



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.



Perspective

Prioritizing second-generation SARS-CoV-2 vaccines through low-dosage challenge studies

Bastian Steuwer^{a,b,*}, Euzebiusz Jamrozik^{c,d,e}, Nir Eyal^{a,f,g,*}^a Center for Population-Level Bioethics, Rutgers University, New Brunswick, NJ, USA^b Rutgers Biomedical and Health Sciences, Newark, NJ, USA^c Ethox Centre and Wellcome Centre for Ethics and Humanities, University of Oxford, Oxford, UK^d Monash Bioethics Centre, Monash University, Melbourne, Australia^e Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia^f Department of Philosophy, Rutgers University, New Brunswick, NJ, USA^g Department of Health Behavior, Society and Policy, Rutgers School of Public Health, Piscataway, NJ, USA

ARTICLE INFO

Article history:

Received 23 December 2020

Received in revised form 3 February 2021

Accepted 10 February 2021

Keywords:

Coronavirus

Vaccines

Human challenge studies

Research design

Ethics

ABSTRACT

The design of human challenge studies balances scientific validity, efficiency and study safety. This Perspective explores some advantages and disadvantages of 'low-dosage' challenge studies, in the setting of testing second-generation vaccines against COVID-19. Compared with a conventional vaccine challenge, a low-dosage vaccine challenge would be more likely to start, and start earlier. A low-dosage challenge would also be less likely to rule out a vaccine candidate that would have potentially been effective, particularly in certain target uses. A key ethical advantage of a low-dosage challenge over a conventional challenge is that both it and its dose escalation process are safer for each participant. Low-dosage studies would require larger numbers of participants than conventional challenges, but this and other potential disadvantages are less serious than they may initially appear. Overall, low-dosage challenges should be considered for certain roles such as prioritizing between second-generation vaccines against COVID-19.

© 2021 The Authors. Published by Elsevier Ltd on behalf of International Society for Infectious Diseases.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Challenge studies for SARS-CoV-2 vaccine efficacy testing

In controlled human infection studies ('challenge studies'), research participants, randomized into an intervention and a control group, are deliberately infected so that researchers can test interventions or investigate other scientific hypotheses. The UK government has announced its support for challenge studies for SARS-CoV-2, which began in early 2021 (Callaway, 2020). First-generation SARS-CoV-2 vaccines have high efficacy in protecting against disease (Grady, 2020), but the longterm safety and effectiveness of these vaccines are currently uncertain (Grady, 2020). Trials of first-generation vaccines were also not primarily designed to detect asymptomatic infection or transmission. By enabling control of the timing of infection, challenge studies excel at demonstrating vaccine efficacy against asymptomatic infection and transmission. Specific challenge designs can also permit

rigorous testing of the duration of vaccine protection and generate other information for improved control measures (Douglas and Hill, 2020; Levine et al., 2020; Eyal et al., 2021). Challenge studies may also help to refine dosing regimens of existing vaccines and determine the degree of protection against particular viral variants.

This Perspective explores the ethical and pragmatic advantages of 'low-dosage' challenge studies. This study design reduces risk to individual volunteers, and may also permit vaccine challenge studies to begin earlier and with greater likelihood after the commencement of initial viral dose escalation studies.

The low-dosage challenge

A low-dosage challenge study here refers to the use of a lower dose of wild-type virus (as opposed to an attenuated strain) than required in conventional challenge studies. In standard challenge study designs, the viral dose that is used is calculated to cause a sufficient proportion of participants in the placebo arm to reach one or more endpoints. Such endpoints can be either disease (e.g. determined by the presence of influenza-like illness), often expressed as 'clinical attack risk', or infection (determined by a

* Corresponding authors at: Center for Population-Level Bioethics, Rutgers University, 112 Paterson St, New Brunswick, NJ 08901, USA.

