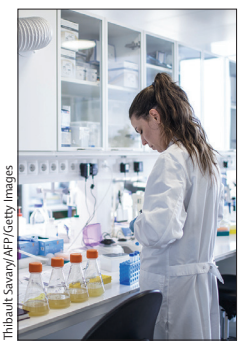
Encouraging results from phase 1/2 COVID-19 vaccine trials



Thibault Savary/AFP/Getty Images

Published Online
July 20, 2020
https://doi.org/10.1016/S0140-6736(20)31611-1

This online publication has been corrected. The corrected version first appeared at thelancet.com on August 13, 2020

See Articles pages 467 and 479

Dystopian realities generate utopian visions. The dramatic emergence of SARS-CoV-2 into our lives and the subsequent COVID-19 pandemic have spawned the active development of nearly 200 vaccine candidates.[1] Science reveals itself to the world in real time in all its glorious uncertainties, but also in all its careful, hard-won, and real achievements. As COVID-19 vaccine trials progress rapidly and with much expectation, two such achievements are published in *The Lancet*.[2,3]

The results of two early phase COVID-19 vaccine trials[2,3] are reported, one from investigators at the Jenner Institute at Oxford University (Oxford, UK), with support from AstraZeneca, and the second from investigators supported by CanSino Biologics in Wuhan, China. Both groups used an adenoviral vector, and both report the vaccine achieving humoral responses to the SARS-CoV-2 spike glycoprotein receptor binding domain by day 28 as well as T-cell responses. Both report local and systemic mild adverse events such as fever, fatigue, and injection site pain. In neither trial was a severe adverse event reported.

Andrew Pollard and colleagues report[2] their phase 1/2 randomised trial of one injection of chimpanzee adenovirus-vectored COVID-19 vaccine. Vaccine formulation at one concentration was tested against a comparator quadrivalent conjugate meningococcal vaccine among 1077 healthy adults (50% male, 90·9% white) aged 18–55 years (median 35 years, IQR 28–44), recruited from five centres in the UK and followed up for 28 days. Local and systemic adverse events such as fatigue, headache, and local tenderness occurred commonly in COVID-19 vaccinees, but were tolerable and mostly ameliorated by paracetamol. No serious adverse events occurred. Neutralising antibodies were generated in more than 90% of participants across different assays. Responses were sustained up to 56 days of observation. A small non-randomly selected, second-dose boosted subset showed strong neutralising responses, and few mild adverse events. Importantly, T-cell responses were induced in all participants.

Wei Chen and colleagues report[3] results from a phase 2 randomised trial of one injection of non-replicating adenovirus-vectored COVID-19 vaccine. Vaccine formulation at two concentrations (ie, 1×10^{11} or 5×10^{10} viral particles per mL) were tested against placebo among 508 healthy COVID-19 unexposed adults (50% male) aged 18-83 years (mean 39·7 years) recruited from one centre in Wuhan, China, and followed up for 28 days. Adverse events such as fever, fatigue, headache, or local site pain occurred by day 28 in 294 (77%) of 382 vaccinees and 61 (48%) of 126 placebo recipients. Male sex was associated with lower occurrence of fever post-vaccination. No serious adverse events occurred. Seroconversion occurred in more than 96% of participants, and neutralising antibodies were generated in about 85%. More than 90% had T-cell responses. People older than 55 years of age had somewhat lower humoral responses (although still higher than placebo), as did people with previous vector immunity, but these factors did not affect T-cell responses. Immunogenicity did not differ by sex.

These trial reports are hugely anticipated. The results of both studies augur well for phase 3 trials, where the vaccines must be tested on much larger populations of participants to assess their efficacy and safety. Overall, the results of both trials are broadly similar and promising, notwithstanding differences in the vector, in the geographical locations of the populations studied, and the neutralisation assays used. Without drawing causal inference, the exploration of associations of age and sex with adverse events and immunogenicity reported by Chen and colleagues, and of longevity of response by Pollard and colleagues, are welcomed, given the differential burden of severe outcomes in older adults, and the emerging science around differential sex-specific vaccine effects.[4] These COVID-19 vaccine trials are small so inferential caution is warranted, but the explorations are laudable. Ethnic diversity in both these trials was very limited.

