Do coronavirus vaccine challenge trials have a distinctive generalisability problem?

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ABSTRACT

Notwithstanding the success of conventional field trials for vaccines against COVID-19, human challenge trials (HCTs) that could obtain more information about these and about other vaccines and further strategies against it are about to start in the UK. One critique of COVID-19 HCTs is their distinct paucity of information on crucial population groups. For safety reasons, these HCTs will exclude candidate participants of advanced age or with comorbidities that worsen COVID-19, yet a vaccine should (perhaps especially) protect such populations. We turn this cliché on its head. The truth is that either an HCT or a field trial has intrinsic generalisability limitations, that an HCT can expedite protection of high-risk participants even without challenging them with the virus, and that an important route to obtaining results generalisable to high-risk groups under either strategy is facilitated by HCTs.

The British government has launched the dose escalation for a SARS-CoV-2 human challenge trial (HCT)[1], and a second British HCT has been approved.[2 i] In a SARS-CoV-2 HCT to investigate vaccines, a limited number of consenting study volunteers in an isolated medical facility would be randomised to receive either the vaccine candidate(s) or control (placebo or a competing vaccine). Sometime later, all would be deliberately exposed to SARS-CoV-2. Within weeks, large differences in infection rates, viraemia, nasal titre (a proxy of infectiousness to others) and other outcome measures between the arms would confirm efficacy, and lack of difference between them would confirm inefficacy.[3–5]

To minimise risk in HCTs, proponents recommend participant isolation, close monitoring and high-priority access to therapeutics and care during and after the trial.[1 3 4 6–8] But in all SARS-CoV-2 HCT plans, the key volunteer protection is recruiting only young adults who are free from major risk factors for severe COVID-19 following infection.[1 3 4 6–8] That exclusionary criterion alone is estimated to reduce the risk of fatality from the HCT (or the viral dose escalation study) to around 3 in 100 000,[9] which is about 100th the risk of perioperative death from live right liver lobe donation.[10–12] Since participation could and should be conditioned on high-quality informed consent, recruitment would be permissible, just like recruitment of live kidney donors.

SARS-CoV-2 HCTs could serve many purposes now. They could accelerate the assessment of both tested SARS-CoV-2 vaccines and of ones in development (which may be easier to store, deliver or purchase around the world) for their largely unknown impact on infection. HCTs could help prioritise between new vaccines for efficacy testing so as to minimise the number of large field trials, whose participants on placebo could now gain vaccine access outside the trial.[13–15] And tested vaccines' high efficacy means that HCTs would greatly simplify any head-to-head vaccine testing deemed necessary. HCTs could also provide other important information—about the correlates and duration of both vaccine-borne and natural immunity, about vaccine success against new strains or in unusual dosing regimens, and more. By readily revealing the correlates of vaccine protection,[16 17] HCTs would facilitate 'immune bridging' studies to assess vaccine impact in, for example, adolescents, currently conducted in the USA with less reliable correlates of vaccine protection (more on this below).

HCT supporters have addressed various critiques of SARS-CoV-2 vaccine HCTs. For example, some critics warned that HCTs are too dangerous or 'uncertain', but HCTs' already-acceptable[3 9 18] risks for consenting volunteers can be reduced further,[15 19] and the uncertainties are not in areas that should count on balance against conducting HCTs.[20] Critics also worried [21] that HCTs generate no information on product safety, but the idea was always that large, brief and benign safety testing would follow HCTs.[3] They decried alleged harm to the communities around trial sites, but participants would remain isolated while infectious,[3] and hospitalisations should be minimal.[9 22] They speculated that HCTs would harm public trust, but the only empirical data available suggest the opposite,[23] and so forth.

