Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
NARRATIVE REVIEW

Testing SARS-CoV-2 vaccine efficacy through deliberate natural viral exposure

Nir Eyal1, 2, 3, *, Marc Lipsitch4

1) Center for Population-Level Bioethics, Rutgers University, New Brunswick, NJ, USA
2) Department of Health Behavior, Society and Policy, Rutgers School of Public Health, Piscataway, NJ, USA
3) Department of Philosophy, Rutgers University, New Brunswick, NJ, USA
4) Center for Communicable Disease Dynamics, Department of Epidemiology, Department of Immunology and Infectious Diseases, Harvard T. H. Chan School of Public Health, Boston, MA, USA

ABSTRACT

Background: A vaccine trial with a conventional challenge design can be very fast 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine candidates, and from the ability of developing countries and small companies to conduct it.

Aims: We set out to identify a challenge design that avoids this part of the long prior process.

Sources: Literature in trial design (including a proof of concept flu challenge trial by B. Killingley et al.), vaccinology, medical ethics, and various aspects of COVID response.

Content: A challenge design with deliberate natural viral exposure avoids the need to grow culture. This new design is described and compared both to a conventional challenge design and to a conventional phase III field trial. In comparison, the proposed design has ethical, scientific, and feasibility strengths.

Implications: The proposed new design should be considered for future vaccine trials.

Introduction

The UK government is planning to support severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) human challenge trials [1,2]. Conventionally performed, challenge trials require (among other things) growing virus in good manufacturing practice (GMP) conditions in specialized laboratories, a lengthy and complex process that may reduce some of their inherent speed advantage [3–5]. To streamline processes in SARS-CoV-2 vaccine testing, and in possible future challenge trials for other directly transmitted pathogens such as influenza, we propose a design that is free from that requirement. Briefly, both the dose escalation and the vaccine challenge trial are conducted by deliberately arranging human interaction that may result in infection. This design could be seen as a cross between conventional challenge trials and standard phase III field trials (herein, FTs). What we shall call a ‘challenge with a natural strain via human interaction’ (CNH) builds on a proof of concept done previously for flu [6]. As we show, it has scientific and logistical advantages over both FT and a conventional challenge trial using a defined strain with intranasal inoculation (CDI). We largely set aside other components of the debate on SARS-CoV-2 vaccine human challenge trials [7–15].

Three designs for vaccine efficacy testing

This section summarizes the characteristics of the design alternatives we consider (see Table 1).

Field trials (FTs)

In a standard phase III field trial (individually randomized controlled trial, or FT), participants (16, 17) are randomized to receive either the vaccine being investigated or a placebo. Several
months later, if and when enough of them become infected, differences in clinical outcomes and infection rates between the two arms indicate vaccine efficacy.

Conventional human challenge with a defined strain through intranasal virus inoculation (CDI)

In conventional challenge trials (CDIs), 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, are placed into isolation and are randomized to receive either the vaccine being investigated or some comparator (e.g. an existing vaccine or a placebo). After ample time for immune response, all are artificially exposed, 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. Treatments may be given to reduce the risk of progression to severe disease. Participants remain in isolation for long enough to prevent secondary transmission.

Challenge with natural exposure to a human infection (CNH)

In an alternative design, a ‘challenge with a natural strain through human interaction’ (CNH), isolated individuals are still randomized to vaccine or placebo, possibly only after being confirmed seronegative, and given time to develop an immune response. But in this design, they are then challenged by exposure to ‘infectors’: naturally infected community members with high viral loads, identified e.g. by providers of rapid-turnaround viral PCR testing—so infectors need not be symptomatic (yet)—or through regular testing of candidate infectors who report any fever or cough, to confirm the presence of SARS-CoV-2 and absence of other respiratory viruses. Included infectors then meet and interact under conditions of close contact with those in whom the vaccine is being tested (‘recipients’). To facilitate natural exposure, windows are kept shut and participants engage in active conversation, singing, or another close-contact activity. To address the likely variability both in infectors’ infectiousness (e.g. in their viral loads and droplet production) and in recipients’ susceptibility to infection, as well as remaining uncertainties about the readiest infection routes of SARS-CoV-2, it is useful to expose each recipient to multiple infectors through multiple group activities. The exposure pattern remains balanced between placebo and vaccine. Differences in clinical illness, infection rates, and/or viral loads between the active and placebo recipients (all blinded) then indicate vaccine efficacy. After the ‘exposure event’, participants remain in isolation to prevent secondary transmission.

