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Abstract: A vaccine trial with a standard challenge design can be faster than standard phase III once it starts, but it requires a long prior process, in part, to grow and standardize challenge virus in the laboratory. This detracts somewhat from its overall promise for accelerated efficacy testing of SARS-CoV-2 vaccine candidates, and from the ability of developing countries and small companies to conduct it. We describe a challenge design that avoids this part of the long prior process. The new design has additional ethical, scientific, and feasibility strengths, compared to standard challenge designs and to standard phase III designs, and should be considered for future vaccine trials.

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Human challenge trials have been proposed as part or full replacement for standard phase III trials, for faster efficacy testing of SARS-Cov-2 vaccine candidates (Eyal, Lipsitch, and Smith 2020, WHO Working Group for Guidance on Human Challenge Studies in COVID-19 2020, WHO 2020b). Oxford University is now planning to conduct human challenge trials before the end of the year, presumably to ensure enough cases to prove efficacy, and to explore other scientific questions (Devlin 2020). Johnson & Johnson and NIAID are reportedly considering such trials as well (Reuters 2020). That may inspire challenge studies for second-generation vaccine testing, say, by developing nations without access to first-generation vaccines. Nearly all dedicated peer-reviewed articles conclude that they could be ethical (Eyal, Lipsitch, and Smith 2020, Plotkin and Caplan 2020, Richards 2020, Kolber 2020, Jamrozik and Selgelid 2020a).

Performed in a standard way, challenge trials require advance preparation that may reduce some of their inherent advantage: growing virus in Good Manufacturing Practice (GMP) conditions in specialized laboratories, then titrating the viral dose for safe challenge in humans necessitates a potentially lengthy and complex process (Cohen 2020, Deming et al. 2020, WHO 2020b). These advance preparations should therefore take place now, in case we later need to rely on standard challenge trials (Shah et al. 2020, Deming et al. 2020).

At the same time, there is merit in considering the scientific, logistical, and safety properties of alternative challenge designs that could circumvent some of this preliminary work. This article describes a trial design that does so. It could be seen as a cross between standard challenge trials and standard phase III trials (herein, "P3"). What we shall call a Challenge with a Natural strain *via* Human Interaction ("CNH") has scientific and logistical advantages over both P3 and a conventional Challenge trial with a Defined strain with Intranasal inoculation ("CDI").

(a) Three designs for vaccine efficacy testing

This section summarizes the characteristics of the design alternatives we consider. They are characterized in Table 1.

Table 1: Viral exposure strain and route for most participants of the respective vaccine efficacy designs discussed in this article.

	Unintended natural exposure	**Challenge**	
		Intranasal inoculation	**Human interaction**
Defined (and potentially GMP) strain	/	A standard challenge, that is, one with exposure to a defined strain through intranasal virus inoculation (**CDI**).	/
Natural strain	Standard randomized controlled trials (**P3**)	/	Challenge with exposure through human interaction to a natural strain (**CNH**)

1. Standard phase III (P3)

In standard phase III (individually-randomized controlled trials, or "P3") trial, participants (who may or may not be restricted to persons seronegative for SARS-CoV-2)(HHS, FDA, and CBER 2020, Lipsitch, Kahn, and Mina 2020) are randomized to receive either the vaccine being investigated or a placebo. Several months later, if and when enough of them became infected, differences in clinical outcomes and infection rates between the two arms indicate vaccine efficacy. The degree of exposure to the virus in both arms depends on personal behaviors and the incidence of SARS-CoV-2 infection in the particular study site throughout the trial and hence, to some degree, the failure of any public health interventions to reduce community transmissions.

2. Standard human challenge with a defined strain through purified virus inoculation strain (CDI)

In standard challenge trials (CDI), artificial exposure to a standardized dose of a laboratory-grown viral strain is used: young and healthy volunteers, perhaps restricted to individuals who are SARS-CoV-2 seronegative, placed into isolation, are randomized to receive either the vaccine being investigated or a placebo. After ample time for immune response, all are artificially exposed, probably *via* intranasal inoculation to a standardized dose of a virus, prepared under GMP. Differences in infection rates, clinical signs and symptoms, viral loads and any other proxies of likely infectiousness between the two arms indicate vaccine efficacy or effectiveness. Participants remain in isolation for long enough to prevent secondary transmission.

