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Safety and efficacy of the Russian COVID-19 vaccine: more information needed

Authors' reply

We thank Enrico Bucci and colleagues for their Correspondence about our open, non-randomised phase 1/2 studies of a recombinant adenovirus type 26 (rAd26) and recombinant adenovirus type 5 (rAd5) vector-based heterologous prime-boost COVID-19 vaccine from Russia.[1]

Here we respond to their Correspondence and to the comments in their open letter.

First, in each figure describing vaccine immunogenicity, numerical values for studied individuals (shown as single dots in the graphs) could be easily determined as corresponding to values indicated on the Y axis. We think that such visualisation of experimental data (showing individual values) is more informative than bars or box plots (which are equally used in scientific articles).

Second, Bucci and colleagues have the impression that some figures contain repeated patterns in the data. We would like to elaborate on this point in greater detail.

In panel A of figure 2,[1] we show that from day 21 to day 28, the values of antibody titres in participants vaccinated with rAd26-S alone did not change. Namely, after double titration, the values of optical densities in the ELISA experiments did not increase by values that allowed progress to the next titration step. To us it is obvious that after a single immunisation, the peak of the immune response is reached 3–4 weeks later. Immunity indicators can reach a plateau, which we observed in the study. Moreover, given the two-fold titration step and the discrete nature of the data, the number of values that a variable can take is limited (800, 1600, 3200, 6400). Accordingly, it is not improbable to obtain the same patterns on the response plateau in small samples.

Comparing IgG titres 21 days after injection of the liquid form of Ad5-S and the lyophilised form of Ad26-S, we underline that geometric mean titres (GMT) as well as individual values are different in indicated groups. In numerous experiments, we showed that the titre of receptor-binding domain-specific antibodies with the introduction of rAd5 was, on average, higher than for Ad26. Similar patterns of value distribution in these cases can be associated with a small number of volunteers in each of the groups (only nine participants) and a small number of discrete values that the variable can take (five dilutions in total).

Next, in most of the participants, antibody titres on days 21 and 28 after a single injection of the lyophilised formulation of rAd5 did not differ. Yet two participants with initially low titres (50 and 400), who Bucci and colleagues seem to have overlooked when describing their concerns about repeated patterns, showed increased titres by 28 days (up to 800). In general, as can be seen from panel A of figure 2,[1] in most participants receiving a single injection of individual components of the vaccine, titres differed slightly or did not change at all in all four studied groups between 21 days and 28 days. This is associated with the peculiarities of the formation of the humoral immune response and the employed method of detection. Again, the antibody response reaches a plateau 21 days after a single vaccination, and titres have generally not changed by the 28th day.

Bucci and colleagues notice that patterns in neutralisation titres (figure 2C[1]) are identical between two groups. They are in fact not identical: the GMTs are different, and the datapoints they have highlighted do not include all individual values in the studied groups. In general, given the higher immunogenicity of rAd5 compared with rAd26, there is nothing strange in detecting that 14 days after the administration of rAd5, the neutralising antibody titres are similar to the neutralising antibody titres at later periods of rAd26 administration. Moreover, given the discreteness of the data (the neutralising antibody titre can take values of 5, 10, 20, 40, etc, with a two-fold step), it is not surprising that participants from different groups have the same neutralising antibody titres.

In figure 3,[1] we present median CD4+ and CD8+ T cell proliferation in percentages, and we detected from 0·1% and higher with a step of 0·1%. 0·1% was the minimum detectable response rate observed in our study. It is not surprising that with an early response, the participants have a minimum value that is discretely estimated at 0·1%. At later timepoints, when the lymphoproliferation is much more significant, such patterns are not formed, as seen in figure 3.[1] It was not unexpected to find that most participants on days 0 and 14 of the study did not show a proliferation in CD4+ and CD8+ cells, and that only a few participants did. In this case, given the indicated step (0·1%) of the presented data, it is also not surprising that participants from different groups before vaccination (0 day) and at first timepoint (14 day) could have the low percentage proliferation values (eg, 0·1%) that cannot be distinguished by our method.

The results showed that when the components were administered separately, and especially at the initial timepoints, there was no significant increase in the number of proliferating CD4+ and CD8+ T cells. Furthermore, as in the case of IgG titre determination, significant differences and scatter of values are observed at later follow-up timepoints, especially in the groups that received the vaccine according to the prime-boost scheme.

Moreover, not all group values are similar. For example, the datapoints in figure 3[1] that Bucci and colleagues highlight in purple boxes in their open letter (containing one value

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For the **open letter** see https://cattiviscienziati.com/2020/09/07/note-of-concern/

each) are different. In panel C of figure 3, CD8+ T cell proliferation is 0·7%, and in panel A, CD4+ T cell proliferation is 0·6%.

In figure 4, in two groups of nine people, seven had undetectable neutralising antibody titres to recombinant adenovirus on day 0. In two volunteers from each group, neutralising antibody titres were 50 and 200. Since the data are discrete, it is not unusual to find a couple of volunteers with the same antibody titres before vaccination.

We confirm that no increase was detected in the titre of antibodies to Ad5 on days 0 and 28 after administration of Ad26. In one participant with antibodies to Ad5, there was no change in the titre of antibodies to Ad5 after administration of Ad26, which confirms the conclusion that there was no cross-reactivity between immune response to different components of the vaccine.

We would like to note, as in the case of the immune response to the target antigen, the scatter of the neutralising antibody titres to recombinant adenovirus in groups with a large number of participants (20 people in groups vaccinated with both components) is much wider than when analysing data in small groups of nine people before vaccination, which is quite logical.

In the methods section of our Article,[1] we provide information about convalescents. To summarise, convalescent plasma was obtained from people who had a laboratory-confirmed COVID-19 diagnosis, had been recovered for at least 2 weeks, and tested negative by PCR twice. The average time from recovery to convalescent plasma collection was about 1 month. Convalescent plasma was collected from people who had mild (fever ≤39°C without pneumonia) and moderate (fever >39°C with pneumonia) disease severity.

Third, Aug 3, 2020, was the last timepoint included in publication for all participants from the phase 2 trial (20 plus 20 participants). 42 days before, all of them were vaccinated (in one day) with rAd26-S. We also want to underline that the second phase of the trial started almost in parallel with the phase 1 trial. June 18, 2020, was day of first vaccination for all participants in the phase 1 trial. Thus, we had enough time (almost 1 month) to collect all blood samples, analyse them, and prepare the manuscript for publication. Indeed, neither clinical trial is finished at the time of writing this Correspondence. One more patient visit (180 days after vaccination) is planned according to protocols, as mentioned in the Article.[1] Data from this timepoint will be published in due course.

We would like to emphasise that all presented data were obtained in experiments and double checked. The coincidences that emerged, especially at the early points (values are low and are close to baseline), are associated with the discreteness of the data, as well as with the small number of participants in the groups. We acknowledged this as a limitation of the study in the discussion section of the Article.

We confirm that individual participant data will be made available on request to DYL and that after approval of a proposal, data can be shared through a secure online platform.

We receive funding from the Ministry of Health of the Russian Federation and have a patent pending for the use of vector constructs for the induction of immunity to severe acute respiratory syndrome coronavirus 2 pending.

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1 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; published online Sept 4. https://doi.org/10.1016/S0140-6736(20)31866-3.