UK's vaccine against SARS-CoV-2 is safe and induces an immune reaction

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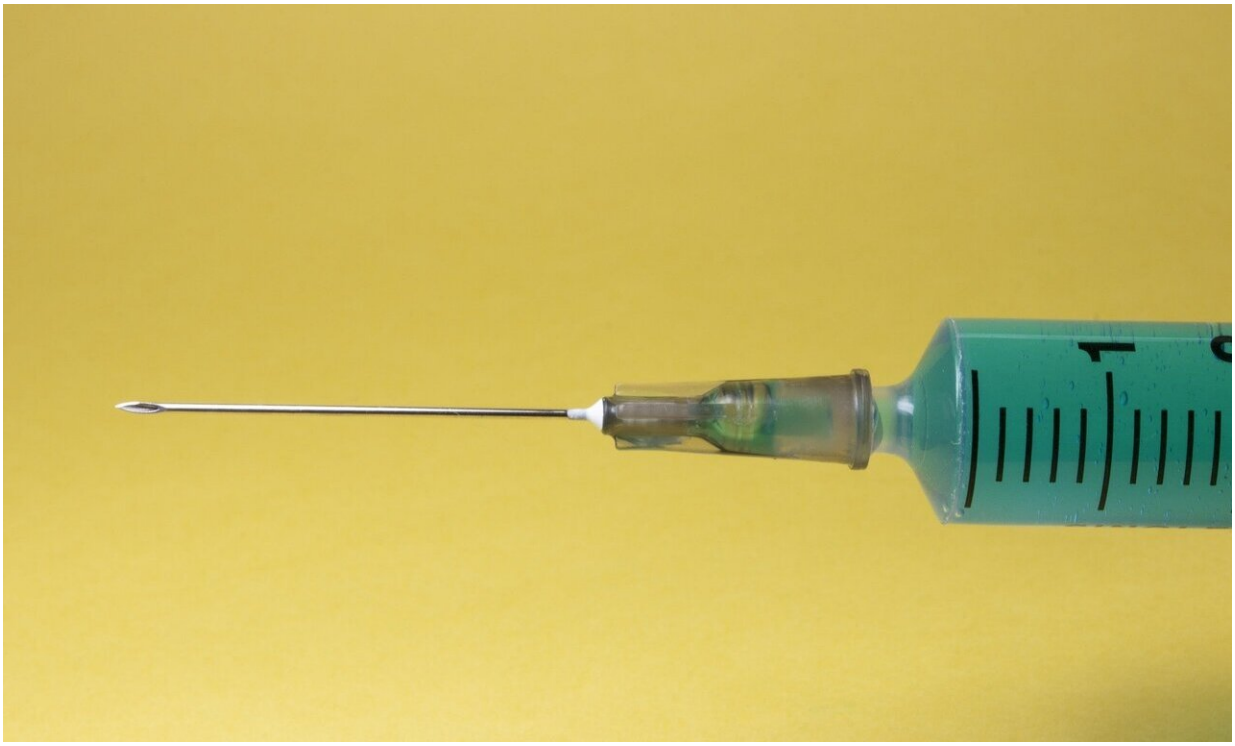

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Promising early stage results from a phase 1/2 clinical trial of the UK's vaccine candidate against SARS-CoV-2 (the virus that causes COVID-19) are published today in *The Lancet*.

The early stage trial finds that the vaccine is safe, causes few side

effects, and induces strong immune responses in both parts of the immune system—provoking a T cell response within 14 days of vaccination (ie, a cellular immune response, it could find and attack cells infected with the virus), and an antibody response with 28 days (ie, humoral immune response, it could find and attack the virus when it was circulating in the blood or lymphatic system).

An ideal vaccine against SARS-CoV-2 should be effective after one or two vaccinations, work in target populations including older adults and those with other health conditions, confer protection for a minimum of six months, and reduce onward transmission of the virus to contacts. The current trial is too preliminary to confirm whether the new vaccine meets these requirements, but phase 2 (in the UK only) and phase 3 trials to confirm whether it effectively protects against SARS-CoV-2 infection are happening in the UK, Brazil and South Africa.

Explaining how the vaccine works, study lead author Professor Andrew Pollard, University of Oxford, UK, says: "The new vaccine is a chimpanzee adenovirus viral vector (ChAdOx1) vaccine that expresses the SARS-CoV-2 spike protein. It uses a common cold virus (adenovirus) that infects chimpanzees, which has been weakened so that it can't cause any disease in humans, and is genetically modified to code for the spike protein of the human SARS-CoV-2 virus. This means that when the adenovirus enters vaccinated people's cells it also delivers the spike protein genetic code. This causes these people's cells to produce the spike protein, and helps teach the immune system to recognise the SARS-CoV-2 virus."

He continues: "The immune system has two ways of finding and attacking pathogens—antibody and T cell responses. This vaccine is intended to induce both, so it can attack the virus when it's circulating in the body, as well as attacking infected cells. We hope this means the immune system will remember the virus, so that our vaccine will protect

people for an extended period. However, we need more research before we can confirm the vaccine effectively protects against SARS-CoV-2 infection, and for how long any protection lasts."