Like all challenges [5], 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, because by the time the dose escalation is over, no person on whom it was done remains acutely infectious, infectors in the actual CNH must be different individuals. Dose escalation should be done with a panel of infectors 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.

Scientific desiderata

An exposure route and dose that mimic target use

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

Titration for likelier infection and mild disease

FT 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).

Generalizability to subgroups at high risk from infection

For trial safety reasons, challenge designs (either CDI or CNH) must exclusively recruit healthy young people [7,9], but target vaccine users include the old and those with risk factors for severe COVID [4,15,18].

Challenge trials followed by safety studies and emergency authorization could start giving high-risk groups indirect protection by e.g. creating a ‘ring’ of vaccinated essential workers around people in retirement homes, during which time an FT could be completed to assess the efficacy of directly vaccinating high-risk groups [19]. Once correlates of protection are identified, potentially through challenge trials [40], immune responses to the vaccine in higher-risk groups can indicate likely protection (or not) in these groups [7]. Either way, only widespread use of a vaccine will reveal its degree of protection for higher-risk subgroups, standard practice for e.g. influenza vaccines [21].

Information on disease severity outcomes

Challenge designs exclude participants at high risk for severe COVID disease if infected. Some commit to treating infected participants with antivirals at a predesignated time point. Thus, challenge designs would not produce information on the vaccine’s effect on severity, an important scientific disadvantage compared to FT.
Information on infection/shedding

It is important to learn the extent to which a vaccine prevents infection and/or reduces infectiousness among those vaccinated persons who do become infected. 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, without necessarily being at high risk of a severe outcome).

An FT may monitor participants for infection, including subclinical infection, perhaps by periodic viral testing and/or end-of-study serological testing for a non-vaccine antigen [16,17,22]. However, the scale of an FT 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. While in principle, FT could with difficulty assess secondary transmissions, current designs do not, and regulators do not expect them to [16]. Challenge trials could 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.

Standardization between trial participants

In CDI the strain and dose of the virus are fully standardized. This reduces variability in outcome and increases statistical power compared to either FT or CNH in which the strain and dose are not fully controlled. But there are some differences between the latter

---

**Table 2**

Three efficacy testing designs for coronavirus vaccines, and their respective strengths. More + signs ordinally designate presumed greater magnitude of benefits; more – signs denote presumed greater magnitude of harms

| Scientific desiderata | Field trials (FTs) | A conventional challenge—with artificial exposure to defined strain through intranasal inoculation (CDI) | Challenge with natural exposure to a human strain (CNH) |
|-----------------------|-------------------|-----------------------------------------------------------------|-------------------------------------------------|
| i. “Natural” exposure route and dose? | Yes | No | Yes |
| ii. Exposure titrated? | No | Yes | Yes |
| iii. Generalizable to subgroups at high risk from infection? | Yes (but may be underpowered to detect that, and subgroups at risk may self-isolate) | No | No |
| iv. Informativeness on disease severity outcomes? | Yes | No | No |
| v. Informativeness on infection/shedding? | Depends on design | 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 | + | + | + |
| i. Fast to reach the scientific endpoint, if the trial goes well? | + (many months in the field) | ++ (GMP + dose escalation + one short stage) | +++ (short dose escalation + one 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. Easy recruitment? | – – | – – | – – |
| iv. Resource-efficient? | + | ++ | +++ |
| v. Summary feasibility profile Safety | + | +++ | +++ |
| 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. Participants’ care in case of infection, disease, adverse event, or long-term sequelae | + | +++ | +++ |
| v. Expected number of vaccine-toxicity-induced adverse events, compared to no trial? | – – | – | – |
| vi. Expected number of severity-enhancement-induced adverse events, compared to no trial? | – – | – | – |
| vii. Expected number of trial-related illnesses due to SARS-CoV-2 exposure, compared to no trial? | – | – – | – |
| viii. Assurance against other-infection trial-related adverse events? | + | + | – |
| ix. Expected number of trial-induced adverse events, compared to no trial? | – – | – | – |
| x. Summary safety profile | + | + | + |
two as well. Exposure in an FT is not standardized at all. In CNH there is partial standardization. CNH can be planned so that multiple recipients share strain, approximate dose, and presumed route of exposure by interacting with the same infector(s) in the exact same way and for the same duration.

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 infector with a confirmed high viral load. He or she then artificially infects several secondary infectors through intranasal inoculation of nasal mucus; long enough afterwards for the secondary infectors’ infection to reach acute phase (verified by rapid-turnaround qPCR), each of the secondary infectors 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 most participants (the recipients) is natural. But in this variant all recipients are exposed to the same strain for mutual comparability. However, the similarity of the strain currently seems unimportant for infection and other outcomes, so the speed advantages of regular CNH seems more important.