E-mail addresses: steuwer@cplb.rutgers.edu (B. Steuwer),

zeb.jamrozik@monash.edu (E. Jamrozik), neyal@cplb.rutgers.edu (N. Eyal).

virological endpoint such as viral load). A World Health Organization (WHO) group on SARS-CoV-2 challenge studies, which included one of the current authors, deemed ‘a 70% clinical attack risk for mild upper respiratory illness accompanied by shedding of SARS-CoV-2’ as a sufficiently high proportion for an efficient vaccine challenge study (World Health Organization, 2020).

Instead of a dosage aimed at 70% risk of influenza-like illness (ILI) in the placebo arm, a low-dosage SARS-CoV-2 challenge could aim at, for example, 35% risk of ILI in the placebo arm. Or it could aim for even lower disease risk (a quarter of the clinical attack risk, a tenth of it, and so forth). Or it could aim for a lower infection ratio (whether symptomatic or not) in the placebo arm, regardless of the clinical attack risk. This option appears suited to the role of prioritizing second-generation vaccines in terms of their impact on blocking infection as well as studying the mechanisms of infection, immunity, and (asymptomatic) transmission. By contrast, a SARS-CoV-2 clinical disease model with a 70% ILI risk would require infecting more than 70% of participants, since some infected participants would remain asymptomatic.

Importantly, to achieve the same statistical power as a conventional challenge study, a low-dosage challenge study would require a larger number of volunteers. The lower the dosage, the more volunteers would be needed. With adequate numbers of volunteers, a low-dosage challenge would have similar statistical power to a conventional challenge study.

In order to determine what (if any) viral dose meets the required endpoint target, challenge studies are nearly always preceded by a dose escalation study. Escalation begins by exposing a few volunteers to increasing doses of virus starting at a low dosage and ends if either (a) there are serious adverse events or (b) there is a sufficiently high rate of the endpoint (using this illustration, 35% of participants experiencing ILI or comparably many infections) being met. If neither occurs, dose escalation continues and further volunteers are exposed to a higher dose.

Others have recently explored different potential scientific applications of low-dosage challenge studies to COVID-19, for a host of non-vaccine-related uses (Hausdorff and Flores, 2021). We explore the advantages and potential disadvantages of low-dosage

challenge over conventional challenge designs in the particular role of developing second-generation vaccines: as an initial efficient test of experimental vaccine efficacy that determines which candidates proceed to standard phase 3 testing (herein, ‘field trials’) (Jamrozik and Selgelid, 2020; Douglas and Hill, 2020; Levine et al., 2020). The advantages and disadvantages are summarized in Table 1 below.

Advantages over conventional challenge designs

Guaranteed start

One worry concerning challenge studies is that there will be serious adverse events (SAEs) in the preceding dose escalation study before it reaches its desired endpoint. A low-dosage challenge would reduce the probability of this occurring, in so far as SAEs are less likely with a lower clinical endpoint target than that of a conventional challenge.

Earlier start

Even when all goes well in the dose escalation, the preliminary process typically takes many weeks and delays the start of vaccine challenge studies (Cohen, 2020; Deming et al., 2020). A dose escalation study with an endpoint reachable with fewer rounds of titration could save many weeks.

Not ruling out efficacious vaccines

Even in environments that put individuals at high probability of SARS-CoV-2 infection (e.g. sharing a berth on a ship, sitting next to an infectious train passenger for many hours), it is rare for $\geq 70\%$ of exposed individuals to be infected and become symptomatic (Liu et al., 2020; Payne et al., 2020; Hu et al., 2020; Prentiss et al., 2020; Popa et al., 2020). This is even less likely for young and healthy individuals, as challenge trial participants would be. So the vast majority of community-acquired infections may well be due to viral doses lower than the dose that would meet the WHO’s 70% ILI

Table 1
Select features of low-dosage challenge studies as compared with higher-dosage challenge studies, and the authors’ assessment of them as advantages (+ or ++), disadvantages (–) or neutral (0).

