers with no comorbidities, controlled viral exposure, and the state-of-the-art treatments that will likely be available by the time the trials begin. Morrison and Rose believe that speeding up the search for an effective vaccine by one day would make human challenge trials worthwhile. We need not put much faith in these admittedly rough numbers to see that the benefits from vaccines can quickly scale to millions or billions of people while the harms are restricted to the tens of people (and hopefully fewer) who would die or suffer long-lasting injury from human challenge trials.

Of course, not all ethicists are consequentialists. Deontologists believe we have duties that limit our conduct even when those duties are expected to lead to 'worse' consequences overall. Nevertheless, I argue, deontologists should recognize the need for challenge trials for two main reasons. First, there are no clear duties or other deontological constraints likely to be violated by human challenge trials, at least given the sorts of autonomous risk-taking we regularly permit. We allow people to take substantial risks for the greater good. Human space travel represents the most vivid case where we knowingly accept a high risk of death from volunteers. Moreover, astronauts accept such risks not principally to save lives but to gather knowledge. Eyal and colleagues offer less risky but closer analogies:

> We ask volunteer firefighters to rush into burning buildings; relatives to donate a live organ to loved ones; healthy volunteers to participate in drug and vaccine toxicity trials with no prospect of improving their health (and some risk of undermining it); relatively healthy volunteers to participate in studies involving long retroviral drug interruptions that risk their health with negligible prospect of improving it; and other challenge studies in which healthy volunteers expose themselves to pathogens.[14]

The most relevant analogy comes from medical personnel who treat patients with COVID-19. They are at much greater risk of developing the disease than the general public, yet we allow them to endanger themselves to benefit their patients. Such sacrifices are all the more noteworthy given research suggesting that healthcare workers are put directly in harm's way due to the higher viral loads they face.[15] They take these risks not in the hopes of saving millions or hundreds of thousands but in the hopes of healing perhaps the hundreds of COVID-19 patients they may encounter. And yet, it is not 'merely permissible' to allow healthcare workers to treat COVID-19 patients but mandatory. It would be morally impermissible for hospital administrators to shut down treatment in the face of the current pandemic (given reasonable assumptions about its risk structure) when they have sufficient staff ready and willing to serve their patients.

Similarly, volunteers for human challenge trials, like healthcare workers, would be well informed of the risks they take (or possibly better informed than healthcare workers today as our knowledge of the virus improves over time). As discussed, volunteers may be gaining net health benefits. Under more conservative assumptions, they may

13 Robert Verity et al, *Estimates of the Severity of Coronavirus Disease 2019: A Model-Based Analysis, Lancet: Infectious Diseases* (published online Mar. 30, 2020).

14 Eyal et al., *supra* note 1, at corrected proof p.9 (citations omitted).

15 Rabinowitz & Bartman, *supra* note 10.

take on risks that are at least roughly on par with those taken by many healthcare workers today. Indeed, they are likely taking on less risk than healthcare workers who practice in their seventies or eighties or have lung disease, cardiovascular disease, or compromised immunity. Moreover, assuming the trials offer no compensation to participants above the payment of costs associated with COVID-19-related illness and injury, subjects may be feel less pressure to put themselves at risk than do healthcare workers whose livelihood may require them to give care during a pandemic.[16]

In fact, policies that prohibit healthcare workers from voluntarily serving patients could be viewed as inappropriately restricting healthcare workers' autonomy. And the same could be said of properly informed human challenge volunteers. A person who volunteers for a challenge study in hopes of benefiting an immune-compromised relative should be allowed to make that decision, and possibly benefit thousands as a side effect. Thus, all things considered, it seems inconsistent to think hospital administrators *must* allow willing healthcare workers to treat COVID-19 patients but think human challenge trials are prohibited or merely permitted.

Second, even if there are deontological constraints at risk, given the *overwhelming* benefits of human challenge trials, based on reasonable assumptions about the toll the novel coronavirus has already taken and will likely continue to take on the world, the risk of violating such constraints is too low—for all but the most dogmatic deontologists—to justify a substantial delay in the search for a safe and effective vaccine.

