Strengthening and accelerating SARS-CoV-2 vaccine safety surveillance through registered pre-approval rollout after challenge tests

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Running head: Strengthening SARS-CoV-2 vaccine safety surveillance following challenge trials

In human challenge trials for SARS-CoV-2 vaccines, a few dozen altruistic young and healthy participants at low risk of severe COVID would be deliberately exposed to the virus in an isolated and controlled medical environment, then given an experimental vaccine or control to assess vaccine efficacy (1-3). The case for challenge trials in the phase III testing of the initial vaccines was primarily that they could reach a statistically meaningful number of cases for efficacy evaluation much faster than a field trial could—albeit without the safety data associated with a much larger field trial (1-3).

With efficacious vaccines now in distribution, however, the case for challenge trials, such as the ones that recently began in the UK (4), takes on a new ethical angle (5). Among other things, challenge trials could now serve for testing, in one population type, new candidate vaccines (e.g., those with suspected greater safety, easier storage and delivery, or sheer availability and affordability around the world) or new vaccine regimens (e.g., half-dose, spaced out vaccinations, a prior vaccine modified to provide better protection against mutated variants of the virus). By contrast, a controlled field trial would require many months of delay, with tens of thousands of participants in areas of high community spread to forgo an approved, already proven vaccine to which they may have access if they do not participate in the trial (6); the ethical and public health implications, and the difficulty recruiting, may be intolerable (5). These complications are much smaller in a challenge trial on fewer than a hundredth that number of participants, who remain isolated while infectious. Before any of the currently available Covid-19 vaccines had been authorized, nearly 40,000 people globally had already expressed willingness to participate in challenge trials (7), and more than 40,000 actually registered on the UK challenge trial website (8).

By and large, however, the present commentary sets aside the general case for challenge trials. It focuses primarily on the best way to evaluate product safety *after a challenge trial substitutes for a field trial to prove efficacy*, where such safety evaluation is needed (an exception may be testing lower or delayed dosing for authorized products). Safety surveillance in this context refers to assessment of an experimental product to rule out any serious and common toxicity; to quantify the frequencies of other clear side effects; and to identify signals of potential risks that may warrant subsequent hypothesis refinement, testing, or simply continued specific surveillance in phase IV. Due to their small sample sizes, challenge trials would provide inherently limited safety data, even combined with earlier safety information (9, 10). To provide sufficient assurance of vaccine safety to support regulatory approvals, challenge trial supporters have so far proposed brief pre-approval safety evaluation on a few thousand volunteers actively monitored for adverse outcomes, including ones from key populations underrepresented in the challenge (11). But even that proposal would leave substantial uncertainty about vaccine safety. For example, finding no occurrence of a given adverse event among 10,000 vaccinated participants of the safety follow-up to a challenge trial only allows 95% confidence that the true rate of that risk is less than one in 3,333 vaccine recipients. Yet serious vaccine-related safety issues can have substantially lower incidence rates, e.g., 1-6 in 100,000 for intussusception after rotavirus vaccine (12), and 1-2 in 1 million for Guillain-Barré syndrome after swine flu vaccination (13). Recent allergy/anaphylaxis (14) and thrombotic thrombocytopenia (15) safety events among vaccinees were of the same scale. We thus propose “registered pre-approval distribution” (RPAD), to test vaccine safety following a challenge trial. Our concept for a safety study consisting of very close monitoring of outcomes in the initial registered users, still prior to full regulatory approval, offers faster and more complete assurance of a candidate vaccine’s safety than either the proposal just mentioned for a safety evaluation in a few thousand subjects after a challenge study or a conventional phase III field study. It is also compatible with continued safety monitoring post-licensure (phase IV) (16-18).

Note that the manuscript does not attempt to provide a complete description of approaches to studying vaccine safety, especially after conventional field trials. Rather, we are focused on vaccine safety studies, when supplemental to challenge trials.

Safety testing for SARS-CoV-2 vaccine candidates following exclusive challenge trials

We propose that vaccine candidates whose efficacy is proven in challenge trials be designated "conditionally approved" (19), and, under emergency use authorization like the US FDA's, made available immediately, but only to patients who give informed consent to receiving an experimental product (20) and to providing rigorous evidence on safety (19). We propose that perhaps the first million recipients would comprise strictly individuals who consent to regular follow-up emails, phone messages, and calls, plus—in case of relevant outpatient clinic visits, hospitalizations, or death—researcher access to their medical records. RPAD participants would thereby gain earlier access to an efficacious vaccine than they might otherwise have. Researchers would gain robust and quantitative pre-marketing evidence for safety outcomes such as serious acute toxicity, enhanced COVID-19 severity (21, 22), and rare events, such as Guillain-Barré syndrome and unusual blood clotting. An RPAD could also provide more- and earlier evidence on the safety of the candidate vaccine in different sub-populations, e.g., the elderly, pregnant, and those with relevant illnesses and medications (5).

