The Ethics of Human Challenge Trials Using Emerging SARS-CoV-2 Virus Variants

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Summary of main points: Researchers are preparing for human challenge trials with emerging SARS-CoV-2 variants. We argue that these trials can be conducted ethically.

Abstract

The world's first COVID-19 human challenge trial using the D614G strain of SARS-CoV-2 is underway in the United Kingdom. The Wellcome Trust is funding challenge stock preparation of the Beta variant (B.1.351) for a follow-up human challenge trial, and researchers at Imperial College London are considering conducting that trial. However, little has been written thus far about the ethical justifiability of human challenge trials with SARS-CoV-2 variants of concern. While vaccine resistance *as such* does not increase risks for volunteers in COVID-19 challenge trials, we explore two specific characteristics of some variants that may initially be thought to make such trials unethical and conclude that SARS-CoV-2 variant challenge trials can remain ethical.

Background

While the authorization of several highly effective vaccines has significantly reduced cases of COVID-19 in some countries, virus variants that may evade authorized vaccines threaten to reverse progress [1].

The Beta and Delta variants are of particular concern. While the CDC [2] reports that "currently authorized mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) provide protection against ... [the Beta variant]," other vaccines which represent the majority of the pre-purchased COVID-19 vaccine doses [3], as well as doses ordered by COVAX [4], show reduced efficacy against this variant.

Interim analysis of Janssen's Phase III trial found that vaccine efficacy in South Africa was reduced to 57% post-vaccination [5]. A Phase IIb trial from Novavax found that their vaccine efficacy against the Beta variant was just 49% [6]. An AstraZeneca study [7] of 2,000 people in South Africa found that "vaccine efficacy against this variant, analyzed as a secondary end point, was 10.4%." This is particularly worrisome, since the AstraZeneca vaccine is the most widely purchased in the world. The African Union has already bought 500,000,000 doses, and South Africa, where the Beta variant is dominant, has had to sell their entire portfolio [8].

The WHO warns that the Delta variant is becoming the dominant strain of SARS-CoV-2 worldwide due to its increased transmissibility [9]. While the Pfizer vaccine remains highly protective against the Delta variant [10], a recent UK analysis found that a single vaccine dose is 35% less effective against the Delta variant than the Alpha variant [11].

The FDA recognizes that the emergence of vaccine-resistant strains warrants immediate preparation of strain-specific booster doses from all authorized vaccine candidates [12]. As a matter of basic preparation, this Perspective adds, the 3-4 month long process of developing challenge stock for all variants that may be vaccine resistant, including both the Delta and Gamma variants, should begin immediately. Commentators skeptical of approving any COVID challenge trial nonetheless proposed laying the groundwork for these trials immediately [13], and their proposal is especially sensible for variant challenges. Given the immense humanitarian benefits of authorizing vaccines that fight a pandemic just weeks or days earlier, the modest cost of viral preparation under Good Manufacturing Practices for human challenge trials is well worth the chance that the challenge stocks are never used.

The limits of conventional studies for variant-specific vaccine boosters

Immunogenicity studies that demonstrate adequate levels of neutralizing antibodies against variants of concern may be indicative of booster efficacy, per regulatory guidance in the United States [12] and Europe [14]. However, these studies face two important limitations. First, while some data show that neutralizing antibodies are predictive of protection against SARS-CoV-2 infection [15], this may not be the case for the Beta variant and future variants markedly more resistant to neutralization [16]. Stronger data describing which immune responses correlate with protection against these variants would facilitate determining the efficacy of boosters by surrogate endpoint. Second, a disadvantage of relying solely on immunogenicity studies to infer

booster efficacy is that no data can be gathered from them on viral shedding and viral activity in the upper respiratory tract [17], significantly narrowing information gathered on viral transmission post-vaccination.

Conventional clinical efficacy trials for boosters also face limitations. First, because efficacy studies require a critical mass of trial participants to encounter a specific strain of the virus, these trials may not produce efficacy results if a different strain predominates in the population during the trial. Second, the strain that predominates in the trial population cannot be reliably predicted in advance of actually conducting the lengthy trial. Third, subdued case rates may cause these trials to take many months, costing lives in the meantime. Fourth, vaccination from a placebo group in a large, non-isolated randomized controlled trial during an epidemic is ethically fraught [18].

The role of human challenge trials with SARS-CoV-2 variants

The UK Medicines & Healthcare products Regulatory Agency (MHRA) and the European Medical Authority (EMA) have both stated that human challenge trials can deliver important evidence about the effect of updated vaccine candidates on variants of concern [17, 19]. The Wellcome Trust has begun funding preparation of the Beta variant challenge stock for a variant challenge model [20], and researchers at Imperial College London are considering conducting a Beta variant challenge trial [21]. Notably, the vaccine resistance of a given variant does not imply that it is more virulent or transmissible, and therefore vaccine resistance *as such* does not

increase risk for challenge volunteers when compared to ongoing characterization studies, in which volunteers are exposed to the challenge agent without first receiving a vaccine. Later, we dedicate a specific discussion to the greater virulence and transmissibility of relevant variants that may be used in challenge trials, and argue that these trials can remain ethical.

Challenge trials can assist in discerning a correlate of protection against different variants of SARS-CoV-2 by investigating the relationship between neutralizing antibody titers presumably caused by efficacious vaccination and a variant challenge [22, 23]. The more evidence that is gathered to establish a robust correlate, the more likely it is that boosters for vaccines can be authorized by surrogate endpoint, accelerating the path to market for boosters that are in early stages of development. Challenge trials could also be used to determine the extent to which subjects who were infected with earlier strains of SARS-CoV-2 can be reinfected with newer variants.