Consider some arguments deontologists might offer. They might argue that those running vaccine trials have special duties to experimental subjects but either have no duties or have much weaker duties to those in the general population who stand to benefit from a vaccine. Moreover, they might argue, vaccine trial personnel potentially cause harm to experimental subjects, but trial delay, if it does anything, merely fails to benefit people. Many deontologists think there is an asymmetry that makes failures to benefit less morally weighty than direct causation of harm. If these views are correct, we cannot simply weigh costs and benefits as a traditional consequentialist might because doing so ignores the special relationship between researchers and subjects as well as the asymmetry between causing harm and failing to benefit.

The long way to respond is to relitigate centuries-old battles between consequentialists and deontologists. Instead, let us assume there are special duties to experimental subjects and that there are no duties to the general public except for general obligations of beneficence (a very conservative assumption given the public funding behind much medical research). Let us further assume that causing harm of a particular magnitude is more serious than failing to provide an equal-sized benefit.

Nevertheless, given the scope of the pandemic, the benefits of a speedier vaccine clearly outweigh the risks from human challenge trials. Except for extreme, absolutist deontologists, even the most precious deontological constraints can and should be

16 There is already substantial volunteer interest in human challenge trials for a COVID-19 vaccine, so participation incentives are likely unnecessary. *See* Conor Friedersdorf, *Let Volunteers Take the COVID Challenge*, The Atlantic, Apr. 21, 2020. Compensation is a tricky issue, though. Make compensation too high, and some will complain that the incentive coerces the neediest to participate. Make compensation too low and some complain that participants aren't treated fairly. (Importantly, considerable empirical evidence suggests that prospective experimental subjects still think rationally even when offered participation incentives. *See, e.g.*, Scott D. Halpern et al, *Regulated Payments for Living Kidney Donation: An Empirical Assessment of the Ethical Concerns*, 152 Annals Internal Medicine 358 (2010).)

violated when the benefits of doing so are sufficiently high. Few in the legal academy have done more to defend deontology than Michael Moore, yet Moore recognizes that:

> Absolutist versions of deontology are implausible in the extreme. Kant's version of the famous Latin saying that justice should be done even though the Heavens fall was 'Better the whole people should perish' from the earth than that an injustice be done. This is the kind of stirring hyperbole that gets people to the barricades; but it is surely utter rubbish if taken as the kind of moral philosophy that any of us should actually live by.[17]

As Moore and many other 'threshold deontologists' recognize, when the value of observing a deontological constraint is dramatically swamped by the harms of observing it, the constraint can and should be broken.

We do not need an especially precise model of the costs and benefits of human challenge trials to see the thrust of the argument. Every risk a single volunteer takes of a negative outcome (above the person's baseline risk when not participating) is likely offset by an expected benefit 1000 or more times larger in magnitude—perhaps much larger, depending on how quickly challenge trials speed us along. Even if several human challenge trials go on at once with, say, 1000 total volunteers, we might see no deaths at all or a small number, some of which might well have occurred anyhow from community exposure. So even if the numbers Morrison and Rose cite are off by an order of magnitude or two, a good case can be made that both consequentialists and deontologists should approve human challenge trials to combat COVID-19 (at least subject to some caveats I discuss at the end).

While threshold deontology has been used to justify breaking even the most serious deontological constraints against torture or deliberately killing innocents, human challenge trials require nothing of the sort. At worst, they involve a modest expansion of the risks we permit experimental vaccine subjects to voluntarily take, and they do so for what is shaping up to be the most serious international medical crisis in generations. What makes human challenge trials mandatory is the comparatively low risk to well-informed volunteers relative to the tremendous gains we reasonably hope to achieve.

