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LETTERS

COVID vaccine efficacy against the B.1.351 ("South African") variant—The urgent need to lay the groundwork for possible future challenge studies

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SARS-CoV-2's B.1.351 ("South African") variant "is markedly more resistant to neutralization by convalescent plasma (9.4 fold) and vaccinee sera (10.3–12.4 fold),"[1,2] raising the specter that that variant could resist the leading authorized spike-based vaccines.[2] Indeed, in earlier lab exams, Moderna's vaccine showed "A six-fold reduction in neutralizing titers … with the B.1.351 variant relative to prior variants."[3] Pfizer-BioNTech's "neutralization of the B.1.351-spike virus was weaker by approximately two thirds."[4] When tested in human volunteers, AstraZeneca's vaccine provided only 10% protection from mild to moderate disease caused by that variant, and its distribution in South Africa was suspended.[5] Janssen's vaccine also did less well in South Africa than elsewhere, presumably due to lower neutralization of infecting viruses.[6]

It is of great urgency to test in human populations whether the leading authorized vaccines, their boosters in development,[7] and other vaccines in development strongly protect against SARS-CoV-2 viral variants. But now that authorized vaccines are being rolled out, and others may soon get emergency authorization, new placebo-controlled phase 3 field trials in nations with wide access to vaccines would have to exclude thousands of study participants from protective vaccines. That would pose substantial risk both to them and to their many contacts around study sites – a formidable ethical and public health challenge.[8] Non-inferiority trials would either require an unacceptably high number of participants and last too long or compromise accepted statistical standards. Trials in countries without vaccine access would be ethically contentious and, even if possible,[9,10] take too long, and cost too much to be done for every variant and booster.

In this new landscape of vaccines gradually becoming available for all adults in rich nations, the quickest and perhaps only viable way to test vaccines for their efficacy against new variants (as well as to test new dosing regimens, discern the correlates and duration of vaccine protection, and rigorously assess vaccine impact on infection and infectiousness) is to conduct *human challenge trials*. In such trials, 1:100–1:1000 the participants of field trials, all selected to be young and healthy with extremely low risk of severe outcomes upon COVID infection,[11] are intentionally exposed to the relevant viral variant, typically by the nasopharyngeal administration of small doses. This is done only after a thorough process to verify their autonomous consent. Trialists then test the relevant vaccine regimen for protection against infection, with suitable controls. To protect wider communities, participants remain in isolation while potentially infectious.

Dose escalation for a human challenge trial of an old SARS-CoV-2 variant has begun in the UK.[12,13] But the advent of new variants and the prospect of further mutations[1] make it urgent to conduct multiple human challenge trials – for multiple variants. *The UK and other governments should now start growing cultures for multiple variants* – typically a 3–4 months-long process. The fact that companies "are already working on developing boosters and new shots specifically designed to address the mutant strains"[12] in no way "reduces the need for human challenge trials,"[12] to reliably test such boosters and new shots in human subjects. While some of the emerging variants (not necessarily B.1.351) are more virulent than old ones,[14] risks in SARS-CoV-2 challenge trials for properly selected participants are so much lower[11] than commonly assumed that the added risk to participants would be well-justified even for these variants by the public health urgency – which that virulence similarly increases. And even if human challenge studies for some emerging variants remain too contentious right now, no human participants would be placed at risk by governments' growing culture to keep options open several months down the road. The UK government had approved the initial SARS-CoV-2 human challenge trials only after months of discussion and notwithstanding initial hesitation.

Human challenge trials are vital tools for rapidly achieving the requisite answers on alarming new viral variants. Now is the time to lay the groundwork for these crucial investigations.

Disclosure of potential conflicts of interest

NE and AC declare having no financial conflicts of interest. NE serves on the board of advisors for 1DaySooner, an organization of intended

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volunteers for SARS-CoV-2 challenge trials–an unpaid position. AC provides unpaid advice to Moderna and J&J on their vaccines. SP works with several companies in the development of SARS-CoV-2 vaccinations.

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