More broadly, challenge trials could offer unprecedented detail regarding viral kinetics and the immune response to variants such as the Beta strain. To quote the UK MHRA guidance on challenge studies for SARS-CoV-2 variants [17], “human challenge studies have the advantage that the course of developing immunity, viral shedding, local suppression of SARS-CoV-2 shedding in the upper respiratory tract and other parameters can be measured in a controlled setting.”

Once a variant challenge stock is prepared, vaccine efficacy in terms of curbing infection and infectiousness can be tested more rapidly in a challenge trial than a field trial. Su et al. have

outlined a plan to assess the efficacy of authorized and updated vaccines against SARS-CoV-2 variants [24]. If unvaccinated volunteers are needed for such a trial but are difficult to find in the UK, trialists can open recruitment from other countries with lower vaccination rates.

In sum, human challenge studies could provide data on variant boosters' efficacy in curbing infection rates, accelerate the discernment of a correlate of protection against virus variants, and advance our understanding of variant pathogenesis.

Human challenge trials against SARS-CoV-2 variants can remain ethical

Human challenge trials involving variants that evade authorized vaccine protection such as the Beta variant could have momentous global public health value, yet little is written about their specific ethics.

The ethical justifiability of COVID-19 human challenge trials with the D614G mutation strain has been endorsed by the World Health Organization [25] and the UK MHRA [17]. As we have argued elsewhere, the risks to the young, healthy volunteers in COVID-19 human challenge trials are far lower than the medical risks of some commonly accepted living organ donations, and the expected global public health value of these trials is dramatically higher [26].

However, a human challenge trial with SARS-CoV-2 variants would raise unique ethical considerations. Here we explore two that may initially motivate opposition—some variants'

greater transmissibility and virulence— and argue that while the trials' risk-reward ratio will depend on the exact strain and type of trial, some vaccine-resistant variant challenge trials can be ethically justified.

Transmissibility

The Alpha, Beta, and Delta variants appear around 50% more transmissible than the strain first identified in Wuhan [27]. However, increased transmissibility, as such, does not directly increase the risks to human challenge participants. What it may do is increase the social value of that challenge trial, which speeds the authorization of a vaccine or booster against a more transmissible and hence, for society, more dangerous, variant.

Greater transmissibility does underline the importance of biosafe quarantine facilities to ensure that infected volunteers do not inadvertently cause community infection. The WHO Working Group has outlined specific standards for biosecure facilities to prevent such transmission [28], and those are already part of operations for challenge trials planned at Imperial College and Oxford University.

Virulence

Limited evidence suggests that the Beta variant is more lethal than the strain first identified in Wuhan [29]. However, a recent study of seven EU countries by Funk et al. found "3.5–3.6 times higher odds of hospitalisation for age groups 40–59" due to the Beta variant. Their analysis did not show increased risk of death from the Beta variant [30].

Since the risks of a severe adverse events in a COVID-19 human challenge trial are already very low— Manheim et al. find that the risk of death for a trial participant is around 0.00025% [31] — a threefold increase in risks for a Beta variant challenge volunteer would remain far lower than common comparator risks like right liver lobe donation, which involves a 0.4% risk of death and a 1.1% risk of lasting disability [32]. The threefold greater risk for young healthy volunteers would also remain well within postulated upper bounds of risk in clinical trials, such as the 1% cap on risk of severe adverse events [33], a standard echoed by critics of challenge trials [34]. If challenge volunteers are vaccinated before the trial, risks will be reduced considerably. To reduce risks further, researchers can also use low-dosage challenge trials with virus variants [35].

Response to Objections

Objection 1: Variant challenge study data may become irrelevant should a further strain become dominant.

It might seem that newer virus variants might rapidly overtake one another, reducing the usefulness of the data from challenge trials of formerly predominant variants. However, the risks of waiting so long that study data becomes irrelevant are *greater* in field studies than challenge studies. The reason is that field studies require a critical mass of trial participants to be exposed to a particular variant. Researchers should prepare challenge stock for each potentially vaccine-resistant strain expeditiously, given the reasonable cost of investment and the reasonable chance that one variant still predominates by the time the data of a challenge trial is reported.

Objection 2: Challenge trials do not produce generalizable efficacy data because ethically, only young, healthy volunteers can participate.

One objection to variant challenge trials is that the resultant data in young, healthy volunteers are unrepresentative of the broader population, which include those at higher risk of medical complications. However, it is not clear that to authorize a vaccine booster we need to verify all effects of a vaccine in all population groups [36]. Even if challenge trial data is insufficient for authorization on its own, the data can still be used in a fast-to-fail approach in which the most promising vaccines are selected for optimized investment. Most importantly, though, challenge trial data may be generalized by discerning the correlates of protection and conducting a rapid and safe immune bridging study in any population group of interest [37].

Objection 3: Challenge trials with new variants can jeopardize public trust.

Some have argued that any COVID-19 human challenge trials would spread distrust in the research process and undermine vaccine confidence [38]. This risk may seem higher in variant challenges. However, the best available evidence on public perceptions on COVID-19 challenge trials and public trust— an international survey of nearly 6,000 respondents— found strong support for challenge testing across all demographic groups [39]. The UK, which is the only country to run COVID-19 challenge trials, has higher vaccine confidence than the US and the

rest of Europe [40], and that confidence has not dropped since rival challenges were approved and launched.

Conclusion

The Beta SARS-CoV-2 variant, and future vaccine-resistant virus variants, threaten to get us back to square one in the fight against the pandemic. Human challenge trials can accelerate the authorization of vaccine boosters and advance our understanding of these variants. While the risk-reward ratio of each trial will depend on the variant and study design, these trials can remain ethical, and researchers should begin preparations for them immediately.

Notes

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