3. Challenge with natural exposure to a human infection (CNH)

In what we shall call a "challenge with a natural strain through human interaction" (CNH), "donors" are naturally-infected community members with high viral loads. To find donors shortly after they are infected, which is when viral loads are highest, researchers can work with providers of viral PCR testing. Alternatively, candidate donors can be tested regularly when they report any fever or cough, to confirm the presence of SARS-CoV-2 and absence of other respiratory viruses. Included donors then meet and interact under close-contact conditions with "recipients"— study participants who are young, healthy, and have undergone recent serologic testing (possibly restricted to those who test seronegative), who will have been isolated and then receive either the vaccine or placebo, randomly allocated. To facilitate natural exposure during interaction, windows are kept shut and participants engage in active conversation and/or another close-contact activity. To address the likely variety both in donors' infectiousness, e.g. in their viral loads and droplet production, and in recipients' susceptibility to infection, as well as remaining uncertainties about SARS-CoV-2's readiest infection routes, it is useful to expose each recipient to multiple donors through multiple activities, e.g. in groups consisting of multiple donors and multiple recipients engaging in multiple activities. Differences in clinical illness, infection rates, and/or viral loads between the active and placebo recipients

then indicate vaccine efficacy. After the “exposure event”, participants remain in isolation to prevent secondary transmission.