Feature	Authors’ assessment	Comments	
Pragmatic considerations	Shorter time to start	++	/
	Likelihood to start	++	/
	Larger financial cost and additional logistics	–	Less acute, given high investment in COVID-19 vaccine research
Scientific considerations	Avoiding type II errors of ruling out efficacious vaccines	++	/
	Avoiding type I errors of not ruling out inefficacious vaccines	0/–	Can be avoided if study is followed by a field trial, or by testing in a branching model together with high-dosage challenges
	External validity	0/+	Higher when there is standardization across multiple sites
Ethical considerations	Reducing risk to individuals	++	Risk reduction due to reduced infection risk and (possibly) dose-severity relationship
	Reducing risk to cohort	0	Unclear whether risk to cohort is higher or lower than conventional challenge trial; commensurate cohort risks with field trial

recommendation in a challenge trial's placebo arm. Low-dosage challenges may therefore be less liable to prematurely rule out vaccines with some degree of efficacy (that is, less liable to a type II error). Based on limited evidence, some vaccines seem to prevent infection via small viral exposures, yet fail against larger viral exposures (Langwig et al., 2019). A vaccine that prevents a significant fraction of community-acquired infections would have powerful herd immunity effects if widely administered, even if it were less efficacious at preventing (higher-dosage) infection or severe disease. Should high levels of herd immunity prove elusive with first-generation vaccines, it would be especially important to identify such a vaccine.

Compatibility with other designs

One approach to study program design would be a 'branching model', wherein different challenge studies are performed for different purposes with a single preliminary dose escalation study. Once a relatively low endpoint is met, the dose escalation study identifies the dose for a first, low-dosage challenge. After this first step, dose titration continues for a second higher dosage challenge study. The combined results of both challenge trials would provide more comprehensive information about potential vaccine performance. Unlike a pure low-dosage challenge, further escalation permits testing vaccine efficacy against higher exposures. Unlike a pure high-dosage challenge, vaccines that may be efficacious against some exposures would not be prematurely ruled out. Alternatively, a higher dose might be necessary for challenge studies to determine certain clinically useful immune correlates of protection. A further advantage of combining low-dosage and high-dosage studies would be to test how seropositive individuals react to vaccination. A branching model could for example test the hypothesis that vaccine boosting after immunity from past exposure results in greater overall protection. The coordination of these different challenge studies in a branching model could therefore increase efficiency and allow a wider array of hypotheses to be tested. A coordinated branching model may also permit the standardization of protocols for multi-site challenge studies. Such standardization could help to improve the external validity of results, increase overall statistical power and reduce the wastage of scientific resources (Roestenberg et al., 2012).

Reduced risk to individual participants

The main ethical advantage of a low-dosage challenge over a conventional challenge is the lower risk for each participant, in two ways. First, a lower viral dose is less likely to infect each individual participant; thus, each person entering the study faces a lower probability for severe outcomes. Second, there may also be a positive dose-response relation between viral dose and the severity of disease, which is a subject of ongoing scientific debate. There is strong evidence from measles (Perry and Halsey, 2004) and cholera (Cash et al., 1974), and weak evidence from SARS-CoV-1 (Chu et al., 2005) and SARS-CoV-2 (Imai et al., 2020; Rubin and Offit, 2020; Gandhi and Rutherford, 2020; Bielicki et al., 2020) that higher viral dosage causes more severe outcomes. In contrast, an influenza challenge study found no statistically significant dose-severity relationship (Memoli et al., 2015). Overall, there is no scientific reason to think that lower viral exposure could, upon infection, make COVID-19 more severe, and good reason to think that it could make it milder. In the face of continuing uncertainty, any reasonable decision-maker should assign some credence to this possibility.

That a low-dosage challenge is safer for each participant than a conventional challenge study addresses concerns that challenge studies must be too risky, even with careful participant selection

and provision of all available therapeutics (Deming et al., 2020; Rosenblatt, 2020; Shah et al., 2020; Kahn et al., 2020). Such concerns are naturally understood to refer to risks to individual participants (Shah et al., 2020), a classical focus of research ethicists (Rid and Wendler, 2011; Miller and Joffe, 2009; Resnik, 2012; London, 2009) and documents on human subject protection (Rid, 2014; Academy of Medical Sciences, 2005; Council for International Organizations of Medical Sciences and World Health Organization, 2016).