As short-term RPAD outcomes are analyzed, detailed recommendations on who should and should not undergo vaccination with the product could be developed, and vaccine approval (or rejection) could be finalized. Longer-term safety outcomes, as they accrue, could be quantified and compared to external population data. This approach could be readily expanded to include comparisons of multiple vaccine candidates. In one form, RPAD might include a concurrent control arm. Now that vaccines are in distribution, placebo control would be seen as unethical because it too would have to deny vaccine access to a large population otherwise eligible for an effective vaccine. However, an active control remains an option. Some systems (perhaps large HMOs or large national insurers with population-wide information like the NHS) may be able to support that particular RPAD design, with a concurrent control using a pre-existing approved vaccine (or regimen) having substantial scientific advantages over an uncontrolled RPAD. Alternatively, one may seek to supplement these with *ad hoc* data collection, to achieve the desired sample sizes faster, with more heterogeneity in practice compared to some health systems. The main complications we envisage here are the even larger size of a non-inferiority design, which would translate into a longer trial, and hence, worse difficulties recruiting the enormous cohort necessary.

In either concurrently-controlled or uncontrolled form, the novel RPAD approach would cut precious time to vaccine availability—certainly for the large cohort in the RPAD protocol and, compared to reliance on field trials, for the population at large, at least compared to the options described above. An RPAD would provide unprecedented data on rare vaccine complications and subgroups. Indeed, RPAD's extensive safety data from a rigorous follow-up of a cohort of 1 million would provide acutely needed assurance of vaccine safety to the vaccine hesitant, and thereby help achieve wider vaccine coverage.

The RPAD approach overcomes four objections.

Rolling out after insufficient testing?

Releasing into 1 million people a vaccine that will have been tested only in a few dozen challenge participants carries some risk of previously undetected toxicity or enhanced COVID-19. This is of course less of a problem in studying a new regimen for an existing vaccine, or a modified vaccine for a variant. Regardless, the invitation treats those million people fairly, inasmuch as RPAD would provide them earlier protection. In high-transmission areas of a lethal pandemic, the promise of early access to a vaccine already proven efficacious is attractive. Of course, risks of common complications may elude early safety surveillance in both animals and small numbers of humans. While exact numbers will not surface before testing, arguably the balance represents at least a (near-) Bayesian "tie" (see Table 1 below). Ethically, individuals' autonomy to participate in research, and the strong public health need to accelerate universal distribution with minimal post-marketing safety issues, permit RPAD.

Some ethicists who view harm as weightier than benefit may be tempted to deny that the risk of vaccination toxicity and enhanced COVID severity for RPAD participants could be justified by the prospective benefits to them from earlier access to potentially safe and efficacious COVID-19 protection. Note however that here, the risks and benefits all accrue to the *very same* people. It is surely permissible to offer autonomous people a "package" of potential harms and benefits that is *not* suspected of being significantly net-harmful to them (an offer that would benefit society).

Undermining public trust in vaccines?

Releasing a vaccine to 1 million participants, as RPAD does, without earlier safety evaluation in thousands, increases the likelihood that serious vaccine side effects might emerge in the RPAD participants. Some might worry that such serious risks would undermine public trust in the vaccine or in vaccines in general (20).

But this risk is precisely why the authorization prior to the RPAD emphatically remains "conditional." So long as the vaccine's "still experimental" status is forefronted, the risk of any safety issue emerging during the RPAD would parallel ones discovered in standard pre-marketing trials. It should be possible to communicate to participants through the informed consent process, and to the public through careful press releases, that safety testing is not over. Indeed, the chance of safety problems arising after final approval is smaller under RPAD than under either smaller safety studies following challenge trials or smaller field trials. RPAD would only make the ensuing product more trustworthy, shielding public trust.

Unfairly blocking early access to some?