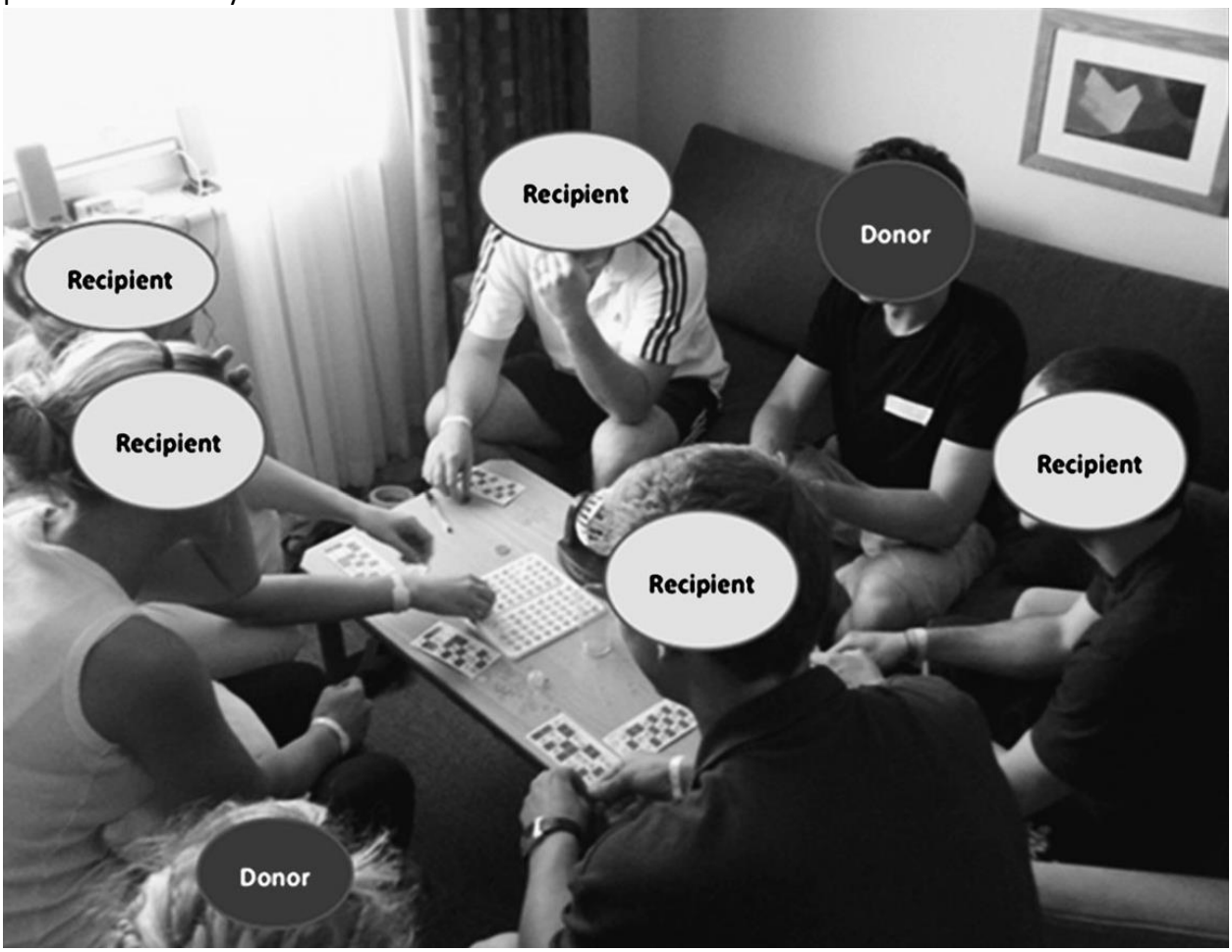

Figure 1: A flu natural exposure challenge (Killingley et al. 2012).

Like all challenges (WHO 2020b), CNH requires a preliminary experiment involving titrated viral dose escalation. In a CNH, what is titrated is the duration of exposure (of a smaller number of unvaccinated volunteers) to highly infectious persons. That establishes a notional minimum period of exposure consistent with the propensity to transmit infection without observed severe disease in the recipients. To address the variety between donors and uncertainty about infection routes, dose escalation is also done with a panel of donors engaged in the same multiple activities as the actual challenge.

We next consider which of the three designs best fulfills each of a variety of scientific, feasibility-, and safety desiderata. Table 2 lists the designs’ respective strengths.

Table 2: Three efficacy testing designs for Coronavirus vaccines, and their respective strengths. More "+" signs ordinally designate presumed greater magnitude.

		Standard Phase III (P3)	A standard challenge—with artificial exposure to a defined strain through purified virus intranasal inoculation (CDI).	Challenge with natural exposure to a human strain (CNH)
Scientific desiderata (discussed in section b)				
i.	**"Natural" exposure route and dose?**	Yes	No	Yes
ii.	**Exposure titrated for likelier infection and mild disease?**	No	Yes	Yes
iii.	**Generalizable to subgroups at high risk from infection?**	Yes (but underpowered to detect that, and subgroups at risk may self-isolate)	No	No
iv.	**Informative on disease severity outcomes?**	Yes	No	No
v.	**Informative on infection/shedding?**	Somewhat	Yes	Yes
vi.	**Standardized exposure between trial participants?**	No	Yes	Partial; near-complete under a possible variant
vii.	**Standardized exposure between trials?**	No	Yes	No
viii.	**Summary scientific profile**	+	+	+
Feasibility (discussed in section c)				
i.	**Fast to reach the scientific endpoint, if the trial goes well?**	+ (many months in the field)	++ (GMP+dose escalation+1 short stage)	+++ (short dose escalation+1 short stage)
ii.	**Fast to identify severe impediments to trial success in reaching an endpoint?**	+ (after many months)	++ (after GMP+dose escalation)	+++ (after dose escalation)
iii.	**Resource-efficient?**	+	+	++
iv.	**Summary feasibility profile**	+	++	++++
Safety (discussed in section d)				
i.	**Participants' risk of infection is equal to or lower than if they did not participate?**	Possibly: so long as participation does not induce risk compensation	No	No
ii.	**A comparatively safe route of exposure?**	No	Possibly	No
iii.	**Participants' risk of vaccine toxicity and disease enhancement is equal to or lower than if they did not participate?**	No	No	No
iv.	**Any adverse event occurs in medical facility?**	No	Yes	Yes
v.	**Small number of participants reduces potential for of adverse events?**	No	Yes	Yes
vi.	**Controlled exposure?**	No	Yes	No
vii.	**Participants' risk of other infections is same as if they did not participate?**	Yes	Yes	No
viii.	**Study likely to give participants better COVID care than alternatively available?**	++	+++	+++
ix.	**Study reduces SARS-CoV-2 risk for staff, contacts, and area residents?**	Possibly	Yes	Yes
x.	**Summary safety profile**	+	+	+