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

**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 FT.

**Summary on scientific strengths**

CNH and FT are scientifically superior to CDI in relying on a ‘natural’ strain, dose, and exposure route. CNH is scientifically slightly superior to FT 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**

**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 FT. Instead of waiting months for natural exposure, in challenge trials exposure is immediate and efficacy outcomes emerge in weeks. CNH removes the need to grow virus under GMP. Once facilities are ready, and if all else goes well, CNH is probably the fastest approach to evaluating efficacy.

**Speed to identifying severe impediments to trial success in reaching an endpoint**

In an FT, only several months into the trial it can 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 [23]. 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 efficacy testing begins.

**Ease of recruitment**

FT must recruit tens of thousands of participants. Either challenge trial requires less than a hundredth the participants, and nearly 40,000 intended volunteers have declared their willingness to participate in challenge trials [24]. Recruiting infectors who are at the acute infection stage could be done by e.g. teaming up with a mobile qPCR testing service. Infectors are presumably not placed at great risk (they are already infected, and are not being vaccinated), so many locals in acute infection may be willing to take that role.

**Resource efficiency**

FTs are notoriously expensive. When multiple vaccine producers compete for participants [25], or when participants can receive a proven vaccine elsewhere, recruitment of thousands of participants can prove very hard. For challenge trials, converting isolation centres and hosting volunteers for many weeks is also expensive (Table 2 assumes, for simplicity, equally expensive). But challenge designs vary in this respect. 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 [26] and for small vaccine developers.

**Summary on feasibility**

Whether a successful trial is possible or not, answers will come faster with CNH than with CDI, which in turn is faster than FT. Given the urgency of a response to the pandemic, this may be the most crucial advantage of CNH. CNH is also more realistic than an FT for developed countries with an available proven vaccine, and more realistic than either FT or CDI for developing nations and small developers, given its need for fewer participants and lower technical demands.

**Safety**

**Participants’ risk of SARS-CoV-2 infection**

Any challenge design introduces a very high risk of infection, one that far exceeds the infection risk that participating individuals would have if they did not participate. But if immunity to COVID-19 disease after natural infection lasts years (even if immunity to the infection is shorter-lived), selecting challenge participants from geographical areas or from professions likely to have a high ongoing risk of infection would reduce the amount of incremental risk of infection from participation [7,12]. FT is free from that added risk.

**Safety of the route of exposure**

It has been proposed that challenge studies involving intranasal inoculation (like CDI) are somewhat safer than ones involving inhalation (like CNH) [6]. While there are also reasons to question the assumption [6], and while there is far more experience with the consequences of natural SARS-CoV-2 exposure than with intranasal inoculation, we shall assume that in that respect CDI is somewhat safer.

**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) [27] 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) [18,28]. 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 an FT because the infection probability per participant is, intentionally, higher.

Care of participants in case of infection, disease, adverse event, or long-term sequelae

When any medical event—including adverse events resulting from infection, from vaccine toxicity, or from disease enhancement—occurs to a participant during a challenge trial, they occur in a controlled medical environment, with early detection and the potential for immediate medical intervention. Likewise, should there be long-term sequelae in a challenge trial, it could be possible to guarantee excellent follow-up care to the tens or hundreds of participants, not a reasonable expectation for the tens of thousands of participants in an FT. So while an FT introduces less risk of infection, challenge designs may provide better prospects to those who experience adverse events, short-term severe disease, or long-term sequelae.

Expected number of vaccine-toxicity-induced adverse events, compared to no trial

The number of participants in a challenge trial who receive the vaccine is typically smaller than that in an FT by a factor of at least 100. That makes an FT far likelier to cause vaccine toxicity events (but see next subsection). Differences in numbers of participants between CDI and CNH are less substantial than the difference between either and FT.

Expected number of severity-enhancement-induced adverse events, compared to no trial

If the overall risk for adverse events from severity enhancement is similar in an FT per virally exposed participant, it remains higher in FT overall. This is for two reasons. First, for a given level of statistical precision, a challenge trial will require fewer participants to experience the outcome during the trial than a field trial would, so there would be fewer vaccinated participants during the trial who would be likely to get exposed to virus and potentially develop enhanced disease than in an FT of the same precision. Second, after a trial ends, vaccinated participants in either trial type would continue to have exposure to the virus, and there are far more vaccinated participants and hence opportunities for enhanced disease following an FT. For these two reasons, an FT is far likelier to have more participants experiencing enhanced disease, if it occurs at all, than a challenge trial.