The flipside of worry about releasing the vaccine too fast to some could be complaints about refusing to vaccinate others earlier. When a challenge trial finds the vaccine safe (albeit in a very small number of individuals) and efficacious (in young and healthy volunteers), perhaps the vaccine should be made widely available to high-priority populations more quickly (23). Is it fair to restrict early availability to RPAD participants only—perhaps not necessarily from high-priority groups; and, further, to condition it on their handing over personal medical information, as RPAD does?

Nothing prevents RPAD participants from being primarily high-priority subjects for vaccination, e.g., frontline health workers, other essential workers, those of advanced years, and so forth. Both in the US for first-generation vaccines (23, 24) and, even more so, in countries without the funds for large vaccine purchase contracts in advance of product efficacy testing (of either first- or later-generation vaccines), wide access will initially be capped by the limited supply of the vaccine; some members of high-priority

populations, somewhere, will not be immediately eligible—and RPAD could focus on recruiting such members. Additionally, experimental vaccines are normally available only through pre-approval studies, whose participants all share their medical information. During the RPAD, the vaccine remains experimental, justifying restricted release.

Administrative impossibility?

But will the US Food and Drug Administration (FDA) and its sister agencies abroad be willing, and legally authorized, to approve this innovative protocol? FDA's non-binding recommendations on SARS-CoV-2 vaccines do not include this idea (25).

But FDA recommendations do not envisage challenge efficacy testing in the first place (25). Our suggestion to FDA and its sister agencies is to consider coupling any future reliance on challenge testing (say, because placebo-controlled field trials are unethical once vaccines are in distribution) with RPAD. The latter would dovetail with directions that some approval agencies already pursue or were advised to pursue. Many countries already have "conditional" approval or systems for post-marketing surveillance, which generate rich information on vaccine safety (26). Even before the current crisis, there were calls for the FDA to take a lifecycle approach to evaluating drug efficacy and safety (19, 27). In the current crisis, the FDA has employed its "emergency use" authority to allow distribution of unapproved vaccines.

Conclusion

RPAD, a novel protocol type for vaccine safety testing following challenge trials, could cut precious time to SARS-CoV-2 vaccine distribution and better protect later vaccine recipients against rare vaccine complications. Four worries about RPAD are answerable, in part because RPAD would in prospect and on balance either benefit or not harm the central stakeholder populations (see Table 1). Approval agencies and vaccine producers should consider RPAD for safety testing following any coronavirus challenge trial with satisfactory efficacy and preliminary safety results.

Population		Major prospective benefits	Major risks	Balance
i. RPAD participants, compared to…	**…their nonparticipation in any trial**	Guaranteed early access to a vaccine with proven efficacy and with limited evidence of safety	a. Vaccine safety issues. b. A limited burden, from RPAD participation.	+ or ? or only a small net risk
	…their own participation in a safety evaluation enrolling a few thousand volunteers, following a challenge trial	0	0	0
	…their own participation in a field trial	a. Guarantee of early access to a vaccine with proven efficacy and limited evidence of safety (whereas in a field trial, control arm participants do not get such access during the trial, and even active arm participants get somewhat less advance assurance of safety and efficacy). b. Less burdensome than participating in a field trial	0	+
ii. The rest of the population, compared to how they would do following…	**…a challenge trial followed by a safety evaluation enrolling a few thousands**	The vaccine was tested in far more participants, and potentially proven free of serious events with incidence of >0.3/100,000.	0	+
	…a field trial	a. The vaccine was tested in far more participants, and potentially proven free of serious events with incidence of >0.3/100,000, potentially including the blood clots that conventional field trials of some authorized vaccines were unable to detect. b. Earlier full distribution than through reliance on a completed field trial.	0 (and see below.)	+
iii. **Members of key populations underrepresented in challenge trials, compared to how they would do following…**	**…a challenge trial followed by a safety evaluation enrolling a few thousands**	As above, as well as the ability to detect special safety issues distinctive to key populations (e.g., serious events with an incidence of 3/100,000 for a subgroup that represents 10% of the general population).	0	+
	…a field trial	Ditto	0 (A challenge would need to be followed by an immune bridging study to assess efficacy in those groups, and there are issues with efficacy information about such groups in field trials as well (28)).	+

Table 1: The balance of major prospective benefits and risks to three central populations from assessing COVID vaccine safety through an RPAD, following challenge-based efficacy testing. The balance of benefits and risks reflects the authors' reasoned judgment.

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Attestation

All authors attest they meet the ICMJE criteria for authorship.

Conflict of Interest Disclosures

NE, TG, and BLS declare having no conflicts of interests.

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