In principle, one could use progressively-lower doses to satisfy lower tolerances for risk to individual participants. Instead of half the risk of ILI (e.g. as suggested earlier, 35% instead of 70%), a lower individual dose could potentially aim at one-tenth that risk (with suitably many more volunteers), or at one-hundredth (ditto), and so forth. Since one could reduce dosage as much as desired, some low-dosage challenge designs should reduce risks such that no critic could dismiss them as too dangerous for individual participants.

Potential disadvantages compared to conventional challenges

Inability to test impact on disease

In all vaccine challenge studies, efficacy against severe disease is harder to detect than in vaccine field trials—precisely because of challenge studies' careful risk reduction strategies, including the exclusion of higher-risk groups (Corey et al., 2020). This limitation may seem to be accentuated in low-dosage challenge studies, which go to even greater lengths to prevent severe disease in the cohort. However, this limitation does not affect the usage of challenge studies to assess impact on infection rather than severe disease (as discussed above) and some other uses (Hausdorff and Flores, 2021).

Potential inefficacy against high-dosage exposures

Another seeming disadvantage of low-dosage challenges compared with conventional ones is their potential higher likelihood of selecting experimental vaccines that are insufficiently protective against high-dosage infections—the flipside of the advantage noted earlier and a type I error (Langwig et al., 2019). However, the doses associated with conventional challenge studies may be rare in target usage (as argued above) in mass population vaccination. Even if higher-dose exposures are common, relative inefficacy against high-dosage exposures would not necessarily undermine low-dosage challenge in their role of weeding out unpromising vaccine candidates in advance of field trials. The low-dosage challenge would help identify, for further study, those vaccine candidates that prevent infection against at least a low dosage. Field trials could then confirm efficacy in target usage.

Higher financial cost

Hosting a larger number of volunteers for an extended period in isolation, and consequently needing more staff hours or larger facilities, as low-dosage challenges require, would cost more. However, these economic costs appear to be outweighed by the benefits of enhanced disease control. Moreover, significant funds are now available for SARS-CoV-2 vaccine development, including challenge studies (Callaway, 2020).

Increased cumulative risk to the study cohort?

Finally, some concerns regarding excessive risk in challenge studies relate to something other than the risk to each participant, but the risk that someone in the cohort of challenge participants

will have a serious adverse event: ‘A single death or severe illness in an otherwise healthy volunteer would be unconscionable . . .’ (Deming et al., 2020; Guarino and Johnson, 2020). Nothing is said here about the probability of death or serious injury for any particular study participant.

First, it is unknown whether risk for the cohort is larger in a low-dosage challenge than in a conventional challenge. In the current illustration of low dosage, the risk of ILI per individual is on average half of what it would be in a conventional challenge, but for statistical reasons at least twice the number of volunteers would be needed. In that respect, the overall risk of SARS-CoV-2 infection in the cohort is higher in a low-dosage challenge. Nonetheless, following any particular infection, the individual risk of severe COVID-19 may remain significantly smaller at lower viral doses (again, a matter currently unknown). Combined, these two effects may increase or decrease overall cohort risk.

Second, either a low-dosage challenge or a conventional challenge study should be deemed cumulatively safe enough for study cohorts, in so far as their cumulative risk is on a par with that of vaccine field trials, which are widely accepted. In particular, vaccine field trials vaccinate > 100 times more participants than conventional challenge studies, and require more viral exposures (Heriot and Jamrozik, 2021). Further, vaccine field trials include risks of other adverse events from vaccine side-effects and potentially from increased risk behavior. Adding up these risks over the substantially larger cohort (tens of thousands of participants), and considering poorly characterized risks of disease severity enhancement (Peeples, 2020; Corey et al., 2020), which can take place in thousands of participants long after the study (Eyal and Lipsitch, 2021), a vaccine field trial may generate a greater cumulative risk of serious adverse events. All in all, a vaccine field trial is not clearly less risky for the cohort than challenge studies.

