

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- to 49-year-olds with positive SARS-CoV-2 polymerase chain reaction tests required hospitalization; their average length of stay ranged from 13.7 to 19.7 days, and their mortality rates ranged from 0.2% to 1.9% (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 $\geq 60\%$ 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

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 (0.2)
30–39	6623	508 (7.6)	14.5	16 (0.7)
40–49	7018	809 (11.5)	19.7	45 (1.9)
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.

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

^bData taken from the Regenstrief Institute COVID-19 Dashboard on 6/22/20.

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

^dPercentage of deaths based on 42 423 positive tests reported by the Indiana State Department of Health.

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

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