The current article answers only one critique, about the 'generalisability' of HCT efficacy findings, according to which, 'SARS-CoV-2 (HCTs) have limited generalisability, as they would need to be conducted with low-risk populations.'[7] As US medical research leaders put the matter, 'partial efficacy in young healthy adults does not predict similar effectiveness among older adults with major cofactors associated with COVID-19 disease.'[24] It was partly on that basis that they and others later decided to reject HCTs for US vaccine testing: 'A model of disease in healthy young volunteers may have questionable scientific validity when extrapolated to older or other

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at-risk populations that have disproportionate morbidity.'[25] A former regulator replied to one of us on TV, 'We know that different people at different ages experience immunity to this virus very differently. Twenty-year olds don't mount the same antibody response as a 65-year-old. They also don't have the same reaction to the virus—it's not as virulent in a 20-year-old as it is in a 75-year-old. So … can you extrapolate the data from a 20-year old to a 65 year old?'[26] A co-leader of the National Institutes of Health (NIH)'s Coronavirus Vaccine Prevention Network recently remarked, 'A 20-year-old in a challenge study isn't really going to give us the answer of will this vaccine keep an older person, someone with chronic kidney disease, from ending up in the hospital.'[27] Scientists[28 29] and ethicists[30] repeated the critique.

By contrast, in conventional phase III field trials (herein 'field trials'), once some participants receive the vaccine and others, the control, all return to their daily lives. Any exposures to the virus, which would help tell the protective effect of receiving the vaccine and not the control, take place only naturally. There are no intentional viral exposures.

Unlike HCTs, field trials leave participants' risk of viral exposure largely intact. Therefore, they can safely recruit high-risk populations. NIH's publicised push to recruit diverse populations to US vaccine field trials fuelled the generalisability critique of HCTs. A review of the various trial designs by NIH ethicists added that unlike HCTs, field trials 'are likely to include participants from known risk groups such as those who are older, have chronic illnesses or are at high occupational risk (eg, healthcare workers, meat-packing plant employees) who are expected to use and benefit from an eventual vaccine.'[31] Multiple news reports of the UK government announcement noted this critique of HCTs. Influential ethicists keep making these claims.[32 33] In-press releases on completed field trials and in regulator discussions on emergency authorisation, efficacy outcomes in various population groups featured prominently.

Let us disentangle three generalisability concerns in these quotations, then show why, far from uniquely raising generalisability concerns, HCTs (either complementary or alternative to field trials) fare no worse, and perhaps better than, standalone field trials on the matter. Literally taken, the generalisability critique of HCTs fails when the proffered alternative is field trials. But there is a small grain of truth to the critique, which we characterise.

THREE GENERALISABILITY CONCERNS

Distinguish three concerns that were expressed as matters of generalisability in some of the above quotes. All these concerns are about alleged paucity of information from an HCT about the vaccine effects on a certain population, but on *what* population?

1. *On people at high risk of exposure to the virus:* The NIH ethicists' review's call for recruiting people 'at high occupational risk (eg, healthcare workers, meat-packing plant employees)'[31] to efficacy trials seems to fall under this variant.
2. *On people at high risk of infection on any exposure:* The former FDA Chief warning, 'different people at different ages experience immunity to this virus very differently',[26] seems to fit here.
3. *On people at high risk of severe disease on any infection:* The co-leader of the coronavirus vaccine prevention Network's concern for 'someone with chronic kidney disease'[27] seems in this vein.

We now address each of these three concerns.

Generalisability to populations at high risk of exposure to the virus

There is simply nothing in HCTs that requires excluding people at high background risk of exposure. In fact, one of us proposed focusing HCT recruitment on such people, for example, on health workers or bartenders at high risk of future exposure, as a way to minimise the added risk from participating in the study.[19]

Generalisability to populations at high risk of infection on any exposure

It is true that a vaccine that prevents infection in young adults need not prevent it in older people. Americans 65 years and older are offered adjuvanted influenza vaccine, which contains an added ingredient that helps create a stronger immune response, because ordinary influenza vaccines were found to be insufficient for protecting that older population.[34] However, that was found after licensure, and the studies detecting insufficient protection in the older population were prompted by signals from the general population. The same goes for the pneumococcal polysaccharide vaccine, which works differently in different age groups.[35] We cannot think of a single vaccine where efficacy data from adequately powered studies of a subpopulation were required before broad approval. Careful follow-up post-approval and, if necessary, studies focusing on older users once the vaccine is widely available, could be used here, too, realising HCTs' speed and other advantages.