Conclusion

When using a challenge study to determine which vaccine candidates should be selected for further testing, low-dosage challenges can remove the main inherent barrier to conducting challenge studies, namely: the potential inexistence of a dose that is both safe enough and enables a study to reach useful endpoints. Additionally, low-dosage challenges permit decision-makers to proceed with vaccine challenge studies at an earlier point in dose escalation. They may mimic some target vaccine indications much better than conventional challenge studies. Low-dosage challenge studies would be less risky for each participant, as would their dose escalation processes. The disadvantages of low-dosage challenge studies over conventional challenge studies for triaging vaccine candidates may be less significant than they appear. Therefore, low-dosage challenges may be useful tools in expediting second-generation SARS-CoV-2 vaccine testing, and specifically in providing estimates of candidate vaccine impacts on infection to select promising candidates for further investigation.

Ethical approval

Approval was not required.

Funding

This work was supported by the NSF [2039320] and the Open Philanthropy Project to BS and NE, the NIAID at the NIH [AI114617-01A1] to NE, and the Wellcome Trust [203132/Z/16/Z and 216355/Z/19/Z] to EJ.

Conflict of interest

EJ previously served on two WHO working groups on SARS-CoV-2 challenge studies. NE serves on the advisory board for challenge trial intended-volunteer group 1DaySooner, an unpaid position.

Acknowledgements

The authors are grateful to Stephen John, Kate Langwig, Marc Lipsitch, Matt Memoli, Stanley A. Plotkin, Nadine Roupheal, participants of a dedicated session of the Center for Population-Level Bioethics (CPLB) seminar, and an anonymous reviewer for this journal for helpful comments.

