Potential conflicts of interest. Author certifies no potential conflicts of interest. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Joerg Hasford

1Institute for Medical Information Processing, Biometry, and Epidemiology, University of Munich, Munich, Germany, and

2Association of Medical Ethics Committees in Germany, Berlin, Germany

References

1. Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. J Infect Dis 2020; 221:1752–6.
2. 1 Day Sooner. COVID-19 human challenge trials. https://1daysooner.org. Accessed 30 May 2020.
3. Metzger WG, Ehni HJ, Kremsner PG, Mordmüller BG. Experimental infections in humans—historical and ethical reflections. Trop Med Int Health 2019; 24:1384–90.
4. Wagner A, Weinberger B. Vaccines to prevent infectious diseases in the older population: immunological challenges and future perspectives. Front Immunol 2020; 11:717.
5. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med 1984; 3:409–22.
6. SIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992; 339:753–70.
7. Centers for Disease Control and Prevention. Vaccine safety datalink. https://www.cdc.gov/vaccinesafety/ensuring_safety/monitoring/vsd/index.html. Accessed 30 May 2020.
8. Drug Safety Research Unit. https://www.dsru.org. Accessed 30 May 2020.
9. Medikura. Patent safety. Digital. https://www.medikura.com/en/home-en/. Accessed 30 May 2020.
10. Lambert SM, Markel H. Making history: Thomas Francis, Jr, MD, and the 1954 Salk poliomyelitis vaccine field trial. Arch Pediatr Adolesc Med 2000; 154:512–17.

Received 30 May 2020; accepted 22 July 2020; published online August 26, 2020.
Correspondence: Joerg Hasford, MD, Institute for Medical Information Processing, Biometry, and Epidemiology, University of Munich, Marchioninistrasse 15, D-81377 Munich, Germany (hasfordibemuni-muenchen.de).

The Journal of Infectious Diseases® 2020;222:1571–2 © The Author(s) 2020. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/infdis/jiaa456

Human Challenge Studies Are Unlikely to Accelerate Coronavirus Vaccine Licensure Due to Ethical and Practical Issues

To the Editor—We write to express some concerns about human challenge studies to accelerate coronavirus vaccine licensure [1]. Human challenge studies are generally considered acceptable if they “are confined to infectious diseases that are either self-limiting or can be fully treated” [2]. Although Eyal et al argue that controlled severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in 20- to 45-year-olds are justified because of potential societal benefit and because they are in an age range “in which the risk of death or serious complications is substantially lower than in older age groups [1],” those risks are very real. In Indiana, 5% to 11.5% of 20–49 years with positive SARS-CoV-2 PCR tests required hospitalization; their average length of stay ranged from 13.7 to 19.7 days, and their mortality rates ranged from 1.7% to 5.6% (Table 1). Although the actual rates may be lower due to lack of universal testing, these risks are substantial. Remdesivir is the only antiviral that has a beneficial effect on coronavirus disease 2019 (COVID-19); it shortens length of stay but has had no statistically significant effect on...

Notes

Disclaimer. The opinions expressed do not necessarily represent those of the Association of Medical Ethics Committees in Germany.
It is clear that SARS-CoV-2 does not cause self-limited disease that can be fully treated.

Informed consent requires that subjects "understand clearly the range of risk", but there are no data on the long-term outcomes of persons with COVID-19. In the absence of data, how could one possibly write an informed consent statement that would fully apprise participants of potential risk?

Eyal et al state that volunteers who participate would receive "excellent care for Covid-19, including priority for . . . life-saving resources . . . in settings converted from those used in influenza challenge studies [1]." There is no acknowledgment of the risk for transmission of SARS-CoV-2 to research unit staff and no discussion of who would be responsible for the financial costs of prolonged hospitalizations should volunteers require intensive care or rehabilitation. If a volunteer became medically disabled, who would be responsible for their long-term financial support and care? A key aspect of respect for persons is the right to withdraw from research studies. Once infected, volunteers would need to stay on the research unit, making the right to withdraw meaningless.