There is an important subtlety here. Challenge trials alone will be too small to fully establish safety. Accordingly, when we proposed challenge trials for efficacy we noted the need to test the safety of the vaccine in a larger cohort of the same order of magnitude as that required for an efficacy trial (tens of thousands) [7]. Thus, the fair comparison is between challenge trial plus the associated safety study versus the FT, erasing some of the safety benefit of challenge trials in the two foregoing paragraphs. That said, participants in the larger safety study associated with a challenge trial would be enrolling after evidence of efficacy had been obtained in the challenge trial, making their participation a better ‘gamble; and a fairer package: they would be taking what is believed to be a low risk of adverse events in exchange for getting demonstrated protection from the vaccine.

Expected number of trial-related illnesses due to SARS-CoV-2 exposure, compared to no trial

An FT need not expose to virus anyone who would not not be exposed had the FT not taken place. Challenge trials of either type include deliberate exposures. That said, the protective selection criteria for a challenge of any form should keep severe COVID disease exquisitely rare in a challenge [9,11] except inasmuch as severity enhancement occurs in such groups after vaccination.

Expected total number of other infections for participants

CNH risks infecting recipients (and in some cases, infectors) with other infections, since there is no purification step for the virus. This, however, is a comparatively minor safety consideration.

Expected total number of trial-induced adverse events, compared to no trial

Events induced by both vaccine toxicity and severity enhancement are more likely to occur (and to be somewhat less manageable and carry sequelae that might be harder to treat fully) in an FT than in either type of challenge. Exposure-induced illness is likely to remain mild in either challenge study, unless there is severity enhancement. The probability of unintended secondary transmissions remains small, as does the significance of any non-SARS-CoV-2 infections. In these respects, a common worry that severe trial-induced adverse events would be unethical or undermine public trust [4,29] is arguably more likely to materialize under FT than under either challenge design.

Summary on safety

While FT has an important strength in adding nearly no risk of infection compared to non-participation in the trial, added risk following infection in challenge trials can be minimized by selecting individuals with low risk of complications and with an expected high future risk of infection, as well as by providing exceptional care during the trial and even thereafter if long-term sequelae result [7,9,10]. 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 an FT. Intranasal inoculation may be somewhat safer than natural inhalation, but for SARS-CoV-2 that difference is speculative.

Challenges have an important safety edge over FT in having fewer participants. Overall, therefore, FT 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) possible in the trial. If we knew in advance that the risk of such adverse events were negligible, FT would be safer overall. But a modest degree of concern about severe adverse events of any kind could tip the balance of cumulative risk in favour 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 serve to warn against challenge studies: “A single death or severe illness in an otherwise healthy volunteer would be unconscionable and would halt progress” [4]. FTs are preferred on that basis [4]. Given current uncertainty about the risk of the various types of adverse event, consistent application of
such onerous demands would have ruled out FTs as well. This reveals the excessive and implausible nature of these demands, which have affected recent US decisions on challenge trials.

Conclusion

The CNH design has real scientific advantages for testing the efficacy of SARS-CoV-2 vaccine candidates. A CNH is worth considering alongside or instead of a conventional challenge design (CDI) and a standard phase III (FT) design.

Author contributions

Conceptualization: NE and ML. Writing—original draft: NE and ML. Writing, review and editing: NE and ML.

Transparency declaration

NE declares having no financial conflicts of interest. He serves on the advisory board of 1DaySooner, an unpaid position. NE’s work was funded by NIAID (AI114617-01A1), Open Philanthropy, and NSF (2039320). ML discloses honoraria/consulting from Merck, Afinivax, Sanofi-Pasteur, Bristol Myers-Squibb, and Antigen Discovery, research funding (institutional) from Pfizer unrelated to COVID-19, and an unpaid scientific advice to Janssen, Astra-Zeneca, One Day Sooner, and Covavax (United Biomedical). ML’s work was supported by Grant Number U54GM088558 from the National Institute of General Medical Sciences, Open Philanthropy, and the Morris-Singer Foundation. The views expressed in this publication are those of the authors and not necessarily those of the US National Institutes of Health.

Acknowledgement

For helpful comments, the authors would like to thank Holden Karnofsky, Josh Morrison, and Jonathan Van-Tam.

