Response to Dawson et al

Dawson et al raise three concerns about human challenge trials to assess the efficacy of SARS-CoV-2 vaccines. First, that current scientific understanding is insufficient to know all the risks to volunteers, including potential long-term effects. However, assuming that the effects of artificial infection resemble those of natural infection, there is substantial evidence that, so long as only young and healthy people are recruited [1-4], the risk of death is comparable with that of live kidney donation [5]. Known and unknown non-lethal complications following infection are also possible, but based on the evidence to date [6], among young people, complications within the duration of follow-up that has been possible in the first months of this pandemic are likely to remain rare. It would be imperative that volunteers in challenge studies have a clear understanding of the known risks and of the possibility of yet unrecognized risks. That includes long-term risks whose frequency is unknowable, a familiar complication inherent in all first-in-human trials—including any phase III trials of novel SARS-Cov-2 vaccines.

Second, Dawson et al question whether autonomous decision making by volunteers overrides concerns about risk, given that "people often make decisions in irrational or idiosyncratic ways", suggesting that irrational decisions are likelier in this case than elsewhere. We note that over 25,000 individuals have already declared willingness to participate in SARS-Cov-2 challenge trials [7] and we think it unlikely that all of these are acting irrationally. Of course, not all may be suitable for a challenge trial and a thorough informed consent process should make a determination on each selected candidate. Procedures for obtaining fully comprehending

consent, familiar to research ethics since the 1980s, have been well established for novel interventions, including those for which risks are ill defined. Dawson et al note, “Given the inherent uncertainty in vaccine development, this kind of optimistic bias could lead people to take risks without seeing the associated benefits”. But this concern could apply to first-in-human vaccine trials, and even in Phase 3 SARS-Cov-2 vaccine trials there is, for example, an uncertain risk of the vaccine inducing enhancing COVID-19 disease [8].

Third, Dawson et al consider that the conduct of challenge studies would imperil public confidence in the COVID-19 research enterprise, potentially undermining the global response to the COVID-19 pandemic. This we question. So long as investigators are open about the possibility of rare events occurring, and this is made public knowledge, if rarely these events do occur (as might also happen in a conventional vaccine trials), we think it unlikely that COVID-19 research or public health response would be impacted, even if, rarely, a volunteer did have the misfortune to suffer from serious disease or died as a result of their participation.

We recognize that challenge trials would raise fewer ethical worries if it was possible to exclude all volunteers at high risk of serious disease, including those genetically predisposed, or if curative treatments existed. But even without these, the risks to volunteers must be balanced against the societal value of reducing the time to identifying efficacious vaccines against a disease which is causing a massive and relentless daily toll.

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