Eyal et al propose that only “people residing in areas with high transmission rates” should be recruited [1]. The idea here is that these participants are likely to get infected anyway and might benefit from receipt of a vaccine. In the United States, African Americans, Hispanics, and Native Americans bear a disproportionate share of SARS-CoV-2 infection.

Targeted recruitment of minority groups runs great risk of exacerbating historical mistrust of biomedical research and racial discord.

Eyal et al justify the increased risk to participants by a more rapid vaccine development time frame [1]. In a practical sense, it is unlikely that a SARS-CoV-2 model could be ready to evaluate vaccines for years. In 2006, all human inoculation experiments were required to be conducted under an Investigational New Drug (IND) application; although our group had already accumulated safety data on 244 participants using one bacterial strain [4], this process took us 17 months. For SARS-CoV-2, sequence analysis of 160 isolates yields 100 distinct genotypes that cluster into 3 types [5]. What preclinical data or whether preclinical data or strain prevalence would drive strain selection for the complex IND process is unclear.

Eyal et al draw parallels between experimental SARS-CoV-2 infection and influenza challenge trials, which are in part justified due to the availability of antivirals should severe symptoms develop [6]. In 2001, experimental infection with influenza was halted in the United States due to a 21-year-old volunteer developing a transient cardiomyopathy after challenge with influenza B [7]. After 2012, 2 influenza A strains were approved for use under an IND, with an initial goal of establishing an infectious dose that would cause mild to moderate disease in ≥60% of the volunteers. Those escalating dose-finding trials involved 46 volunteers over a 15-month period for an H1N1 virus and 37 volunteers over a 19-month period for an H3N2 virus [8, 9]. Thus, the time needed to standardize a SARS-CoV2 infection model will be substantial. Expediting IND approval or the dose-ranging studies increases the risk of subject harm.

Finally, human challenge studies would not provide adequate data regarding vaccine safety. Eyal et al indicate that a challenge trial would have to be followed by a placebo-controlled safety study with 3000 vaccinated participants [1], the minimum recommended for a phase III trial [10]. They suggest that only short-term safety issues would need to be assessed, which would shorten the time frame to some extent. However, if significant medium- or longer-term safety problems emerge postlicensure, the potential damage to vaccine confidence in general would be incalculable.

## Notes

**Financial support.** This work was funded by the National Institutes of Allergy and Infectious Diseases, National Institutes of Health (Grant R01 AI1137116; to S. M. S.) and the National Center for Advancing Translational Sciences, National Institutes of Health (Grant UL1TR002529; to M. A. O.).

**Potential conflicts of interest.** G. D. Z. reports personal fees from Sanofi Pasteur and personal fees from Merck, outside the submitted work. M. A. O’s spouse is an employee for Eli Lilly, Inc. and she receives personal fees from Merck and Bayer USA, outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

---

**Table 1. Indiana COVID-19 Data for “Low-risk” Age Groups**

| Age Group | Positive PCR Tests | No. Hospitalized | LOS (Days) | Deaths |
|-----------|--------------------|-----------------|------------|--------|
| 20–29     | 5888               | 297 (5.0)       | 13.7       | 5 (1.7) |
| 30–39     | 6623               | 508 (76)        | 14.5       | 16 (3.1)|
| 40–49     | 7018               | 809 (11.5)      | 19.7       | 45 (5.6)|
| All ages  | 41 389             | 6788 (16.4)     | 19.5       | 2350 (5.5)|

Abbreviations: COVID-19, coronavirus disease 2019; LOS, length of stay; PCR, polymerase chain reaction.

*Excerpt as indicated, data represent number of persons and their percentage in parentheses in each age group.

*Data taken from the Regenstrief Institute COVID-19 Dashboard on 6/22/20.

*Data taken from the Indiana State Department of Health COVID-19 Dashboard on 6/22/20.