While I argue that human challenge trials are ethically mandatory given the considerations raised by Eyal and colleagues, there are a few important caveats. First, I assume but do not necessarily endorse the assumptions they make about COVID-19 and its likely progress. Their assumptions certainly seem reasonable. But if, for example, a vaccine candidate had a high risk of making subjects more susceptible to harm from coronaviruses,[18] that particular candidate vaccine might pose an unfavorable risk-return trade-off—particularly when human and financial resources to conduct trials are limited. Similarly, while one expert, Stanley Plotkin, thinks a human challenge

17 Michael S. Moore, *The Rationality of Threshold Deontology*, 371, 371 *in* Moral Puzzles and Legal Perplexities Essays on the Influence of Larry Alexander (Heidi M. Hurd ed., 2019) (footnotes omitted). For one way to understand threshold deontology, see Adam J. Kolber, *Punishment and Moral Risk*, 2018 U. Illinois L. Rev. 487, 530–31.

18 *See, e.g.*, Yushun Wan et al, *Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry*, 94 J. Virology (March 2020). Eyal and colleagues suggest challenging small groups of volunteers sequentially to rule out increased danger from subsequent infections and note that the risk of such paradoxical effects are better addressed in smaller human challenge trials than larger traditional trials.

trial could give us key efficacy information in 2–3 months, another expert, Myron Levine, believes that given the special attention and urgency that will be given to finding a novel coronavirus vaccine, human challenge trials may not speed discovery of a cure by very much.[19] This might also be true if there are sufficiently high-risk groups (perhaps healthcare workers) who will be exposed to the virus in the ordinary course of their lives such that we can get efficacy results relatively quickly without deliberate infection. Clearly, if Eyal and colleagues are mistaken about key assumptions, it could substantially change the analysis.

Second, there is no uniform, generic group of 'vaccine trial personnel'. Rather, there are many people with distinct roles, responsibilities, and places in the organizational hierarchy. They do not each have the power to decide how a trial will be run. Since 'ought' usually implies 'can', people have no moral obligation to run a challenge trial if they lack the power to do so. Still, those who authorize or run trials might have weaker obligations. For example, they may be obligated to raise the possibility of challenge trials or to present arguments in their favor.

Third and most importantly, there are some considerations that Eyal and colleagues do not address that could complicate the analysis. For example, if many human challenge trials are run, someone may contract COVID-19 and die or be seriously injured who would not have suffered such complications had the person not volunteered. (I'm not sure how we could know what would have otherwise happened given that subjects will be drawn from places where the virus represents a substantial risk, but it's enough of a worry if people perceive that a subject was seriously harmed who would not have been otherwise.) From my perspective, we should be grateful for the subject's sacrifice for the greater good to the extent the subject knowingly accepted additional health risk. Some, however, might seize upon the story to call vaccines or vaccine trials into question. So even if human challenge trials are ethically mandatory based on the considerations Eyal and colleagues address, there might be risks of bad publicity or other down-the-line effects that must also be considered as matters of realpolitik.

Irrational fear of vaccines or vaccine research can itself cause harm because vaccines work best when used by a substantial portion of the population. Similarly, those running vaccine trials may have regulatory or liability concerns associated with human challenge trials. Whether such concerns are well-founded or not, it is better to run a traditional trial than a trial that will consume resources and face so much regulatory scrutiny that it never actually benefits anyone. Such concerns can be difficult to assess but are important to manage nonetheless because trials will not be approved swiftly if they garner too much lawyerly headwind.

Therefore, I argue, given reasonable empirical assumptions, human challenge trials are ethically mandatory subject to certain hard-to-assess considerations related to public relations, navigating legal and regulatory requirements, and other issues of realpolitik. The important point is that the ethics of human challenge trials for the novel coronavirus are straightforward, though we cannot entirely ignore the complex psychological and political factors that ultimately affect how vaccine trials are perceived by others even when they are conducted with the best motivations and intentions.

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19 Jon Cohen, *Speed Coronavirus Vaccine Testing by Deliberately Infecting Volunteers? Not So Fast, Some Scientists Warn*, SCIENCE, Mar. 31, 2020.