Scientific desiderata

i. An exposure route and dose that mimic target use

In both P3 and CNH, the strain, dose, and exposure route (inhalation and perhaps some contact), are "natural," as in ordinary life. This may initially sound less scientific than the unique intranasal inoculation of lab-grown defined virus in CDI. But it is an advantage, because experimental exposure that resembles the exposures that vaccines will target arguably reveals more about how protective they would be in actual usage. This is an important advantage of P3 and CNH over CDI.

ii. Titration for likelier infection and mild disease

P3 does not require dose escalation. By contrast, CDI and CNH, which deliberately expose participants to virus, must titrate that exposure to likelier infection (as well as safety), either by varying the quantity of culture inoculated (CDI) or by varying the exposure length (CNH). In CNH, the dose escalation process can be less reliable than in CDI, which uses the same strain in the same quantity and same exposure route for all recipients.

iii. Generalizability to subgroups at high risk from infection

A common critique of challenge designs (applicable both to CDI and to CNH) is that, for trial safety reasons, they must exclusively recruit healthy young people (WHO Working Group for Guidance on Human Challenge Studies in COVID-19 2020, Eyal, Lipsitch, and Smith 2020), yet target vaccine users may include the old and those with risk factors for severe COVID (Corey et al. 2020, Deming et al. 2020).

This comparative advantage is exaggerated given that even a P3 trial that includes high-risk participants is likely to be underpowered to detect variation between population subgroups, and in a P3, high-risk populations (if included at all) are especially likely to self-isolate zealously.

Inasmuch as challenge designs can be used to establish correlates of protection (which they can do better than P3 can), immune responses to the vaccine in higher-risk groups may then be used to infer likely protection (or not) in these groups. Whatever approach is used for the initial trials, observational studies will probably be needed following widespread use of a promising vaccine to estimate the degree of protection for higher-risk subgroups, as is done routinely for influenza vaccines (Darvishian et al. 2014).

iv. Information on disease severity outcomes

Both by excluding participants at high risk for severe COVID disease if infected (as all proper challenge designs do)(WHO Working Group for Guidance on Human Challenge Studies in COVID-19 2020) and by treating infected participants with antiviral medications at a predesignated timepoint (as some variants now being considered would do), challenge designs

would not produce information on the vaccine's effect on severity. While protective of participants, this is an important scientific disadvantage compared to P3. One of the FDA's endpoints for vaccine trial is reduction in severe disease (HHS, FDA, and CBER 2020), and some of the initial vaccine candidates may be likelier to prevent severe disease than to affect infection and infectiousness (Branswell 2020).

v. Information on infection/shedding

It may be even more important to learn from trials the extent to which a vaccine prevents infection and/or reduces infectiousness among those vaccinated persons who do become infected. Only by doing so can a vaccine contribute to herd immunity and to indirect protection of those who do not receive it or in whom it is less effective. If a vaccine affects neither of these outcomes, it cannot build herd immunity and does not get us closer to a sustainable end to the pandemic. Confirming impact on infection and on infectiousness also informs the number of vaccine doses to purchase (fewer are needed to protect a population if herd immunity is achievable) and for vaccine rationing decisions (if a vaccine reduces infection risk or infectiousness, then it may be better deployed to those who transmit most, while a vaccine that only reduces illness in all will be better deployed to those at high risk of severe outcomes). Accordingly, infection remains a strongly recommended endpoint for the FDA (HHS, FDA, and CBER 2020).

A P3 may monitor participants for infection, including subclinical infection, perhaps by periodic viral testing and/or end-of study serologic testing for a nonvaccine antigen (Lipsitch, Kahn, and Mina 2020, HHS, FDA, and CBER 2020, Kahn et al. 2019). However, the scale of a P3 places limits on the frequency of such testing, while either challenge design would have constant access to participants for frequent viral testing, one or more times per day. Challenge trials could therefore provide much more detailed and quantitative information about the effect of a vaccine on the probability of infection and viral shedding if infected, a likely predictor of infectiousness.

vi. Standardization between trial participants

In CDI, the strain and dose of virus is fully standardized. This will reduce variability in outcome and increase statistical power, compared to either P3 or CNH, in which strain and dose are not fully controlled. But there are some differences between the latter two as well. Exposure in P3 is not standardized at all. In CNH there is partial standardization. First, CNH can be planned so that multiple recipients share strain, approximate dose, and presumed route of exposure—by interacting in the exact same way and duration with the same donor(s).