References

- Academy of Medical Sciences. Microbial challenge studies of human volunteers—a guidance document from the Academy of Medical Sciences. 2005. <https://acmedsci.ac.uk/file-download/34796-Microbia.pdf>.
- Bielicki M, Züst R, Siegrist D, Meyerhofer D, Cramer GAG, Stanga Z, et al. Social distancing alters the clinical course of covid-19 in young adults: a comparative cohort study. *Clin Infect Dis* 2020;ciaa889, doi:<http://dx.doi.org/10.1093/cid/ciaa889>.
- Callaway E. Dozens to be deliberately infected with coronavirus in UK ‘human challenge’ trials. *Nature* 2020;586:651–2, doi:<http://dx.doi.org/10.1038/d41586-020-02821-4>.
- Cash RA, Music SI, Libonati JP, Snyder MJ, Wenzel RP, Hornick RB. Response of man to infection with *Vibrio cholerae*. I. Clinical, serologic, and bacteriologic responses to a known inoculum. *J Infect Dis* 1974;129:45–52, doi:<http://dx.doi.org/10.1093/infdis/129.1.45>.
- Chu CM, Cheng VCC, Hung IFN, Chan KS, Tang BSF, Tsang THF, et al. Viral load distribution in SARS outbreak. *Emerg Infect Dis* 2005;11:1882–6, doi:<http://dx.doi.org/10.3201/eid112.040949>.
- Council for International Organizations of Medical Sciences, World Health Organization. International Ethical Guidelines for Health-related Research Involving Humans. 2016. <https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>.
- Cohen J. Speed coronavirus vaccine testing by deliberately infecting volunteers? Not so fast, some scientists warn. *Science* 2020;2020, doi:<http://dx.doi.org/10.1126/science.abc0006>.
- Corey L, Mascola JR, Fauci AS, Collins FS. A strategic approach to COVID-19 vaccine R&D. *Science* 2020;368:948–50, doi:<http://dx.doi.org/10.1126/science.abc5312>.
- Deming ME, Michael NL, Robb M, Cohen MS, Neuzil KM. Accelerating development of SARS-CoV-2 vaccines – the role for controlled human infection models. *N Engl J Med* 2020;383:e63, doi:<http://dx.doi.org/10.1056/NEJMp2020076>.
- Douglas AD, Hill AVS. Immunological considerations for SARS-CoV-2 human challenge studies. *Nat Rev Immunol* 2020;20:715–6, doi:<http://dx.doi.org/10.1038/s41577-020-00472-0>.
- Eyal N, Caplan A, Plotkin SA. Human challenge trials of covid-19 vaccines still have much to teach us. *BMJ Opin* 2021;.
- Eyal N, Lipsitch M. Testing SARS-CoV-2 vaccine efficacy through deliberate natural viral exposure. *Clin Microbiol Infect* 2021;27:P372–7, doi:<http://dx.doi.org/10.1016/j.cmi.2020.12.032>.
- Gandhi M, Rutherford GW. Facial masking for COVID-19 – potential for “variation” as we await a vaccine. *N Engl J Med* 2020;383:e101, doi:<http://dx.doi.org/10.1056/NEJMp2026913>.
- Grady D. Early data show Moderna’s coronavirus vaccine is 94.5% effective. *New York Times*; 2020 11 November <https://www.nytimes.com/2020/11/16/health/Covid-moderna-vaccine.html>. [Accessed 3 February 2021].
- Guarino B, Johnson CY. Volunteers sign up to put their lives on the line for a coronavirus vaccine. *Washington Post*; 2020 15 June <https://www.washingtonpost.com/health/2020/06/15/volunteers-sign-up-put-their-lives-line-coronavirus-vaccine/>. [Accessed 3 February 2021].
- Hausdorff WP, Flores J. Low dose exposures to SARS-CoV-2 to understand and prevent severe COVID-19. *Int J Infect Dis* 2021;103:37–41, doi:<http://dx.doi.org/10.1016/j.ijid.2020.11.171>.
- Heriot GS, Jamrozik E. Not in my backyard? COVID-19 vaccine development requires someone to be infected somewhere. *Med J Aust* 2021;214:150–152.e1.
- Hu M, Lin H, Wang J, Xu C, Tatem AJ, Meng B, et al. Risk of coronavirus disease 2019 transmission in train passengers: an epidemiological and modeling study. *Clin Infect Dis* 2020;ciaa1057, doi:<http://dx.doi.org/10.1093/cid/ciaa1057>.
- Imai M, Iwatsuki-Horimoto K, Hatta M, Loeber S, Halfmann PJ, Nakajima N, et al. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. *Proc Natl Acad Sci* 2020;117:16587–95, doi:<http://dx.doi.org/10.1073/pnas.2009799117>.
- Jamrozik E, Selgelid MJ. COVID-19 human challenge studies: ethical issues. *Lancet Infect Dis* 2020;20:E198–203, doi:[http://dx.doi.org/10.1016/S1473-3099\(20\)30438-2](http://dx.doi.org/10.1016/S1473-3099(20)30438-2).
- 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 Natl Acad Sci 2020;117:28538–42, doi:<http://dx.doi.org/10.1073/pnas.2021189117>.
