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.

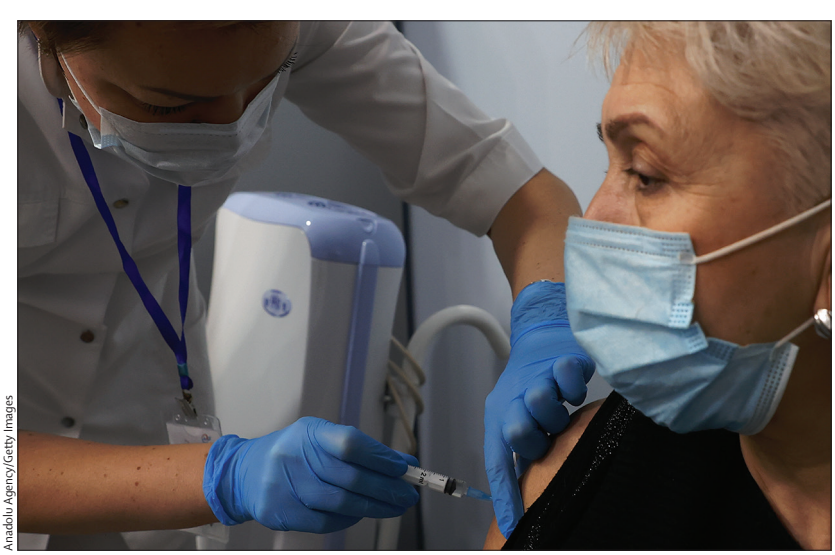
Sputnik V COVID-19 vaccine candidate appears safe and effective

Published Online
February 2, 2021
https://doi.org/10.1016/
S0140-6736(21)00191-4

See Articles page 671

Denis Logunov and colleagues[1] report their interim results from a phase 3 trial of the Sputnik V COVID-19 vaccine in *The Lancet*. The trial results show a consistent strong protective effect across all participant age groups. Also known as Gam-COVID-Vac, the vaccine uses a heterologous recombinant adenovirus approach using adenovirus 26 (Ad26) and adenovirus 5 (Ad5) as vectors for the expression of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein. The use of two varying serotypes, which are given 21 days apart, is intended to overcome any pre-existing adenovirus immunity in the population.[2] Among the major COVID vaccines in development to date, only Gam-COVID-Vac uses this approach; others, such as the Oxford–AstraZeneca vaccine, use the same material for both doses. The earlier vaccine for Ebola virus disease, also developed at Gamaleya National Research Centre for Epidemiology and Microbiology (Moscow, Russia), was similar, with Ad5 and vesicular stomatitis virus as the carrier viruses,[3] and the general principle of prime boost with two different vectors has been widely used experimentally.[4]

The recombinant adenovirus route to protection is shared with the Oxford–AstraZeneca vaccine, which uses a chimpanzee adenovirus (ChAdOx),[5] the Johnson & Johnson vaccine that uses only Ad26[6] whose detailed results are expected soon, and the CanSinoBIO-Beijing Institute of Biotechnology Ad5-based vaccine whose phase 3 trial began in September, 2020.[7] The carrier viruses are modified and cannot initiate a productive infection; they enter cells, express the spike protein, and then stop (because they cannot continue the normal virus lifecycle), although a high-sensitivity analysis also showed that a few Ad genes were expressed, albeit at a low level.[8] The vaccine-infected cells are eventually destroyed by the very immunity they are designed to elicit. Recombinant adenoviruses have been used widely as vaccine vectors because they can accommodate large genetic payloads and, although unable to replicate, they trigger the innate immunity sensors sufficiently to ensure robust immune system engagement.[9] Consequently, they do not need an adjuvant and can provide immunity after just a single dose.[4] Their physical robustness is thought to allow storage at temperatures around –18°C, which is feasible for many supply chains. The downside of recombinant adenovirus-based vaccines is that large doses are required, typically 10^{10} or 10^{11} particles, which makes large demands on the manufacturing and quantitation required for rollout on a global scale.



Anadolu Agency/Getty Images

What then of the Sputnik V COVID-19 vaccine data published here? The earlier phase 1/2 data published in September, 2020, showed promising safety results and gave an indication that the immune response was at a level consistent with protection.[10] Recipients generated robust antibody responses to the spike protein, which included neutralising antibodies, the proportion of the total immunoglobulin that inhibits the virus binding to its receptor. They also showed evidence of T-cell responses, consistent with an immune response that should not quickly wane. The interim report of the phase 3 data now presented[1] includes results for more than 20 000 participants, 75% of whom were assigned to receive the vaccine, and the follow-up for adverse events and infection. With a planned study power of 85%, those recruited were aged 18 years and older, were about 60% male, and were almost all white. Comorbidities, a known risk for COVID-19 severity, were present in about a quarter of those who entered the trial. 62 (1·3%) of 4902 individuals in the placebo