It is possible to construct a variant of CNH that exposes all recipients to a single viral strain. In that variant, trialists first identify in the community a *single donor*, with confirmed high viral load. He or she then artificially infects several *secondary donors* through nasal intranasal inoculation of nasal mucus; long enough afterwards for the secondary donors' infection to reach acute phase (verified by qPCR with rapid turnaround), each of the secondary

donors spends time in close quarters with a small group of vaccinated and placebo recipients. This variant resembles CNH in that the source of the strain is not laboratory-grown and is not defined or GMP, and in that the exposure of the recipients, who comprise most participants, is natural. But this variant has the advantage that all recipients are exposed to the same strain, making their results more mutually-comparable. However, the similarity of the strain currently seems unimportant for infection and other outcomes. On balance, therefore the speed advantages of other CNH seems more important.

In short, standardization between trial participants is a substantial advantage of CDI over P3, and only a modest advantage over CNH.

vii. Standardization between trials

Standardization of strain and dosage can also facilitate comparison of different vaccines, across trials (or in trials where different active arms have different vaccines). In that respect, CDI has a limited advantage over CNH and over P3.

viii. Summary on scientific strengths

CNH and P3 are scientifically superior to CDI in relying on a "natural" strain, dose, and exposure route. CNH is scientifically slightly superior to P3 and slightly inferior to CDI for having partial standardization between participants and between trials, but these differences matter less. In still other ways, all three alternatives are similar. Overall, CNH may have a slight scientific advantage over the two alternatives.

Feasibility

i. Speed to reaching the scientific endpoint, if the trial goes well

Overall, both CDI and CNH are likely to be faster than confirming vaccine efficacy through P3. Instead of waiting many months for natural exposure that may or may not come, exposure in challenge trials happens immediately, and efficacy outcomes emerge within weeks. Moreover, CNH removes the need to grow virus under GMP. Still, all challenge designs require conversion of isolation facilities to the purpose and a dose escalation of some sort. Once those are complete, because challenge designs are otherwise so much faster than standard phase III, the fastest challenge, namely, CNH, is probably the fastest approach to evaluate efficacy if all goes well.

ii. Speed to identifying severe impediments to trial success in reaching an endpoint

In the case that the trial turns out to be infeasible, potentially far more time is lost in a P3 than in a CDI or in a CNH. In a P3, only several months into the trial can it become clear, in ways that were unpredictable when the trial began, that incidence is declining at the trial site, precluding

meaningful results. This has in fact happened after several months of investment in a SARS-CoV-2 vaccine in the UK (Blakely and Philp 2020).

Acute barriers can surface in challenge designs as well, but they would surface earlier. During dose escalation for either CDI or CNH, it may already become clear that no safe dose is likely to infect enough controls for efficient trial conduct. But that discovery comes only a few weeks after process inception, enabling early abortion of the project, and before efficiency testing is even launched.

iii. Resource efficiency

P3 trials are notoriously expensive. With 26 vaccine candidates in clinical investigation (WHO 2020a), and global need for multiple vaccines, there is already competition for participants in trials (Hopkins and Loftus 2020). Trials may turn out to be barely manageable even after some vaccines are proven and some drop out of consideration. Converting isolation centers and hosting volunteers for many weeks is also expensive (Table 2 assumes for simplicity, equally expensive). But there is a difference between different challenge designs. Growing virus in GMP lab conditions can only be done in some developed nations. CNH, which does not require lab-produced virus, is more feasible for developing nations in direct need of a vaccine (Jamrozik and Selgelid 2020b) and for small vaccine developers.

iv. Summary on feasibility

Whether a successful trial is possible or not, answers will come faster with CNH than with CDI, which is, in turn, faster than P3 in situations where no trial site promises to remain high-incidence for the duration of efficacy testing. Given the urgency of responding to the pandemic, this is the most crucial advantage of CNH. In addition, CNH is also more realistic for developing nations and small developers than CDI.