*Percentage of deaths based on 42 423 positive tests reported by the Indiana State Department of Health.
References
1. Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. J Infect Dis 2020; 221:1752–6.
2. Miller FG, Grady C. The ethical challenge of infection-inducing challenge experiments. Clin Infect Dis 2001; 33:1028–33.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - preliminary report. N Engl J Med 2020. doi:10.1056/NEJMoa2007764
4. Janowicz DM, Ofner S, Katz BP, Spinola SM. Experimental infection of human volunteers with Haemophilus ducreyi: fifteen years of clinical data and experience. J Infect Dis 2009; 199:1671–9.
5. Forster P, Forster L, Renfrew C, Forster M. Phylogenetic network analysis of SARS-CoV-2 genomes. Proc Natl Acad Sci U S A 2020; 117:9241–3.
6. Sherman AC, Mehta A, Dickert NW, Anderson EJ, Roupheal N. The future of flu: a review of the human challenge model and systems biology for advancement of influenza vaccination. Front Cell Infect Microbiol 2019; 9:107.
7. Ison MG, Campbell V, Rembold C, Dent J, Hayden FG. Cardiac findings during uncomplicated acute influenza in ambulatory adults. Clin Infect Dis 2005; 40:415–22.
8. Memoli MJ, Czajkowski L, Reed S, et al. Validation of the wild-type influenza A human challenge model H1N1pdmMIST: an A(H1N1)pdm09 dose-finding investigational new drug study. Clin Infect Dis 2015; 60:693–702.
9. Han A, Czajkowski LM, Donaldson A, et al. A Dose-finding study of a wild-type influenza A(H3N2) virus in a healthy volunteer human challenge model. Clin Infect Dis 2019; 69:2082–90.
10. Singh K, Mehta S. The clinical development process for a novel preventive vaccine: an overview. J Postgrad Med 2016; 62:4–11.

Reply to Hasford and to Spinola et al
TO THE EDITOR—We proposed human challenge trials (HCTs) as a possible alternative or complement to conventional phase 3 trials for expedited severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine efficacy testing [1]. Hasford [2] argues that a large, simple, randomized trial, as proposed by Yusuf et al [3], could work better. We note that the latter design is similar to that implemented by the World Health Organization for the SOLIDARITY platform trial [4]. If vaccine efficacy can be assessed rapidly in such trials, then HCTs might prove unnecessary, but preparing for HCTs would still be a valuable hedge against the possibility of too low an incidence of coronavirus disease 2019 (COVID-19) in field trials in such a fluid situation.

Spinola et al argue that HCTs are generally limited to diseases that can be fully treated. We recognize that COVID-19 is not in that category, but have explained elsewhere why the risks remain tolerable [5, 6]. We note also that since we wrote our original manuscript, 2 specific therapies have been shown to reduce the risks to patients hospitalized with COVID-19 [7, 8], and it is possible that further treatments will be developed in the coming months that reduce the risks even further. It is true that we necessarily have no information on the long-term outcomes associated with SARS-CoV-2 infections. The informed consent statement must include specification that there may be long-term effects of which we are currently unaware. As we explained elsewhere, this in no way invalidates participants’ informed consent [9]. Nor does the uncertainty otherwise make the trials impermissible [10]. We agree with Spinola et al that such trials should not target minority groups for recruitment [5].

Spinola et al argue that “it is unlikely that a SARS-CoV-2 model could be ready to evaluate vaccines for years.” But the circumstances of the COVID-19 pandemic have changed the paradigm for the time it takes to develop and test new vaccines. If sufficient resources are devoted to developing HCTs for SARS-CoV-2 vaccines, then we believe they could be available much sooner. Of note is the recent report that HCTs might be conducted at Oxford University “by the end of this year” [11].

Spinola et al are also concerned that HCTs would not provide adequate data regarding vaccine safety and that, even with a parallel large short-term safety trial, such testing could not detect long-term adverse effects. However, even in the type of conventional phase 3 trial that it is hoped might produce efficacy data in 3–6 months sufficient to justify widespread vaccine use [4], longer-term adverse effects will remain unknown, and must be studied in postlicensure studies.

Notes
Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases (grant number AI114617-01A1 to N. E.); National Science Foundation (grant number 2039320 to N. E.); National Institute of General Medical Sciences (grant number...