Surely, however, the thought may arise, it would be even better to avoid that compromise, and confirm vaccine efficacy in older patients prior to its first approval. This thought does not jeopardise some uses of HCTs, for example, to merely decide which field trials to conduct. But our fuller response is that both ongoing SARS-CoV-2 field trials and any realistic alternative fail to confirm efficacy in older populations, for two reasons. First, even when older people join a vaccine field trial, it is not powered to confirm efficacy in each subpopulation, just in the study population as a whole. Even limited oversampling of older people would not change this simple statistical fact. Of course, one could run an entire similarly sized study with just older adults but presumably that is not normally feasible (certainly not for all relevant high-risk groups—see below). SARS-CoV-2 vaccines' success rates in certain subpopulations was widely publicised. But any trial that discovered only that would be clearly underpowered. So these widely publicised findings would also seem to be somewhat underpowered and much less telling than they were made out to be.

Second, this complication is not easy to address, for any trial. Even a field trial that recruited an equal number of older and younger participants would in practice remain unlikely to reach sufficient case numbers for meaningful results about older participants. The reason is that high-risk patients will typically self-isolate zealously, preventing exposures sufficient for meaningful results on that subgroup in particular.

Thus, the lack of efficacy data on older patients is in no way unique to HCTs. Unfortunately, all feasible efficacy designs are likely to be, in practice to only slightly different degrees, inconclusive about the specific efficacy in older patients. While limited oversampling in field trials can be substantial enough to provide 'signals' about efficacy in older populations (and in other high-risk groups), lack of statistically valid proof remains a universal issue—and some of the large field trials that recently supported vaccine authorisation had only few cases in older participants. For similar reasons, it is only after these trials that we are discovering that

some of these vaccines may not always generate enough antibodies in those living with obesity.[36]

What can be done, then? Two things. First, a vaccine that an HCT has shown to block infections in young healthy people (and proven safe in a short follow-up study)[3] could be authorised for emergency use and rolled out, starting immediately to build herd immunity in young and healthy people, such as nursing home staff, or essential workers who cannot self-isolate. That would already provide indirect protection to higher risk groups, for example, nursing home residents.[37 38] Depending on the numbers, that may turn out to be the best way of protecting everyone, including the latter. Likewise, vaccinating children against seasonal influenza is an efficient way of protecting the old. In COVID-19, during initial vaccine rollout with exclusive approval in young and healthy populations, field trials that permit the direct protection of high-risk populations could be completed. That would be a net gain for older patients. While awaiting direct protection they could already start receiving indirect protection.

Second, as even opponents of HCTs concede, 'the experimental control provided by [an HCT] has distinct advantages over field studies for discerning correlates of protection, given the precise timing of infection and the ability to measure immune responses at early and predetermined time points.'[25] A correlate of protection is 'an immune response that is responsible for and statistically interrelated with protection' against a pathogen, for example, an antibody uniquely present in those participants in whom the vaccine worked.[39 40] Discerning the correlates of vaccine protection (which was attempted in field trials, but could be done more easily and thus probably more accurately in HCTs) would enable short and relatively safe immune bridging studies in which high-risk participants receive the vaccine (with no viral exposure) and investigators examine whether it induces in them these precise correlates at sufficient rates, a strong proxy of vaccine efficacy in them.[4] If older adults, the obese or still other high-risk populations 'mount a very different antibody response than healthy young adults', the bridging study would be able to discover that rapidly. Indeed, neither trial design covers all population groups, and in the USA, trials to assess vaccine impacts on children and adolescents are currently planned, recruiting or active. Some of those trials use the emergence of correlates of protection as endpoints (a standard placebo-controlled efficacy trial would be hard to justify now) and would have been more reliable if, thanks to HCTs, those correlates had been discerned earlier on.