Safety

i. Participants' risk of SARS-CoV-2 infection

Challenge designs introduce very high risk of infection and one that exceeds participants' baseline risk, namely the risk that they would be at had they not participated. P3 is nearly free from that added risk (in HIV prevention studies it was hypothesized that participants, believing they may be protected, would behave less safely (Eaton and Kalichman 2007), but that was not observed) (Painter et al. 2017, Gust et al. 2016).

The increased risk of undergoing deliberate infection in challenge trials is an important safety advantage of P3 over challenge designs. But if immunity to COVID-19 disease after natural infection lasts years (even if immunity to for SARS-Cov-2 infection may be shorter-lived), it can be mitigated by selecting challenge participants from geographical areas or from professions

where baseline risk of infection is considered likely to become or remain high anyhow (Eyal, Lipsitch, and Smith 2020, Eyal 2020).

ii. Safety of the route of exposure

It has been proposed that challenge studies involving intranasal inoculation (like CDI) are somewhat safer than ones (like CNH) involving natural routes of exposure, because inhalation is thought more liable to generate severe disease (Killingley et al. 2012). While there are also reasons to question the assumption (Killingley et al. 2012), and while there is far more experience with the consequences of natural SARS-CoV-2 exposure than with intranasal inoculation, we suspect that controlled intranasal exposure is somewhat safer than uncontrolled natural exposure, providing a possible safety advantage for CNH over CDI.

iii. Risk to each participant of vaccine toxicity and disease enhancement

All these trials present new risks, both from vaccine toxicity (which earlier clinical testing does not fully rule out due to small numbers)(Lipsitch and Eyal 2017) and from enhanced disease severity from SARS-CoV-2 infection following vaccination (which earlier clinical testing, in individuals unexposed to the virus, does not rule out at all) (Corey et al. 2020). These risks remain unknown. Per participant, the probability of experiencing an adverse event due to the vaccine alone (not related to the challenge) is equal in all designs. Per participant, the probability of enhanced disease, if it occurs at all, is greater in a challenge trial than in P3 because the infection probability per participant is higher, by design.

iv. Participants' location in case of an adverse event

When any medical event, including adverse events resulting from infection, from vaccine toxicity, or from disease enhancement, occur to a participant in a challenge trial, they occur in a controlled medical environment, with early detection and the potential for immediate medical intervention. In contrast, in P3, they usually occur outside such an environment (unless they coincide with a study visit). So while P3 introduces less risk of infection, challenge designs may provide better prospects to those who experience resulting severe disease.

v. Expected total number of adverse events

If overall risk for adverse events from vaccination (including disease enhancement) is similar or only somewhat lower in P3 per participant, it remains higher in P3 overall, for three reasons. First, the number of participants in a challenge trial who receive the vaccine would typically be smaller than the one in a P3 by a factor of at least 100. Second, because a P3 will typically have a lower proportion of all participants experiencing the outcome than a challenge trial, in order to achieve equivalent power, a P3 would need more individuals who get infected in the control arm than would a challenge trial . Therefore, by randomization, the P3 would also have more individuals in the vaccinated arm who receive exposure sufficient to infect a control participant.

Consequently, if the vaccine enhances disease severity in a proportion of those vaccinated persons who are exposed to the virus (Corey et al. 2020), it follows that a P3 should have more participants experiencing enhanced disease than a challenge trial does. Third, but for severity enhancement, severe COVID disease is expected to remain exquisitely rare in a challenge, given the selection criteria (Jamrozik and Selgelid 2020a, WHO Working Group for Guidance on Human Challenge Studies in COVID-19 2020). Therefore, a common worry, that severe adverse events could undermine public trust in COVID research or response (Dawson, Earl, and Livezey 2020), is likelier to materialize under P3 than under either challenge trial. While CDI is likelier to involve somewhat fewer participants than CNH, differences in numbers of participants are less substantial than the difference between either and P3.

vi. Risk of other infections for participants

CNH risks infecting recipients (and in some cases, donors) with other infections, since there is no purification step for the virus. Neither of the other designs creates this extra risk. We believe however that this net risk of other infections is a modest safety consideration, since it is just the risk of normal human interaction.

vii. Study effect on SARS-CoV-2 risk for study staff and area residents not participating in the study

A P3 must take place in a concurrently-high transmission area. It is likely to affect local response, either negatively (by giving its many trial participants and cases priority access to care at the expense of local patients and by encouraging risk behavior) or positively (by infusing the area with high-quality resources and by inoculating many residents with a vaccine that may turn out to be efficacious).