References

[1] Devlin H. Coronavirus vaccine: Oxford team aim to start lab-controlled human trials. The Guardian; 2020.
[2] Kirka D. UK may take part in COVID-19 vaccine ‘challenge studies’. Telegraph 2020.
[3] Cohen J. Speed coronavirus vaccine testing by deliberately infecting volunteers? Not so fast, some scientists warn. Science 2020.
[4] Deming ME, Michael NL, Robb M, Cohen MS, Neuzil KM. Accelerating development of SARS-CoV-2 vaccines — the role for controlled human infection models. New Engl J Med 2020;383:e63.
[5] Who. Feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adults volunteers. Geneva: WHO; 2020.
[6] Killingley B, Enstone JE, Greaves J, Gilbert AS, Lambkin-Williams R, Cauchemez S, et al. Use of a human influenza challenge model to assess person-to-person transmission: proof-of-concept study. J Infect Dis 2012;205:35–43.
[7] Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccines licensure. J Infect Dis 2020;221:1752–6.
[8] Plotkin SA, Caplan A. Extraordinary diseases require extraordinary solutions. Vaccine 2020;38:3887–8.
[9] WHO Working Group for Guidance on Human Challenge Studies in COVID-19. Key criteria for the ethical acceptability of COVID-19 human challenge studies. Geneva: WHO; 2020. Contract No.: WHO/2019-nCoV/Ethics_criteria/2020.1.
[10] Shah SK, Miller FG, Darton TC, Duenas D, Emerson C, Lynch HF, et al. Ethics of controlled human infection to study COVID-19. Science 2020;368:832–4.
[11] Jamrozik E, Selgelid MJ. COVID-19 human challenge studies: ethical issues. Lancet Infect Dis 2020.
[12] Eyal N. Why challenge trials of SARS-CoV-2 vaccines could be ethical despite risk of severe adverse events. Ethics Hum Res 2020.
[13] Steel R, Buchak L, Eyal N. Why continuing uncertainties are no reason to postpone challenge trials for coronavirus vaccines. J Med Ethics 2020;46:808–12.
[14] Grady C, Shah S, Miller F, Danis M, Nicolini M, Ochoa J, et al. So much at stake: ethical tradeoffs in accelerating SARS-CoV-2 vaccine development. Vaccine 2020;38:5381–7.
[15] Kahn JP, Henry LM, Mastroianni AC, Chen WH, Macklin R. Opinion: for now, it’s unethical to use human challenge studies for SARS-CoV-2 vaccine development. Proc Nat Acad Sci 2020.
[16] Hhs, FDA, CBER. Development and licensure of vaccines to prevent COVID-19—guidance for industry. 2020.
[17] Lipsitch M, Kahn R, Mina MJ. Antibody testing will enhance the power and accuracy of COVID-19-prevention trials. Nat Med 2020;26:818–9.
[18] Corey L, Mascola JR, Fauci AS, Collins FS. Accelerating development of SARS-CoV-2 human challenge studies. Nat Rev Immunol 2020.
[19] Lipsitch M, Dean NE. Understanding COVID-19 vaccine efficacy. Science 2020;370(6518):763–5. https://doi.org/10.1126/science.abe5938.
[20] Douglas AD, Hill AVS. Immunological considerations for SARS-CoV-2 human challenge studies. Nat Rev Immunol 2020.
[21] Darvishian M, Bijlsma MJ, Hak E, van den Heuvel ER. Effectiveness of seasonal influenza vaccine in community-dwelling elderly people: a meta-analysis of test-negative design case-control studies. Lancet Infect Dis 2014;14:1226–39.
[22] Kahn R, Hitchings M, Wang R, Bellan SE, Lipsitch M. Analyzing vaccine trials in epidemics with mild and asymptomatic infection. Am J Epidemiol 2019;188:467–74.
[23] Blakely R, Philip C. Oxford vaccine team chases coronavirus to Brazil. The Times; 2020.
[24] 1DaySooner staff. The COVID challenge. 2020. Available from: www.thecovidchallenge.org.
[25] Hopkins JS, Loftus P. Coronavirus researchers compete to enroll subjects for vaccine tests. Wall Street J 2020.
[26] Jamrozik E, Selgelid MJ. Human infection challenge studies in endemic settings and/or low-income and middle-income countries: key points of ethical consensus and controversy. J Med Ethics 2020;1–5.
[27] Lipsitch M, Eyal N. Improving vaccine trials in infectious disease emergencies. Science 2017;357:153–6.
[28] Haynes BF, Corey L, Fernandes P, Gilbert PB, Hotez PJ, Rao S, et al. Prospects for a safe COVID-19 vaccine. Sci Transl Med 2020;12:eaax9948.
[29] Dawson L, Earl J, Livezey J. SARS-CoV-2 human challenge trials: too risky, too soon. J Infect Dis 2020;222:514–6.