The new trial included 1,077 healthy adults aged 18-55 years with no history of COVID-19, and took place in five UK hospitals between 23 April and 21 May 2020. The data included in the paper covered the first 56 days of the trial and is ongoing.

The participants either received the new COVID-19 vaccine (543 people) or the meningococcal conjugate vaccine (534 people). 113 participants (56 given the COVID vaccine, and 57 in the control group) were also asked to take paracetamol before and for 24 hours after their vaccination to help reduce vaccine-associated reactions (as the COVID-19 vaccine was given in a high dose to help induce a strong immune response).

All participants gave additional blood samples and underwent clinical assessments to determine if the vaccine was safe and whether it provoked an immune response. Participants were also asked to record any adverse events throughout the trial.

The participants were split into four groups. Group 1 (88 people) had additional safety monitoring to form the phase 1 part of the trial, and had antibody and T cell responses assessed. Group 2 (412 people) had extra blood taken to assess for antibody and T cell responses, and group 4 (567 people) had serum taken to assess for antibody response only. In groups 1, 2 and 4 half the participants received the COVID-19 vaccine and half received the control vaccine. Group 3 (10 people) received only the COVID-19 vaccine, and were given an extra dose of vaccine 28 days after the first dose to determine safety and whether this boosted antibody and T cell responses.

The vaccine was found to have an acceptable safety profile and there were no serious adverse events. Fatigue and headache were the most commonly reported reactions (around 70% [340/487] of all participants given the COVID-19 vaccine only reported fatigue, and 68% [331/487] reported headache, compared with around 48% [227/477] and 41% [195/477], respectively, of participants in the control group without paracetamol). Other common side effects included pain at the injection site, muscle ache, malaise, chills, feeling feverish, and high temperature.

Participants taking paracetamol around their vaccination had reduced pain, chills, feeling feverish, muscle ache, headache, and malaise in the two days following vaccination. In addition, in the 10 people who received the extra dose of the COVID-19 vaccine, side effects were less common after the second dose.

The authors found that there were strong antibody and T cell responses from the vaccine. T cell responses targeting the SARS-CoV-2 spike protein were markedly increased (in the 43 participants studied), peaking 14 days after vaccination (median 856 spot-forming cells per million peripheral blood mononuclear cells), with this level declining slightly by day 56 of the trial (to median 424 spot-forming cells per million peripheral blood mononuclear cells) . The T cell response did not increase with a second dose of the vaccine, which is consistent with other vaccines of this kind.

Antibody responses peaked by day 28 (median 157 ELISA units—studied in 127 participants) and remained high until the measurement at day 56 in the trial (median 119 ELISA units—studied in 43 participants) for those given a single vaccine. This response was boosted by a second dose (median 639 ELISA units at day 56 in these 10 participants).

28 days after vaccination, neutralising antibody responses against SARS-

CoV-2 were detected in 32 of 35 participants (91%) (when measured in MNA80 neutralisation assay), and in 35 of 35 participants (100% - when measured in PRNT50 neutralisation assay) who received a single dose of the COVID-19 vaccine. These responses were present in all participants who had a booster dose of the vaccine (nine of nine participants in MNA80 assay at day 42, and ten of ten in Marburg VN assay on day 56).

The authors found that taking paracetamol did not affect immunogenicity of the COVID-19 vaccine.

Co-author, Professor Sarah Gilbert, University of Oxford, UK, says: "There is still much work to be done before we can confirm if our vaccine will help manage the COVID-19 pandemic, but these early results hold promise. As well as continuing to test our vaccine in phase 3 trials, we need to learn more about the virus—for example, we still do not know how strong an immune response we need to provoke to effectively protect against SARS-CoV-2 infection. If our vaccine is effective, it is a promising option as these types of vaccine can be manufactured at large scale. A successful vaccine against SARS-CoV-2 could be used to prevent infection, disease and death in the whole population, with high risk populations such as hospital workers and older adults prioritised to receive vaccination."

The authors note some limitations, including that more research is needed to confirm their findings in different groups of people—including older age groups, those with other health conditions, and in ethnically and geographically diverse populations. The authors note that these groups are being recruited in their ongoing phase 2 and 3 trials of the vaccine in the UK, Brazil and South Africa. In the current trial, 91% (979/1,077) of participants were white and the average age of participants was 35 years.

They also note that a small number of participants had detectable

neutralizing antibodies and T cell responses against SARS-CoV-2 spike protein before vaccination, likely to be due to past asymptomatic infection as potential participants with recent COVID-19-like symptoms or with a history of positive PCR test for SARS-CoV-2 were excluded from the study.

The authors say the participants recruited in this study will be followed-up for at least one year to continue to study the vaccine's safety and the immune response it provokes.

Writing in a linked Comment discussing both Articles, lead author Assistant Professor Naor Bar-Zeev (who was not involved in the two studies), International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, USA, says: "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... 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."

However, he warns of the preliminary nature of the two vaccine candidates. He continues: "The platform [adenovirus vectored vaccines] 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."

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