Both trials used adenovirus vectors to deliver and study the COVID-19 vaccine, an innovative and efficient means of vaccine development in the midst of a pandemic. Capable of generating humoral, cellular, and innate responses, adenovirus-vectored vaccines have much potential. The platform only achieved European Commission regulatory licensure on July 1, 2020, with the Ebola vaccine. Much remains unknown about these and other COVID-19 vaccines in development, including longevity of response and immunogenicity in older adults or other specific

groups, such as those with comorbidities who are often excluded from clinical trials, or ethnic or racial groups more severely affected by COVID-19.[5–8] What should phase 3 trials look like? They should be rapid, pragmatic, and large enough to address efficacy in subgroups of interest. Will a single dose be sufficient in older adults, or is a booster dose required? Does longevity of response or rates of waning differ with a two-dose regimen, and does longevity of clinical protection require cell-mediated responses? Are there host-specific differences in immunogenicity by age, sex, or ethnicity? Do T-cell responses correlate with protection irrespective of humoral titres? Are there specific adverse events in pregnant women? As hotspots for infection shift, trial designs that are responsive to differential risk, or that are enriched for networks of infection, should be deployed.

The safety signals from these two important trials are reassuring. But when things are urgent, we must proceed cautiously. The success of COVID-19 vaccines hinges on community trust in vaccine sciences, which requires comprehensive and transparent evaluation of risk and honest communication of potential harms. Hand in hand with the trajectory of vaccine study, pharmacovigilance infrastructure is urgently needed, including surveillance for asymptomatic infection among vaccinated and unvaccinated persons if both absolute and relative risk of adverse vaccine outcomes, such as enhanced disease, are to be determined.[9] These should be implemented in parallel with phase 3 trials and in preparation for phase 4 roll-out. Such infrastructure will be needed across a wide range of populations and settings, and for the spectrum of upcoming COVID-19 vaccines.

Equitable distribution of future COVID-19 vaccines also requires detailed evaluation of local country needs and priorities, community engagement, and trust. Global planning is underway,[10,11] but should be underpinned and informed by specific local realities. Only this way can these very encouraging first early-phase randomised trial results yield the global remedy for which we all yearn.

We declare no competing interests.

*Naor Bar-Zeev, William J Moss
nbarzee1@jhu.edu

International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21231, USA

1 Lurie N, Sharfstein JM, Goodman JL. The development of COVID-19 vaccines: safeguards needed. *JAMA* 2020; published online July 6. https://doi.org.10.1001/jama.2020.12461.
2 Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; published online July 20. https://doi.org/10.1016/S0140-6736(20)31604-4.
3 Zhu F-C, Guan X-H, Li Y-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2020; published online July 20. https://doi.org/10.1016/S0140-6736(20)31605-6.
4 Bischof E, Wolfe J, Klein SL. Clinical trials for COVID-19 should include sex as a variable. *J Clin Invest* 2020; **130:** 3350–52.
5 Williamson EJ, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19 death in 17 million patients. *Nature* 2020; published online July 8. https://doi.org.10.1038/s41586–020–2521–4.
6 Price-Haywood EG, Burton J, Fort D, Seoane L. Hospitalization and mortality among Black patients and white patients with COVID-19. *N Engl J Med* 2020; **382:** 2534–43.
7 Truelove S, Abrahim O, Altare C, et al. The potential impact of COVID-19 in refugee camps in Bangladesh and beyond: a modeling study. *PLoS Med* 2020; **17:** e1003144.
8 Costantine MM, Landon MB, Saade GR. Protection by exclusion: another missed opportunity to include pregnant women in research during the coronavirus disease 2019 (COVID-19) pandemic. *Obstet Gynecol* 2020; **136:** 26–28.
9 Graham BS. Rapid COVID-19 vaccine development. *Science* 2020; **368:** 945–46.
10 Usher AD. COVID-19 vaccines for all? *Lancet* 2020; **395:** 1822–23.
11 The Lancet. Global governance for COVID-19 vaccines. *Lancet* 2020; **395:** 1883.

Childhood adversity and death of young adults in an affluent society

Adversity in childhood can induce health, social, and economic problems that persist throughout the adult years and might be fatal. Systems for child protection, poverty alleviation, and family support are designed to minimise harm, and it is reasonable to expect that the impact of adversity should be lowest in affluent countries that have comprehensive social services. However, research from high-income countries has shown startling links between childhood adversity and premature death. Brown and colleagues[1] in the USA, for example, followed up 17 000 adults who self-reported multiple adversities (eg, child abuse, neglect, and mental illness or imprisonment of a family member) and found that they died 19 years earlier than peers with no such adversities

See **Articles** page 489