Vaccine 38 (2020) 3987–3988

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Extraordinary diseases require extraordinary solutions

The world is experiencing a major pandemic with a high mortality. One can hope that the outbreak will end spontaneously after most people are infected, but the SARS-2 coronavirus may become endemic and continue to cause cycles of respiratory disease and fatal pneumonias. A vaccine that is shown to give immunity is the only practical way of preventing the virus from continuing to cause widespread serious and often fatal illness and economic destruction. Developing one and distributing an efficacious vaccine as quickly as possible is a moral imperative for the world.

Vaccine development is usually a long process, requiring years to move from animal tests to a series of human trials to regulatory licensure. Safety of a vaccine must be confirmed by extensive animal work, followed by the inoculation of dozens of humans, then escalating to thousands. The demonstration of efficacy normally depends on collecting and comparing cases in thousands of individuals who randomly receive vaccine or placebo [1]. That process normally takes months to years, during which SARS-2 will infect and possibly kill millions. Acceleration of that standard process is necessary.

However, the recognition that new viruses continue to emerge and cause human disease, often leading to epidemic diseases has stimulated vaccine developers to rethink the usual path of development. For example, this path was shortened in the case of the Ebola outbreak in West Africa by comparing disease in two regions, in one of which vaccine had been distributed. That process allowed demonstration of efficacy in 10 months from the first clinical trials [2]. Others, including ourselves, are proposing to obtain preliminary safety and efficacy data in human volunteers to accelerate use of an effective vaccine.

Considering the rapid spread of the SARS-2 coronavirus and its mortality rate, which exceeds that of the 1918–19 influenza epidemic, a vaccine is urgently needed [3]. Multiple candidates have been proposed and many are in clinical trials, but the question remains as to whether emergency use of a SARS-2 vaccine should await collection of controlled data from large populations that are experiencing epidemic SARS-2 disease or whether to expedite vaccination by moving quickly through animal studies and doing human challenge studies in volunteers [4]. Human volunteer challenge studies have been done previously with several agents, yielding important information [5,6]. Of course, such studies put volunteers at risk of disease and death and deaths have occurred in drug studies. The ethics of such trials, as well as their acceptability to regulators as a step towards emergency use of a candidate vaccine are foremost and require immediate discussion.

In the case of SARS-2 infection a challenge study could take advantage of the lower rate of death in 18–29 year olds. In that age group in China, the death rate was 0.03%, not negligible but relatively uncommon [7]. Nevertheless, a challenge study would require controls who receive no vaccine and who might become ill. Possible rescue treatments are being tested, such as remdesiver, convalescent serum, and other modalities which could be used in case of a severe disease after challenge, or administered as soon as virus positivity is confirmed [8]. Morally those volunteering would need to be free from coercion of any sort and their consent revalidated by research ethic committees. Volunteers might include those who are at high risk of exposure to the virus in the ordinary course of their work or living arrangements. Still, despite the danger we believe it is ethical to ask now for volunteers who would be informed about the known and unknown risks. They would be carefully screened and selected for their understanding of the risks for death and disability. Meanwhile, it will take some weeks to prepare a pool of challenge virus and to verify treatment modalities such as antivirals and antibodies. The availability of top tier researchers at high level medical facilities would be essential to the acceptability of these challenge studies.

The first step in a SARS-2 challenge study would be to administer virus to volunteers who have serologic evidence of prior infection. That step would determine whether immune responses are protective and give some information about which immune responses are important. Subsequent studies would include vaccinees and seronegative controls. Challenges would be done first with low doses to determine the minimal infectious dose. Analysis of immune responses in vaccinees who resist infection would give important information about correlates of protection, allowing judgments to be made about the probable efficacy of vaccines developed subsequently.

The production of a challenge virus under Good Manufacturing Practices conditions will take time and challenge studies should not be done before there is agreement among regulators and ethicists that the results of those studies are acceptable means to confirm efficacy. If vaccine development moves more rapidly perhaps challenge studies will not be necessary. However, regulators and ethicists should take into account the time required for an efficacy study and the likelihood that control groups in typical phase 3 efficacy studies of SARS-2 vaccines will suffer more deaths than in carefully done human challenges, to say nothing about simultaneous deaths in people not in the studies exposed to circulating virus. Moreover, it would be possible for regulators to allow emergency use based on the results of challenge studies, and to continue collecting data in the usual fashion for licensure at a later date. Deliberately causing disease in humans is normally abhorrent, but asking volunteers to take risks without pressure or coercion is

https://doi.org/10.1016/j.vaccine.2020.04.039

not exploitation but benefitting from altruism. We are aware of multiple offers from people willing to volunteer for the challenge studies. As Shakespeare put it, "Desperate diseases by desperate measures are relieved."

References

[1] Plotkin S, Robinson JM, Cunningham G, Iqbal R, Larsen S. The complexity and cost of vaccine manufacturing - An overview. Vaccine 2017;35(33):4064–71. doi: https://doi.org/10.1016/j.vaccine.2017.06.003.

[2] Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!). Lancet 2017;389(10068):505–18. doi: https://doi.org/10.1016/s0140-6736(16)32621-6.

[3] Taubenberger JK, Morens DM. The 1918 influenza pandemic and its legacy. Cold Spring Harb Perspect Med 2019. doi: https://doi.org/10.1101/cshperspect.a038695.

[4] Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. Preprint at DASH http://nrs.harvard.edu/urn-3:HUL.InstRepos:42639016 (March 24, 2020).

[5] Sherman AC, Mehta A, Dickert NW, et al. The future of flu: a review of the human challenge model and systems biology for advanceent of influenza vaccinology. Front Cell Infect Microbiol 2019 Apr;17(9):107. doi: https://doi.org/10.3389/fcimb.2019.00107.

[6] Lambkin-Williams R, Noulin N, Mann A, Catchpole A, Gilbert AS. The human viral challenge model: accelerating the evaluation of respiratory antivirals, vaccines and novel diagnostics. Respir Res 2018;19(1):123. doi: https://doi.org/10.1186/s12931-018-0784-1.

[7] Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 2020. doi: https://doi.org/10.1016/s1473-3099(20)30243-7.

[8] Yan Y, Shin WI, Pang YX, Meng Y, Lai J, You C, et al. The first 75 Days of novel coronavirus (SARS-CoV-2) outbreak: recent advances, prevention, and treatment. Int J Environ Res Public Health 2020;17(7). doi: https://doi.org/10.3390/ijerph17072323.

Stanley A. Plotkin *
Pediatrics, University of Pennsylvania, PA, USA
* Corresponding author at: 4650 Wismer Road, Doylestown, PA 18902, USA.
E-mail address: stanley.plotkin@vaxconsult.com

Arthur Caplan
Bioethics, New York University, NY, USA

Available online 20 April 2020