Clinical Infectious Diseases

EDITORIAL COMMENTARY

The Value of Human Challenges in Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Development

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The epidemic of coronavirus disease 2019 (COVID-19) rolls on, at least in the rule-recalcitrant population of the United States, but also in countries that are too poor and disorganized to provide conditions for self-isolation. Aside from the increasing toll of death and disability, the economic and social effects of the epidemic are disastrous and grow day by day, exceeding anything seen since the 1918–19 influenza outbreak or the depression of the 1930s. We have only 2 hopes for salvation: the exhaustion of susceptible individuals by natural infections or the development of a preventive vaccine. The former hope would require acceptance of many deaths and overflowing hospitals, while the latter hope depends on an effective vaccine being licensed for widespread use.

Normally, licensure of a vaccine requires many years of development, including a large safety and efficacy trial in which vaccinees are compared to placebo recipients with respect to reactions and to the incidence of the disease for which the vaccine was developed. In this pandemic, that would mean a requirement for sufficient COVID-19 disease and possibly deaths in the placebo group, with less disease in the vaccine group. Meanwhile, those not in a trial would still be subject to the ravages of the disease.

Is there another way to confirm that a vaccine against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is protective, and thus to accelerate its use? A number of people, including Nguyen et al [1] in this issue and others [2–7] elsewhere, have proposed the use of human challenge trials as a way of confirming the protective ability of candidate vaccines, in order to allow emergency use in high-risk groups and to facilitate the way to eventual licensure and use in the general population. However, there are obvious objections to such a strategy, summarized by the adage that all physicians learn: "above all, do no harm." It is repugnant to think that something we do may cause disease and perhaps death, even if the goal in the long term is to save lives.

The idea behind human challenge trials is to recruit young, healthy volunteers who have the lowest chance of serious disease, who would be given vaccine candidates and then be challenged with SARS-CoV-2 in order to determine whether the vaccines protect. However, there would also have to be prior challenges of unvaccinated volunteers to determine the optimal infectious dose, and also challenges of some volunteers who have had prior COVID-19 infections, to confirm that immune responses can give subsequent protection.

Obviously, the ethical issues around human challenge trials are many. However, numerous ethicists have weighed in on this issue. Although some have disagreed [8, 9], the majority have accepted human challenge trials done in informed volunteers as ethical under the current circumstances. Some ethicists have pointed out that organ donation by volunteers is an accepted practice, despite a low but definite risk of death or disability, which is equivalent to the risk of COVID-19 in the young age group of volunteers [10]. The organization to which the authors of the paper by Nguyen et al [1] belong, One Day Sooner, represents literally thousands of volunteers for SARS-CoV-2 challenges.

Aside from the ethical issues, the principal objection to human challenge trials with SARS-CoV-2 is the absence of a reliable rescue medication for the treatment of serious disease. To mitigate disease severity, one could begin treatment with Remdesivir, convalescent serum, and steroids as soon as a lower respiratory tract infection is confirmed, but one must bear in mind that as of this writing, no therapy is confirmed to be completely effective. Nevertheless, by confining studies to young (18–25 years old) and healthy volunteers, current data suggest a very low risk of severe disease.

In evaluating the idea of human challenges with SARS-CoV-2, one must balance the risks of those challenges against the risks associated with the usual process of vaccine development and evaluation. Table 1 attempts to contrast

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Table 1. Rapid Development of Severe Acute Respiratory Syndrome Coronavirus 2 Vaccines Human Challenge Studies vs Traditional Phases 1–3

Human Challenges	Phases 1–3
Advantages	
Quick readout on protection by vaccines	Enable licensure
Determine immunity after prior natural infection	Large safety data base
Identify correlates of protection	Tests efficacy in multiple age groups
Can compare multiple vaccines	Data from large populations
Leads to provisional use in high-risk people	Results based on natural exposures to varying doses
Disadvantages	
Possible serious disease and death in volunteers	Placebo groups will have serious disease and death
Results might not extrapolate to the elderly	Longer path to widespread use
Virus dose may be artificially low	Need for a large population, even more for multiple vaccines
Establishment of correct dose might take longer than expected	…
Insufficient safety data for licensure	…

the advantages and disadvantages of each approach. Clearly, there are unknowns that should obviate dogmatism, but it appears to this observer that human challenge experiments are worth preparing for and potentially putting in motion, particularly considering the large number of current vaccine candidates and the difficulties of conducting Phase 3 trials for all of them.

Clearly, human challenges in a pandemic disease with associated fatality, such as COVID-19, must be seriously evaluated before launching them. The manufacture of a challenge virus will take some weeks, as will organizing a site in which the challenged volunteers can be isolated and receive medical care. However, the objection of some that those steps will take so long that the value of human challenge studies will be negated is a self-fulfilling prophecy: the longer we argue, the less the value of the proposed idea. If vaccines are rapidly tested and made available through the usual Phases 1–3, human challenge trials might be obviated and could always be cancelled. However, a committee of the World Health Organization and a committee of the National Institutes of Health have both given provisional approval to human challenges [11, 12]. The longer we hesitate, the less the value of human challenge trials.

Note

Potential conflicts of interest. S. A. P. is a consultant to numerous companies and biotechs, none of which have indicated interest in human challenge trials. 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.

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