group and 16 (0·1%) of 14 964 participants in the vaccine group had confirmed SARS-CoV-2 infection from day 21 after first vaccine dose (the primary outcome). A time-resolved plot of the incidence rate in the two groups showed that the immunity required to prevent disease arose within 18 days of the first dose. That protection applied to all age groups, including those older than 60 years, and the anecdotal case histories of those vaccinated but infected suggest that the severity of disease decreases as immunity develops. Three fatalities occurred in the vaccine group in individuals with extensive comorbidities, and were deemed unrelated to the vaccine. No serious adverse events considered related to the vaccine were recorded, but serious adverse events unrelated to the vaccine were reported in 45 participants from the vaccine group and 23 participants from the placebo group. Vaccine efficacy, based on the numbers of confirmed COVID-19 cases from 21 days after the first dose of vaccine, is reported as 91·6% (95% CI 85·6–95·2), and the suggested lessening of disease severity after one dose is particularly encouraging for current dose-sparing strategies.

The development of the Sputnik V vaccine has been criticised for unseemly haste, corner cutting, and an absence of transparency.[11] But the outcome reported here is clear and the scientific principle of vaccination is demonstrated, which means another vaccine can now join the fight to reduce the incidence of COVID-19.

We declare no competing interests.

*Ian Jones, Polly Roy
i.m.jones@reading.ac.uk

School of Biological Sciences, University of Reading, Reading RG6 6AJ, UK (IJ); Department of Infection Biology, London School of Hygiene & Tropical Medicine, London, UK (PR)

1 Logunov DY, Dolzhikova IV, Shcheblyakov DV, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021; published online Feb 2. https://doi.org/10.1016/S0140-6736(21)00234-8.

2 Barouch DH, Kik SV, Weverling GJ, et al. International seroepidemiology of adenovirus serotypes 5, 26, 35, and 48 in pediatric and adult populations. *Vaccine* 2011; **29:** 5203–09.

3 Dolzhikova IV, Zubkova OV, Tukhvatulin AI, et al. Safety and immunogenicity of GamEvac-Combi, a heterologous VSV- and Ad5-vectored Ebola vaccine: an open phase I/II trial in healthy adults in Russia. *Hum Vaccin Immunother* 2017; **13:** 613–20.

4 Lu S. Heterologous prime-boost vaccination. *Curr Opin Immunol* 2009; **21:** 346–51.

5 Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397:** 99–111.

6 Sadoff J, Le Gars M, Shukarev G, et al. Safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial. *medRxiv* 2020; published online Sept 25. https://doi.org/10.1101/2020.09.23.20199604 (preprint).

7 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; **396:** 479–88.

8 Almuqrin A, Davidson AD, Williamson MK, et al. SARS-CoV-2 candidate vaccine ChAdOx1 nCoV-19 infection of human cell lines reveals a normal low range of viral backbone gene expression alongside very high levels of SARS-CoV-2 S glycoprotein expression. *Res Square* 2020; published online Oct 20. https://doi.org/10.21203/rs.3.rs-94837/v1 (preprint).

9 Liu J, Ewald BA, Lynch DM, et al. Magnitude and phenotype of cellular immune responses elicited by recombinant adenovirus vectors and heterologous prime-boost regimens in rhesus monkeys. *J Virol* 2008; **82:** 4844–52.

10 Logunov DY, Dolzhikova IV, Zubkova OV, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. *Lancet* 2020; **396:** 887–97.

11 Cohen J. Russia's claim of a successful COVID-19 vaccine doesn't pass the 'smell test,' critics say. *Science* 2020; published online Nov 11. https://doi.org/10.1126/science.abf6791.

Next-generation COVID-19 vaccines: here come the proteins

Published **Online**
January 29, 2021
https://doi.org/10.1016/S0140-6736(21)00258-0

See **Articles** page 682

Since publication in January, 2020, of genomic information about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] many efforts have been made around the world to develop a vaccine against this virus. Three vaccines with more than 90% efficacy are licensed and beginning roll-out in some countries as of January, 2021,[2–4] which is a true feat of scientific endeavour and international efforts. However, SARS-CoV-2 continues to be a major threat worldwide and development of new COVID-19 vaccines remains essential.

In *The Lancet*, Peter Richmond and colleagues[5] report their phase 1, first-in-human, dose-finding and adjuvant justification study testing a stabilised trimeric spike subunit protein vaccine (SCB-2019). This vaccine differs from those already approved as it uses a stabilised protein trimer as the antigen. The researchers used Trimer-Tag, a protein derived from the C-terminus of human type I procollagen,[6] which preserves the trimeric conformation of the SARS-CoV-2 spike protein and has not previously been used in clinical trials. Trimer-Tag technology provides an alternative trimer stabilisation strategy to the molecular clamp derived from HIV proteins.[7] A phase 1 clinical trial of a SARS-CoV-2 vaccine (NCT04495933) was halted in December, 2020, because