Thus, possibly the surest path to credible results on SARS-CoV-2 vaccine effects in older people and on other populations barred from HCTs passes through identifying the correlates of vaccine protection, at which HCTs are better than field trials.

Generalisability to populations at high risk of severe disease on infection

The concern for populations with concomitant conditions that make them likelier to develop severe disease if infected (like kidney disease, diabetes, cardiovascular issues and, again, advanced age) is easier to answer. Everything just said in response to the concern about older people's susceptibility to infection applies to all these populations, and more. So first, kidney patients, and other people with relevant comorbidities, are likely to self-isolate more zealously than low-risk people, and none of the current field trial is powered to say anything specific about them. They would be protected indirectly by a vaccine approved in other people who otherwise might infect them. And if evidence on the effects in those with related comorbidities is required even before initial marketing, the surest way to gather that evidence goes through identifying correlates of vaccine protection, which is best done in HCTs.

In fact, some of these corrective measures would be unnecessary in people who have kidney disease or cardiovascular issues, for example. Unlike advanced age and, as a proportion to vaccine dosage, potentially obesity,[36] these particular comorbidities (many of which correlate with advanced age) do not as such clearly spark 'a very different antibody response' than that of healthy young adults. In kidney patients, for example, doubt about the effects of vaccines on infection, shedding and the likely accomplishment of herd immunity hardly arises—only about using the vaccine to prevent progression to severe disease. That brings us to the next point, the grain of truth in the generalisability critique.

The grain of truth in the generalisability critique

The research leaders quoted above add that an HCT 'may not recapitulate the pulmonary pathophysiology seen in some patients.'[24] This separate concern, about how much the vaccine prevents disease progression, is not about generalisability to this or to that patient population, but about a certain outcome of interest. The concern is that HCTs would be uninformative on whether a vaccine that may protect against infection also prevents disease and, especially, severe disease. It would only reveal what the vaccine does to prevent infection, shedding, and hence progress towards herd immunity. Indeed, the concern may arise that an HCT that shows no effect on infection and shedding might erroneously weed out a vaccine that would have greatly reduced severity in those infected.

This is indeed an important downside of HCTs compared with field trials, but five rejoinders must be made. First, SARS-CoV-2 vaccine field trials' primary endpoints concerned only mild disease and they were not powered to confirm impact on severe cases.[41] Second, when HCTs show that a vaccine prevents nasopharyngeal replication, they—importantly—reveal also potential protection of the lungs. Third, a key role for a vaccine is to reduce infections, faciliate herd immunity and, with other containment measures, end the pandemic. Assessing vaccines in that crucial role is easier with HCTs than in field trials. Fourth, HCTs can complement field trials, with the former assessing vaccine impact on rates of infection and of likely infectiousness (as well as on other outcomes) and the latter assessing impact on rates of disease and severe disease. Fifth, the specific division of labour between HCTs and field trials could assign HCTs a merely 'confirmatory' function: when efficacy in reducing infection is confirmed in an HCT, that would suffice for vaccine approval (so long as there are also encouraging findings from large and credible yet relatively brief and benign follow-up safety and immune bridging studies that establish effects in diverse populations); but HCT's failure to show effect would not lead to disapproval, just to dependence on the results of a field trial—and the latter may yet show that the vaccine reduces disease progression.

CONCLUSION

Efficacy data obtained by HCTs are not directly generalisable to older populations, but in practice, field trials also have partial generalisation problems. The most protection would come to high-risk populations from use of both designs, so that during completion of a field trial, they can already start benefiting from indirect protection, thanks to a prior HCT. Even if no field trial is performed, or direct data on some groups is lacking even after they are performed, immune bridging studies could give us that information. And the best way to discern the correlates of vaccine protection necessary for immune bridging studies is an HCT.

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