Challenge trials of either type need not take place in concurrently-high transmission areas (for ethical reasons, we recommended recruiting from areas where transmissions are likely to be high at *some* points in the future) (Eyal 2020). Worry may arise that in challenge trials, "even with strict facility engineering controls, stringent discharge criteria, and experienced personnel, there is a potential risk of community spread of the challenge virus" (Deming et al. 2020). However, SARS-Cov-2 already circulates in communities, keeping any added *relative* risk very small. Indeed, if either infection or the vaccine instigate even partial immunity, contacts' risk of getting infected is likelier to *decline* on balance.

Overall, each of the trial types may reduce risk to "study bystanders" (Eyal 2019), but the relative magnitudes are uncertain. Dramatic positive or negative effects on struggling communities are likelier in P3, suggesting that they (in that respect, more than challenge designs, which are assumed to require such engagement)(Deming et al. 2020, Shah et al. 2020) would benefit from local community engagement.

viii. Quality of care available to study participants

Any type of challenge study recruits far fewer participants than P3, and, for SARS-CoV-2, would keep all in a controlled environment. Providing excellent COVID care (e.g. guaranteed access to the most effective treatments) is much easier than in a P3. That matters more to participants from areas with likely future surges in demand for services (Eyal, Lipsitch, and Smith 2020, Eyal 2020).

ix. Summary on safety

While P3 has an important strength in adding nearly no risk of infection compared to nonparticipation in the trial, challenge trials' added infection risk can be minimized by selecting individuals with low risk of complications and expected high future risk of infection, as well as by providing excellent COVID care (Eyal, Lipsitch, and Smith 2020, WHO Working Group for Guidance on Human Challenge Studies in COVID-19 2020, Shah et al. 2020). All these designs add risks from vaccine toxicity and from disease severity enhancement, which are more manageable in challenges that take place in medical environments with frequent monitoring than in P3. intranasal inoculation may be somewhat safer than natural inhalation, but the difference is at this point a matter of speculation for SARS-CoV-2.

Challenges have an important safety edge over P3 in having fewer participants. Overall, therefore, P3 creates less risk from trial participation per participant, but challenge designs may be less risky if one adds up the risks of participation for all participants. The balance depends on the risk of adverse events (toxicity plus enhancement) we consider possible in the trial. If we knew in advance that the risk of such adverse events were negligible *a priori*, P3 would be safer in total. On the other hand, a modest degree of concern about severe adverse events of any kind could tip the balance of cumulative risk in favor of challenge designs. For a vaccine with a perfect safety record in prior phases of testing, this balance remains uncertain, as prior phases do not evaluate enhancement. Onerous safety demands were applied to challenge studies and thought to favor P3, e.g. "A single death or severe illness in an otherwise healthy volunteer would be unconscionable and would halt progress" (Deming et al. 2020); given current uncertainty about the risk of the various types of adverse event, consistent application of such onerous demands would have ruled out P3 as well. That reveals the excessive and implausible nature of these demands, which affected recent US policy on challenge trials.

Conclusion

These considerations argue that, for testing the efficacy of SARS-Cov-2 vaccine candidates, a CNH design is worth considering alongside or instead of a standard challenge design (CDI) and a Phase III (P3) design.

The strengths of these designs are complementary, with the P3 having advantages in understanding disease progression, for example, and challenge designs having advantages of

speed and feasibility (especially CNH) and understanding effects on infection and shedding. CNH shares with P3 the advantage of mimicking the target route of infection.

Running more than one type of trial simultaneously would also hedge our bets and maximize the chance that at least one reaches meaningful results in timely fashion (Gerhard, Strom, and Eyal In preparation). Even if multiple trials are conducted, the momentous stakes in finding a gamechanger countermeasure against this pandemic may keep the balance of personal risks to societal benefits low enough for each trial.

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