Kingdom, or Scandinavia) or by patient reporting. Vaccine safety information can be collected by established systems like the Vaccine Safety Datalink in the United States [7], prescription event monitoring programs (eg, the Drug Surveillance Research Unit in the United Kingdom [8]), or by direct patient safety reporting on websites, including those accessible with smartphones [9], which can be specifically designed for vaccine trials. Among the advantages of using the LSRT design are that it allows central randomization of large numbers of volunteers within a short time and rapid collection of the relevant outcomes at a low cost compared to the conventional phase 3 trials with many follow-up visits and extensive monitoring. Adaptive design features (eg, modification of the eligibility criteria considering the accruing safety information) are feasible as well. Given the wide entry criteria, the results provide external validity for large parts of the population compared to any challenge trial, which would need to focus on participants with extremely low risks for developing serious COVID-19. As there will be very many people who would like to participate in such a vaccination trial, the sample sizes needed should be achieved within a very short time.

When the LSRT double-blind design is used, the validity of the results is assured and it does not generate the serious ethical issues inherent in challenge trials. Regarding the Salk vaccine, large randomized trials with sample sizes of more than 70 000 were done in the early 1950s [10] and such LSRTs should be feasible in 2020. Thus, the sponsors of vaccine trials and the drug regulatory agencies should start the preparatory work now to be ready once an investigational vaccine is ready to be administered on a large scale.

Notes

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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

mortality [3]. 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.

Table 1. Indiana COVID-19 Data for "Low-risk" Age Groups[a]

Age Group	Positive PCR Tests[b]	No. Hospitalized[b]	LOS (Days)[b]	Deaths[c]
20–29	5888	297 (5.0)	13.7	5 (1.7)
30–39	6623	508 (7.6)	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)[d]

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

[a]Except as indicated, data represent number of persons and their percentage in parentheses in each age group.

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

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

[d]Percentage of deaths based on 42 423 positive tests reported by the Indiana State Department of Health.

Notes

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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

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