- Langwig KE, Gomes MGM, Clark MD, Kwitny M, Yamada S, Wargo AR, et al. Limited available evidence supports theoretical predictions of reduced vaccine efficacy at higher exposure dose. *Sci Rep* 2019;9:3203, doi:<http://dx.doi.org/10.1038/s41598-019-39698-x>.
- Levine MM, Abdullah S, Arabi YM, Darko DM, Durbin AP, Estrada V, et al. Viewpoint of a WHO advisory group tasked to consider establishing a closely-monitored challenge model of COVID-19 in healthy volunteers. *Clin Infect Dis* 2020; ciaa1290, doi:<http://dx.doi.org/10.1093/cid/ciaa1290>.
- Liu Y, Eggo RM, Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2. *Lancet* 2020;395:e47, doi:[http://dx.doi.org/10.1016/S0140-6736\(20\)30462-1](http://dx.doi.org/10.1016/S0140-6736(20)30462-1).
- London AJ. Clinical research in a public health crisis: the integrative approach to managing uncertainty and mitigating conflict. *Seton Hall L Rev* 2009;39:1173–202.
- Memoli MJ, Czajkowski L, Reed S, Athota R, Bristol T, Proudfoot K, et al. Validation of the wild-type influenza a human challenge model H1N1pdMIST: an A(H1N1) pdm09 dose-finding investigational new drug study. *Clin Infect Dis* 2015;60:693–702, doi:<http://dx.doi.org/10.1093/cid/ciu924>.
- Miller FG, Joffe S. Limits to research risks. *J Med Ethics* 2009;35:445–9, doi:<http://dx.doi.org/10.1136/jme.2008.026062>.
- Payne DC, Smith-Jeffcoat SE, Nowak G, Chukwuma U, Geibe JR, Hawkins RJ, et al. SARS-CoV-2 infections and serologic responses from a sample of U.S. Navy Service members – USS Theodore Roosevelt, April 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:714–21, doi:<http://dx.doi.org/10.15585/mmwr.mm6923e4>.
- Peebles L. News feature: avoiding pitfalls in the pursuit of a COVID-19 vaccine. *Proc Natl Acad Sci* 2020;117:8218–21, doi:<http://dx.doi.org/10.1073/pnas.2005456117>.
- Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis* 2004;189:S4–S16, doi:<http://dx.doi.org/10.1086/377712>.
- Popa A, Genger JW, Nicholson MD, Penz T, Schmid D, Aberle SW, et al. Genomic epidemiology of superspreading events in Austria reveals mutational dynamics and transmission properties of SARS-CoV-2. *Sci Transl Med* 2020;12:eabe2555, doi:<http://dx.doi.org/10.1126/scitranslmed.abe2555>.
- Prentiss M, Chu A, Berggren KK. Superspreading events without superspreaders: using high attack rate events to estimate N^2 for airborne transmission of COVID-19. *medRxiv* 2020;, doi:<http://dx.doi.org/10.1101/2020.10.21.20216895>.
- Resnik DB. Limits on risks for healthy volunteers in biomedical research. *Theor Med Bioeth* 2012;33:137–49, doi:<http://dx.doi.org/10.1007/s11017-011-9201-1>.
- Rid A, Wendler D. A framework for risk-benefit evaluations in biomedical research. *Kennedy Inst Ethics J* 2011;21:141–79, doi:<http://dx.doi.org/10.1353/ken.2011.0007>.
- Rid A. Setting risk thresholds in biomedical research: lessons from the debate about minimal risk. *Monash Bioeth Rev* 2014;32:63–85, doi:<http://dx.doi.org/10.1007/s40592-014-0007-6>.
- Roestenberg M, O'Hara GA, Duncan CJA, Epstein JE, Edwards NJ, Scholzen A, et al. Comparison of clinical and parasitological data from controlled human malaria infection trials. *PLOS One* 2012;7:e38434, doi:<http://dx.doi.org/10.1371/journal.pone.0038434>.
- Rosenblatt M. Human challenge trials with live coronavirus aren't the answer to a Covid-19 vaccine. *STAT News*; 2020 June 23. <https://www.statnews.com/2020/06/23/challenge-trials-live-coronavirus-speedy-covid-19-vaccine/>. [Accessed 3 February 2021].
- Rubin D, Offit PA. We know crowding affects the spread. It may affect the death rate. *New York Times*; 2020 April 27. <https://www.nytimes.com/2020/04/27/opinion/coronavirus-crowds.html>. [Accessed 3 February 2021].
- Shah SK, Miller FG, Darton TC, Duenas D, Emerson C, Fernandez Lynch H, et al. Ethics of controlled human infection to study COVID-19. *Science* 2020;368:832–4, doi:<http://dx.doi.org/10.1126/science.abc1076>.
- World Health Organization. Feasibility, potential value and limitations of establishing a closely monitored challenge model of experimental COVID-19 infection and illness in healthy young adult volunteers. 2020. <https://www.who.int/publications/m/item/feasibility-potential-value-and-limitations-of-establishing-a-closely-monitored-challenge-model-of-experimental-covid-19-infection-and-illness-in-healthy-young-adult-volunteers>.